The Clinical Value of Sentinel Lymph Node Biopsy In Melanoma Staging, Regional Disease Control, and Survival

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The regional lymph nodes are commonly the first site of melanoma metastasis. Even within a nodal basin, there may be regional spread to surrounding lymph nodes before progression to distant sites. Therefore, surgical excision of regional lymph nodes has been a focus of melanoma treatment for decades. There are three potential goals of surgery, any one of which may justify the procedure for an individual patient when the benefits of treatment are judged to outweigh the risks and morbidity:

1) **staging** (where information about lymph node status provides an accurate prognosis and guides subsequent treatment);

2) **regional disease control** (to prevent symptomatic growth of regional metastases); and

3) **improved patient survival** (because tumor burden is reduced or eliminated so that the metastatic process is interrupted or delayed).

**The Role of Surgical Lymphadenectomy in Stage III Patients**

The benefits of surgical lymphadenectomy (whether sentinel lymph node biopsy and completion lymphadenectomy or therapeutic lymphadenectomy) in Stage III melanoma patients have been debated for decades. However, even if some questions remain, the issue of its utility can now be put to rest with the publication of the seminal Multi-center Selective Lymphadenectomy Trial I (MSLT-1), the largest and longest-running melanoma surgical trial ever.

In the evolution of melanoma care, it has repeatedly been demonstrated that less can be more. Once, at first sight of a primary tumor, entire limbs were sacrificed to prevent metastasis. Not long ago, 3-5-cm margins around the primary were standard in surgical excision, whereas now 1-cm margins are routine. And just a generation ago, primaries deemed high-risk most often led to complete elective regional lymph node dissection (ELND). This practice ended with the gradual acceptance of sentinel lymph node biopsy (SLNB), the now standard tissue-sparing surgical technique developed by Dr. Donald Morton in the early 1990s. However, the role of SLNB in clinical practice continues to be debated.

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conducted, led by the late Dr. Donald L. Morton. The results of this 20-year prospective randomized clinical trial clearly demonstrate the staging value of the sentinel lymph node biopsy (SLNB) procedure, and in a predetermined cohort of microscopically node-positive patients with a primary melanoma thickness of 1.2—3.5 mm (a subset of intermediate thickness melanomas), also demonstrate the disease-free and disease-specific survival advantage of early surgical intervention involving complete excision of regional node metastases.

After 35 years of uncertainty and controversy, the results of MSLT-1 provide important new insights into the value of surgical excision of regional lymph nodes in melanoma patients. Balch and colleagues proposed in 1979 that tumor thickness could guide surgical management and partitioning of patients based on their relative risk for regional and distant metastases. Thus, patients with thin melanomas (defined at that time as those less than 0.75 mm in thickness) would have a low risk for regional or distant metastases and, therefore, would not benefit from regional lymphadenectomy. Nor, at the other extreme, would patients with thick melanomas (defined in 1979 as > 4.0 mm in thickness), who would have such a high risk of distant metastases that they would receive no therapeutic benefit from lymphadenectomy (but would still derive staging value).

At that time, Balch, et al hypothesized that patients with intermediate-thickness melanomas (those ranging from 0.76 to 4.0 mm) might benefit from lymphadenectomy because they would have a high enough risk of regional node metastasis to justify the operation but a low enough risk of initial distant metastases to benefit from regional treatment and prevention of further dissemination to distant sites. They concluded, “The rationale of elective RND is improved survival in patients with intermediate-thickness lesions (0.76 to 3.99 mm), while it is [also] justifiable as a staging procedure for lesions exceeding 4.0 mm thickness.”

This hypothesis was the scientific underpinning for the subsequent randomized Intergroup Melanoma study of elective lymphadenectomy, begun in 1983 and first reported in 1996; the randomized surgical trial conducted by the World Health Organization Melanoma Program on trunk melanomas (Trial #14); and the first Multicenter Selective Lymphadenectomy Trial known as MSLT-1, which began in 1994, culminating in the final report 20 years later in the New England Journal of Medicine. Sentinel Lymph Node Biopsy

In 1992, the management of melanoma changed forever, with the landmark publication by Morton, Cochran and colleagues detailing the sentinel lymph node biopsy (SLNB) technique. This procedure enabled surgeons to remove just one or two key lymph nodes (the “sentinel nodes”) to determine whether micrometastases from a primary melanoma had reached the regional lymph node basin; if the sentinel nodes proved negative for metastases, the rest of the nodes in the basin could be spared, and if the sentinel nodes proved positive, the patient could elect to have the rest of the nodes in the basin removed. Others confirmed these findings, further demonstrating its staging value and its reproducibility across institutions. Morton, Cochran, and colleagues worldwide then embarked on a monumental project to determine the overall value of this surgical procedure in a randomized prospective study, MSLT-1.

MSLT-1 accrued 2,001 patients, of
whom 1,560 with melanomas ≥1.2mm in thickness were evaluable.² (An additional 232 patients with melanomas ≤1.2 mm thick were separately randomized, but the results of this cohort have not been reported because to date too few metastatic events have occurred to make a valid comparison.) The primary objective of the study was to compare overall survival for all patients randomly assigned to either 1) SLNB and, if positive for metastases, a completion lymphadenectomy (watch-and-wait) on patients who later developed clinical evidence of nodal metastases. A predefined secondary objective of MSLT-1 was to compare survival for those patients who had completion lymphadenectomy for nodal metastases diagnosed by SLNB with that of patients who had a delayed lymphadenectomy for palpable metastases. The latter took an average 19.3 months to become clinically apparent (M. Faries, personal communication). Such a delay was, at least theoretically, a critical time period during which the metastatic process may have further disseminated and eventually caused the demise of a greater proportion of patients in this cohort with clinically detectable nodal metastases compared to those whose regional metastases were removed when the tumor burden was subclinical. It is also notable that in the delayed lymphadenectomy patients, there was regional spread within the nodal basin, since the number of metastatic nodes increased during this time as well—from an average of 1.4 metastatic nodes in the immediate completion lymph node dissection (CLND) group compared to 3.3 metastatic nodes in the delayed CLND group (p<0.001). Biopsy-based management improved 10-year melanoma-specific survival by 44 percent (p=0.006) for patients with intermediate thickness melanomas and nodal metastases, but not for those with melanomas >3.5mm thick (Figure 1). A sophisticated latent subgroup statistical analysis also demonstrated a significant treatment benefit in the intermediate thickness cohort.²¹⁶

Staging Value

The staging information provided by SLNB is of particular value because it reliably identifies patients with nodal micrometastases.¹⁻¹⁷ In MSLT-1 as in several previous large studies, SLN status was the most important and statistically powerful predictor of survival outcome (Table 1).² Used in conjunction with Breslow thickness, ulceration, and other prognostic features of the primary melanoma, it allows for accurate predictions of metastatic risk and survival outcome. Information based on SLN status is also valuable for counseling SLN-positive patients about the need for completion lymphadenectomy to improve regional disease control, reduce operative morbidity (as compared with the morbidity associated with later, possibly more radical, regional surgery and often radiation therapy for palpable nodal recurrence), reduce the relative risk of recurrence by 26 percent, and potentially improve survival if nodal metastases are present.¹⁻¹⁷ In addition, the information about their SLN status can be used to counsel patients regarding enrollment into melanoma clinical trials, and can serve as the basis for discussing a screening and follow-up regimen based on risk for subsequent development of metastases. Patients who are SLN-negative can be reassured that their prognosis is relatively improved; these patients are less likely to require adjuvant treatments and/or frequent follow-up.¹⁻¹⁰⁻¹⁷

The results of MSLT-1 clearly demonstrate the important staging role of SLNB in a defined group of patients (those with intermediate thickness and thick melanomas), as well as a survival benefit in those with intermediate thickness melanomas. Just as importantly, it partitions the majority of melanoma patients with T2 to T4 melanomas who have negative sentinel nodes into a better prognostic group who can safely be spared more aggressive treatments, including potentially toxic systemic therapies.

These results reinforce guideline recommendations for SLNB made by the American Society of Clinical Oncology.

### Table 1. Multivariate hazard ratios for disease recurrence and death among patients with intermediate-thickness melanoma who underwent sentinel-node biopsy, according to prognostic indicator

<table>
<thead>
<tr>
<th>PROGNOSTIC INDICATOR</th>
<th>DISEASE RECURRENT</th>
<th>DEATH FROM MELANOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HAZARD RATIO (95% CI)</td>
<td>P VALUE</td>
</tr>
<tr>
<td>Sentinel-node status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(positive vs. negative)</td>
<td>2.64 (1.92-3.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Breslow thickness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(per 1-mm increase)</td>
<td>1.62 (1.31-2.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ulceration (present vs. absent)</td>
<td>1.40 (1.04-1.89)</td>
<td>0.03</td>
</tr>
<tr>
<td>Site of melanoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm or leg</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Trunk</td>
<td>1.42 (1.03-1.94)</td>
<td>0.03</td>
</tr>
<tr>
<td>Head or neck</td>
<td>1.20 (0.77-1.86)</td>
<td>0.42</td>
</tr>
<tr>
<td>Sex (male vs. female)</td>
<td>0.94 (0.70-1.26)</td>
<td>0.66</td>
</tr>
<tr>
<td>Age (per 1-yr increase)</td>
<td>1.01 (1.00-1.02)</td>
<td>0.07</td>
</tr>
<tr>
<td>Clark level (IV or V vs. III)</td>
<td>1.27 (0.94-1.71)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

the Society of Surgical Oncology, the American Joint Committee on Cancer, and other organizations (Table 2).1,17,20 MSLT-1 demonstrates that there is a role for surgical removal of regional metastases, both for its staging value and, by intercepting the metastatic process, potentially increasing survival rates in some patients. Knowing the pathological status of the regional lymph nodes is also an essential eligibility criterion for entry into adjuvant therapy clinical trials.

Should Patients with Thin (T1) Melanomas Ever Be Considered for SLNB?

Most experienced melanoma surgeons would also offer SLNB to patients who have T1 melanomas (i.e., not thicker than 1.0 mm) if the tumors have characteristics that substantially increase the likelihood of regional node micrometastasis. This would include patients with T1 melanomas with primary tumor ulceration, a mitotic rate ≥ 1/mm² and/or Clark level IV/V invasion—especially if tumor thickness exceeds 0.75 mm. Ulceration, mitotic rate and Clark level are considered to be especially relevant in patients who have no significant comorbidity, who are younger than 40-45 years, or whose primary tumor depth is uncertain because of a tumor-positive deep margin in the biopsy specimen.21

What the Critics Say

Some still question the value of SLNB, and the MSLT-1 findings have not dissuaded them. Some, for example, maintain that SLN status is not a useful enough prognostic indicator, and that similar prognostic information can be obtained with less morbidity by examining the features of the primary melanoma.22-25 This proposal ignores evidence from two large multicenter clinical trials (the Sunbelt Trial and MSLT-1) which specifically examined this question.26,27 In both these trials, sentinel node status provided the best prediction of outcome, with hazard ratios of 2.8 (p<0.0001) and 2.4 (p<0.01) respectively compared to the prognostic value of Breslow thickness and ulceration.26,27 The latter parameters, of course, can only indicate the likelihood that metastatic disease is present in regional nodes, whereas SLNB determines whether metastatic disease in the regional nodes is actually present. Both sources of information, the primary tumor and the lymph node, provide independent prognostic information, and both are valuable.

Others assert that the improvements in disease-free survival and (for those with intermediate thickness melanomas) disease-specific survival associated with management based on SLN status are of no clinical significance, since they are not definitively proven to lead to increased overall survival. But most clinicians and patients would disagree strongly. Detractors make much of SLNB’s morbidity, but in the modern era it is associated with much lower morbidity than occurred in early studies, and any morbidity is generally mild and transient. What cannot be disputed is that early CLND, performed when a positive SLN is identified, is a much less morbid procedure than delayed complete lymph node dissection for palpable or bulky nodal metastases, performed therapeutically only when nodal disease becomes clinically apparent. In the latter circumstance the surgical morbidity is much greater, the volume of nodal disease has more than doubled, and so too has the risk of postoperative lymphedema.19

Another suggestion made by those who oppose SLNB is that some “false-positive” sentinel nodes (with micrometastases that would never actually advance to clinical metastases) might lead to unnecessary radical surgery and morbidity.24 However, the comprehensive data collected in MSLT-1 provide no statistical support whatsoever for this theory.27

Conclusions

There is now convincing, irrefutable evidence demonstrating the staging value of SLNB for specific cohorts of melanoma patients. This evidence is derived from multiple prospective studies, especially the randomized MSLT-1.
It may also be offered to patients with primary melanomas <1.0 mm (but preferably ≥0.75 mm) in thickness if there are adverse pathologic features such as ulceration or a high mitotic rate.1,17,20,21

Currently the second MSLT (MSLT-2) is ongoing. This Phase III trial examines the value of completion lymph node dissection vs. SLN alone in patients found to have SLN metastases, since nodal metastases in 80-90 percent of such patients are limited to the sentinel node(s). The primary outcome measure will be melanoma-specific survival, and secondary outcome measures will be both disease-free survival and recurrence over 10 years of follow-up. MSLT-2 has completed accrual of nearly 2,000 subjects, and results will be available with additional follow-up, clarifying one of the last significant questions in the initial management of this disease.

**References**


How Long Will Sentinel Node Biopsy Remain Standard in Melanoma?

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Sentinel lymph node biopsy (SLNB) has been a source of debate in melanoma ever since Donald Morton introduced the technique in the early 1990’s. Some continue to consider it a costly, invasive technique that is unjustifiable since it has shown no survival benefit. This attitude has softened in the past 10 years, since hundreds of publications and studies have confirmed the prognostic value of SLNB. Its global use in staging, therapy selection, and trial inclusion criteria has strengthened its place de facto in clinical practice. SLNB proponents accurately consider it the best-ever staging method for melanoma, and argue that SLNB limits the use of radical/complete node dissection (CLND) to patients who need it, although no one truly knows who needs it until nodal disease becomes clinically detectable.

Hopefully, the day could soon be coming when SLNB fades into the sunset, as we keep improving our analytic ability to find molecular and immunological information establishing stage and prognosis in blood tests and the primary tumor itself. Given the negative primary endpoint results from the recent publication of the large Multicenter Selective Lymphadenectomy Trial-I (MSLT-I) by Morton, et al in the New England Journal of Medicine,1 and new research calling into question the survival benefits of CLND in patients with positive sentinel nodes,2 routine use of this controversial procedure could be replaced by other strategies.

The Pivotal Results of MSLT-I

The results of MSLT-I were long awaited to answer the many questions about SLNB and determine whether it should continue to be used. In the trial, 1,661 patients were randomized either to the SLNB arm (with SLNB followed by immediate CLND for a positive biopsy) or to the observation arm, with simple surveillance of the patient (“watch and wait”) and CLND only in the eventuality of clinically detectable nodal recurrence. The primary endpoint was overall survival, with secondary endpoints of recurrence-free or disease-free survival (RFS or DFS), survival with tumor-positive or tumor-negative nodes, and incidence of sentinel node metastases versus clinically detectable nodes. Unfortunately, a close look at the results shows that the trial falls short in answering several major questions about SLNB.

**SLNB as a Marker**

To be of utility, a marker has to be correlated to prognosis. It also has to show a good positive and negative predictive value for individual selection of high-risk patients.

**Is SLNB of prognostic value?**

Definitively YES. This has been established in many papers and was confirmed by MSLT-I. It is however only a statistical marker, with rather low individual predictive capability. Indeed, 62 percent of patients with intermediate thickness primaries and positive SLNBs, and 48 percent of thick melanoma patients with positive SLNBs, are alive at 10 years. More important, negative SLNBs also have a low individual predictive value, since 15 percent of intermediate thickness patients with negative nodes and 35 percent of thick melanoma patients with negative SLNBs will nonetheless die from melanoma within 10 years.

**Is a positive SLNB a sound way to identify patients at risk of extensive nodal disease and/or disseminated metastatic disease?**

Positive SLNBs may overestimate metastases, producing false positive markers for metastatic progression. There is no way of knowing exactly which micrometastases in the nodes will sooner or later become true nodal metastases. It is dubious that ALL micrometastases will turn into macro-metastases; some will simply disappear under immune system pressure. The authors of MSLT-I argue that since cumulative rates of nodal involvement were ultimately comparable in the two arms of the trial (immediate SLNB vs. delayed CLND), this proves that all tumor micro-deposits in the nodes will sooner or later become true nodal metastases. This is a post-hoc deduction for which the trial was not designed. Comparing cumulative rates of nodal involvement in the two arms of MSLT-I may be much more difficult to interpret than the authors think, given the possibility of nodal metastases outside the area explored by SLNB, and the fact that time could have a great impact on the respective rate of nodal involvement in the two arms. Which arm patients were in influences the date of detection of nodal disease and the date and probability of nodal recurrence versus extra-nodal recurrence.

A negative SLNB does not exclude metastatic progression. We are not speaking here of the technically false negative for SLNB (where a positive SLNB is simply missed due to technical or anatomical reasons). We are speaking about a truly negative SLNB in patients who will nonetheless develop metastatic disease. One reason this can occur is that in patients with negative SLNBs, nodal micrometastases outside the sentinel node might develop into macro-metastases. Second, the sentinel node concept is an anatomical criterion, just like tumor thickness or ulceration. As such, there can be delay before biological aggressiveness can have clear anatomical expression. In other words, a biologically aggressive primary melanoma detected very early (a situation that increasingly occurs) might have a low Breslow thickness not typically calling for SLNB, or might express so little nodal tumor deposit that it results in a negative SLNB, even if it already has a high potential to kill. Early detection of melanoma before its aggressiveness can be picked up by anatomical criteria such as SLNB may explain why more and more patients who ultimately die from melanoma are coming from AJCC Stage IIA and IIB groups, and not from Stage III (positive SLNB).3

Although statistically correlated to

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2 New research calling into question the survival benefits of CLND in patients with positive sentinel nodes.
3 Positive SLNBs may overestimate metastases, producing false positive markers for metastatic progression. There is no way of knowing exactly which micrometastases in the nodes will sooner or later become true nodal metastases.
prognosis, SLNB status is not a reliable marker to predict the course of an individual patient’s disease.

The Issue of Survival Benefits

SLNB was adopted by the medical community based on the hypothesis that it was not only a marker, but a marker that could directly or indirectly benefit the patient by improving survival or at least quality of life. The answers to a few simple questions tell us whether SLNB truly offers such benefits.

Does SLNB improve surgical management of melanoma in a way that offers an overall survival (OS) benefit? More specifically, does early intervention (SLNB + CLND for a positive sentinel node) offer a melanoma-specific survival benefit?

Even the trial authors acknowledge that MSLT-1 did not demonstrate clear utility in improving overall survival, which happened to be their primary endpoint. When comparing survival between patients who have CLND after positive SLNBs are found against patients who have therapeutic LND only after clinically detectable nodal metastases are found, there is no significant advantage for the SLNB arm in 10-year melanoma-specific survival. Nonetheless, attempting to show some 10-year-survival advantage, the authors of MSLT-1 found it only among those with intermediate tumor thickness – 62 percent 10-year survival in the SLNB arm vs. 41 percent in the observation arm. The advantage did not hold true for patients with thick melanomas. This survival comparison by subgroups is post-hoc, not randomized. Comparability would suppose that all patients from the SLNB arm with a positive SLNB would eventually have had invasive, palpable nodal disease if they had been in the observation arm. But this is uncertain.

Does CLND add a survival benefit to SLNB alone?

Another problem with MSLT-1 from the start was taking for granted that any patient with a positive sentinel node would definitely benefit from CLND. The utility of CLND after SLNB, however, is still an open question. To test this hypothesis properly, after finding positive sentinel nodes in patients, researchers would have to perform CLND on one group of patients while leaving the rest of the nodal basin intact in a comparable control group until the nodes became palpable, and then observe which group lived longer. The results of a recent German trial reported at the 2015 American Society of Clinical Oncology annual meeting argue against the survival value of CLND after a positive SLNB. With 483 patients studied and a median follow-up of 35 months, patients randomly assigned to undergo or not undergo CLND after a positive SLNB were statistically indistinguishable with respect to distant metastasis-free survival, recurrence-free survival, and melanoma-specific survival.

On the heels of this small study, we now await the results of Morton, et al’s far longer, larger follow-up study to determine if CLND offers an OS benefit?

As a selection criterion for adjuvant therapy, does knowing SLNB status improve medical management in a way that offers an OS benefit?

SLNB began being used long ago to select melanoma candidates for therapy with interferons, which proved to have a limited adjuvant benefit. Support for SLNB has taken on a new dimension in recent years with the development of effective targeted therapy and immunotherapy in advanced metastatic melanoma: many researchers believe that the successful FDA-approved checkpoint blockade therapies (anti-CTLA-4 and anti-PD-1) for stage IV patients might save even more lives if used earlier as adjuvant therapies. The prognostic capabilities of SLNB make it a potentially useful tool in indicating these treatments at earlier stages, for two main reasons: 1) It can target the highest-risk patients, and 2) it can limit useless toxicity in patients at low risk.

However, use of SLNB in selecting candidates for new adjuvant therapies is relevant only if most patients who will eventually develop systemic metastases are initially detected by a positive SLNB; and as we have noted, this is far from a given, since more and more patients who die from melanoma are coming from AJCC Stage IIA and IIB groups because of earlier diagnosis. Thus, even a new immune or targeted drug with a demonstrated strong adjuvant impact on OS in a population of SLNB-positive patients may not ultimately have an impact on melanoma mortality, since more and more of the future victims of multimetastatic melanoma may not be patients with a positive SLNB.

If CLND is not found to have tangible, meaningful survival benefits (and to date we have seen nothing to suggest it will), the reasons for employing SLNB will be strongly diminished if not altogether eliminated.

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Could SLNB be not only useless but deleterious? Could it reduce survival?

There are obvious drawbacks to performing any invasive procedure that is ultimately of limited or no benefit. The question of reducing survival is not irrelevant, since tumor cells in the sentinel node might well present a pattern for priming the immune system against melanoma, and it conceivably could be damaging to destroy this pattern. However, to date, there is no argument to support this. In MSLT-I, no survival disadvantage was found in the SLNB arm, suggesting that any deleterious immune effect was negligible.

Conclusions

For all our arguments, SLNB is still probably inevitable for now, mainly because it is a pillar of the current universally accepted AJCC staging system required for all patient trials. But while SLNB is the best statistical prognostic marker for melanoma populations, this does not mean that using it as a marker is of any benefit or relevance to patients; it is still uncertain whether using it to assign adjuvant therapy with new potent drugs will impact on melanoma mortality. To better select patients for early adjuvant treatment, we need very early (biological) and reliable individual predictive markers, whereas SLNB is a rather late (anatomical), merely statistical marker with poor positive and negative predictive value. Our need for individual biological markers will become more and more crucial, since patients who ultimately die from melanoma are coming more and more from so-called “low-” or “intermediate-risk” populations, and less and less from “high-risk” groups; the absolute number of “low-risk” and “intermediate-risk” patients (AJCC stages II A, IIB, and IIIA) is simply much higher than the number of patients with “high-risk” melanoma (AJCC stages III B and C).

In the end, SLNB is a costly and invasive intervention. In the next several years, if it does not show some definitive benefit, it will inevitably be replaced in staging by tumoral and/or circulating molecular markers, and/or patient immune profiling, which will provide more individual predictive information with less morbidity.

References


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morbidity for numerous melanoma patients who formerly might have undergone ELND but proved to have negative sentinel nodes, and has allowed more precise staging to inform therapeutic decisions and improve stratification for clinical trials. However, SLNB for melanoma has remained controversial, with some critics arguing against its therapeutic value in the absence of definitive evidence that it improves survival, and others even questioning its value as a staging tool.

Unfortunately, the controversies were not resolved with the publication in 2014 of Morton, et al’s long-awaited Multicenter Selective Lymphadenectomy Trial-I (MSLT-I), the longest, largest study of SLNB and LND ever undertaken. The results were mixed, with a negative result for the primary analysis of the effect on overall survival and a positive finding for a variably interpreted secondary analysis confined to a subset of patients with regional metastases. The controversy is compounded by disagreement on the role of completion LND in patients with positive sentinel nodes. Preliminary data from a recent German study provide an initial answer to the question, and Morton, et al’s follow-up study, the pending MSLT-2 analysis, is exploring the issue in a much greater number of patients.

Our lead story in this issue of The Melanoma Letter, by Drs. Charles Balch, Mark Faries, and John Thompson, presents an authoritative and detailed review of SLNB in melanoma, with special attention to the results of MSLT-I. Our second story, by Dr. Jean-Jacques Grob, explores the questions remaining about the efficacy of SLNB, reviews the German data on completion LND, and looks forward to an era of increasingly precise staging/prognostication based on molecular studies of the primary tumors and blood. These two complementary stories provide a fairly comprehensive update and perspective on this important subject.

Dr. Morton died in 2014 before MSLT-1 could be published, but not before his brilliantly conceived and researched technique came to be considered a vital staple of melanoma staging and treatment, especially for patients with tumors of intermediate thickness, who were considered (and subsequently proven by MSLT-I) to be the group most likely to benefit from SLNB. Whatever the ultimate fate of the technique, it was a milestone achievement in the evolution of the field.

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