Sentinel Lymph Node Biopsy in Melanoma

Sentinel lymph node (SLN) biopsy was first described by Morton et al. (*1*) in 1992 in patients with malignant melanoma. Many others over almost 100 y had made significant scientific contributions that ultimately led to the development of the technique (*2–4*); however, it was Morton's group from the John Wayne Cancer Center that condensed the principle of the technique now used around the world. SLN biopsy allows the accurate staging of regional lymph node fields by surgical removal and targeted histologic examination of only those lymph nodes receiving direct lymph drainage from the tumor site and, on average, only 1 or 2 nodes need to be removed to achieve this. It has become the standard of care in melanoma (*5*) and breast cancer (*6*) and is increasingly being applied to other solid cancers that have the propensity to metastasize to the regional lymph nodes.

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Despite this rapid acceptance into clinical practice, SLN biopsy was controversial at its conception and uncertainties remain. When the initial description of SLN biopsy by Morton et al. (*1*) was presented for publication, it was rejected by major surgical journals. It can only be presumed that this occurred because, in the opinion of the reviewer, SLN biopsy went against standard teaching in surgical oncology at the time—that is, "Do not node pick. The lymph node field should be subjected to an elective dissection or left alone." Since publication in the *Archives of Surgery*, however, this article has become one of the most frequently cited in surgical oncology.

An unexpected consequence of SLN biopsy when applied to large numbers of patients with melanoma was the discovery that lymphatic drainage of the skin was much more variable in individuals than was previously thought. In fact, several new lymphatic drainage pathways were discovered. These included drainage from the skin of the back to triangular intermuscular space nodes (*7*); drainage through the posterior body wall to nodes in the retroperitoneal, intercostal, paravertebral, and paraaortic regions (*8*); and frequent drainage to interval nodes that lay outside standard node fields (*9,10*). When this variability in individual lymphatic drainage is considered it becomes apparent that in previous trials of elective dissection of draining lymph nodes in patients with melanoma (*11,12*), the wrong field was being dissected in up to 30% of patients.

The article by Rossi et al. (*13*) in this issue of *The Journal of Nuclear Medicine* is further evidence of the robust nature of SLN biopsy when used in clinical practice to stage the regional lymph nodes in melanoma patients. In this Italian multicenter study there were regional differences in the activity injected, the timing of injections before surgery, and the number of peritumoral injections given intradermally—yet a very high rate of SLN node identification was achieved. There was also a true-positive SLN rate for metastasis of 16.9% and a false-negative rate of 14%, both results similar to previous studies including those from single institutions (*1,14,15*). They did find an inverse correlation between the number of peritumoral intradermal injections given and the number of excised SLNs. This will need to be confirmed before a recommendation for more peritumoral injections can be made.

Despite the rapid clinical acceptance of SLN biopsy and the apparent ease with which it can be performed accurately in many different institutions and countries, some controversies remain.

IS SLN BIOPSY ACCURATE IN STAGING REGIONAL NODE FIELDS?

The original method described by Morton et al. (*1*) required many operations to be performed before the surgeon became competent. Two of the 3 surgeons in the study who had performed 36 and 46 procedures, respectively, were able to locate the SLN in the regional node field only 75% of the time. Since then, however, with the introduction of the γ-probe to be used intraoperatively (*16*) and preoperative lymphoscintigraphy (LS) that allows the surgeon to be directed right to the location of the SLN (*17*), identification rates have risen so that SLNs are found in close to 100% of patients and the results of the Italian multicenter trial are typical in this regard. A further very important, but sometimes overlooked, advantage of SLN biopsy is that a histopathologist faced with only 1 or 2 nodes to examine, rather than the contents of a whole node field, can use serial sections and immunohistochemical staining methods to significantly increase the detection rate for micrometastasis (*18*). Reverse transcription polymerase chain reaction (RT-PCR) methods have also been adapted for use in lymph node sections (*19*) and

Received Oct. 14, 2005; revision accepted Nov. 11, 2005.

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the result is an unprecedented level of accuracy for detecting metastatic deposits in the regional nodes. These approaches when combined with SLN biopsy mean the regional node field will be accurately staged in about 98% of patients (*14,15*).

In the case of patients with breast cancer there is no evidence that SLN biopsy is associated with an increase in local recurrence in the regional node field (*20*). Rates of 0.25% are typical and this has not been changed by the introduction of SLN biopsy to patient management. Patients with breast cancer, however, frequently receive adjuvant chemotherapy or radiation therapy to the node field that is likely to eliminate any residual cancer remaining in a missed SLN or lying in the interstitial tissues of the node field. With melanoma, where there is currently no reliably effective therapy for disseminated disease, if a melanoma metastasis is missed it is likely to declare itself and this is reflected in the false-negative rates for SLN biopsy in melanoma of 10%–15% (*13–15*). These rates of local recurrence are similar to those seen after elective dissection of a lymph node field in melanoma. Despite this false-negative rate, node staging using SLN biopsy remains more accurate than the old method of elective node dissection because the routine examination of the large number of lymph nodes in such a specimen using hematoxylin–eosin staining was associated with a false-negative histologic examination in up to 10%–16% of patients compared with immunohistochemisty staining of the nodes (*21,22*).

DOES SLN BIOPSY INCREASE THE RATE OF IN-TRANSIT RECURRENCE?

Because it is imperative for any physician when managing a patient to "first do no harm," this question must be answered in the negative before we can comfortably adopt SLN biopsy as a standard technique. There was a report in a small number of patients that a significant increase in in-transit metastasis was seen in patients undergoing elective node dissection after a positive SLN biopsy compared with a therapeutic dissection when clinical metastasis became evident in the lymph node field (*23*). In-transit metastasis occurred in 23% and 8% of these patients, respectively. It is important to note, however, that the mean thickness of the melanomas in the SLN biopsy–positive group was significantly greater than that in the other group (3.8 vs. 2.9 mm; $P = 0.023$). Increasing Breslow thickness is a major cause of higher rates of in-transit disease and it can only be presumed that differences in the patient populations studied such as this resulted in the findings observed. Four large studies have since shown no increase in the incidence of in-transit metastasis. Over a 10-y period, 2,018 patients at the Sydney Melanoma Unit were treated by wide local excision of the melanoma site alone or wide local excision plus SLN biopsy. In-transit metastasis occurred in 4.9% and 3.6% of these patients, respectively (*24*). A separate study at the MD Anderson Cancer Center in Houston showed in-transit metastasis occurred in 12% of patients who had a positive SLN biopsy and 3.5% of patients in whom the SLN biopsy was negative (*25*). Further work at the John Wayne Cancer Center has confirmed these findings (*26*), and the preliminary results of the prospective randomized multicenter selective lymphadenectomy trial (MSLT I) (*27*) also showed no increase in the incidence of in-transit metastasis associated with SLN biopsy. It would seem, therefore, that the nature of the individual patient's melanoma determines the likelihood of in-transit metastasis and not the SLN biopsy procedure.

IS SLN BIOPSY LESS MORBID THAN ELECTIVE LYMPH NODE DISSECTION?

Removal of just 1 or 2 SLNs to stage a lymph node field should cause fewer postoperative complications compared with a full elective dissection of the field and this has been borne out in practice (*28*). Postoperative complications occur in about 40% of patients after elective dissection of a node field, whereas SLN biopsy causes postoperative complications in only 10%. The most severe complications such as lymphedema are also much less common. In fact, the reduced morbidity associated with SLN biopsy is one of the major factors that have driven its acceptance by patient advocates, because 70%–80% of patients have normal SLNs (*13–15*) and require no further lymph node surgery.

DOES SLN BIOPSY IMPROVE SURVIVAL?

There is some evidence that early excision of regional lymph node metastasis confers a slight survival benefit in patients with melanoma (*29*). Preliminary results of MSLT I were presented recently (*27*). This trial compared SLN biopsy, followed by immediate elective dissection of the node field if the SLN was positive, to a delayed therapeutic node dissection when a clinical metastasis was found in the node field. A disease-free survival benefit was found over 5 y in the SLN biopsy group (78% vs. 73%; $P = 0.01$) and there may be a survival benefit in the SLN biopsy–positive group compared with the group who developed a clinical recurrence. Five-year survival was 71% after immediate elective lymph node dissection when the SLN biopsy was positive and 55% in the patients who had a delayed therapeutic lymph node dissection for clinical nodal recurrence ($P = 0.0033$). There is argument about whether these are matched patient groups but the trial is ongoing and its results may eventually answer this question. At the Sydney Melanoma Unit the surface location of SLNs is marked on the skin with a permanent tattoo of carbon black ink and clinical follow-up includes periodic targeted ultrasound examination of these SLNs. It has been our experience that when a clinical recurrence does appear in the

draining node field it occurs in the SLN immediately beneath the skin tattoo, which is evidence that, in fact, the 2 patient groups are matched and that the survival benefit is in fact real. This is the subject of ongoing research at our institution. For the moment, however, it is prudent to regard SLN biopsy as primarily an accurate method of staging the regional lymph nodes.

WILL SLN BIOPSY BE NEEDED WHEN WE HAVE BETTER GENETIC CHARACTERIZATION OF THE PRIMARY TUMOR?

Advances in molecular medicine are beginning to offer the prospect of a detailed analysis of the metabolic and genetic changes present in an individual patient's primary cancer (*30*). This may also give important information as to the tumor's metastatic potential. In this situation would there be any point in performing SLN biopsy? Cure or control of cancer will ultimately require addressing the most aggressive clones of the cancer in each patient. The metastatic cancer cells that lodge in the SLN have, by their behavior, identified themselves as such aggressive clones and, therefore, it is these metastatic cells that will need to be characterized to optimize therapy. It may even be possible to "disarm" the oncogenic mechanisms (*31*) that have caused malignant change in an individual patient's melanoma as we learn more about the biology and metabolism of this tumor. It seems plausible, therefore, that in the future a combination of SLN biopsy and genetic techniques to characterize the metastatic cancer cells will be the approach followed.

AT A TIME WHEN WE HAVE NO RELIABLY EFFECTIVE THERAPY FOR DISSEMINATED MELANOMA WHAT IS THE POINT OF DOING SLN BIOPSY?

When dealing as medical practitioners with a patient who presents with any disease there are several aspects to address—the diagnosis, treatment, and prognosis associated with the particular disease and its stage at presentation. In patients with melanoma the status of the SLN is the most significant prognostic factor (*32–36*). Five-year survival in patients with a SLN biopsy positive for melanoma metastasis is 73% compared with 97% when the SLN biopsy is negative. The SLN biopsy result, however, contributes only marginally to current decisions regarding the treatment of individual patients with melanoma. Most patients today are better informed about their disease than in the past and an accurate estimate of life expectancy is expected and is important knowledge for the majority. Setting one's affairs in order and perhaps taking that "dream trip" with the family are worthwhile goals since most patients with melanoma feel well physically until very near the end. For the prognostic accuracy SLN biopsy provides alone, it would seem worthwhile offering to your patients with melanoma.

There is also, however, an increasing knowledge accumulating on the genetic changes occurring in melanoma cells when they become malignant (*30,31,37*). This knowledge is opening the door to several new therapeutic approaches that offer the hope of controlling the growth of malignant melanoma if not curing it. For any new therapy to be proven requires randomized controlled trials of patients who have had accurate staging performed. SLN biopsy is vital to determine the status of the regional lymph nodes and will be an important part of the randomization of patients into future therapy trials for melanoma.

CAN SLN BIOPSY BE PERFORMED ACCURATELY AFTER PREVIOUS SURGERY OF THE EXPECTED DRAINING NODE FIELD?

It is well known that previous surgery to lymph nodes can alter lymphatic drainage pathways. We have seen drainage from a leg melanoma site to a SLN in the contralateral groin (*38*) in a patient who had undergone a minor lymph node excision biopsy in the ipsilateral groin and others have seen similar patients (*39*). We have also seen direct drainage from a melanoma site next to the right nipple to a SLN in the right internal mammary chain in a patient who had undergone an elective dissection of the right axilla 20 y earlier for lymphoma (*40*). In both of our cases, the SLN in these unexpected locations was positive for melanoma metastasis. Therefore, though there is no doubt previous surgery to a node field causes unusual drainage pathways to be seen in some patients, LS and SLN biopsy can nevertheless still accurately stage the draining lymph nodes wherever they may be located.

CAN HIGH-RESOLUTION ULTRASOUND EXAMINATION OF THE SLN AND ITS BASIN REPLACE SLN BIOPSY?

Ultrasound using high-frequency probes in the 10- to 15-MHz range now enables the internal structure of lymph nodes to be examined in some detail. The normal structure of a lymph node including the hilum and subcapsular sinus as well as the surface outline and shape of the node can be defined. Most of the lymph nodes that drain the skin can be accessed with such high-frequency probes though there are exceptions such as the deep iliac and obturator nodes that can sometimes drain the lower limb and SLNs in the retro-peritoneal, paravertebral, and paraaortic regions that are sometimes seen draining the skin of the back (*8*). The closer the node is to the skin surface the easier is its examination with high-frequency ultrasound and thus the best lymph node images are obtained in the groin of thin patients and the cervical chains. The axilla is a more difficult region to examine with ultrasound. There is no doubt that ultrasound is more accurate than clinical palpation in detecting metastatic disease in lymph nodes (*41*) and this is particularly so when used as part of clinical follow-up in patients with melanoma (*42*), but how

well does ultrasound detect metastasis in the SLN compared with histologic examination after excision biopsy of the SLN? In this role ultrasound does not perform well because of the simple fact that most melanoma metastasis at presentation is microscopic and current ultrasound machines have a resolution limit for metastasis of 2–4 mm, depending on the depth of the node from the skin (*43,44*).

False-negative rates of 61%–79% were recorded in 2 prospective studies in which preoperative ultrasound was followed by biopsy and histologic examination of the SLN (*43,44*). Both of these studies had a specificity of 100% so that a positive ultrasound for metastasis in this situation could be used to anticipate an elective dissection of the field once the SLN has been removed. Ultrasound will not replace SLN biopsy to stage the SLN as external scanning methods will never be capable of detecting a small cluster of metastatic cells in a lymph node, something that can be quite obvious using immunohistochemical staining methods.

CONCLUSION

From the experience accumulated over the past 13 y since Morton et al. (*1*) originally described the technique of SLN biopsy in melanoma patients, several things have become clear.

The SLN biopsy method can accurately stage regional node fields and this is done with reduced operative and postoperative morbidity. It is a robust method that has been shown to be accurate in many different countries using many different radiocolloids and imaging and surgical protocols.

The targeted histologic examination of the SLN using serial sections, immunohistochemical stains, and more recently RT-PCR has led to unprecedented accuracy in nodal staging.

The technique can be successfully applied to any solid tumor that has the propensity to metastasize to regional lymph nodes. SLN biopsy is now the standard of care in patients with melanoma and breast cancer and is moving toward this in many other cancers.

Despite rapid advances in the molecular characterization of cancer, SLN biopsy is likely to remain a part of patient management as it allows the most aggressive clones of the tumor (those that have metastasized) to be examined. Future management is likely to involve a combination of surgical and molecular techniques.

SLN biopsy is safe and does not increase the chance of local recurrence in the node field or in-transit recurrence between the primary site and the draining node field.

Disease-free survival does seem to be improved by SLN biopsy and there may be some improvement in overall survival but this is yet to be definitively proved. Its use, however, even in cancers that have no currently effective therapies for disseminated disease, can be justified on the basis of providing the most accurate prognostic information and staging for entry into therapeutic trials of new treatments.

Ultrasound of the SLNs cannot replace SLN biopsy and it would seem unlikely that any external scanning method will do so in the future.

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