The Current Role of Sentinel Lymph Node Biopsy in Breast, Melanoma, and Gastrointestinal Cancers

a report by

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In the two decades that have passed since Morton and colleagues[1] introduced their landmark technique for the identification of sentinel lymph node (SN) metastasis in patients with malignant melanoma, sentinel lymph node biopsy (SLNB) has proved to be a remarkable tool in the treatment of solid cancers and has dramatically changed the manner in which regional nodal disease is managed.

The SN concept is that lymphatic flow away from a primary tumor drains through one, or sometimes several, first or SNs as it enters the regional nodal basin. By definition, these nodes receive their drainage directly from the tumor and not from any other nodes. Cancer spread through the lymphatics should first be deposited in the SN and detailed examination of that node should accurately predict the status of the remaining nodal basin. This not only identifies those patients who are most likely to benefit from a completion nodal dissection (CLND), but also results in more accurate pathological staging.

Although SLNB was originally introduced in the management of malignant melanoma, the technique was also rapidly and successfully applied to invasive breast cancer.[2] Since then, clinicians have investigated the applicability of SLNB to an ever-increasing number of malignancies, including thyroid cancer, lung cancer, multiple gastrointestinal malignancies, and even head and neck cancer.[3–6] The ultimate role of the SN technique is yet to be determined for many of these different malignancies, and refinements to both technique and indication are frequently proposed as worldwide experience increases. This article will focus principally on the current role of SLNB in the management of malignant melanoma, invasive breast cancer, and colon cancer—the three malignancies with the greatest amount of collective data available upon which recommendations can be based. Specific details for the SN technique in treating these cancers and others are sufficiently described elsewhere and will not be emphasized to any great extent here.

Malignant Melanoma

Prior to the arrival of the SLNB era, management of the draining nodal basins in patients with cutaneous malignant melanoma was a hotly contested issue. Many clinicians favored elective lymph node dissection (ELND) in patients who had no clinical or radiographic evidence of nodal involvement, in the belief that interceding prior to the development of obvious nodal disease would provide patients with the best chance of a complete cure.[7] Others countered that because ELND benefited only the 10–20% of patients who had occult nodal disease, its routine use for clinically normal regional nodes would subject at least 80% of patients to a potentially morbid operation from which they could gain no benefit. In addition, they argued, there was no clear survival benefit for the small percentage of patients who actually had nodal disease compared with those who underwent delayed lymph node dissection (DLND) after nodal involvement became clinically apparent.[8] Several large, randomized multi-institutional studies failed to demonstrate a clear survival advantage for ELND despite earlier retrospective reports espousing significant benefit.[9,10]

The technique for SN identification introduced by Morton in 1992 represented a substantial solution to the issues outlined above.[1] The procedure, which combined pre-operative lymphoscintigraphy, intradermal vital blue dye injection, and intraoperative mapping of the SN, proved to be remarkably consistent and accurate, particularly for a newly described technique. Application of the hand-held gamma probe followed soon afterwards, allowing realtime use of radioactive colloid tracer in conjunction with blue dye to increase SN yield, shortening the learning curve for the technique, and further reducing false-negative rates. Multiple investigators have confirmed the high accuracy of this technique, with SN identification rates approaching 98% in most studies and false-negative rates of <1% (see *Table 1*).[11–15]

The Intergroup Melanoma trial first reported results for ELND in patients with intermediate thickness (1–4mm) melanoma in 1996 with follow-up results reported in 2000.[16,17] This trial was initiated in response to criticisms about previous randomized trials that failed to demonstrate benefit in ELND yet lacked the sophistication to analyze specific patient subgroups with primary

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Table 1: Results of Sentinel Lymph Node Biopsy in All Nodal Basins for Malignant Melanoma

Investigator	Number of Cases	Localization Method	Accuracy (%)
Morton[1]	223	BD	82
Krag[11]	121	BD/RAC	98
Thompson[12]	118	BD	96
Albertini[13]	106	BD/RAC	96
Leong[14]	163	BD/RAC	98
Essner[15]	247	BD/RAC	98

BD = blue dye; RAC = radioactive colloid.

cutaneous melanoma that might indeed receive a survival advantage from the procedure. Although no survival benefit was shown for the group as a whole, younger patients with thinner lesions and favorable prognostic features (no ulceration) did appear to benefit. This study was quickly embraced as evidence that there was indeed some role for ELND in patients with intermediate thickness primary melanoma. As the popularity and acceptance of SLNB spread, clinicians reassessed the indications for nodal staging in the melanoma population as a whole, while critics argued that there continued to be no clear evidence that early identification and nodal dissection for patients with occult nodal metastasis was beneficial. The Multicenter Selective Lymphadenectomy Trial (MSLT) group was formed to address these questions and others about the benefit of SLNB in patients with primary cutaneous melanoma.[18] MSLT-1 randomized 1,269 patients with intermediate-thickness melanoma to either wide local excision (WLE) alone or WLE plus SLNB. Patients in the WLE alone arm underwent DLND if they developed clinical evidence of nodal disease, and patients in the WLE plus SLNB group underwent CLND if a tumor-positive SN was found. Interim results of this study, reported in 2006,[18] were striking in that they not only showed a significant survival advantage for patients with occult nodal metastasis who underwent SLND/CLND, but also showed that patients managed with SLND had a longer disease-free survival interval. The results of this trial supported widely existing consensus opinion that patients with primary cutaneous melanoma of intermediate depth (1–4mm) should undergo SLNB in conjunction with WLE of the primary lesion.

Patients with either thick (>4mm) or thin (<1mm) primary melanoma had typically not been considered as candidates for ELND in the pre-SLNB era. Those with thin primary lesions were historically felt to have such a low risk (5%) for occult nodal metastasis that exposure to the morbidity of ELND could not be justified given the high likelihood that they would receive no oncological benefit from the operation. A number of investigators documented the negative prognostic impact of regional nodal recurrence in large cohorts of thin melanoma patients, and have proposed a paradigm shift in the application of SLNB for selected patients in this group.[19] Other clinicians have reported their institutional results for SLNB in this group, confirming a consistently low incidence of occult nodal metastasis and a variability of tumor/patient characteristics that correlated with nodal status.[20–22] We recently reported our own results for SLNB in a large group of thin melanoma patients and confirmed the important prognostic significance of SN status in this patient group, in terms of both recurrent disease and melanoma-specific survival.[23] Thick melanoma patients have traditionally not been offered surgical staging of the regional nodal basin because their high risk for occult distant metastases was felt to be prohibitive and also more indicative of outcome than nodal status. Again, with the arrival of the SN era, clinicians challenged conventional indications for surgical nodal staging. For example, Gershenwald et al. reported their experience with 131 thick melanoma patients who underwent SLNB and confirmed not only the accuracy of the technique but also that nodal status is the most important prognostic indicator in this patient group.[24]

Current National Cancer Care Network (NCCN) recommendations call for all patients with primary cutaneous melanoma >1mm in depth in the absence of clinically evident nodal metastasis or known distant disease to undergo SLNB as part of their primary surgical management.[25] Patients with thin primary lesions (<1mm) are not advised to undergo routine SLNB in the absence of potential risk factors, such as tumor ulceration, younger age, tumor depth >0.75mm, vertical growth phase, elevated mitotic rate, and questionable tumor depth, as sometimes occurs with a shave biopsy. However, it is unclear whether these factors correlate sufficiently with nodal status to make confident decisions regarding the need for nodal staging. Future studies may help to more accurately define factors for risk stratification in this patient group, resulting in more reliable patient selection.

Breast Cancer

Perhaps more than with any other malignancy, management of the regional nodal basins in breast cancer has undergone a dramatic change since the first applications of the SN technique to this disease. As recently as 10 years ago the majority of patients with invasive breast cancer underwent some form of axillary lymph node dissection (ALND) at the time of tumor resection. This provided critical staging information in these patients that was important not only from a prognostic standpoint but also in terms of appropriate patient selection for increasingly effective adjuvant therapies. Despite the frequent and long-term use of this approach, several aspects of routine staging ALND in early-stage invasive breast cancer remained problematic. Consider the morbidity of ALND. Even with a relatively limited dissection to remove level I and II echelon nodes, significant rates of extremity lymphedema, weakness, paresthesia, limited mobility, and debilitating pain occur.[26] Furthermore, routine drain placement is required and post-operative wound complications are not unusual. Just as importantly, limited ALND can often miss the involved node(s) or, alternatively, the involved node may be included in the nodal dissection specimen but go undetected by the examining pathologist.

> Although sentinel lymph node biopsy was originally introduced in the management of malignant melanoma, the technique was also rapidly and successfully applied to invasive breast cancer.

The initial application of the SN technique in invasive breast cancer was reported by our group in 1994.[2] In that study, 172 patients underwent lymphatic mapping using vital blue dye alone. In 174 procedures (two patients had bilateral synchronous cancers), the SN correctly predicted the status of the axillary nodal basin on completion dissection 95.6% of the time. Although there was a steep learning curve to the procedure with an SN identification rate of 58% in the first 50 cases compared with almost 80% of the final 50 cases, these findings immediately validated the idea that the SN technique, which had proved to be reliable in cutaneous melanoma, could also be applied to solid tumors of the breast.

Since that initial report, multiple investigators have confirmed the accuracy and reliability of the technique in patients with invasive breast cancer.[27–30] As was also the case with malignant melanoma, numerous studies have shown a complementary role for the use of pre-operative lymphatic mapping and intraoperative localization with radiolabeled pharmaceuticals. However, unlike malignant melanoma, lymphatic drainage of the breast is predictable enough that the use of blue dye alone is sufficient in the majority of cases should that be the surgeon's preference.

The role of SLNB in patients with early invasive breast cancer seems broadly accepted. Patients with clinical stage I or II disease in the absence of clinically evident nodal metastasis have a 20–30% risk for occult nodal disease, and therefore are reasonable candidates for surgical nodal staging, particularly when one considers the effect of increasingly effective systemic therapies in this disease.[31] Few would argue that SLNB has emerged as the nodal staging procedure of choice for patients with early invasive breast cancer, given not only the dramatic decrease in morbidity compared with conventional nodal dissection but also the ability of pathologists to more accurately detect small deposits of cancer when able to focus on select nodes. Growing evidence suggests that status of the SN has prognostic implications, even for patients with very small or microscopic metastatic disease.[32,33]

Current matters of debate regarding the use of SLNB in breast cancer center largely on its role in patients with locally advanced disease or those with ductal carcinoma *in situ* (DCIS). Large, bulky tumors often preclude the routine use of breast conservation in patients with breast cancer. Instead, these patients may often undergo neoadjuvant systemic therapy with the hope of shrinking the primary tumor enough to allow for successful segmental mastectomy. Given the effectiveness of this approach in achieving breast conservation, it is no surprise that nodal status often changes during the course of therapy. Many believe that, in order to be accurate, the SN technique must be applied prior to the initiation of systemic therapy in these patients.[34] This translates into additional cost and morbidity as patients ultimately have to undergo two operative procedures. Furthermore, the benefit of SLNB is somewhat diminished, as a higher percentage of these patients will have a tumor-positive node in the pre-operative setting and will require a completion dissection. Although evidence for strong recommendations regarding the role of SLNB in the setting of planned neoadjuvant chemotherapy is lacking, some national guidelines recommend pre-therapy SLNB and post-therapy CLND if the SN is tumor-positive, independent of tumor response to systematic therapy.[25] Others have found SLNB accurate and helpful after neoadjuvant chemotherapy, because prognosis is determined by post-treatment nodal staging. The common use of adjuvant radiotherapy further complicates the issue.

> Sentinel lymph node biopsy has radically transformed the surgical management of breast cancer and malignant melanoma and is now routine in the care of these patients.

Table 2: Prospective Multi-institutional Trials of Sentinel Lymph Node Biopsy in Patients with Colon Cancer

Investigator	Number of Patients	False-negative Rate (%)	Upstaging* (%)
Bertagnolli[38]	72	54	1.2
Bilchik[39]	132	7	23.6
Bembenek[40]	315	46	21
Stojadinovic[41]	82	10	10.7
Lim[42]	120	41	

**Sentinel node initially deemed tumor-negative by hematoxylin and eosin (H and E) staining but interpreted as tumor-positive after use of ultra-staging techniques (multisectioning, immunohistochemistry [IHC], and/or reverse transcriptase-polymerase chain reaction [RT-PCR]).*

Although DCIS represents pre-invasive malignant change, studies have demonstrated a 1–2% rate of occult nodal metastasis. While this risk was not substantial enough to warrant routine ALND in the pre-SLNB era, the availability of the SN technique has lessened concerns about excessive morbidity. In addition, many patients with DCIS are currently diagnosed via image-guided biopsy, which results in a higher risk for upstaging to invasive disease when the primary tumor is completely excised. However, those patients treated with breast conservation can undergo successful SLNB after upstaging at a second operation in most instances. Clearly, the majority of patients with DCIS diagnosed by core needle biopsy need not be offered SLNB routinely. Instead, a selective approach is warranted in patients with higher risk for invasive disease, such as those with a palpable mass, high nuclear grade, possible microinvasion, or a large radiographic area of disease.[35] Patients undergoing mastectomy for DCIS should also be strongly considered for SLNB given the high risk for discovering invasive disease in the mastectomy specimen and the inability to reliably perform selective nodal sampling afterwards, especially in the setting of immediate reconstruction using free flaps.

Gastrointestinal Malignancies

Colon Cancer

The successful use of the SN technique in the surgical management of patients with malignant melanoma and breast cancer has led clinicians to widely investigate the role of SLNB in other malignancies, most notably colorectal cancer (CRC). The rationale for the use of SLNB in patients undergoing resection for CRC is based on the way in which nodal status determines which patients are selected for adjuvant systemic therapy. Growing evidence suggests that a substantial percentage of pathologically node-negative stage I and II patients treated with conventional segmental mesenteric resection and nodal analysis are actually understaged and thereby denied important and increasingly effective systemic therapy. Recurrence rates in node-negative patients as high as 25% support this notion.[36]

In 1998, our group described the application of the SLNB concept to a variety of solid malignancies, including CRC.[3] A prospective follow-up study in 2000 that focused on gastrointestinal malignancies included 50 patients with CRC and demonstrated the manner in which *in vivo* SLNB could alter the extent of surgical resection.[37] In that same year, Saha et al. reported their experience with 86 patients diagnosed with localized CRC. SNs were identified in 85 of 86 patients.[6] In the 56 patients with a tumor-negative SN, SLNB correctly predicted the remainder of the nodal dissection in 94% of cases. In 15 of 29 node-positive patients, the SN was the only site of nodal metastasis and seven had micrometastasis only in the node. These findings

suggested that a substantial number of patients undergoing resection for CRC could be upstaged by use of the SN technique.

Since the publication of these initial studies, several prospective multi-institutional trials have been reported regarding the use of SLNB in CRC (see *Table 2*).[38–42] Collectively, these reports have highlighted both the promise and the limitations of SN applications in CRC. As SLNB in CRC does not result in a more limited or less morbid operative intervention, and only occasionally alters the intra-operative plan, the real potential benefit to the technique appears to lie in providing more accurate staging information and better selecting patients for potentially life-saving adjuvant therapy. A majority of studies indicate that SLNB with increased nodal sectioning and assessment of hematoxylin and eosin (H&E)-stained negative nodes with immunohistochemistry (IHC) and/or reverse transcriptase-polymerase chain reaction (RT-PCR) techniques results in the upstaging of a substantial number of patients who would otherwise be deemed node-negative. However, less clear is the significance of this microscopic nodal disease in terms of both disease-related outcome and selection for adjuvant systemic therapy. Our group recently reported interim results regarding the prognostic impact of micrometastases, and a mean follow-up of 25 months in 152 CRC patients found no recurrences in patients deemed node-negative after SLNB by H&E, IHC, and RT-PCR compared with six recurrences in patients who were tumor-node-positive according to IHC or RT-PCR staining.[43] Lim et al. found equivalent outcomes in patients with SNs positive by IHC only compared with those who were truly node-negative.[42]

Additional issues regarding SLNB in CRC patients include the need for considerable surgeon experience, a variable false-negative rate with frequently aberrant lymphatic anatomy, and the marginal results achieved in patients with rectal cancer. The precise role of SLNB in the management of CRC is yet to be determined. Further evidence is needed to assess the true importance of metastatic nodal disease that is too small in volume to be detected with conventional histopathological techniques. As collective experience with this potentially important treatment tool increases, the role of SLNB in early CRC may assume an importance that approaches the role of SLNB in other malignancies such as melanoma and breast cancer. However, until that time arrives, SLNB in CRC is best used in the context of prospective clinical trials and as an adjunct to, but never in place of, adequate mesenteric resection.

Other Applications

Sentinel node techniques have been applied to other gastrointestinal cancers as well. Experience with SLNB in gastric cancer is growing steadily worldwide, with the greatest expertise rapidly accumulating in Japan, where the disease is most prevalent.[44] Multicenter trials are under way in Japan and elsewhere to fully assess the efficacy and impact of SN identification in gastric cancer, but early reports demonstrate success in SN identification consistent with other gastrointestinal malignancies. There may be a particular relevance for this technique in gastric cancer given the complexity of lymphatic drainage from the stomach and the well-described tendency for early nodal metastasis to occur well removed from the primary tumor. Development of a reliable SN technique in esophageal cancer is in the early stages of investigation, but may ultimately prove to be useful in better selecting patients for attempts at curative *en bloc* resection.

Summary

SLNB has radically transformed the surgical management of breast cancer and malignant melanoma and is now routine in the care of these patients. This transformation has led to ongoing investigations into the applicability of the technique in other solid-organ malignancies, most notably CRC. Although SLNB shows promise in many of these other cancers, its exact role remains largely undefined in these other malignancies and is best used in the setting of a clinical trial. ■

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