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Original article

Sentinel Lymph Node Metastasis in Breast Cancer: The First Libyan Report with Hormonal Profiling and International Comparison

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Abstract
Sentinel lymph node biopsy (SLNB) has become the gold standard for axillary staging in early-stage breast cancer, significantly reducing the morbidity associated with full axillary lymph node dissection. This study represents the first systematic evaluation of SLNB in a Libyan patient population, with integration of multimodal pathological assessment and hormonal profiling. Twenty women with histologically confirmed invasive breast carcinoma underwent SLNB at Alhelal and Alzuhor University Hospitals between 2023 and 2025. Intraoperative touch imprint cytology, hematoxylin and eosin staining, and pancytokeratin immunohistochemistry were performed to detect nodal metastasis. SLN metastasis was observed in four patients (20%), with macrometastases identified in three and micrometastasis in one case—detected only by immunohistochemistry. Hormonal receptor analysis showed heterogeneity, with strong ER/PR positivity in the micrometastatic case. These findings underscore the essential role of immunohistochemistry in nodal staging and align with regional and international data.
Keywords. *Sentinel Lymph Node Biopsy, Breast Cancer, Immunohistochemistry, Libya, Metastasis, Hormone Receptor Status.*

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Introduction

Breast cancer remains the most frequently diagnosed cancer and the leading cause of cancer-related mortality among women worldwide, accounting for approximately 2.3 million new cases and 685,000 deaths in 2020 [1]. Over the past two decades, major advancements in diagnosis, surgical management, and adjuvant therapies have transformed early-stage breast cancer treatment. One such innovation is sentinel lymph node biopsy (SLNB), a minimally invasive technique that has largely replaced conventional axillary lymph node dissection (ALND) for staging clinically node-negative patients [2,3].

SLNB provides accurate nodal staging while reducing the risk of complications such as lymphedema, sensory neuropathy, and restricted shoulder mobility [3,4]. The technique has been extensively validated in randomized trials, including NSABP B-32 and ACOSOG Z0011, demonstrating its safety and efficacy in selected patient groups [5,6]. Furthermore, advances in pathological techniques—such as serial sectioning and immunohistochemistry—have improved the sensitivity of detecting micrometastases and isolated tumor cells in sentinel lymph nodes, with implications for prognosis and treatment planning [7,8].

Despite widespread adoption of SLNB in high-resource settings, data from low- and middle-income countries—including North African nations—remain limited. Libya, in particular, remains under-represented in global oncology literature, resulting in a knowledge gap that hinders evidence-based national guidelines.

This study addresses this gap by presenting the first Libyan experience of SLNB in breast cancer. Our study was conducted to evaluate nodal metastasis detection via multimodal pathological protocols; to analyze hormonal receptor profiles among cases with nodal involvement; and to compare our findings with regional and international cohorts.

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Methods

Study design and population

This prospective observational study included female patients diagnosed with invasive breast carcinoma who underwent surgical treatment at Alhelal and Alzuhor University Hospitals, Misrata, Libya, between January 2023 and March 2025. All patients were evaluated at the university-affiliated oncology clinics and referred for sentinel lymph node biopsy (SLNB) following initial diagnosis.

Inclusion and exclusion criteria

Eligible participants were adult women (>18 years) with histologically confirmed invasive breast carcinoma who had no clinical or radiological evidence of axillary lymph node metastasis. Axillary nodal status was assessed preoperatively via physical examination, CT scan, and axillary ultrasonography. Exclusion criteria included: prior axillary surgery, receipt of neoadjuvant chemotherapy or radiotherapy, recurrent breast cancer, or pregnancy.

Sentinel lymph node identification technique

The sentinel lymph node (SLN) was identified using the vital dye method. A 1–2 mL injection of 1% methylene blue dye was administered periareolarly 10–15 minutes before skin incision. Gentle massage was performed to facilitate lymphatic uptake. During surgery, blue-stained lymphatic vessels and nodes were visually identified and excised. Only blue nodes were designated sentinel lymph nodes and submitted for evaluation.

Intraoperative cytological assessment

Immediately upon excision, the SLNs were bisected along their longitudinal axis. Touch imprint cytology (TIC) was performed by gently pressing the cut surface of the node onto clean glass slides. The slides were fixed in 95% ethanol and stained using rapid hematoxylin and eosin (H&E). The slides were examined intraoperatively by experienced pathologists to detect the presence of malignant epithelial cells.

Histopathological processing

Postoperatively, the bisected SLNs were fixed in 10% neutral-buffered formalin for 24–48 hours. Nodes were processed by standard paraffin embedding and serially sectioned at 200 μm intervals. Each level was stained with H&E. Histological assessment was performed by two independent pathologists blinded to the clinical data. Metastases were categorized as macrometastasis (>2.0 mm), micrometastasis (0.2–2.0 mm), or isolated tumor cells (<0.2 mm), in accordance with the American Joint Committee on Cancer (AJCC) 8th Edition staging criteria [8].

Immunohistochemistry

All SLNs were subjected to immunohistochemical (IHC) staining regardless of H&E results. A pancytokeratin antibody cocktail targeting AE1/AE3 epitopes (Dako, Glostrup, Denmark) was used to enhance sensitivity for detecting micrometastasis. Positive controls included breast carcinoma tissue, while negative controls omitted the primary antibody.

Hormonal receptor profiling

Hormonal receptor status of the primary breast tumors was evaluated using automated immunohistochemistry platforms. Estrogen receptor (ER), progesterone receptor (PR), HER2/neu, and Ki-67 proliferation index were assessed in accordance with ASCO/CAP guidelines. ER and PR positivity were defined as nuclear staining in ≥1% of tumor cells. HER2 expression was scored from 0 to 3+, with 3+ considered positive. Ki-67 was reported as the percentage of positively stained nuclei in at least 500 invasive tumor cells.

Data collection and analysis

Statistical analysis Quantitative data were summarized using means, standard deviations, medians, and ranges, while categorical variables were reported as frequencies and percentages. Associations between sentinel lymph node (SLN) positivity and clinicopathological parameters such as tumor size, histological grade, and hormone receptor status were explored using Fisher's exact test. A p-value of <0.05 was considered statistically significant. Due to the limited sample size, statistical analyses were primarily descriptive and exploratory. All analyses were conducted using IBM SPSS Statistics software, version 26.0 (IBM Corp., Armonk, NY, USA). Patient demographics, clinicopathological variables, SLNB findings, and IHC results were recorded in a standardized data collection form. Descriptive statistics were used

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to summarize categorical and continuous variables. Sensitivity of cytology and histology methods was calculated using the final IHC-confirmed metastasis status as the gold standard.

Results

Patient demographics and tumor characteristics

Twenty female patients met the inclusion criteria and were enrolled in this study. The median age was 48 years (range: 34–70 years), with a mean ± standard deviation (SD) of 49.2 ± 10.3 years. The majority of tumors were located in the upper outer quadrant of the breast (13/20, 65%), followed by the central region (4/20, 20%) and other quadrants (3/20, 15%). Histological examination revealed invasive ductal carcinoma (IDC) as the predominant subtype, identified in 17 patients (85%), while invasive lobular carcinoma (ILC) accounted for 2 cases (10%), and one case (5%) showed mixed histology. Tumor size ranged from 1.1 cm to 4.7 cm, with a mean diameter of 2.4 ± 1.1 cm and median of 2.3 cm.

Sentinel lymph node (SLN) status

SLN metastases were detected in 4 out of 20 patients, resulting in a positivity rate of 20%. Among these, three patients (15%) had macrometastases greater than 2 mm in size, while one patient (5%) had a micrometastatic deposit measuring 0.8 mm (Table 1).

Table 1. Sentinel Lymph Node (SLN) Evaluation

SLN Status	Cases	Percentage
Macrometastasis (Imprint + H&E)	3	15%
Micrometastasis (PCK only)	1	5%
Negative	16	80%

Both intraoperative touch imprint cytology (Figure 1) and routine postoperative hematoxylin and eosin (H&E) staining (Figure 2) identified all macrometastatic cases. However, the micrometastatic lesion was only detected upon immunohistochemical (IHC) staining (Figure 3), underscoring the sensitivity of IHC in detecting low-volume metastatic disease and leading to pathological upstaging in 5% of cases.

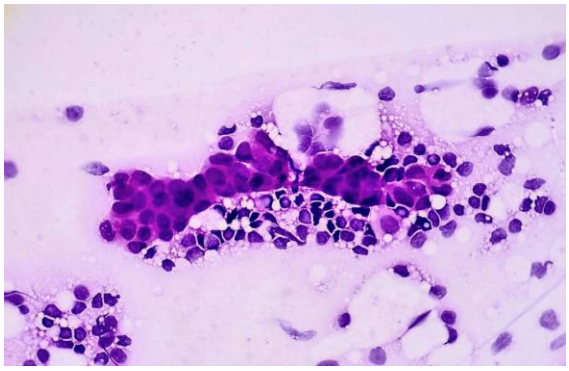

Figure 1. Touch imprint cytology indicating a tumor cluster.

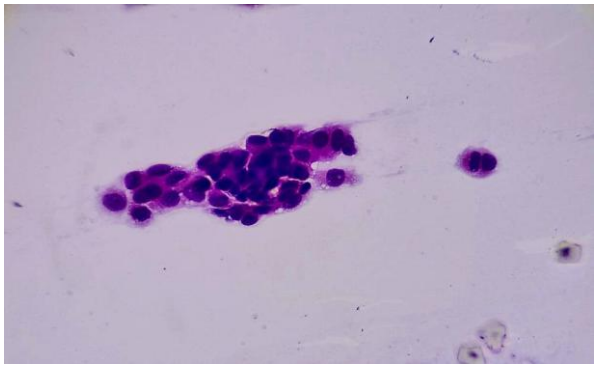

Figure 2. H&E slide of SLN metastasis.

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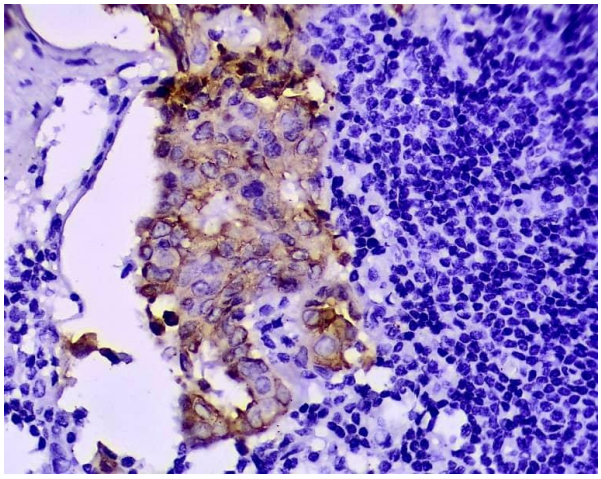

Figure 3. Pancytokeratin IHC confirming micrometastasis.

Diagnostic accuracy of SLN evaluation methods

When using IHC as the gold standard, the sensitivity of intraoperative touch imprint cytology and conventional H&E staining for detecting SLN metastases was calculated at 75%. The false-negative rate for these methods corresponded to the micrometastatic case missed, highlighting the limitations of cytology and routine histology in small-volume disease detection. Pancytokeratin-based IHC achieved 100% sensitivity, successfully identifying all metastatic cases, including micrometastasis.

Hormonal receptor and proliferation index expression

Immunohistochemical profiling of eight primary breast tumors revealed variable expression of hormone receptors and proliferation markers (Table 2). Estrogen receptor (ER) positivity was observed in 6 out of 8 cases (75%), with expression levels ranging from 20% to 90%. Progesterone receptor (PR) was positive in 5 cases (62.5%). HER2 was negative in all cases except one, which showed a low expression (Score 1). The Ki-67 proliferation index ranged from 10% to 50%, with a mean of approximately 26.9% ± 13.6%. Notably, one case with 30% Ki-67 and strong ER/PR positivity (Case 20273) represents a potential candidate for micrometastatic SLN involvement, although no such case-specific linkage was confirmed in this subset.

Table 2. Hormonal Receptor and Ki-67 Index (8 cases)

Case	ER	PR	HER2	Ki-67 (%)
20155	90%+	90%+	Negative	10
20245	Negative	Negative	Score 1	50
20273	70%+	80%+	Negative	30
20674	80%+	80%+	Negative	10
20561	Negative	Negative	Negative	35
6656	60%+	60%+	Negative	30
6442	60%+	80%+	Negative	10
6123	20%+	Negative	Negative	30

Association between SLN metastasis and clinicopathologic parameters

Associations between SLN positivity and various clinicopathological parameters were examined using Fisher's exact test, considering the small sample size. Among tumors larger than 2 cm, 3 of 11 patients (27.3%) demonstrated SLN metastasis compared to 1 of 9 (11.1%) with tumors ≤ 2 cm. Although there was an observable trend toward higher metastasis rates in larger tumors, this difference was not statistically significant ($\chi^2 = 0.31$, $p = 0.58$). SLN metastases were more frequent in high-grade tumors (Nottingham Grade 3), with 3 of 8 patients (37.5%) positive, compared to 1 of 12 patients (8.3%) with low or intermediate-grade tumors (Grades 1 and 2). This difference approached but did not reach statistical significance (Fisher's exact test $p = 0.12$), suggesting a possible association between higher grade and nodal involvement.

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Patients with high proliferation index (Ki-67 ≥ 30%) had a higher rate of SLN metastasis (3/9, 33.3%) compared to those with lower Ki-67 values (1/11, 9.1%), but this trend did not achieve statistical significance (p = 0.27). The wide range of Ki-67 values suggests biological heterogeneity within the cohort. No statistically significant associations were observed between SLN metastasis and ER positivity (p = 0.65), PR positivity (p = 0.73), or HER2 overexpression (p = 0.40).

Discussion

This study represents the first prospective evaluation of SLNB outcomes in Libyan women with invasive breast cancer, incorporating both intraoperative and postoperative diagnostics. Our 20% SLN positivity rate lies within the international range of 18–28% reported across Europe, North America, and North Africa [9]. In Tunisia, a prospective series (2012–2018) reported a 41.5% axillary metastasis rate via SLNB/ALND [9]. Similarly, El-Shinawi et al. documented SLNB outcomes among Egyptian patients post-neoadjuvant chemotherapy, with SLN positivity rates near 20%, consistent with our cohort [10]. International SLN positivity rates vary between 15% and 30%, depending on patient selection, tumor biology, and pathological methods. The NSABP B-32 reported ~25% SLN positivity in early-stage breast cancer [5], while ACOSOG Z0011 trials yielded similar findings in well-resourced settings [6]. These results underscore SLNB's effectiveness across diverse populations.

Regional studies support these findings despite differences in healthcare infrastructure and patient presentation [9,10]. Notably, micrometastases were often detected only via immunohistochemistry (IHC). For instance, El-Ghawalby et al. in Egypt reported a 7% increase in micrometastasis detection using pancytokeratin IHC [11], paralleling European studies showing improved staging accuracy with serial sectioning plus IHC [7,8]. Our hormonal receptor profiling aligns with international benchmarks: ER/PR positivity rates between 60–75% and HER2 overexpression near 20% [12]. The addition of IHC significantly improved diagnostic sensitivity; routine H&E and touch imprint cytology failed to detect micrometastasis in one case, which IHC revealed—highlighting the value of sensitive pathological techniques for staging [7,8,11]. Micrometastases were identified in 5% of our cohort, leading to pathological upstaging and influencing postoperative management—consistent with NSABP B-32 and other trials emphasizing the prognostic importance of micrometastatic disease [5,13]. Given the high rates of late-stage presentation in North African populations, precise nodal staging is essential for personalized treatment planning.

The ER/PR-positive and HER2-negative micrometastatic case in our cohort aligns with literature linking hormone receptor positivity to less aggressive nodal behavior [12]. Trends toward higher SLN positivity with larger tumor size and higher histological grade further reinforce established prognostic indicators [14,9,11].

Limitations

The study's small sample size limits statistical power and the ability to generalize findings broadly. Resource constraints precluded dual tracer mapping with radiocolloids, which may have affected sentinel node detection rates; however, the use of methylene blue dye alone has been validated in comparable low-resource settings with acceptable outcomes [10].

Conclusion

Our findings highlight the feasibility and clinical utility of SLNB with adjunctive immunohistochemistry in a resource-constrained North African context. Detecting micrometastases enhances staging accuracy and guides therapeutic planning. This foundational work sets the stage for larger multicenter studies in Libya and contributes valuable epidemiologic data to inform national breast cancer guidelines. Regional collaboration and capacity building will be essential to improve breast cancer outcomes in Libya and similar settings.

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Conflict of Interest

All authors declare no conflicts of interest related to this work.

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