

## Sentinel lymph node biopsy for melanoma: therapeutic procedure or diagnostic test?

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Although sentinel lymph node (SLN) biopsy is considered standard of care by many surgical oncologists and dermatologists, it remains controversial among others. Clinical practitioners in both surgery and dermatology have used the same available evidence to both support and refute the sentinel node hypothesis and the role SLN biopsy should play in the management of cutaneous melanoma. Much of the disagreement centers on whether one views SLN biopsy as a therapeutic intervention meant to improve survival or a diagnostic test meant to stratify risk and select patients for further therapy. This article will review the available data, including the most recent data from the Multicenter Selective Lymphadenectomy Trial-I (MSLT-I), the first prospective randomized study of SLN biopsy in melanoma.

**KEY WORDS:** Melanoma - Biopsy - Sentinel lymph node biopsy.

Although it is still the greatest source of debate among physicians who treat melanoma, the importance of the regional nodal basin in the management of melanoma was recognized in the late 1800's.<sup>1</sup> Today, the great majority of patients with primary cutaneous melanoma present with clinically negative (nonpalpable) regional lymph node basins, but 1/5<sup>th</sup> of these patients harbor occult regional metastases. Prior to the introduction of lymphatic mapping and sentinel lymph node (SLN) biopsy by Morton *et al.*,<sup>2</sup> this posed a clinical dilemma. Patients and their physicians were faced with two choices. With the

understanding that primary melanomas often spread to regional nodal basins before metastasizing widely, some surgeons advocated elective lymph node dissection (ELND). This approach hinged on the idea that early clearance of tumor deposits in the regional nodal basin could prevent subsequent dissemination and improve survival, an idea supported by retrospective studies.<sup>3,4</sup> Elective node dissection, though, exposed the 80% of patients who were node-negative to the morbidity of a nodal dissection.

The alternative approach was that of limiting node dissections to those patients with documented metastases, the therapeutic lymph node dissection (TLND). Clinically node negative patients underwent wide excision alone. If they developed clinically palpable nodal disease, but were without evidence of distant disease, they underwent TLND. This spared the node negative patients the morbidity of a lymph node dissection, but risked the possibility that in the time period between the primary excision and when the nodal recurrence became evident, melanoma cells may have metastasized systemically from the node, losing the chance for cure.

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This dilemma ultimately led to several randomized trials, each of which showing no overall survival advantage to elective node dissection, but perhaps some benefit among certain subsets of patients.<sup>5-8</sup> The Inter-group Melanoma Surgical Program randomized 740 stage I and II melanoma patients to ELND or observation.<sup>6</sup> While there was no difference in survival between the two groups overall, in a subgroup analysis, ELND was seen to confer a survival benefit in patients with nonulcerated melanomas and in patients with tumor thickness between 1 and 2 mm. This data suggested, although by no means proved, that there did exist a portion of patients for whom the early removal of microscopic disease from the regional nodes would improve survival. The results of these trials prompted many surgeons to abandon ELND while others chose to use ELND selectively. As there was no way to specifically identify patients with microscopic disease, surgeons based the decision to perform ELND on clinical features such as patient age, gender, tumor location, tumor thickness and the absence of ulceration.

This point became moot with the introduction of lymphatic mapping and SLN biopsy, a minimally invasive procedure capable of identifying that very subset; patients with melanoma harboring synchronous occult microscopic disease in the lymph nodes. With this procedure, the management of melanoma changed swiftly, allowing node-negative patients to avoid unnecessary lymphadenectomies without sacrificing accurate staging. Today, SLN biopsy is considered standard of care by most surgical oncologists for staging the regional lymph nodes of patients with primary cutaneous melanomas  $\geq 1$  mm thickness. Patients with thin melanomas ( $< 1$  mm) have a low incidence of regional metastases, and so SLN biopsy is not routinely recommended. In some cases, however, the presence of other adverse features (ulceration, mitotic rate, young age, or Clark's level IV or V tumors) may prompt SLN biopsy in patients with melanoma  $< 1$  mm.<sup>9, 10</sup>

Despite the clinical acceptance of SLN biopsy, its application is not without controversy and there is broad disparity of opinions regarding SLN biopsy among dermatologists.<sup>11-14</sup> While some of this debate may be fueled by the shift in who is responsible for the treatment of melanoma (although this is only a minority of melanoma patients as most do not fall within the current guidelines for SLN biopsy<sup>15</sup>), there are

many unanswered questions and legitimate concerns that had not been addressed by current trial data. Should SLN biopsy be accepted as the standard of care in the management of melanoma? To best answer this question, one must address several issues surrounding the procedure and ask not only whether SLN delivers what is expected of it, but what precisely is expected of it.

The SLN technique is designed to identify the lymph node or nodes that accurately represent the status of the draining nodal basin. The concept is not a new one. In the mid-19<sup>th</sup> century, Virchow described the concept of lymphatic drainage from a given body site to a specific lymph node. Based on studies in cats and humans with vital dye, Braithwaite first described the "glands sentinel" as the lymph node which drains a particular area. In 1960, Gould described a "sentinel node" that directly drained the parotid gland and proposed that a radical neck dissection should be performed if this node contained micrometastatic disease. And, in 1976, Cabanas suggested that the sentinel node of the penis could be used to determine the need for regional node dissection for penile cancer. However, the use of intra-operative lymphatic mapping to identify the sentinel node was truly brought forward by Donald Morton for the treatment of malignant melanoma.

The hypothesis underpinning SLN biopsy is that while the mechanism by which melanoma cells metastasize to the lymph nodes is a complex and difficult to predict process, the manner in which they metastasize is orderly and definable by mapping the lymphatic drainage from the site of the melanoma. Typically, two methods are employed for identifying the sentinel node; a blue dye and a radiolabelled colloid solution. The radiolabelled colloid is injected 1 to 4 h pre-operatively and the blue dye is injected intradermally at the site of the primary tumor a few minutes before the sentinel node biopsy incision is made. The surgeon then uses a hand-held gamma probe to identify the "hot spot" marking the location of the sentinel node, thereby minimizing the size of the skin incision needed. Once the incision is made, the surgeon identifies the sentinel node by either following blue-stained lymphatics or by finding the areas with the highest signal.

The prevailing argument is that identification and removal of the SLN will accurately stage the patient. This presumes two things. First, the lymph node(s) that take up the tracers are truly the nodes most likely to harbor micrometastases if present. In other words,

it is highly unlikely that if the SLN is negative (has no identifiable micrometastases) there are melanoma cells in other lymph nodes. The second presumption is that the identification of melanoma cells in the SLN portends a poor prognosis as compared with patients who are SLN negative. In other words, is this a true staging procedure that stratifies patients by projected outcome? If these two presumptions are true, then the next question is whether there are any interventions available to improve outcome among SLN positive patients. If not, then outside of accurate staging for research purposes, SLN biopsy provides minimal benefit to the patient and is not justified outside of a clinical trial. If so, the final question is whether the potential benefit to the patient is worth the cost and morbidity of the procedure.

#### Does the sentinel lymph node accurately reflect the status of the regional basin?

The SLN biopsy typically begins with the injection of a radiolabeled colloid tracer in 4 quadrants around the melanoma or biopsy scar. Lymphoscintigraphy then demonstrates the anatomic locations of the SLN(s) in the draining basin(s). The patient comes to the operating room where a fat-soluble blue dye is injected in a similar manner. The hand-held gamma probe is used to identify the vicinity of the SLN within each basin by means of elevated counts and a small incision is made in the skin. Any lymph node within the basin that is blue or has blue-stained lymphatics, or has high counts on the gamma probe is excised and labeled a "sentinel node." Any lymph node that is clinically suspicious on digital examination of the basin is also excised for pathologic examination. The procedure is completed when all blue nodes have been removed and counts have dropped to 10% of the highest node count *ex vivo*. This approach will identify the SLN in over 97% of cases.<sup>16-18</sup> The incision is closed and the sentinel node(s) are sent to pathology. An equally important aspect of the SLN biopsy is the pathologic analysis of the specimens. Step sectioning of the harvested nodes increases detection of micrometastases. If step sectioning and routine hematoxylin and eosin (H&E) staining is negative for metastasis, then immunohistochemical staining for melanoma markers such as S-100, Melan-A, and HMB-45 is performed.<sup>19-22</sup>

Does the SLN truly reflect the lymph node status? As one can imagine, there are several missteps that

TABLE I.—Possible mechanisms of false negative sentinel lymph node (SLN) biopsy.

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- <sup>99m</sup>Tc-labeled colloid sulfur and lymphoscintigraphy fail to identify correct basin(s).
  - Tracer travels to correct basin but moves past SLN to second-tier lymph nodes (may be related to time between injection and procedure).
  - Tracer travels to correct basin but collects in NSLN (serial *versus* parallel drainage).
  - Surgeon fails to remove all true sentinel nodes (background counts do not drop to <10% of highest node *ex vivo*).
  - Tumor emboli within lymphatics block flow of tracer into the SLN.
  - Clinically involved nodes, without tracer uptake, missed by surgeon.
  - Lack of thorough pathologic evaluation of the SLN (no step sectioning, lack of immunohistochemistry)
  - Crush or cautery artifacts preclude identification of micrometastases.
  - Microscopic disease in lymph node not identified despite appropriate methods.
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can occur during the procedure that can lead to a false-negative finding—calling the patient node-negative when in reality spread to the regional nodes did occur (Table I). Initial studies of the false negative rate for SLN biopsy were pathologic in nature. Patients who underwent lymphatic mapping and SLN biopsy had a complete node dissection so that the status of the SLN could be compared to the status of the nonsentinel lymph nodes (NSLN). Multiple studies have demonstrated that, when the SLN is negative, the likelihood of finding disease in any NSLN is quite low.<sup>16, 23, 24</sup> This finding, however, assumes that the <sup>99m</sup>Tc-labeled colloid sulfur and lymphoscintigraphy accurately identified all draining basins. For example, if a flank melanoma metastasized to the inguinal nodes, but the lymphoscintigram only showed drainage to the axillary basin, then the absence of disease in the axillary sentinel and nonsentinel nodes does not mean that this is a true negative.

The second measure of the accuracy of the SLN in predicting the nodal status is the regional recurrence rate among patients who are SLN negative. Several single-institution series have demonstrated a relatively low false-negative rate in this situation, although follow-up for some of these series has been limited.<sup>23, 25-27</sup> The most recent data comes from the Multicenter Selective Lymphadenectomy Trial-I (MSLT-I); a prospective, randomized trial comparing wide local excision alone to wide local excision and SLN biopsy, with complete lymph node dissection for SLN positive patients.<sup>28</sup> In this trial, the false negative rate was 3.4% at 5 years.

The regional recurrence rate, however, does not

absolutely define the accuracy of the SLN procedure either. For patients who have micrometastases limited to the SLN but missed by the pathologist on histologic examination, they would be false negatives but would not clinically recur because the SLN was excised. In one series, 4.1% of patients who developed a nodal recurrence after a negative SLN had re-evaluation of the SLN and 80% had evidence of missed occult metastasis.<sup>27</sup> It is certainly feasible that a portion of patients who did not recur also had missed occult metastases. It is also possible that some false-negative cases may have residual microscopic disease in a NSLN that simply didn't recur, possibly kept in check by the immune system or capable of spread but incapable of growth and survival. On the other hand, patients who suffer a regional recurrence may have been truly node negative at the time of their SLN biopsy, but in-transit disease in the lymphatic vessels may have reached a node subsequent to that procedure.

Therefore, the precise accuracy of SLN biopsy could be questioned for either method of assessing the false negative rate. However, when one looks at the compilation of data, combining both the low rate of identifying disease in the NSLN on completion dissection after a negative SLN with the low regional recurrence rate after a negative SLN biopsy not followed by CLND, the evidence to date strongly supports the SLN hypothesis.

### **Does finding a positive sentinel lymph node imply a worse prognosis?**

While the evidence strongly suggests the SLN is the most likely to harbor micrometastatic cells if they exist, this is meaningless if these cells are clinically insignificant. If the SLN procedure finds melanoma cells that are not indicative of the metastatic potential of the cancer, then it is of little benefit. One example of this might be if a great number of the foci identified within the SLN were there secondary to mechanical dislodgement, incapable of spread on their own. Another example would be if a high percentage of patients had melanomas capable of true spread to the lymph nodes but incapable of further growth or hematogenous spread. In these cases, SLN positive patients would have a prognosis not too dissimilar to SLN negative patients.

As with the accuracy of the procedure, the prognostic worth of the procedure is also strongly sup-

ported by the literature. There is an overwhelming preponderance of evidence that SLN status is the most significant factor for clinical outcome and is a critical component of melanoma staging.<sup>29-33</sup> Despite the fact that SLN biopsy is often restricted to patients with tumors between 1 and 4 mm in depth, studies have validated the prognostic significance of the SLN biopsy in both thin (<1 mm) and thick (>4 mm) melanoma.<sup>34-38</sup> In the MSLT-I trial, the status of the SLN was the most important prognostic factor, with the 5 year survival dropping from 90% among SLN negative patients to 72% among SLN positive patients.<sup>28</sup>

While the literature supports that the SLN procedure is both accurate and provides the most important prognostic information available, this still does not in itself justify the procedure (outside of the context of a clinical trial or for research purposes). Prognostic signs offer an accurate assessment of the likelihood of recurrence and death so physicians and patients make choices as to the relative risks and benefits of either surgery or adjuvant therapy. But what if there are no choices for additional therapy? While one might argue that having accurate prognostic information is beneficial to patients, the true benefit of prognostic and predictive markers lies in our ability to intervene in those patients with potentially poor outcomes. Simply knowing patient A has a worse outcome than patient B is relatively meaningless unless we can offer patient A something to improve that outcome.

When one talks of staging cancer patients, it is typically with adjuvant therapy in mind. While their options are limited, high-risk melanoma patients do have one adjuvant therapy available to them; high-dose interferon (HDI) with interferon alpha-2b (Intron-A). Adjuvant HDI is a controversial topic. While three studies have clearly demonstrated a benefit to disease-free survival for HDI, only two of these three studies demonstrated an overall survival benefit<sup>39, 40</sup> while one found no survival advantage.<sup>41</sup> Furthermore, an ideal subset of high-risk melanoma patients who benefit the most from HDI has not been identified. A discussion of the relative pros and cons of adjuvant IFN is beyond the scope of this paper.<sup>42-45</sup> However, if after reviewing the data one agrees that the evidence supports at least offering patients adjuvant HDI, then the prognostic information provided by the SLN procedure is crucial.

The other avenue by which SLN biopsy may provide a survival benefit to patients is through additional

surgery, specifically a completion lymph node dissection (CLND) in patients found to harbor micrometastases. If one excludes any potential improvements in survival obtained with HDI, then the true benefit of identifying node-positive patients is if survival is improved by the early eradication of that disease, as compared with delaying surgery until those patients would recur.

### **Is the sentinel lymph node biopsy a therapeutic procedure that improves survival?**

There are several arguments that one can make in favor of sentinel node biopsy irrespective of whether overall survival is improved. SLN biopsy will provide accurate staging for appropriate counseling, decision-making and prognostication. In this way, surveillance patterns may be adjusted accordingly, increasing surveillance of high risk individuals while the 80% of patients who are found to be node negative can be spared some of the anxiety (and the health care system can be spared some of the cost) of an intensive surveillance schedule. There is indirect evidence that SLN biopsy and immediate CLND will provide better regional control than delayed CLND.<sup>27, 46, 47</sup> In addition, the CLND for a positive SLN has decreased complications as compared with CLND for palpable disease.<sup>48</sup> As patients who recur after wide local excision alone often have more advanced regional disease (multiple involved nodes, extranodal extension), they often require radiation therapy to optimize regional control.<sup>49</sup> The use of SLN biopsy would decrease the need for this, and the associated cost and morbidity. These relative advantages can be argued back and forth, however the most important question, and argument for the routine application of SLN biopsy, is whether identifying this disease at an early stage and removing it before it is clinically apparent improves survival.

Another way to frame this question is whether, in the *interim* of time between when the primary melanoma is treated and regional metastases are identified, could melanoma cells have spread from the nodes to other sites and recur as distant metastases that would have been prevented had the nodes been excised at the time of the primary wide excision? If the answer to that question is yes, the next question is how large a subset of patients would this represent? Patients with clinically node negative melanoma essentially fall into 4

categories, only one of which would realize a survival benefit:

1. Patients with no metastases to the regional nodes. Obviously these patients would not experience any survival advantage to the SLN biopsy, and they represent the overwhelming majority of patients (approximately 75% to 80%).

2. Patients with microscopic disease in the SLN who have not yet metastasized but will in the time it takes those regional mets to be clinically detectable. This is the group that does benefit from SLN biopsy and the subsequent CLND.

3. Patients with microscopic disease in the SLN who still have no distant disease when they suffer their regional recurrence and undergo a TLND.

4. Patients with microscopic disease in the SLN who already have distant disease when their primary melanoma is discovered. This is the biggest question mark. If almost all patients with microscopic disease in their nodes already harbor distant metastases, then groups 2 and 3 would represent such a small fraction of the SLN positive patients that it is unlikely that SLN biopsy and CLND for node positive patients would impact survival in any more than a negligible way. However, clinical evidence does not support this notion, as multiple prospective studies have demonstrated a significant percentage of long-term survivors with stage III disease.

The relative distribution of patients into these four categories is dependent upon multiple factors. First and foremost is the biology of melanoma and those factors that may favor lymphatic *versus* hematogenous spread. These fractions will also change with earlier diagnosis of melanoma, the accuracy of SLN biopsy and our ability to detect regional and distant metastases on imaging. Therefore, the role that SLN biopsy may play in the management of melanoma is in a constant state of flux, and could be impacted tomorrow by improvements in early diagnosis, imaging studies or adjuvant therapies.

As for today, is SLN biopsy, with CLND for node positive patients, a therapeutic surgical procedure? If one considers SLN biopsy a therapeutic procedure, one must seek a survival advantage among all patients to whom the procedure is applied. Using this threshold, which many have done in arguments against the use of SLN biopsy, then the answer is clearly no. Prior to the onset of SLN biopsy, the overriding question in melanoma surgery was whether ELND would

improve survival over delaying lymph node dissection until there was clinical evidence of recurrence. Despite retrospective data supporting ELND,<sup>3,4</sup> four prospective randomized trials failed to demonstrate any survival advantage to the ELND *versus* a watch and wait approach.<sup>5-8</sup>

Would we expect SLN biopsy to change that? It seems unlikely. It is true that the SLN biopsy procedure will identify aberrant lymphatic drainage pathways and intercalated nodes (also known as ectopic or interval nodes) that would have been missed otherwise. However, this would be a small benefit, offset by a false negative rate resulting in node-positive patients not undergoing node dissection. The SLN biopsy primarily serves to limit the morbidity of the node dissection to those patients harboring microscopic disease. Its direct impact on survival is unlikely to be significantly different than ELND as 80% of the patients are still going to be node negative and not realize any survival benefit from the procedure. The survival benefit obtained from early eradication of nodal microscopic metastases would have to be large to demonstrate that benefit in a randomized study (or the study would have to accrue a number of patients beyond what is feasible to achieve statistical significance). As expected, there has to date been no survival advantage to SLN biopsy compared with observation alone in MSLT-I (with a 5-year melanoma-specific survival rate of 86.6% in the observation group and 87.1% in the biopsy group,  $P=0.58$ ).<sup>28</sup>

Many who argue against SLN biopsy use that data to support their arguments that SLN biopsy should never be done outside a clinical trial as it infers no survival benefit to the patient population as a whole.<sup>11, 12</sup> However, is this the correct yardstick by which we measure SLN biopsy?

### **Is the sentinel lymph node biopsy a diagnostic procedure that identifies patients who may benefit from further surgery?**

Let us say hypothetically that we had a serum test that identified patients at a high likelihood of harboring regional metastases. The test was inexpensive and had minimal morbidity, save those complications associated with phlebotomy, and was accurate in about 95% of cases (with both a high sensitivity and specificity). If performing CLND on those patients who had a positive serum test was shown to improve their

survival, would you order the test? Obviously the answer is an overwhelming yes. We order similar tests for a variety of malignancies every day. Upon diagnosis melanoma patients often undergo chest X-rays, a host of blood tests, CT scans and PET scans even though none of these have been shown to impact survival.<sup>50</sup> It is, therefore, hard to imagine there is any practitioner who would not order our imaginary blood test if it truly identified patients for whom survival might be improved by further surgery.

Following this logic, the question is whether SLN biopsy functions in the same manner, as a diagnostic test meant to identify a portion of patients who may benefit from intervention. If the answer is yes, then the only remaining question is whether the costs and side effects of this surgical diagnostic test (obviously more substantial than a blood test or an X-ray) are justified by the benefit to the patient.

To assess the performance of a diagnostic test, one must ask whether it accurately identifies a patient population who derives benefit from further intervention, in this case a survival benefit. As a diagnostic procedure, SLN biopsy is meant to identify node-positive patients, so one must ask whether survival is improved in this subset by CLND. This benefit must be further tempered against the false negative rate of the procedure.

Prior to the MSLT-I trial, there was significant evidence that subsets of patients might benefit from early removal of nodal metastases. As discussed previously, the Intergroup Melanoma Surgical Program, while demonstrating no overall survival difference between ELND and observation, did show in subgroup analysis a survival benefit to ELND in patients with nonulcerated melanomas and in patients with tumor thickness between 1 and 2 mm.<sup>6</sup> Further evidence comes from the World Health Organization (WHO) Melanoma Group Program 14 Trial, which randomized patients with truncal melanoma to wide excision plus ELND or wide excision plus observation, with subsequent lymph node dissection if patients recurred.<sup>7</sup> Again, there was no overall survival benefit, but when survival of patients with microscopic disease on ELND were compared with those who had regional recurrences, the survival was significantly improved in the ELND group (48.2% *vs* 26.6%,  $P=0.04$ ). While this data is strongly suggestive, it certainly does not prove that even among node positive patients the node dissection provides that degree of

benefit, as there may be patients who were node positive on ELND who would not have recurred had the nodes been left in place.

This all leads to the recently reported *interim* results of the Multicenter Selective Lymphadenectomy Trial I (MSLT-I) which is the first prospective randomized trial to specifically address the survival benefit of the SLN biopsy. As stated, to date there has been no significant difference in survival between the patients randomized to SLN biopsy *versus* those randomized to excision alone. However, when one compares the melanoma specific survival among those patients who were SLN positive to those patients who recurred after excision alone, there was a significant improvement in survival in the SLN group. Among the node positive patients, the 5-year survival rate with CLND for a positive SLN was 72.3% *versus* 52.4% for patients who underwent CLND for a recurrence (HR 0.51; 95% CI, 0.32 to 0.81; P=0.004). When one includes the false negative patients (those patients with a negative SLN biopsy who had a regional recurrence) in the SLN biopsy group, there is still a significant improvement in survival (66.2% *vs* 54.2%; HR 0.62; 95% CI 0.40 to 0.95; P=0.02).<sup>28</sup>

Certainly, the same criticisms of the WHO Program 14 data could be applied here; that there may have been a significant number of patients positive on SLN biopsy who would not have recurred had they not undergone SLN biopsy. The initial report, in fact, did suggest more patients who were SLN positive than recurred. However, with longer follow-up, there were nearly the same numbers of patients who were either SLN positive or recurred after a false negative SLN as there were patients who had a regional recurrence after wide excision alone. The cumulative incidence of regional metastases in both the observation group and the biopsy group were equal by 10 years of follow-up (about 20% in both groups).<sup>51</sup> This suggests a very small number, if any, of patients who had nodal metastases that would not ultimately suffer a regional recurrence.

This data, therefore, would strongly suggest that SLN as a diagnostic procedure will accurately identify patients who will experience a survival benefit from further intervention, specifically completion node dissection (and possibly further benefit from adjuvant HDI). It is hard to argue against its effectiveness as a staging procedure. Thus, the argument surrounding the appropriateness of SLN biopsy shifts from whether

there is a benefit (there clearly is) to whether the costs and morbidity of a surgical staging procedure are justified. Again, if this were a simple blood test or X-ray meant to identify patients who would experience a significant decrease in mortality with further intervention, there would be no argument as to its worth.

The morbidity of the SLN procedure is low. Several studies document postoperative complications after SLN biopsy in the range of 5%.<sup>46, 52, 53</sup> Complications are relatively minor, primarily consisting of wound infection, seroma or hematoma. Allergic reaction to the blue dye is rare but potentially serious. Lymphedema after SLN biopsy is uncommon, and despite early concerns, SLN biopsy does not increase the likelihood of in-transit recurrences.<sup>28, 54</sup> The cost is another question. Much of the controversy surrounding the use of SLN biopsy centers on the increased costs of a procedure that benefits a small subset of patients. For patients deemed appropriate candidates, surgical therapy shifts from an office-based procedure, which can be done for approximately \$1 000 to \$1 750, to one where i.v. sedation or general anesthesia is utilized, nuclear medicine is involved, and a time-consuming pathologic evaluation of the sentinel nodes is necessary. This raises the cost of treating melanoma to between \$7 150 and \$15 223.<sup>55, 56</sup> Are these costs justified? In previous cost analyses of SLN biopsy, the answer was yes, but this was only if one considered the survival benefit associated with HDI or compared to ELND.<sup>57, 58</sup> This final outstanding question; whether SLN biopsy is worth the cost, should be subjected to a cost-analysis taking into account the most recent information gained from the MSLT-I study, and compared to other diagnostic or therapeutic practices in oncology.

## Conclusions

The SLN procedure for melanoma patients should be thought of and evaluated as a staging procedure as opposed to a therapeutic procedure. Attempts to judge the merits of the procedure as a therapeutic intervention will always come up lacking, as 80% of these patients are node negative and will derive no direct survival benefit from the procedure. However, as a diagnostic procedure, SLN biopsy fulfills all of the criteria. It is highly accurate in identifying a subset of patients who 1) have a significantly worse prognosis and 2) will benefit from further intervention. Certainly there are outstanding questions. Whether the cost and

morbidity of this staging procedure are justified can be debated, but can only be truly addressed by a cost-benefit analysis that takes into account the most recent available data. It is also impossible to completely separate the diagnostic aspect of the procedure from the therapeutic, as to look at the SLN one must remove it and thus remove some (and possibly all) of the regional disease (in essence an oncologic version of Heisenberg's uncertainty principle). In many patients, the SLN will be the only node(s) in which disease is identified pathologically, although nonsentinel nodes are not subjected to the same thorough pathologic examination as the sentinel nodes. Unfortunately, predicting those patients that may not require CLND has proven unreliable.<sup>59-61</sup> The true benefit of the completion node dissection is presently being prospectively addressed in the Multicenter Selective Lymphadenectomy Trial II (MSLT-II), which randomizes patients with a positive SLN to CLND or observation with serial ultrasounds of the regional basin.

Based on the available evidence, it is logical to consider SLN biopsy a standard diagnostic evaluation for patients with cutaneous melanoma >1 mm and perhaps some patients with melanoma <1 mm.<sup>9, 10, 56, 62, 63</sup> As with all interventions in oncology, there is no black and white. Patients should be presented with available data, with a balanced discussion of the risks and the potential benefits. Models exist to help predict the likelihood of finding a positive SLN that can help individualize the discussion.<sup>64, 65</sup> It is reasonable that patients may weigh the pros and cons and opt to forego the procedure and proceed with wide excision alone. However, given the present level of evidence; the prognostic information SLN biopsy will provide, the potential benefit should they be SLN positive, and the future options they may have (HDI, clinical trial participation) it does not seem reasonable to make this decision for them.

### Riassunto

*Biopsia del linfonodo sentinella nel melanoma: procedura terapeutica o test diagnostico?*

Sebbene la biopsia del linfonodo sentinella venga considerata il gold standard da parte di molti chirurghi oncologi e dermatologi, essa continua ad essere oggetto di discussione da parte di altri. I clinici, sia chirurghi che dermatologi, hanno utilizzato la stessa evidenza disponibile sia a favore che contro l'ipotesi del linfonodo sentinella e sul ruolo che la sua biopsia dovrebbe giocare nella gestione del melanoma cutaneo. Molto del disaccordo nasce da un diverso punto di vista della biopsia del linfonodo sentinella, se considerarla

un intervento terapeutico per migliorare la sopravvivenza o se considerarla un test diagnostico per stratificare il rischio e selezionare i pazienti per una terapia ulteriore. Questo articolo riassumerà i dati disponibili, compresi quelli più recenti forniti da *Multicenter Selective Lymphadenectomy Trial-I (MSLT-I)*, il primo studio prospettico randomizzato sulla biopsia del linfonodo sentinella nel melanoma.

PAROLE CHIAVE: Melanoma - Biopsia - Linfonodo sentinella.

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