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Review

Clinical aspects of sentinel node biopsy

Hiram S Cody III

The Breast Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, and Cornell University Medical College, New York, New York, USA

Correspondence: Hiram S Cody III, MD, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA. Tel: +1 212 639 8261; fax: +1 212 794 5812; e-mail: codyh@mskcc.org

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Abstract

Sentinel lymph node (SLN) biopsy requires validation by a backup axillary dissection in a defined series of cases before becoming standard practice, to establish individual and institutional success rates and the frequency of false negative results. At least 90% success in finding the SLN with no more than 5–10% false negative results is a reasonable goal for surgeons and institutions learning the technique. A combination of isotope and dye to map the SLN is probably superior to either method used alone, yet a wide variety of technical variations in the procedure have produced a striking similarity of results. Most breast cancer patients are suitable for SLN biopsy, and the large majority reported to date has had clinical stage T1-2N0 invasive breast cancers. SLN biopsy will play a growing role in patients having prophylactic mastectomy, and in those with 'high-risk' duct carcinoma *in situ*, microinvasive cancers, T3 disease, and neoadjuvant chemotherapy. SLN biopsy for the first time makes enhanced pathologic analysis of lymph nodes logistically feasible, at once allowing greater staging accuracy and less morbidity than standard methods. Retrospective data suggest that micrometastases identified in this way are prognostically significant, and prospective clinical trials now accruing promise a definitive answer to this issue.

Keywords: breast cancer, lymph node metastasis, lymphoscintigraphy, sentinel node

Introduction

Some of the best ideas in clinical medicine are simple ones, and SLN biopsy is one of these. The hypothesis that one or a few lymph nodes receive the first drainage from a tumor site, and that a regional node dissection and its morbidity might be avoided if the SLNs prove negative, is logical and intuitive. First suggested by Cabanas [1] in the context of penile cancer and conceived in its modern form in a 1992 report by Morton *et al* [2], SLN biopsy is rapidly emerging as a new standard of care in melanoma and breast cancer. The procedure has promise but remains investigational in patients with head and neck, urologic, gynecologic, and colorectal cancers. SLN biopsy's immediate potential is greatest among patients with breast cancer, by far the most significant group numerically, and will be the focus of this overview. Among an estimated 184,200 new cases of breast cancer in the United States last year [3], about 60% (110,000) had disease limited to the breast and might have avoided a conventional axillary lymph node dissection (ALND) through SLN biopsy.

By the end of 1999, 41 peer-reviewed pilot studies using radioisotope [4–19] or blue dye [20–30] methods, or a combination of both [31–42] (Table 1), report the results of SLN biopsy validated by a 'backup' ALND in breast cancer patients. SLNs were identified in 90% of cases, correctly identified 93% of axillary node-positive individuals, and were the only site of nodal metastasis in 47% of these. An

ALND = axillary lymph node dissection; FNA = fine-needle aspiration; SLN = sentinel lymph node.

Table 1

Cumulative results of sentinel lymph node (SLN) biopsy, 1993–1999

Method	SLN found	False negative SLN	Accuracy overall
Isotope [4–19]	2112/2292 (92%)	54/779 (7%)	1942/1996 (97%)
Blue dye [20–30]	714/886 (81%)	23/245 ((9%)	691/717 (96%)
Combined [31–42]	1071/1155 (93%)	21/417 (5%)	1042/1063 (98%)
Total	3897/4333 (90%)	98/1441 (7%)	3675/3776 (97%)

Data presented as *n* (%). False negative SLN, (false negative SLN)/(true positive axilla); accuracy overall, (true positive SLN + true negative SLN)/(total cases in which SLN was found).

increasing number of centers, having completed validation studies of SLN biopsy, offer patients the option of no further axillary surgery if the SLN is negative. Despite this encouraging debut, SLN biopsy is a new operation, has a definite learning curve, and is highly multidisciplinary, requiring the cooperation of nuclear medicine physicians, surgeons, and pathologists. The techniques pertinent to each specialty continue to evolve, and many of these aspects remain the subject of debate. We have performed more than 3000 SLN biopsy procedures since 1996, and the following represents a distillation of our experience, recently reviewed in detail [43], and that of other workers.

Protocol design and learning curve issues

The benefit of SLN biopsy seems clear, but the technique is a new one, the long term consequences are not fully defined, and the medicolegal risks are unknown. Institutions beginning to perform this procedure should do so under a formalized Institutional Review Board protocol, in which selection and technique are carefully specified, patients are fully informed, a backup axillary dissection is carried out to validate the early experience, and careful audits of individual and institutional results (short and long term) are maintained. A success of 90–95% in finding the SLN and no more than 5–10% false negative results would seem reasonable targets for validation trials.

We have found that success in localizing the SLN continued to improve over our first 500 cases, and that one-half of our false negative results occurred within the first six cases of each surgeon [44]. Cox *et al* [45] found that, to identify the SLN, surgeons required an average of 23 cases to achieve 90% success and 53 cases to achieve 95% success, although the SLN was falsely negative in only 2% of their node-positive patients [39]. While most authorities recommend that each surgeon initially perform 20–30 SLN procedures with a backup ALND, fewer validated cases may be necessary. McMasters *et al* [46], in a remarkable multi-institutional trial involving 806 patients and 99 surgeons, found that the frequency of successful mapping and of false negative results was identical whether the participating surgeons had prior experience of more than or fewer than 10 SLN operations.

SLN may be identified by either radioisotope or blue dye methods and, while each technique by itself enjoys the vocal support of a few investigators [10,21], an emerging international consensus (and our own experience [33,47,48]) supports the use of both methods in combination. We continue to find that about 10% of SLN, and 10% of positive SLN, are found by either dye or isotope alone, and presumably would have been missed by reliance on a single method. McMasters *et al* [46] demonstrate that false negatives occur half as often with a combined technique as with a single-agent SLN mapping technique.

Case selection

Most of the reported experience with SLN biopsy includes patients with clinical stage T1-2N0 invasive breast cancers. SLN biopsy has an emerging role in microinvasive cancers and in selected cases of duct carcinoma *in situ*, particularly those with a high risk of occult invasion (evidenced by a palpable mass or extensive disease requiring mastectomy). While neither group is normally considered for a conventional ALND, about 10% of microinvasive or high-risk duct carcinoma *in situ* patients harbor micrometastases in their SLN [49]. SLN biopsy is reasonable at the time of a prophylactic mastectomy, to avoid the need for reoperative ALND if invasive cancer is unexpectedly found in the breast (as is the case in perhaps 5% of prophylactic mastectomies). SLN biopsy works well for nonpalpable cancers requiring needle localization [50], and in the setting of a prior surgical biopsy [47]. While equally accurate for T1 and T2 cancers [51,52], high false negative rates occur in T3 cancers and in patients with surgical disruption of the axillary lymphatics by a large upper outer quadrant biopsy cavity. Diagnosis should, for this reason, be by fine-needle aspiration (FNA) or core needle biopsy whenever possible. Even in the setting of advanced disease, SLN biopsy may play a role in estimating response to neoadjuvant chemotherapy [53]. Finally, SLN biopsy is reasonable in selected patients with clinically palpable axillary nodes thought to be reactive, as long as the surgeon maintains a low threshold for default to conventional ALND.

Nuclear medicine aspects

Overall, radioisotope mapping of the SLN succeeds more often than blue dye (92% versus 81%; Table 1). Intuition would suggest that tracer injection into or directly adjacent to the tumor would most accurately identify the SLN. A number of studies, however, have found that SLN identified by intraparenchymal, 'subdermal', intradermal or subareolar injections [18,28,32,54,55] stage the axilla with comparable accuracy, and that the entire breast and its overlying skin function as a single lymphatic unit in most patients [56]. This may explain why such a wide variation in isotope techniques (dosage of isotope, carrier particle, route/timing/volume of injection, and definition of a successful result) produces such a similarity of outcome. We have achieved optimal success using blue dye injected intraparenchymally and unfiltered [57] Tc-99m sulfur colloid in 0.05 cm^3 saline injected intradermally [54] into a single site directly over the tumor, at a dose of 0.1 mCi for same-day and 0.5 mCi for day-before injection. In our most recent experience, we have identified the SLN in 97% of cases.

Preoperative lymphoscintigraphy is essential in the management of melanoma, and can indeed also show unexpected patterns of lymphatic drainage (supraclavicular, internal mammary, Rotter's node) in about 20% of breast cancer patients [58]. Because gross recurrence in these nonaxillary sites is a very rare event in early-stage breast cancer, the clinical relevance of this finding is uncertain, and the role of routine preoperative lymphoscintigraphy in breast cancer patients remains a matter of debate.

Surgical aspects

SLN biopsy is usually a straightforward and simple operation [43]. Before the procedure on the breast (excision or mastectomy), blue dye is injected into the breast just superolateral to the tumor (or biopsy) site, and isotope counts are taken from the axilla and the injection site in the breast using a hand-held gamma probe. An axillary incision is made, and the surgeon identifies and removes the SLN by looking for blue-stained lymphatic vessels or nodes and using the gamma probe to identify focally 'hot' nodes. All blue and/or hot nodes are removed until the axillary background counts fall below a threshold value; most authors report a median of two SLN per patient. Once the surgeon has passed the validation phase in which backup ALND is performed routinely, the SLN are submitted for frozen section and either tumor excision or mastectomy is performed while waiting for the pathologists's report. ALND is performed if the SLNs contain tumor or if there are clinically suspicious nonSLNs palpable at the time of surgery. Clinically suspicious nonSLNs were present in more than one-half of our false negative SLN biopsy procedures [43,47], suggesting that gross tumor involvement of the nodes may impair the uptake of both isotope and dye by the 'true' SLN. Careful intraoperative palpation of the axilla is an essential component of SLN biopsy, and the surgeon facing suspicious findings should not hesitate in defaulting to ALND.

Pathologic aspects

Frozen section analysis of the SLN, if positive, allows an immediate ALND, sparing the patient a reoperation. While limited in its ability to detect micrometastases (which predominate in the smallest invasive cancers), the frozen section of the SLN demonstrates sensitivity ranging from 40% for T1a to 60% for T2 cancers [59].

Lymph nodes in ALND specimens are normally examined by a single hematoxylin and eosin stained section. When nodes found to be negative by this standard method are further studied with serial sectioning and immunohistochemical stains for cytokeratins, missed metastases are found in 10–20% of cases [60]. The overwhelming majority of studies with adequate statistical power demonstrate that these missed metastases are prognostically significant, associated with a 10–15% worsening of disease-free survival [60–62]. SLN biopsy for the first time makes enhanced pathologic analysis logistically feasible, and allows the identification of a group of patients whose increased risk of systemic relapse might otherwise go unrecognized. While SLN biopsy is itself subject to a small percentage of false negative results, the proportion of false negatives with a conventional pathologic analysis of the axillary nodes is perhaps 10-fold greater.

A striking parallel to the presented findings arises from two German studies [63,64], in which the bone marrow of breast cancer patients harvested at the time of their surgery was examined for micrometastases using immunohistochemical staining. Both demonstrate, firstly, a strong correlation of micrometastases with stage of disease and, secondly, an 'independent' prognostic significance of bone marrow micrometastases that equals or exceeds that of axillary node status.

Breast cancer is a disease characterized by heterogeneity, and nowhere is this heterogeneity more apparent than at the level of the SLN. Enhanced pathologic analysis using immunohistochemical and serial sections may identify SLN containing single metastatic cells, tiny groups of cells, micrometastatic clusters, or even large macrometastases found on a directed retrospective review of the hematoxylin and eosin stained sections. These gradations suggest that not all nodal metastases are the same, but they rather represent a spectrum of risk, posing a dilemma for the oncologist trying to ascertain the necessity of systemic adjuvant treatment. Even with the maturity of clinical trials now in progress, the prognostic significance of occult SLN metastases will remain a matter of controversy.

Follow-up

The follow-up of patients after SLN biopsy, as for breast cancer patients in general, is for life. While local recurrence has been reported in the regional node basin after SLN biopsy for melanoma [65], no such recurrences have

been observed in breast cancer patients after a negative SLN biopsy, either in our experience or that of others [66]. Such recurrences will recur, but we ultimately expect that that the rate of isolated axillary relapse after a negative SLN biopsy will be comparable with that after a conventional axillary dissection, 1% or less. We expect the other long term morbidities of SLN biopsy to also be substantially less than that of axillary dissection, if not zero. Early results from a prospective study of our own patients demonstrate a substantial reduction in postoperative sensory phenomena for SLN biopsy compared with axillary dissection; long term studies also address the relative risk of lymphedema and cellulitis.

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