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Frozen section evaluation of breast carcinoma sentinel lymph nodes: a retrospective review of 1,940 cases

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Abstract

Many sentinel lymph node biopsies (SLNBs) are evaluated intraoperatively by frozen section, which may impact the need for further axillary dissection (AD). However, the need for AD in patients with small metastases has been recently called into question, meaning that frozen SLNB may be unnecessary. Furthermore, frozen section can compromise tissue for further study. At our institution, we grossly evaluate all SLNB and freeze half of the node. Here, we evaluate the frozen SLNB discrepancy rate using this method, focusing on cause of discrepancy and need for further surgery. We reviewed surgical pathology records for all breast cancer resections with frozen section of SLNB examined from 2003 to 2012. For cases with a frozen section discrepancy, we compiled clinicopathologic data. In total, 1,940 cases involved frozen section evaluation of SLNB. In 95 cases (4.9 % of total cases, 23.8 % of positive node cases), the SLNB was called negative on frozen but positive on final examination (false negatives). The majority of missed metastases are isolated tumor cells or micrometastases. A trend was observed toward fewer patients receiving completion AD after a discrepant frozen SLNB in the later years of the study. The protocol of freezing half of a SLNB is a reasonable method, with results similar to or better than other studies. The main adverse outcome is the need for separate AD; however, additional positive nodes are

uncommon. The trend of fewer patients getting additional AD after a discrepant frozen SLNB suggests that clinicians may be using this information differently recently.

Keywords

Sentinel lymph node biopsy; Frozen section; Breast cancer

Introduction

Sentinel lymph node biopsy (SLNB) remains the standard of care for the assessment of clinically negative axillary lymph nodes in patients with invasive breast carcinomas [1–3]. Accurate diagnosis of a SLNB can direct the surgeon with regards to the need for axillary dissection (AD), as well as affecting post-operative treatment decisions including radiation therapy [4]. Furthermore, an accurate negative diagnosis on SLNB can spare the patient from the increased risk of lymphedema that accompanies AD or post-operative treatments.

Although the American Society of Clinical Oncology guidelines recommend paraffin embedding of lymph nodes with standard hematoxylin and eosin staining (H&E), surgeons often request intraoperative assessment of SLNB to guide further treatment decisions while still in the operating suite [2]. A recent update of these guidelines did not alter this recommendation, and only briefly commented on the role of immunohistochemistry (IHC) in detecting micrometastases and isolated tumor cells (ITCs) [3]. Such assessment can consist of either H&E-stained frozen sections or touch prep cytologic assessment [5]. The potential benefits of using intraoperative frozen section versus touch prep cytology include the preservation of tissue architecture including metastasis size via the former method, while the potential disadvantages of the frozen section method include loss of fatty nodal tissue and possible frozen section artifact impacting interpretation. There is no standardized method for frozen section evaluation of SLNB, resulting in wide inter-institutional variability in the amount of tissue examined on frozen section and the number of levels examined per frozen specimen [6]. Although there is some concern about frozen section analysis of SLNBs impairing detection of metastases, mathematical modeling has shown that this is not a likely scenario [7].

At our institution, gross evaluation is first done to determine the number of nodes and if any are grossly suspicious, and then half of the SLNB tissue is frozen for intraoperative assessment. We believe this method allows for sufficient representation of the SLNB on frozen section, while preserving an ample amount of tissue unaltered by frozen section artifact for subsequent paraffin sections and IHC, hormone receptor studies, and molecular studies, if necessary.

The sensitivity, specificity, and positive and negative predictive values of intraoperative SLNB assessment are subject to a number of factors, including tissue sampling, block sampling, and misinterpretation of the frozen section. We performed a 10-year retrospective review of SLNB specimens with intraoperative evaluation via frozen section to evaluate sensitivity, specificity, positive and negative predictive values, reasons for discordance between the frozen section and final diagnoses, and clinical follow-up.

Methods

Case review

We searched the Pathology Data Systems at Johns Hopkins Hospital for all breast procedures (mastectomy, lumpectomy, or biopsy) performed over approximately a 10-year period, from 01/01/2003 to 09/01/2012, with any part identified as “sentinel lymph node” by the surgeon ($n = 2,546$). Cases evaluated by touch prep analysis or other cytologic method were not included. From these cases, we examined those with a frozen section diagnosis recorded ($n = 1,940$), noting the frozen section and final diagnoses.

For any cases with a discrepancy between the frozen section and final diagnoses, we noted the reason for the discrepancy (i.e., tissue sampling, block sampling, misinterpretation, or IHC needed to detect metastasis). “Tissue sampling” was defined as finding a metastasis in the non-frozen half of the lymph node; “block sampling” was defined as finding a metastasis in a deeper level of the frozen portion of lymph node (i.e., present on the frozen section control slide only); “misinterpretation” was defined as misinterpretation of a focus of metastatic carcinoma; and “IHC needed” was defined as the presence of a metastatic focus only visible by IHC. The reason for such a discrepancy is routinely recorded as part of an in-house quality control measure, but for any cases where the reason for the discrepancy was not recorded or was unclear, the frozen sections and paraffin-embedded slides were reviewed by two pathologists to properly attribute the reason for discrepancy.

Clinicopathologic data

For patients with a discrepancy between the frozen section and final diagnoses, we compiled clinicopathologic data including patient age, histologic tumor type, tumor size, and metastasis size as well as follow-up data including subsequent AD, chemoradiation treatment, and survival. Micrometastases were defined as a metastatic focus greater than 0.2 mm but less than or equal to 2.0 mm; ITCs were defined as a focus of metastatic carcinoma measuring less than or equal to 0.2 mm, or fewer than 200 cells. At the time of manuscript preparation, all patients had at least 12 months of clinical follow-up available.

Immunohistochemistry

Consistent with established recommendations, our standard practice is to *not* reflexively perform cytokeratin IHC on sentinel lymph nodes from all patients with breast carcinoma [8, 9]. We do perform cytokeratin IHC upfront on sentinel lymph nodes from patients with known invasive lobular carcinoma, as the metastatic foci may be subtle and mimic benign histiocytes; we only perform IHC on sentinel lymph nodes for invasive ductal carcinoma if a suspicious focus is noted on H&E.

Statistics

A Fisher’s exact test was performed in Microsoft Excel.

Results

Intraoperative frozen sections for breast sentinel lymph nodes were performed on 1,940 surgical cases over an approximately 10-year period. The comparison of frozen section and final diagnoses is shown in Table 1. Using our method of freezing half of the sentinel lymph node, the sensitivity of frozen section diagnoses was 76.3 %, and the specificity was 99.9 %; the positive predictive value was 99.7 %, while the negative predictive value was 94.0 %.

Frozen section discrepancies

In 95 of 400 cases with positive nodes (23.8 %), the sentinel lymph node was called negative for carcinoma on frozen section, but was positive for a metastasis in the final diagnosis; these cases were classified as false negatives. These false-negative cases accounted for 4.9 % of the 1,940 total cases with intraoperative assessment. The majority of the discrepancies (74 %) were due to tissue sampling (39 %, Fig. 1) or block sampling (35 %, Fig. 2), and IHC was needed to detect the metastases in an additional 20 % of cases. Only 6 % of the discrepancies (only 0.3 % of all frozen sections) were due to misinterpretation, or failure to recognize a metastatic focus on the original frozen section.

One case (0.05 %) had a frozen section diagnosis of “one lymph node with scattered tumor cells identified” but a final diagnosis of “rare atypical cells only seen on the frozen section.” IHC for AE1/AE3 was performed on both the frozen section control tissue, and the remaining tissue and was negative. Although the atypical cells noted in the frozen diagnosis could indeed have represented a metastasis, due to the negative IHC, we conservatively classified this case as a false positive. The remaining 1,844 cases were correctly diagnosed on the frozen section.

Clinicopathologic data of false-negative frozen SLNB

The clinicopathologic data of the patients with false-negative frozen SLNB are shown in Table 2. The 95 patients with false-negative frozen SLNB ranged in age from 22 to 82 years old (median, 52 years old). Metastatic ductal carcinoma accounted for 64 (67 %) cases, lobular carcinoma accounted for 20 (21 %) cases, and the remaining 11 (12 %) cases were mammary carcinomas with features of both ductal and lobular carcinoma. The primary tumor size ranged from 0.1 to 6.0 cm (median, 1.7 cm). The metastasis size ranged from 0.05 to 16 mm (mean, 1.9 mm; median, 1.1 mm). 26 false-negative cases (27 %) were classified as ITCs (not greater than 0.2 mm) in the final diagnosis, 40 (42 %) were classified as micrometastases (0.2 to 2.0 mm), and 29 (31 %) were classified as macrometastases (greater than 2.0 mm) (Fig. 3). Of the 19 cases in which immunostains were needed to detect the metastasis, 11 (58 %) were classified as ITCs, 7 (37 %) were classified as micrometastases, and 1 case (5 %) was a 2.5 mm macrometastasis. There were six cases with metastases measuring >0.5 cm, and the majority of these (67 %) were metastatic lobular carcinomas with false-negative frozen SLNB due primarily (85 %) to tissue or block sampling. One was due to misinterpretation or failure to identify a small focus (0.5 cm) of subtle subcapsular tumor cells in a case of metastatic lobular carcinoma.

As of last follow-up, 88 (93 %) patients with a false-negative frozen SLNB were alive, while 7 (7 %) had died. A follow-up AD was performed in 39 (42 %) patients; of these 39 patients, additional positive lymph nodes were found in 6 (15.4 %). Of the six patients with positive nodes at follow-up AD, three (50 %) had metastases involving only one node in the follow-up specimen; the other three patients had metastases in two, three, and thirteen nodes, respectively. In five (83 %) of these patients, the carcinoma was ER and PR positive; one of these patients showed weak Her2 positivity by IHC, while the other patients were negative. One (17 %) patient's carcinoma was negative for ER, PR, and Her2. All five of these patients with clinical follow-up information received additional post-operative chemotherapy. Eight (9 %) additional patients underwent AD during the initial operation, despite the negative frozen section diagnosis.

Twenty-seven (69 %) of these 39 patients who underwent follow-up AD were diagnosed between 2003 and 2008, while only 12 (31 %) were diagnosed between 2009 and 2012 (Fig. 4). Stated another way, 53 % of patients with false-negative SLNB from 2003 to 2008 were taken back for additional axillary surgery, whereas only 27 % from 2009 to 2012 were taken back ($p < 0.05$). The decrease in AD does not reflect a decrease in the overall rate of intraoperative SLNB, as 852 (44 %) of the 1,940 intraoperative assessments occurred during this time period.

Discussion

SLNB is a safe and an accurate method of screening the axillary lymph nodes in women with breast cancer [2, 3, 10–12]. Furthermore, a negative SLNB can spare the patient from the morbidity that accompanies a complete AD [2, 3, 10–12]. One specific surgical scenario we have encountered in our clinical practice in which intraoperative SLNB has particular utility is in patients undergoing a mastectomy with immediate reconstruction (i.e., deep flap reconstruction). In these circumstances, the intraoperative knowledge that the patient has a positive SLNB and is likely to receive post-mastectomy radiation therapy may lead the surgeons to abort the immediate reconstruction and instead opt for placement of a temporary tissue expander with delayed reconstruction. In this case, the surgeons are able to avoid the known complications associated with post-mastectomy radiation therapy and immediate reconstruction. Furthermore, should the patient require a subsequent AD, an intraoperative SLNB has the potential of avoiding the risks associated with a second surgery and anesthesia exposure, which are not trivial.

However, recent studies have called into question the need for intraoperative SLNB assessment in situations where additional AD is unlikely to be performed even if a metastasis is detected in the sentinel lymph node. The ACOSOG Z0011 study showed no difference in local or regional recurrence between patients with 1–2 positive sentinel lymph nodes who were randomized to either SLNB only or SLNB and AD [13]. This study also showed that the use of SLNB alone compared with AD did not result in inferior survival in a limited patient population (clinically negative axillae, tumors smaller than 20 mm, and 1–2 positive nodes) [14]. By applying the Z0011 criteria, it is estimated that approximately 75 % of patients undergoing breast-conservation surgery could avoid additional AD [15]. Similarly, while a retrospective study found occult metastases to be a prognostic factor in

clinically negative lymph nodes [1], a prospective study showed the survival in patients with these occult metastases to be only 1.2 % lower [16], implying that clinically negative lymph nodes do not require intraoperative assessment. Regardless of the ultimate determination as to the necessity of SLNB evaluation, if the findings of the sentinel lymph node are no longer driving intraoperative decision making, the need for intraoperative assessment of sentinel lymph nodes is called into question. Furthermore, some have called into question the necessity of any histologic SLNB evaluation [17, 18], suggesting that pre-operative ultrasound with optional fine-needle aspiration of suspicious nodes can guide the decision regarding AD.

Reflecting this uncertainty surrounding the need for intraoperative assessment of SLNB is the clinical heterogeneity in both the methods used (i.e., frozen section vs. touch prep) and the amount of tissue submitted for intraoperative assessment. The College of American Pathologists has published guidelines for the processing of sentinel lymph nodes, but they focus on the grossing and processing of these specimens for permanent histology with no mention of the proper technique for intraoperative assessment [19]. Thus, a review of the relevant literature will show a wide variety of techniques used for intraoperative assessment of SLNB [20].

In this study, we evaluated the diagnostic performance of our method of intraoperative assessment of SLNB—that is, freezing half of the sentinel node while preserving the other half for routine histology. After comparing the frozen and final diagnoses, we then evaluated the reasons for discrepancy between the diagnoses and examined the clinicopathologic data of patients with false-negative frozen diagnoses. We found that the majority of false-negative diagnoses result from patients with either ITCs or micrometastases, which are of debatable clinical significance and clearly carry a better prognosis than macrometastases. Furthermore, the majority of false negatives were due to either block or tissue sampling errors, with few cases the result of misinterpretation at the time of frozen section. This result is generally similar to the findings of a study examining the appropriateness of diverting half of a node for ancillary studies and research protocols [21].

Based on these findings, we conclude that the protocol of freezing half of a sentinel lymph node is a reasonable method that results in a high correlation between the frozen and final diagnoses, although it does not entirely eliminate sampling error. The results of this current study do not resolve the debate of the clinical utility of intraoperative SLNB, yet rather present a viable method for the frozen section analysis when deemed clinically appropriate. Furthermore, this method preserves ample amounts of tissue for optimal histologic evaluation and further diagnostic studies such as IHC or in situ hybridization. Importantly, false-positive diagnoses are exceedingly rare, meaning that this method of frozen section evaluation does not result in unnecessary and potentially harmful additional procedures.

We also show that only 15 % of patients with a false-negative frozen diagnosis who receive additional AD have additional positive lymph nodes, supporting the concept that many patients have at most limited axillary involvement and can be followed clinically and radiographically. Reflecting this trend, the rate of follow-up AD was lower in the later years

of the study, suggesting increased recognition of this movement toward conservative management [22].

Although this study was a retrospective review, it is the largest of its type in the limited literature examining the frozen assessment of SLNB. Our clinicopathologic data included 10 years of patients with at least 12 months of follow-up, as well as complete data about surgical follow-up. The rates of false-positive and false-negative SLNB may vary depending upon the patient demographics including incidence of nodal metastases (specifically macrometastases) at a given institution, such that patient selection for intraoperative SLNB may bias the outcomes across institutions. However, we found similar or better rates of false-negative diagnoses than studies with smaller numbers of SLNBs and less comprehensive follow-up [4, 23–29]. These comprehensive data show that this method of frozen section analysis of SLNB produces excellent specificity (with most false negatives being due to small tumor burden and tissue sampling, rather than misinterpretation) in addition to allowing for rapid evaluation of the size of metastasis in grossly suspicious nodes.

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Fig. 1.

Representative false-negative intraoperative frozen sentinel lymph node biopsy due to “tissue sampling.” In this representative case with negative frozen section diagnosis, the diagnosis was changed to positive after a metastasis was detected in the non-frozen half of the lymph node on H&E (**a** $\times 4$, **b** $\times 20$) and cytokeratin immunostain (**c** AE1/AE3 immunostain, $\times 20$) (“tissue sampling” error)

Fig. 2. Representative false-negative intraoperative frozen sentinel lymph node biopsy due to “block sampling.” In this representative case with negative frozen section diagnosis (**a** H&E $\times 20$), the diagnosis was changed to positive for isolated tumor cells (**b** H&E $\times 20$) after tumor cells were found on the deeper level in the permanent section, confirmed as carcinoma by immunohistochemistry for cytokeratin (**c** AE1/AE3 immunostain, $\times 20$) (“block sampling” error)

Fig. 3.

Size classification of metastases after false-negative intraoperative frozen sentinel lymph node biopsy. The majority of the metastases seen on the permanent section of the sentinel lymph node biopsies, after a false-negative intraoperative frozen section, were either isolated tumor cells (27 %) or micrometastases (42 %), with 31 % macrometastases (>2 mm)

Fig. 4. Follow-up axillary dissection (AD) rates. These *charts* illustrate the trend toward decreased follow-up AD in the later portion of the study, with 53 % of patients with false-negative frozen SLNB undergoing follow-up AD between 2003 and 2008 and 27 % of these patients undergoing follow-up AD from 2009 to 2012

Table 1

Comparison Between the frozen section diagnosis and final diagnosis on sentinel lymph node biopsies

	Final diagnosis positive for carcinoma	Final diagnosis negative for carcinoma	Total
Frozen section positive for carcinoma	305	1	306
Frozen section negative for carcinoma	95	1,539	1,634
Total	400	1,540	1,940

Table 2

Clinicopathologic features of patients with false-negative intraoperative frozen sentinel lymph node biopsies

Age	Median 52 years, range 22–82 years
Metastasis size	Median 1.1 mm, mean 1.9 mm, range 0.05–16 mm
Primary tumor type	Ductal 64 (67.4 %), lobular 20 (21.1 %), mammary not otherwise specified 11 (11.6 %)
Primary tumor size	Median 1.7 cm, range 0.1–6.0 cm
Survival (as of 1/1/2014)	Alive 88 (92.6 %), dead 7 (7.4 %)
Discrepancy reason	IHC needed 19 (20 %), block sampling 33 (34.7 %), tissue sampling 37 (38.9 %), interpretation 6 (6.3 %)
Additional axillary dissection	Yes 39 (41.9 %)