

Intraoperative Axillary Lymph Node Assessment for Metastatic Breast Carcinoma: Frozen Section versus Imprint Cytology/Touch Preparation

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Abstract

Sentinel lymph node biopsy has been introduced as an appropriate and safe procedure to assess axillary lymph node status in certain groups of patients with breast cancer. Intraoperative frozen section and imprint cytology/touch preparation of the axillary (sentinel) lymph nodes are the most commonly used methods to detect metastatic breast cancer. Despite the comparable performance characteristics of these two methods in some studies, a wider range of false negative rates was reported with imprint cytology/touch preparation (21-66%) compared to frozen section (5.4-26%) in the neoadjuvant setting. Most of the false negative neoadjuvant cases were shown to have small tumor deposits (< 2 mm), but some were related to poor quality of imprint cytology/touch preparation secondary to therapy induced histologic changes or interpretation challenge due to lobular histotype. The practicing pathologist should be aware of the challenges/limitations of intraoperative imprint cytology/touch preparation in neoadjuvant setting such as cases with biopsy-proven lymph node metastasis prior to neoadjuvant therapy or tumors with lobular histotype.

Keywords: Intraoperative axillary lymph node assessment; Metastatic breast carcinoma; Touch preparation; Imprint cytology; Frozen section; Neoadjuvant; Non-neoadjuvant

Introduction

Axillary lymph node status is an independent prognostic factor in patients with invasive breast cancer and in earlier days, axillary lymph node dissection (ALND) was considered to be the standard of care for nodal staging.

Sentinel lymph node (SLN) biopsy has been introduced as an appropriate and safe procedure to assess the axillary lymph node status in non-neoadjuvant patients with clinically node-negative or limited node-positive early breast cancer [1-4]. Currently, SLN biopsy is also offered to post-neoadjuvant patients with operable breast cancer, especially when the nodes are clinically negative [5,6].

In many practices, intraoperative SLN assessment was adopted to eliminate second surgeries for completion ALND. Intraoperative frozen section [7] and imprint cytology/touch preparation [8,9] are the most commonly used methods to detect metastatic breast cancer. Although some studies reported comparable sensitivity and specificity between intraoperative frozen section and imprint cytology/touch preparation [10,11], the reliability of imprint cytology/touch preparation was questioned in the neoadjuvant setting [12].

In this short commentary, intraoperative frozen section and imprint cytology/touch preparation were discussed regarding their reliability and challenges/limitations to detect metastatic breast cancer in the neoadjuvant setting.

Discussion

Neoadjuvant therapy can induce histologic changes such as fibrosis, histiocytic infiltration, lymphocyte depletion, hyalinization and mucinous/myxoid changes [13], particularly in pre-treatment positive lymph nodes demonstrating tumor regression. These histologic changes may challenge the pathologist during intraoperative axillary lymph node assessment.

Intraoperative frozen section of SLN was shown to have similar sensitivity and specificity in the neoadjuvant setting compared to the non-neoadjuvant setting [6,10,14]. The limitations of frozen section were described as tissue folding, tissue shattering or loss in fatty lymph nodes, and smaller tissue representation due to incomplete facing of frozen tissue block(s) [6,15]. In the neoadjuvant setting, false negative rate of frozen section was reported from 5.4% to 26% [6,14,15]. False negative cases were more commonly found with isolated tumor cells or micrometastasis on permanent

sections rather than macrometastasis [6,15,16]. Regarding the histopathologic tumor features, false negative cases were more likely to be estrogen receptor (ER) positive, human epidermal growth factor receptor-2 (HER-2) negative and histologic grade 1, which reflects the lower rates of pathologic complete response after neoadjuvant therapy in these tumors [6,15,16].

In some studies, intraoperative imprint cytology/touch preparation of SLN showed acceptable sensitivity and specificity [17] or even similar performance characteristics compared to frozen section in the neoadjuvant setting [10]. However, false negative rate was reported with a wider range from 21% to 66% [10,12,18,19]. The limitations of imprint cytology/touch preparation were described as interpretation challenge for lobular histotype, poor quality of imprint cytology/touch preparation secondary to therapy induced histologic changes in pre-treatment positive lymph nodes and undersampling due to small tumor deposits (< 2 mm) [12,19]. Regarding the histopathologic tumor features, false negative cases were more likely to be lobular histotypes, ER positive, HER-2 negative and lower histologic grade [19].

In our previous study, macrometastasis were more frequently missed in the neoadjuvant setting by imprint cytology/touch preparation compared to the non-neoadjuvant setting [19]. Most of these patients were known to have biopsy-proven axillary lymph node metastasis prior to neoadjuvant therapy. On permanent sections, these cases demonstrated tumor cells embedded within fibrotic stroma interfering with the quality of imprint cytology/touch preparation [19]. Lobular histotype was a well-known pitfall due to dyshesive nature of tumor cells on touch preparations [12,20], and 32% of our false negative cases were lobular histotype in the neoadjuvant setting [19].

Intraoperative axillary lymph node assessment starts with the clinical history, followed by gross and microscopic examination. The following information has utmost importance: tumor histotype, any presurgical treatment and any prior axillary lymph node sampling (if yes for the latter, final diagnosis on the lymph node biopsy, and any clip placed at time of lymph node biopsy). On gross examination, lymph nodes should be sectioned at ≤ 2 mm intervals. If a clip was placed during the prior axillary lymph node biopsy, the presence or absence of the clip-containing node(s) should be documented, specifically to ensure the removal of previously biopsy-proven positive lymph node(s). If there is no gross evidence of metastatic carcinoma, the entire lymph node should be submitted for microscopic examination [13].

As discussed above, the false negative rates of imprint cytology/touch preparation in the neoadjuvant setting were quite variable which would reflect different performance characteristics in different institutions. This was not surprising since there were differences in study designs such as preparation method (imprint versus scraping), experience in preparation of the imprint

cytology/touch preparation, involvement of a cytopathologist during intraoperative assessment and sample bias (variable case distribution for macrometastasis versus micrometastasis & isolated tumor cells, lobular versus ductal histotypes, or previous lymph node metastasis). In any way, the practicing pathologist should be aware of the challenges/limitations of imprint cytology/touch preparation for intraoperative axillary lymph node assessment in patients that have received neoadjuvant therapy, and particularly in cases with pre-treatment biopsy-proven lymph node metastasis or tumor of lobular histotype [12,19].

Conclusion

Overall, intraoperative frozen section of SLNs seems to have a better sensitivity and specificity in detecting metastatic breast cancer compared to imprint cytology/touch preparation [11,21]. In the neoadjuvant setting, imprint cytology/touch preparation has been reported with a wider range of false negative rates which aligns with the variable performance characteristics in different institutions. The small size of metastatic tumor deposits (< 2 mm) is one of the major discrepancy reasons which may not change the axillary management of non-neoadjuvant patients if only limited lymph node(s) is involved. However, in the neoadjuvant setting, intraoperative diagnosis of low volume axillary (sentinel) lymph node disease may be an indication for ALND [22,23]. For imprint cytology/touch preparation, the practicing pathologist should be aware of the challenges/limitations of this detection method in certain clinical scenarios such as patients with biopsy-proven lymph node metastasis prior to neoadjuvant therapy or lobular histotype.

Competing Interest

The authors declare no competing financial interest.

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