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Is Routine Intraoperative Frozen-Section Examination of Sentinel Lymph Nodes in Breast Cancer Worthwhile?

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Background: Routine intraoperative frozen section (FS) of sentinel lymph nodes (SLN) can detect metastatic disease, allowing immediate axillary dissection and avoiding the need for reoperation. Routine FS is also costly, increases operative time, and is subject to false-negative results. We examined the benefit of routine intraoperative FS among the first 1000 patients at Memorial Sloan Kettering Cancer Center who had SLN biopsy for breast cancer.

Methods: We performed SLN biopsy with intraoperative FS in 890 consecutive breast cancer patients, none of whom had a back-up axillary dissection planned in advance. Serial sections and immunohistochemical staining for cytokeratins were performed on all SLN that proved negative on FS. The sensitivity of FS was determined as a function of (1) tumor size and (2) volume of metastatic disease in the SLN, and the benefit of FS was defined as the avoidance of a reoperative axillary dissection.

Results: The sensitivity of FS ranged from 40% for patients with T1a to 76% for patients with T2 cancers. The volume of SLN metastasis was highly correlated with tumor size, and FS was far more effective in detecting macrometastatic disease (sensitivity 92%) than micrometastases (sensitivity 17%). The benefit of FS in avoiding reoperative axillary dissection ranged from 4% for T1a (6 of 143) to 38% for T2 (45 of 119) cancers.

Conclusions: In breast cancer patients having SLN biopsy, the failure of routine intraoperative FS is largely the failure to detect micrometastatic disease. The benefit of routine intraoperative FS increases with tumor size. Routine FS may not be indicated in patients with the smallest invasive cancers.

Key Words: Sentinel lymph nodes—Frozen section—Macrometastases—Micrometastases.

Sentinel lymph node (SLN) biopsy represents a new standard of care for the patient with clinically node-negative breast cancer. Thirty-two published studies of SLN biopsy validated by a back-up axillary dissection (and comprising nearly 3600 cases)[1–32] confirm that SLN biopsy is both feasible and accurate, reliably detecting axillary metastases in 97% of all patients, and 93% of node-positive cases. Many institutions are completing their own validation trials and beginning to offer SLN biopsy on its own, with no further axillary surgery for SLN-negative patients.

In this setting, the value of routine intraoperative SLN frozen section (FS) is controversial, with wide variation in results and recommendations. If positive, FS has the obvious advantage of allowing an immediate axillary dissection and thereby avoiding reoperation. On the other hand, FS is costly, time-consuming, and subject to false-negative results. Which patients, if any, benefit from routine FS of the SLN? The goal of this study was to address this question by examining the results of FS among our first 1000 SLN biopsy procedures for breast cancer.

MATERIALS AND METHODS

Between September 1996 and January 1999, 1000 consecutive patients had SLN biopsy for clinical stage

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T1–2N0 breast cancer at Memorial Sloan Kettering Cancer Center, using blue dye and isotope in combination. A total of 890 patients had routine intraoperative FS of their SLN and comprised the study group for this analysis. The remaining 110 patients participated in validation studies and had a planned back-up axillary dissection, without FS.

The methodology and results of our first 60[27] and first 500[33] SLN biopsy procedures have been described previously in detail. Successful mapping by blue dye required the identification of a blue-stained SLN or a blue-stained lymphatic directly contiguous with a non-blue node. Successful isotope mapping required the ex vivo counts of the SLN to exceed the postexcision axillary background by at least four to five times.

Whenever possible (depending on node size), half of each SLN was immediately frozen and banked for research protocols. Among our first 1000 SLN biopsy procedures, samples from 1800 SLN were banked in this fashion, corresponding to the median yield of 2 SLN per patient. A portion of the remaining nodal tissue was taken for FS and examined by a single hematoxylin and eosin (H&E) stained section. All FS were prepared by histotechnologists. The remaining frozen tissue (submitted as a "frozen section control") and all remaining unfrozen nodal tissue were fixed and embedded in paraffin. Serial sections were taken at 50-μm intervals and stained both with H&E and with immunohistochemical (IHC) stains for CAM5.2 and AE1:AE3 (Becton Dickinson Immunocytometry Systems, San Jose, CA). An average of three H&E and two IHC-stained sections were analyzed per SLN.

The benefit of FS was defined as the proportion of all patients having FS in whom the FS was positive, thereby allowing an immediate axillary dissection and avoiding reoperation for this reason. The sensitivity of FS was defined as (true positive)/(true positive + false negative), the false-negative rate as (false negative)/(true positive + false negative), and the positive predictive value as (true positive)/(true positive + false positive). Based on a complete pathologic review of all positive SLN, metastases were classified as micrometastatic (tumor deposits $\leq$ 2 mm in greatest dimension) or macrometastatic (deposits $>$ 2 mm). Patients classified as macrometastases included those who had a mixture of micro- and macro-metastases, whereas those classified as micrometastases had only micrometastases. The significance of frequency differences between subgroups was determined by χ^2.

RESULTS

Among the 890 patients, FS correctly diagnosed 58% of those who were SLN-positive (135 of 231). Among patients with positive SLN, the median age was 53 years (range, 21–85) and median tumor size was 1.5 cm (range, 0.1–4.5 cm). A total of 202 (87%) had infiltrating ductal, 24 (10%) infiltrating lobular, and the remaining 5 (3%) colloid, medullary, or tubular cancers. There was a single false-positive FS (in a patient with a benign nevus rest), yielding a positive predictive value of 99.3%. All other incorrect results were false-negatives.

The overall results of FS (Table 1) indicated that both SLN positivity and FS sensitivity increased with tumor size ($P = .002$) and that false-negative FS was less frequent for larger tumors. The size of SLN metastasis could be determined for 224 of the 231 SLN-positive patients; 51% (115) had micrometastases and 49% (109) had macrometastases. The proportion of SLN-positive patients with micrometastases was inversely related to tumor size: 73% of T1a, 58% of T1b, 54% of T1c, and 35% of T2 lesions had micrometastasis ($P = .016$). FS was far less sensitive in detecting micrometastases (Table 2) than in detecting macrometastases (Table 3, $P < .001$). For the patients with micro- (Table 2) and macrometastases (Table 3), FS sensitivity was relatively independent of tumor size ($P = .09$ and $P = .74$, respectively).

The 115 patients classified as having micrometastases included a mixture of those whose SLN were positive on H&E and/or IHC, and 68% of the SLN micrometastases

TABLE 1. *Overall results of intraoperative frozen section of the SLN*

Tumor size	Patients (n)	SLN+ (%)	Sensitivity* (FS+/SLN+) (%)	False-negative rate (FS−/SLN+) (%)	Benefit (FS+/total) (%)
T1a	143	15 (10)	6/15 (40)	9/15 (60)	6/143 (4)
T1b	249	50 (20)	25/50 (50)	25/50 (50)	25/249 (10)
T1c	379	108 (29)	59/108 (55)	49/108 (45)	59/379 (16)
T2	119	58 (48)	45/58 (76)	13/58 (23)	45/119 (38)
Total	890	231 (26)	135/231 (58)	96 (42)	135/890 (15)

FS, frozen section, SLN, sentinel lymph node; sensitivity, (true positive)/(true positive + false negative); false-negative, (false negative)/(true positive + false negative); benefit, (true positive)/(total patients).

* $P = .002$.

TABLE 2. *Sensitivity of SLN frozen section for patients with micrometastases*

Tumor size	Proportion micrometastatic (%)	Sensitiviy* (%)	False-negative (%)
T1a	11/15 (73)	2/11 (18)	9/11 (82)
T1b	28/48 (58)	3/28 (11)	25/28 (89)
T1c	57/106 (54)	14/57 (25)	43/57 (75)
T2	19/55 (35)	8/19 (42)	11/19 (58)
Total	115/224 (51)	28/115 (17)	87/115 (83)

* $P = .09$.

TABLE 4. *SLN micrometastases detected only with IHC*[a]

Tumor size	Proportion micrometastatic (%)	Frozen section negative (%)	IHC only positive (%)
T1a	11/15 (73)	9/11 (82)	7/9 (78)
T1b	28/48 (58)	25/28 (89)	17/25 (68)
T1c	57/106 (54)	43/57 (75)	27/43 (63)
T2	19/55 (35)	11/19 (58)	9/11 (82)
Total	115/224 (51)	88/115 (77)	60/88 (68)

IHC, immunohistochemistry.
[a] IHC only performed in patients with negative frozen section.

(Table 4) were diagnosed only by IHC. Although with larger tumors the SLN were less likely to contain micrometastases, the yield of IHC staining in the micrometastatic subset was also relatively independent of tumor size.

DISCUSSION

An increasing number of institutions are completing validation studies of SLN biopsy in breast cancer and beginning to accept a negative SLN as adequate axillary staging. In this setting, the role of routine intraoperative FS of the SLN will come under scrutiny. Although clearly of benefit when positive (by allowing an immediate axillary dissection and avoiding reoperation), FS consumes operative time, increases the pathologist's workload, is costly, and is subject to false-negative results.

Dixon et al.[34] recently examined the role of axillary node FS in breast cancer outside the setting of SLN biopsy. In 88 consecutive patients having either mastectomy or breast conservation, they sampled four axillary nodes and compared the results of FS with permanent sections. FS detected metastatic disease in 19/26 node-positive patients, for a sensitivity of 73%, and they concluded that FS was not sufficiently accurate to be used as part of an axillary node sampling procedure.

In the more focused setting of SLN biopsy for breast cancer, five previous studies examine the role of intraoperative pathologic assessment (Table 5), using a variety of methodologies. Interpretation of the results is made difficult by variations in technique. Enhanced *intraoperative* analysis of the SLN (with the addition of serial sections, touch prep [TP], and even IHC stains) will increase the apparent sensitivity of FS, whereas enhanced postoperative analysis of the paraffin sections (using serial sections and IHC) may identify more positive SLN, decreasing the apparent sensitivity of FS. The use of enhanced methods both intraoperatively and postoperatively adds another element of variation.

TABLE 3. *Sensitivity of SLN frozen section for patients with macrometastases*

Tumor size	Proportion macrometastatic (%)	Sensitivity* (%)	False-negative (%)
T1a	4/15 (27)	4/4 (100)	0/0 (0)
T1b	20/48 (42)	18/20 (90)	2/20 (10)
T1c	49/106 (46)	44/49 (90)	5/49 (10)
T2	36/55 (65)	34/36 (94)	2/36 (6)
Total	109/224 (49)	100/109 (92)	9/109 (8)

* $P = .74$.

In the two smallest studies, Flett et al.[21] (using FS) and Rubio et al.[35] (using TP) demonstrate sensitivities of 84% (18 of 21) and 94% (16 of 17), in detecting positive SLN. The early, larger experience of Veronesi et al.[2] is more comparable to our own. Intraoperative FS identified metastatic disease in 64% (32/50) of SLN-positive cases. Turner and Giuliano[36] were able to increase the sensitivity of their intraoperative examination by combining FS and TP, and of their paraffin sections by adding IHC staining to the routine H&E. Their sensitivity of 74% using H&E staining of the SLN increased to 83% with the addition of IHC. The ultimate intraoperative examination of the SLN is that described by Veronesi et al.[16] in a follow-up report to his initial study. Unsatisfied that routine FS with H&E staining detected only 68% of SLN-positive cases, he describes the "exhaustive intraoperative frozen section method," in which a FS analysis of the entire SLN was performed: 15 or more pairs of 4-μm FS (stained with both H&E and a rapid IHC method) were taken until the entire node was sampled, leaving no tissue for permanent sections. The procedure he describes, taking "40–50 minutes" and requiring multiple pathologists and technicians, would be prohibitive for any institution with lesser resources than his own.

Intraoperative FS appears equally limited in its ability to detect SLN metastases in patients with melanoma, about 20% of whom are node-positive. Separate studies by Gibbs et al.[37] and Clary et al.[38] report sensitivities for FS ranging from 29% to 56% and note the value of serial sections and IHC staining in detecting disease missed by

TABLE 5. *Reported results of intraoperative pathologic examination of the SLN*

Author	# SLN+ pts	Intraoperative methodology	Paraffin section methodology	Sensitivity (FS+/SLN+) (%)	False negative (FS−/SLN+) (%)	Benefit (FS+/total) (%)
Flett et al.[21]	21	FS	H&E	18/21 (86)	3/21 (14)	18/56 (32)
Rubio et al.[35]	17	TP	H&E	16/17 (94)	1/17 (6)	16/53 (30)
Veronesi et al.[2]	50	FS	H&E	32/50 (64)	18/50 (36)	32/160 (20)
Turner and Giuliano[36]	72	FS+TP	H&E	53/72 (74)	19/72 (26)	53/278 (19)
	111	FS+TP	IHC	92/111 (83)	19/111 (17)	92/278 (33)
Veronesi et al.[16]	81	FS	H&E	55/81 (68)	26/81 (32)	55/192 (29)
	52	FS+IHC[a]	—	52/52 (100)	0/52 (0)	52/119 (44)

SLN, sentinel lymph node; FS, frozen section; TP, touch prep (imprint cytology); H&E, hematoxylin-eosin; IHC, immunohistochemistry; sensitivity, (true positive)/(true positive+false negative); false-negative, (false negative)/(true positive+false negative).
[a] FS and immediate IHC taken of the *entire* SLN.

FS. Both authors suggest that routine intraoperative FS not be performed and raise the possibility of missed micrometastases within the tissue consumed by FS. Neither group emphasizes the consequence of not performing intraoperative FS for melanoma: a reoperation rate of 20%.

Our data in 231 SLN-positive patients demonstrate that (1) the sensitivity of intraoperative FS (58% overall) is dependent on tumor size, (2) this dependence reflects the increasing proportion of macrometastases in patients with larger tumors, and (3) that within the subsets of patients with SLN micro- or macro-metastases, this size dependence is lost. As Turner et al.[36,39] also show, the failure of intraoperative FS analysis of the SLN is largely the failure to detect micrometastatic disease. In identifying this group of patients, IHC staining is an essential element. Among our 88 SLN-positive patients with micrometastases missed by FS (Table 4), 68% were detected by IHC.

The major benefit of intraoperative FS is that a positive result allows an immediate axillary dissection and avoids the need for reoperation, a distressing event for many breast cancer patients. This benefit accrued to only 4% (6/143) of our patients with T1a cancers and increased with tumor size to include 38% (45/119) of those with T2 tumors (Table 1). Veronesi et al.'s[16] "exhaustive intraoperative frozen section" addresses the issue of benefit at one end of the spectrum, with an analysis so thorough that FS of the SLN is always correct and that no patient should need reoperation because of a false-negative result. At the other extreme is Dixon et al.,[34] who argue (in the context of axillary sampling) that a sensitivity for intraoperative FS of 73% is too low to justify its routine use. This latter viewpoint may in part reflect a general reluctance of surgical pathologists in the United Kingdom to perform FS for any reason (J. Hartley, personal communication, 1999). We believe that intraoperative FS of the SLN is indicated in most patients with invasive breast cancer, and our own practice, based on the above data, is to perform FS on the SLN of all patients with invasive breast cancers larger than 5 mm, in whom axillary dissection will be performed if the FS is positive.

This practice may change over time. First, not all SLN-positive patients may require axillary dissection and a positive FS of the SLN is of no benefit to the patient if the rest of the axilla is negative. We are developing predictive models to define subgroups of SLN-positive patients with disease limited to the SLN.[40] Second, a major clinical trial[41] (Z0011, sponsored by the American College of Surgeons Oncology Group) is asking whether *any* SLN-positive patients require axillary dissection, and randomizes SLN-positive patients to either axillary dissection or observation. Finally, in the managed care era, more detailed analyses are required to determine the exact point at which the cost of intraoperative FS exceeds the benefit. Considered in the simplest way, the total charge at our institution for a single reoperation exceeds that of a FS by 20–30 times. A sophisticated cost-benefit analysis of SLN biopsy in general, and of SLN FS in particular, is beyond the scope of this article and much needed.

CONCLUSION

The sensitivity of intraoperative FS of the SLN in breast cancer patients is tumor size dependent, and false-negative FS result largely from the failure to detect micrometastases. The benefit of intraoperative FS in avoiding reoperative axillary dissection ranged from 4% for T1a to 38% for T2 cancers. Routine FS may not be indicated for patients with the smallest invasive tumors.

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