



The accuracy of intraoperative frozen section analysis of sentinel lymph nodes in patients with breast cancer

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ABSTRACT

Background: The biopsy of sentinel lymph nodes (SLNs) has widely replaced conventional axillary lymph node dissection (ALND) for assessing the axillary lymph node (LN) status. Rapid intraoperative frozen section (FS) analysis of SLNs enables surgeon to perform ALND during the same operative procedure. However, there is an ongoing controversy regarding the accuracy and usefulness of FS for the evaluation of SLNs. The aim of the study was to investigate the accuracy of FS analysis in the management of patients with breast cancer.

Patients and Methods: Between 2007 and 2014, 214 breast cancer patients who underwent SLN biopsy procedure with intraoperative FS were included in this retrospective study. The SLNs were examined using standard FS procedures, and each section was stained with hematoxylin and eosin (H and E) only. The remaining tissues were then further sectioned and examined with H and E postoperatively. The results of FS and permanent sections were compared (the sensitivity, specificity and accuracy of FS were calculated).

Results: FS analysis detected LN metastases in 50 patients, while the permanent histopathologic examination detected metastases in another 9 patients. The sensitivity of FS for all kinds of metastases was 84.7%, but it reached up to 98% for macrometastases, and the specificity was 100%. FS allowed immediate completion of ALND in 50 patients (96%) with positive SLNs, and second-step surgery was only performed in 2 patients with discordant FS results.

Conclusion: FS examination of SLNs is a reliable and safe procedure for the diagnosis of LN metastasis. FS provides immediate completion of ALND in case of metastatic disease in the SLNs.

Key words: Accuracy, breast cancer, frozen section, sentinel lymph node

Introduction

Axillary lymph node (LN) status has remained one of most important prognostic and determinant factors in patients with breast carcinoma [1-3]. In the past, complete axillary lymph node dissection (ALND), which means clearance of the axillary LN (including Level I and II LNs) even if there is not any metastatic disease, was the standard approach. As the published

literature has reported that axillary dissection (AD) has no impact on the survival in node-negative patients, sentinel lymph node biopsy (SLNB) is currently accepted as the gold standard technique for assessing the axillary LN metastasis [4,5]. Since the status of the sentinel nodes accurately predicts the status of the remaining axillary LNs, many complications associated to ALND (lymphedema, seroma, paraesthesiae, pain

syndrome, etc.,) may be avoided in SLNB negative patients [6,7].

However, there is a controversy concerning the histopathologic (HP) examination of the excised sentinel lymph nodes (SLNs), especially regarding the utility of the frozen section (FS). Examination of the SLN by FS is accepted to be less accurate than analysis of routine permanent sections [3]. In some institutes the evaluation of the SLN is performed with permanent HP examination, and therefore, if the SLN is reported as “positive” for the metastatic disease, a second-step surgery for completion of ALND will be inevitable for the patient. Any patient would want to avoid a second operation if possible. Second-step surgery is associated with increased postoperative morbidity, cost and anxiety [7], and it will cause a delay for adjuvant treatment. On the other hand, a rapid and accurate FS analysis of the SLNs allows immediate therapeutic ALND, if metastases are detected in the SLNs.

Aim

The aim of this study was to investigate the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FS in the evaluation of SLNs, in patients with breast cancer.

Patients and Methods

This retrospective study included the results of 207 patients with clinically node negative breast cancer who underwent a SLN biopsy procedure between 2007 and 2014. The patients were operated by three different team of the breast and endocrine surgery unit. Blue dye or a combination of techniques (blue dye and radioactive colloid) were used for localizing SLNs.

If blue dye injection was preferred, periareolar subcutaneous or subdermal injection of 2-4 ml blue dye (patent blue V dye) was performed in localizing the SLN, then, subsequent breast massage for about 5 min with warm compresses was carried out to disseminate the dye toward the axilla. In case of radiocolloid agent use, periareolar injection of radiocolloid agent was handled on the morning of the surgery. While the operation was going on, SLNs were excised before the primary tumor and were sent for the FS procedures.

Upon arriving at the pathology department, the SLNs were longitudinally bisected through the hilus, however, if the pieces were thicker than 5 mm further

sectioning was performed. SLNs were evaluated by standard FS procedures, each section was prepared and stained with hematoxylin and eosin (H and E) only. Immunohistochemistry (IHC) staining procedure was not routinely used for the FS analysis of SLNs. SLNs were evaluated by different pathologists, but a senior one was consulted for controversial cases. If no metastasis was detected with H and E staining, the case was reported as not having LN metastasis, but, waiting for the results of permanent sections was advised before any treatment decision. Permanent sections were later prepared from the remaining tissues after FS analysis. Routine postoperative HP examination was carried out with multiple-step sections following fixation. These samples were further examined by H and E, staining. IHC techniques were only reserved for the SLNs morphologically highly suspicious for metastatic disease, however, reported as “reactive” with H&E staining.

The positivity of SLN metastasis was reported according to the microscopic size of the tumor infiltrate as follows: Macrometastases (>2.0 mm); micrometastasis (>0.2-2.0 mm). Isolated tumor cells (ITCs) or small cell clusters not <0.2 mm were designated as ITCs. SLN metastases that were not diagnosed on FS but diagnosed on permanent HP examination were considered as false-negative.

If the FS analysis of SLNs detected macrometastases or micrometastases, the patient underwent immediate completion ALND during the same operation. The patients with ITCs or reactive LN did not receive any further surgical treatment to their axilla.

The clinicopathological characteristics of the patients, tumor characteristics (grade, histologic type, receptor status), SLN status, immediate or delayed ALND status were recorded. Accuracy, sensitivity, specificity, positive predictive value and negative predictive value of FS were calculated by comparing the FS analysis of the SLNs with the results of routine H and P examination.

Results

There were 214 patients included in this retrospective study and all of the patients underwent FS examination for the SLNs. There were 124 (58%) cases of mastectomy and 90 (42%) cases of lumpectomy. While invasive carcinoma constitutes 97.5% (202) of

cases, ductal carcinoma in situ was present in 2.5% (5) of cases (Table 1).

A total of 382 SLNs were collected from 214 patients and the median number of SLNs examined per patient was 1.8 (range 1-5). The time for the intraoperative FS analysis was approximately 25 min (15-40). The final pathology (permanent sections) results revealed LN metastasis in 59 patients (27.5%), of whom 9 (1 macrometastasis, 5 micrometastases and 3 ITCs) were diagnosed as negative by the FS examination (Table 2).

Five additional micrometastases (5 of 8 patients) and all of the ITCs (3 patients) were only diagnosed

on permanent sections. FS analysis of these 8 patients revealed no metastatic disease in the SLNs.

While there were 9 false-negative results on FS analysis, there was no false positive case, therefore, the specificity of FS analysis was 100% for all kinds of metastases (macro-micro metastasis and ITC). The sensitivity of FS for macrometastasis was 98% (47/48) and decreased to 84.7% for all kinds of metastases, including macro- micrometastasis and ITCs. The negative predictive value was 91.9% for macrometastasis. The false-negative rate was 2% and 62.5% for macrometastasis and micrometastasis, respectively (Table 3).

With the help of FS examination of SLNs, 50 of 59 patients, whose permanent H and P results revealed axillary LN metastases, underwent immediate completion ALND. Only 2 patients (3.3%) had to undergo a second-step surgery for completion of ALND; the remaining 7 patients with microscopic metastatic disease (4 micrometastases and 3 ITCs) did not receive any further axillary surgery.

Discussion

FS examination of SLNs is a safe and efficient procedure with a sensitivity of 98%, a specificity of 100% and an accuracy of 98.5% for macro-metastases. In terms of all kinds of metastases (macro-micrometastases and ITCs), the sensitivity of FS is low (80.2%) but the specificity is still high (100%). This technique allowed 96% (47) of patients with positive SLNs to appropriately undergo immediate ALND as a result of the intra-operative FS. Thus, the accuracy of FS avoided a second operation with increased morbidity and possible delay in postoperative adjuvant therapy.

The sentinel node (SLN) biopsy, being a less invasive technique compared to ALND, has become a standard procedure and it is proposed to the patients having clinically not negative breast cancer [7]. Histologic examination of the SLNs may be carried out intraoperatively (FS) or postoperatively (permanent sections). Rapid intraoperative examination of SLNs would be a preferable option, since it allows immediate completion ALND in case of axillary metastases. However, FS analysis of the SLNs is known to be less accurate than permanent sections [8].

Today, the false negative result of FS constitutes a major problem that may discourage surgeons. Al-

Table 1. Demographic and pathologic characteristics of the patients.

Characteristic of tumor	Number of patients (%)	Number of patients (n)
Infiltrative ductal carcinoma	79	169
Infiltrative lobular carcinoma	7	15
Others	14	30
Stage 0	2.3	5
Stage I	46.2	99
Stage II	43.4	93
Stage III	7.9	17
Grade I	8.8	19
Grade II	52.3	112
Grade III	38.8	83

Table 2. Comparison of the result of FS analysis and permanent HP examination.

Type of metastases	FS (n)	Routine HP examination (n)
Macrometastases	47	48
Micrometastases	3	8
Isolated tumor cell	0	3
Total	50	59

FS: Frozen section, SLN: Sentinel lymph nodes

Table 3. The results of FS analysis for the evaluation of SLNs.

Parameters	Percentage
Sensitivity	84.7
Specificity	100
False negative rate	15.2
Positive predictive value	100
Negative predictive value	94.5
Accuracy	95.7
Sensitivity for macrometastases	98

FS: Frozen section, SLN: Sentinel lymph nodes

though FS can accurately detect most of the macrometastases, the detection rate for micrometastases and ITC falls to undesired low levels [3,9]. In a review in the *British Journal of Surgery*, it was reported that the FS sensitivity ranges from 57% to 74% and the specificity ranges from 99% to 100% [10]. False negative results may be decreased by the combination of FS and rapid IHC staining. On the other hand, IHC staining is not a feasible method for small centers since it requires additional time and specialized team. In addition, IHC staining allows detecting small (tiny, micrometastases) metastases that do not alter patient management and it may cause unnecessary completion of ADs with increased morbidity.

In the current concept, patients with positive SLNs should be treated with completion ALND [11]. However, since both micrometastases and ITC do not require additional surgical approach to the axilla, IHC staining during intraoperative SLN examination is not routinely proposed [11].

Despite the advantages of FS analysis of SLNs, the procedure adds time and cost to the operation and it is still associated with a significant (25%) false negative rate [12,13]. Therefore, some centers are not in favor of FS and prefer to reserve FS evaluation of SLNs for patients who have a significantly increased risk of nodal positivity.

The ACOSOG Z0011 and IBCSG 23-01 trials compared the overall survival in SLN-positive patients. A group of patients underwent completion ALND for positive SLN and another group did not, even if they had positive SLN. They reported that there was not a significant difference between the two groups in terms of overall survival [14,15]. These two studies have started to question the role of completion ALND, even in the management of SLN-positive disease. Therefore, the trend of evaluating SLNs intraoperatively with FS has decreased in the recent years. From Memorial Sloan Kettering Cancer Center, Weber et al. reported that the utilization rate of FS for SLN examination among the surgeons has declined from 100% to 62% during the last 10 years [16].

The rates of ITCs and micrometastases were found low in our study when compared to other reports [17,18]. However, in our institute, IHC staining was

not routinely used and FS analysis of the SLNs was handled with H and E staining only. It is accepted that ITCs do not alter the management of patient. Therefore, we did not perform further axillary surgery in case of ITCs.

Our study has two main limitations. First, it is a retrospective study. Second, our method of intraoperative analyzing of SLN is not homogenous and it is operator-dependent. While most of the SLNs were evaluated by standard FS analysis and H and E dye only, a few others underwent a combined technique (FS and imprint cytology).

In the study of Alessandro Sanguinetti and co-workers, FS examination was reported to have a high false negative rate, with a sensitivity of 83.3% for macrometastasis, 40% for micrometastasis, and only 18.2% for ITCs [3].

Conclusion

Our retrospective study showed that intraoperative FS analysis of the SLNs is a reliable and safe procedure in the management of patients with breast cancer. Thus, if the result is positive for metastatic disease, intraoperative FS enables surgeon to complete ALND during the same operative procedure, thereby avoiding the need for a second-step surgery. However, FS may fail to detect ITCs and micrometastases, especially in cases with small tumors.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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