Intraoperative Frozen Section Evaluation of Sentinel Lymph Nodes in Breast Carcinoma: Single-Institution Indian Experience

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Abstract Sentinel lymph node biopsy is an established way of predicting axillary nodal metastasis in early breast cancer. Intraoperative frozen sections (FS) of sentinel lymph nodes (SLNs) can be used to detect metastatic disease, allowing immediate axillary lymph node dissection. The purpose of this study was to evaluate the accuracy of intraoperative frozen sections in evaluation of sentinel lymph nodes in cases of breast cancer. Between March 2006 and August 2010, a total of 164 patients with clinically node-negative operable breast cancer were subjected to sentinel lymph node biopsy of axillary lymph nodes using preoperative peritumoral injection of radioactive colloid and methylene blue. Intraoperative identification of sentinel nodes was done using a handheld gamma probe and identification of blue-stained nodes. The nodes were sent for frozen section examination. The results of frozen section were compared with the final histopathology. Out of the 164 cases, metastases were detected in SLN by frozen section in 38 cases. There were three false-negative cases (all showing micrometastasis on final histopathology). FS had sensitivity of

92.6 %, specificity of 100 %, and overall accuracy of 98.1 %. The positive predictive value was 100 %, and the negative predictive value was 97.6 %. FS for diagnosis of metastasis of SLNs is reliable. Patients with negative SLNs by the FS diagnosis can avoid reoperation for axillary lymph node dissection. However, FS may fail to detect micrometastases, especially in cases with small tumors.

Keywords Breast cancer · Frozen section · Sentinel node · Axillary clearance

Introduction

Axillary lymph node (ALN) status remains one of the most important prognostic factors in breast carcinoma. Sentinel lymph node (SLN) biopsy was described in the early 1990s to permit an accurate staging of ALN status, and over a decade, it has substantially changed the therapeutic paradigm for women with breast cancer [1–3]. SLNB has proven to be an accurate staging procedure in breast cancer patients and has replaced axillary lymph node dissection (ALND) in the clinically node-negative axilla [4].

Although SLN procedure has led to a more thorough inspection of these lymph nodes in general, their specific examination varies substantially throughout Europe and the USA. Several institutions, such as those in France, perform it as a two-stage procedure where the sentinel node is harvested and sent for histopathology examination (HPE) and subsequent treatment is done as a second-stage procedure, depending on the final HPE. On the other hand, at institutions such as NCI Milan, Italy, it is done as a single-stage procedure subjecting the SLN to frozen section (FS) and proceeding as per FS diagnosis. In our institution, SLN biopsy

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(SLNB) was introduced in the early 2000s and has been performed regularly since then. As part of a validation study, SLNB using both gamma probe and blue dye had a false-negative rate of 3.7 % with overall sensitivity, specificity, positive predictive value, and negative predictive value of SLNB of 96.2, 100, 100, and 98.6 %, respectively [5].

Examination of the SLN by FS is known to be less accurate than analysis of permanent sections, but it avoids reintervention for ALND if metastases are detected in sentinel node on FS. However, the procedure is costly and increases the operation time. It is well known that with conventional FS techniques, it is easier to miss the metastases in SLN than with permanent section techniques. Hence, the intraoperative assessment of SLNs must be performed with accuracy and efficiency.

We describe the results of routine intraoperative FS at our center and evaluate the reliability of intraoperative FS diagnosis of SLNs in early breast cancer patients. This study aimed to estimate the sensitivity, specificity, negative predictive value, and false-negative rate of FS protocol of our center in the detection of sentinel node metastases.

Patients and Methods

It was a prospective study conducted between March 2006 and August 2010. A total of 164 consecutive patients with clinically node-negative early breast cancer were included in the study. SLNB was performed using a combination of radioactive colloid and blue dye. One milliliter of Tc-99-labeled radioactive sulfur colloid (equivalent to 1 mCi) was injected in the subareolar region 2 h before surgery. SLNs were marked using a handheld gamma probe. After induction of anesthesia, 4–5 mL of methylene blue was injected peritumorally. Intraoperatively, SLNs were identified by their blue color (blue nodes) and handheld gamma probe (hot nodes). In all cases, the excised SLNs were submitted for immediate FS diagnosis. While awaiting the results, a lumpectomy or total mastectomy was performed. Patients diagnosed as having positive SLNs on the basis of the FS diagnosis immediately underwent ALND.

Pathological assessment of SLN was done by intraoperative FS evaluation as per the recommendations provided by the College of American Pathologists [6]. SLNs were bisected along the longitudinal axis, and 2-mm-thick multiple sections were taken and stained with hematoxylin and eosin (H&E). Hence, on an average, 12–14 sections were made depending on the size of the lymph node. Larger nodes were sectioned at three different levels. Two oncopathologists examined the sections independently. The entire procedure took 15–20 min. The remaining frozen tissues were fixed in formalin, embedded in paraffin, and sectioned. The SLNs were later diagnosed using permanent sections

and H&E staining without additional immunohistochemistry (IHC) or serial sections. Other dissected non-SLNs were also examined using the same methods.

The results of FS and permanent section were compared with the pathological diagnosis for the SLNs. The standard was based on the results for the permanent section.

Results

For this study, we collected 368 SLNs from 164 patients with breast carcinoma who underwent SLN mapping during these 4 years. The median number of SLNs examined per patient was 2 (range, 1–5). The median age of patients in our study was 54 years (range, 21–76 years). Figure 1 depicts the characteristics of the tumor in the study population. Overall, 41 of 164 cases (25 %) were found to have nodal metastases in the final pathology. In three cases, the FS diagnoses were negative, but the permanent section diagnoses were positive (false-negative rate, 7.3 %). All three patients had micrometastasis on permanent section. FS could pick up micrometastasis in another six cases (Fig. 2). Comparison of results of FS and permanent sections are given in Table 1.

FS had a sensitivity of 92.6 %, specificity of 100 %, and overall accuracy of 98.1 %. The positive and negative predictive values were 100 and 97.6 %, respectively.

Discussion

Knowledge of the SLN status at the time of primary surgery is desirable because it potentially avoids an unpleasant return to the operating room for deferred axillary dissection once the diagnosis of lymph node metastasis is made. The potential psychological advantages for the patients and the effects on survival of the avoidance of systemic treatment delay are not well studied.

Several methods of intraoperative evaluation have been described. These include FS and touch preparation, scrape

Fig. 1 Tumor characteristics in the patient population

Fig. 2 Pictures of pathological evaluation of SLN. **a** FS of SLN metastases; **b** subcapsular micrometastases missed by frozen section seen on final HPE (high-power view); **c** FS of sentinel node micrometastases

cytology, IHC stain, and an exhaustive method of serial intraoperative sectioning described by Veronesi et al. [7–11]. The latter is appealing because the entire lymph node is step-analyzed during the operation. However, it is very difficult to implement because it requires human and financial resources not easily available in most centers. The sensitivity of intraoperative evaluation in the literature is variable ranging from 44 to 94 % as depicted in Table 2 [8, 12–29]. This large variation is probably related to the different histopathological techniques used for FS analysis, the number of serial sections, the use of IHC, and the proportion of SLN macrometastases in that group of patients. Only a few series have studied a cohort of more than 200 patients.

Attempts to improve the sensitivity of intraoperative examination have included step sectioning the lymph node, using anti-keratin IHC at the time of FS and using cytological preparations from the SLN [30–32]. Some of these techniques increase the laboratory workload at the time of FS quite dramatically, but sensitivities (in reports with >100 patients) have been as high as 93 %. Recently, Krogerus compared two FS techniques [33]. Lymph nodes were either bisected, then cut twice at five levels on both sides, or were

cut at a thickness of 1–1.5 mm with a razor blade followed by two sections and touch preparations from each piece. The authors claimed that the second method was less labor intensive and found more metastases, but the sensitivity for detection of carcinoma was actually higher using the first technique, because there were no false-negative cases.

In 2004, the European Working Group for Breast Screening Pathology (EWGBSP) reported a high degree of variability among European pathology institutes for SLN examination [34]. Two years later, Czerny et al. and EWGBSP stipulated that intraoperative assessment of SLN can be carried out by FS based on institutional resources [35, 36]. In our series, intraoperative evaluation was done as per the recommendations provided by the College of American Pathologists [6].

Table 1 Comparison of frozen section and final histopathology

Frozen section	Final HPE	Patients	Parameter
+	+	38	True positive
–	–	123	True negative
–	+	3	False negative
+	–	0	False positive
Parameter	Calculations		Values (%)
Sensitivity	$\frac{TP}{TP+FN}$	$\frac{38}{41}$	92.6
Specificity	$\frac{TN}{TN+FP}$	$\frac{123}{123}$	100
False negativity	$\frac{FN}{TP+FN}$	$\frac{3}{41}$	7.3
PPV	$\frac{TP}{TP+FP}$	$\frac{38}{38}$	100
NPV	$\frac{TN}{TN+FN}$	$\frac{123}{126}$	97.6
Accuracy	$\frac{TP+TN}{TP+TN+FP+FN}$	$\frac{161}{164}$	98.1

PPV positive predictive value, NPV negative predictive value, TP true positive, FP false positive, TN true negative, FN false negative

Table 2 Literature review

Study	Number of patients	Type	Sensitivity (%)
Hill [12]	405	FS	87
Zurrida [13]	192	FS	68
Weiser [14]	890	FS	58
Chao [15]	203	FS	68
Tanis [16]	262	FS	74
Gulec [17]	157	FS	44
Menes [25]	117	FS	78
Smidt [8]	148	CY	67
Ratanawichitrasin [18]	55	CY	82
Lee [19]	65	CY	65
Llatjlos [20]	76	CY	67
Henry-Tillman [21]	247	CY	94
Kane [22]	150	CY	54
Csemi [23]	60	CY	83
Lambah [24]	53	CY	82
Menes [25]	117	CY	57
Shiver [26]	133	CY	56
Karamlou [27]	142	CY	75
Mullenix [28]	71	CY	48
Creager [29]	678	CY	52

FS frozen section, CY cytology

It has also been reported that the sensitivity of FS may be higher for larger tumors because the proportion of macrometastases in these patients increases. In the present study, the sensitivity of FS was 92.6 % and the specificity was 100 %. There were three false negatives in our study. The metastatic foci in the false-negative cases were found on a permanent section that was adjacent to the FS surface and belonged to the category of micrometastasis (≤ 2 mm). These results suggest that FS is most accurate at detecting the foci of nodal metastases that are >2 mm in size. The failure of routine intraoperative FS is largely caused by the failure to detect micrometastatic disease [13]. In literature, the false-negative rate has been highly variable, ranging from 5.5 to 54 % [15, 37].

The use of step sectioning and IHC has increased the chances of finding occult metastases and micrometastasis in SLNs [9, 15, 20, 21]. Nodal tumor burden is a continuum from a single cell to bulky palpable disease, and prognosis should follow tumor burden when all other intrinsic biologic factors are equal. However, the significance of detection of micrometastasis is not clear in terms of predicting further nodal involvement, prognosis, and indications for adjuvant systemic treatment. The significance of isolated tumor cells detected only by IHC may be even less. It remains unclear how often these isolated tumor cells reflect metastases capable of further growth and dissemination. Researchers from the NSABP B-32 trial concluded that there was no clinical benefit of additional evaluation, including immunohistochemical analysis, of initially negative sentinel nodes in patients with breast cancer, and thus, routine IHC in SLN was not indicated [38]. Regardless of whether they are detected in initial sections or in additional deeper levels, isolated tumor cell clusters and micrometastases have less prognostic significance than macrometastases and should be classified separately. According to the guidelines in the seventh edition of the American Joint Committee on Cancer staging manual, micrometastasis is defined as tumor deposits 0.2–2.0 mm in size and are grouped as pN1mi. Any deposits <0.2 mm are considered as pN0 with the short hand i+ or i- indicating whether IHC staining was performed with positive or negative results [39]. Studies on the clinical significance of these cells have had mixed results, and the results of long-term follow-up are not yet available [40–44].

A recent analysis of population-based data from the National Cancer Institute's Surveillance, Epidemiology, and End Results national cancer database showed that the presence of micrometastasis not >2.0 mm in lymph nodes is associated with an overall decrease in survival at 10 years of 1, 6, and 2 % for T1 (not >2.0 cm), T2 (>2.0 cm but not >5.0 cm), and T3 (>5.0 cm) tumors, respectively, compared to patients with no nodal metastases detected [45]. Thus, for the usual sentinel node patient with a tumor <2.0 cm, this study suggests that there is little expected detrimental impact associated with the

presence of micrometastasis. However, the study does suggest that for larger tumors, detection of micrometastasis may be more important. A prospective randomized trial on the clinical significance of micrometastasis is being carried out at NCI Milan, Italy, by Veronesi et al. where patients with micrometastasis in the axillary nodes are randomized into an axillary clearance and observation arm. Various studies including the ACOSOG Z0010 trial have showed that presence of micrometastases does not change the overall survival in breast cancer [46, 47]. A Swiss group analyzed pooled data from five different hospitals and drew the same conclusion that presence of micrometastases makes no difference in overall survival and recurrence of disease when ALND was not performed in this group of patients [48].

Conclusion

Intraoperative FS evaluation of SNLs is a reliable and safe procedure for diagnosis of SLN metastasis, allowing immediate axillary dissection in a one-stage surgical procedure. However, FS may fail to detect micrometastasis, although as yet, this is not a reliable indication for ALND.

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