Sentinel lymph node biopsy and melanoma: 2010 update

Part II

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This article will discuss the evidence for and against the therapeutic efficacy of early removal of potentially affected lymph nodes, morbidity associated with sentinel lymph node biopsy and completion lymphadenectomy, current guidelines regarding patient selection for sentinel lymph node biopsy, and the remaining questions that ongoing clinical trials are attempting to answer. The Sunbelt Melanoma Trial and the Multicenter Selective Lymphadenectomy Trials I and II will be discussed in detail. (J Am Acad Dermatol 2010;62:737-48.)

Learning objectives: At the completion of this learning activity, participants should be able to discuss the data regarding early surgical removal of lymph nodes and its effect on the overall survival of melanoma patients, be able to discuss the potential benefits and morbidity associated with complete lymph node dissection, and to summarize the ongoing trials aimed at addressing the question of therapeutic value of early surgical treatment of regional lymph nodes that may contain micrometastases.

Key words: melanoma; Multicenter Selective Lymphadenectomy Trial; sentinel lymph node biopsy.

DO SENTINEL LYMPH NODE BIOPSY AND EARLY COMPLETE LYMPH NODE DISSECTION IMPROVE OVERALL SURVIVAL COMPARED TO OBSERVATION AND THERAPEUTIC DISSECTION AFTER THE DEVELOPMENT OF CLINICALLY PALPABLE NODES?

Key point

• No randomized trial has yet shown that early surgical removal of the positive lymph nodes improves overall survival compared to delayed resection

There is currently no definitive evidence from randomized trials that a positive sentinel lymph node biopsy (SLNB) followed with complete lymph node dissection (CLND) can improve overall survival (OS) from melanoma. In the years preceding the publication of the interim results of the first Multicenter Lymphadenectomy Trial (MSLT-1), a number of smaller, nonrandomized studies had shown equivocal results, although most of these studies revealed a potential OS benefit to small subsets of patients with a positive SLN who have had immediate CLND compared with groups of patients followed for nodal relapse after wide local excision (WLE) alone.1-8

Since the publication of the review by Johnson et al,6 there have been two nonrandomized retrospective studies published by Nowecki et al9 and van Akkooi et al10 comparing the OS of patients who underwent

Abbreviations used:

CLND: complete lymph node dissection
DFS: disease-free survival
ELND: elective lymph node dissection
IHC: immunohistochemical staining
MR: mitotic rate
MSLT: Multicenter Selective Lymphadenectomy Trial
NSN: nonsentinel node
OS: overall survival
RT-PCR: reverse transcriptase polymerase chain reaction
SLN: sentinel lymph node
SLNB: sentinel lymph node biopsy
TLND: therapeutic lymph node dissection
WLE: wide local excision
immediate CLND after positive SLNB versus those who underwent therapeutic lymph node dissection (TLND) after developing clinically palpable nodes following WLE alone.\textsuperscript{9,10} Again, the results of these retrospective studies were only suggestive of potential therapeutic benefit and they underscored the importance of the ongoing prospective randomized trials designed to evaluate more accurately this question. Currently, only the results from the third interim analysis of the MSLT-1 have been published and will be discussed below.

THE MULTICENTER SELECTIVE LYMPHADENECTOMY TRIAL

Key points

- The Multicenter Selective Lymphadenectomy Trial is an 18-institution multinational trial initiated in 1994 and closed to accrual in 2002 that tested the theory that sentinel node biopsy, followed by immediate completion lymphadenectomy if the sentinel node was positive, would improve disease-free and overall survival in patients.
- The third interim analysis of Multicenter Selective Lymphadenectomy Trial is discussed in detail.

The MSLT-1 consisted of 1347 patients with clinically localized melanoma (stage I/II) $\geq 1$ mm or $\geq$ Clark level IV who were $<10$ weeks from their initial biopsy. Patients were randomized to receive WLE plus observation (40%) or WLE plus lymphatic mapping and SLNB (60%), followed by CLND if the sentinel lymph node(s) (SLN[s]) contained histologic evidence of tumor. Patients randomized to WLE plus observation underwent delayed TLND if clinically palpable nodes developed during the follow-up period.

The results of the third of five planned interim analyses were published by Morton et al\textsuperscript{11} in 2006. The analysis focused on the subgroup of patients with intermediate-thickness melanomas (1.2-3.5 mm). As mentioned in part I of this review, the MSLT-1 data clearly showed that SLNB provides important prognostic information and is therefore a valuable staging tool.\textsuperscript{11} Detailed analysis of the interpretation of the third interim analysis of the MSLT-1 with regard to disease-free survival (DFS) and OS (Fig 1) are discussed in detail in the upcoming sections.

WHAT ARE THE INTERPRETATIONS OF THE RESULTS OF THE THIRD INTERIM ANALYSIS OF MSLT-1?

Early removal of micrometastatic disease has not been shown to improve overall survival.

At the time of the third interim analysis of the MSLT-1, no improvement in OS was seen in the total group randomized to receive SLNB followed by CLND if the SLN was positive compared to those randomized to WLE and observation, with nearly identical 5-year melanoma specific survivals of 87.1\% versus 86.6\% ($P = .58$).

Those who believe that early removal of the nodal basin may benefit a subset of patients with micrometastatic disease argue that the MSLT-1 and the elective lymph node dissection (ELND) trials that preceded it were underpowered to detect a survival difference. Before the MSLT-1, both the Intergroup Melanoma Surgical Trial and the World Health Organization Melanoma Programme (WHO Clinical Trial #14) showed a trend toward increased survival with ELND compared to nodal observation, but the differences did not reach statistical significance.\textsuperscript{4,12} It has been suggested that both studies were underpowered to detect a difference in survival, because only 20\% of patients included in these trials could have potentially benefited from a CLND. This same argument has been made for the results of the MSLT-1, highlighting that 80\% of the patients randomized to SLNB did not have a positive SLN, which diluted any potential survival benefit of immediate lymphadenectomy in the 20\% of patients with SLN micrometastases.\textsuperscript{13}

In a paper titled “How should we view the results of the MSLT-1?” Ross et al\textsuperscript{14} explain how the MSLT-1 was underpowered to detect a survival difference (ie, why the primary endpoint was not
met): given that only 19% of patients randomized to undergo SLN were found to have a positive SLN, only this group could theoretically benefit from early therapeutic intervention. Previous studies have shown that only 15% to 20% of patients with a positive SLN will have evidence of further nodal disease within that basin, which leaves a potential survival advantage to only 3% to 4% of the total study group, which was too small for a study of this size to detect. To detect a survival benefit in such a small percentage of patients, a much larger total study population of up to 10,000 subjects would be required.\(^{15}\)

**SLNB does not appear to increase the frequency of local/in-transit recurrence**

Before the MSLT-1, previous studies had conflicting results regarding a possible link between SLNB and an increased risk of in-transit metastases.\(^{16-19}\) The third interim analysis of the MSLT-I showed no significant difference in frequency of local/in-transit recurrence between the SLNB and observation groups at 5 years (7.7% vs 8.4%; \(P = .38\)). These results are further supported by a large retrospective study by Kang et al\(^{20}\) in which 30 years of data from 4412 patients treated at the John Wayne Cancer Institute were analyzed. This review analyzed the incidence of in-transit metastases after WLE alone, WLE plus SLNB, and WLE plus ELND for clinically localized melanoma, and found no significant differences in either in-transit metastases overall or as a first recurrence. In addition, two large studies from MD Anderson Cancer Center in Texas and from the Sydney Melanoma Unit in Australia analyzed patients with primary melanoma who underwent SLNB and concluded that performing SLNB in patients with melanoma treated by WLE does not increase the overall incidence of in transit metastasis.\(^{19,21}\)

**Improved 5-year DFS for patients undergoing SLNB versus observation group**

In the MSLT-1, patients undergoing SLNB were found to have an increase in the likelihood of 5-year DFS compared to those in the observation group (78.3 vs 73.1; \(P = .009\)). This apparent survival benefit has been criticized on the basis that nodal metastases are classically the first metastases to present clinically, and the patients in the SLNB and immediate CLND group already had their nodes removed. It has been suggested that the MSLT-1 investigators should have compared the groups based on time to first nonnodal recurrence in order to compare fairly DFS between the two groups.\(^{22}\) Morton concedes this point, but states that CLND in patients with a positive SLNB lowers risk of nodal failure, which is a major cause of anxiety among patients.\(^{23}\) However, one could question whether the major source of anxiety is limited to recurrence in the nodal basin or simply recurrence of any type.
Improved 5-year OS for the subgroup of patients with positive SLN undergoing immediate CLND versus patients in the observation group who underwent TLND after developing clinically positive nodes

The most controversial conclusion from the MSLT-1 relates to Morton’s initial interpretations of the secondary endpoint that compared OS of the selected subgroups of patients in the SLNB arm who underwent early CLND after pathologic detection of metastases with those in the observation arm who had TLND after detection of clinically palpable nodes. Morton et al initially reported 5-year survival rates of 72% versus 52%, respectively ($P = .004$), a result criticized on the basis that post hoc analysis of previously randomized subgroups is statistically invalid and should not be performed. Thomas has argued that the 20% OS difference reported after post hoc analysis was caused by an improper assumption that all micrometastases found in the SLNB group would have inevitably progressed to clinically meaningful disease if left untreated. Thomas has termed this potential subgroup of patients with clinically insignificant micrometastases “prognostic false positives,” which falsely elevate the OS rate of the SLNB group by including patients that would have never progressed to clinically meaningful disease. In addition, Thomas stated that Morton et al did not properly account for the 26 patients in the biopsy arm who initially had false negative SLNs but progressed to palpable nodal recurrence and had delayed lymphadenectomy, all of whom had the same prognosis as the 78 patients in the observation arm who later developed clinically palpable nodes. As a result of these criticisms, Morton subsequently reanalyzed these data, this time including only the patients with comparable prognostic factors and the subset of initially false negative patients that developed recurrence in the same basin. The recomputed 5-year OS rates were adjusted to 66.2% versus 52.4% ($P = .02$), with a smaller OS difference of 14% compared to the previous 20%. Despite this recalculation, Thomas has maintained that recently reported provisional results of the fourth interim analysis of the MSLT-1 concur with the concept of “prognostic false positivity,” indicating that survival differences between these two groups are a result of inclusion of a subset of patients with clinically insignificant micrometastases.

Most recently, Morton has stated that an evaluation of 10 years of MSLT-1 follow-up data provides evidence that all micrometastases will indeed become clinically relevant if left untreated. At 10 years of follow-up, the percentage of patients randomized to observation after WLE and who experienced lymph node basin metastases has increased to 20.5 ± 2.6%, which equals the percentage of patients (20.8 ± 1.7%) with nodal metastases detected by SLNB or by nodal relapse after false negative results. By suggesting that these groups do, in fact, have comparable nodal metastasis rates, the conclusion is that all nodal metastases will eventually become clinically palpable, therefore validating the survival benefit found in the post hoc analysis of the MSLT-1. In support of this argument, others have also cited the WHO Clinical Trial #14 where patients were randomized to ELND versus observation. In this study, the regional nodal metastatic rate was 30.5% in the observation arm compared to 22% of the patients randomized to immediate ELND, indicating a delay between initial metastasis to the SLN and spread to the nonsentinel nodes (NSNs) in that lymphatic basin. However, because histopathologic evaluation was not as thorough for these ELND specimens as for a SLNB, it is likely that some real percentage of reportedly negative ELND specimens contained undetected micrometastases, which would have increased the percentage of positive ELNDs closer to that of the observation group.

Morton’s findings from this reanalysis of the MSLT-1 data strongly argue, but do not prove, that most if not all lymph node micrometastases have the potential to develop into clinically palpable nodes. However, predicting which nodal micrometastases will evolve to clinical significance depends on factors that are not currently quantifiable, including individual tumor biology and a given patient’s immune response to that tumor.

DOES IMMEDIATE COMPLETE LYMPH NODE DISSECTION AFTER POSITIVE SENTINEL LYMPH NODE BIOPSY RESULT IN IMPROVED REGIONAL DISEASE CONTROL?

Key point

- Therapeutic lymph node dissection for clinically evident disease has increased operative difficulty and postoperative morbidity when compared to immediate complete lymph node dissection in patients with positive sentinel lymph node biopsy

The presence of significant regional nodal disease, either in the setting of recurrence or as an initial presentation, has been shown to impact patient quality of life negatively, increase the difficulty of surgically clearing the nodal basin, and increase postoperative complications, including both postoperative lymphedema (41% vs 24%; $P = .025$) and the wound infection rate (28% vs. 14%; $P = .02$).
From the published MSLT-1 third interim analysis, immediate CLND results in more effective regional control than TLND after detection of clinically palpable nodal disease. This study revealed that patients who had immediate CLND following positive SLN on average had 1.4 nodes involved versus 3.3 nodes in the TLND arm (1.4 vs 3.3; P < .001). The percentage of patients who had four or more positive nodes after immediate CLND was only 1.6% compared to 25.7% of patients undergoing TLND (P < .001). This suggests that WLE and observation results in an increase in detectable tumor burden.11

Studies have also shown that TLND, once clinically palpable nodes are evident, is technically more difficult than SLNB plus immediate CLND, and is associated with a higher surgical morbidity.6,26,30 A recent retrospective review by Sable et al30 sought to determine if there was a difference in morbidity in patients who undergo immediate inguinal lymph node dissections after a positive SLN compared to those who had TLND performed after detection of clinically evident disease.30 They found that patients who underwent TLND after clinically detectable disease had significantly worse prognostic indicators, such as an increased number of involved nodes (3.0 vs 1.96; P = 0.0013), a higher percentage of patients having more than four involved nodes (29% vs 9%; P < 0.001), and greater frequency of extranodal extension (47% vs 5%; P < .001).30 Extranodal extension is associated with higher surgical failure rates, and is often followed by adjuvant radiation therapy (XRT) to the local node basin in an attempt to obtain adequate regional control, leading to further morbidity from the side effects of XRT.31 In this study, patients who underwent immediate CLND after positive SLN had a lower rate of wound complications and lymphedema compared to those who had TLND for clinically evident disease.30 Therefore, in terms of operative difficulty and postoperative morbidity, early disease control with immediate CLND in patients with positive SLNB has a significant benefit over TLND.

MORBIDITY ASSOCIATED WITH SENTINEL LYMPH NODE BIOPSY AND COMPLETE LYMPH NODE DISSECTION

Key point

- Sentinel lymph node biopsy is a low morbidity procedure, but complete lymph node dissection has a higher rate of acute and long-term complications

There are several studies that have reported morbidity and complication rates associated with SLNB and CLND.29,32-35 The two largest randomized, prospective studies that have performed morbidity analysis on patients undergoing these procedures are the MSLT-I and Sunbelt Melanoma trial. The MSLT-I reported that when comparing WLE alone to WLE plus SLNB, the rates of total complications, which included wound separation, seroma/hematoma formation, infection, and skin graft failure, were very similar (13.9% vs 13.8%). However, when SLNB was compared to SLNB plus CLND, the total complication rate increased almost fourfold (10% vs 37%).36 The Sunbelt Melanoma trial revealed a total complication rate of 4.6% with SLNB and 23.2% for CLND after a positive SLN. In conclusion, SLNB alone is a relatively low morbidity procedure. However, most patients with positive SLN will go on to have CLND, which is associated with much higher rates of morbidity and complication.32 However, as discussed earlier in this review, CLND has lower complication rates than TLND.30

PATIENT SELECTION FOR SENTINEL LYMPH NODE BIOPSY

Key points

- On average, the incidence of nodal metastasis in patients with thin melanoma (≤ 1 mm) is 5% to 6%
- Patients with thick melanomas have overall poor prognosis

SLNB is routinely recommended for patients with clinically negative nodes and primary lesions with >1 mm thickness. Based on Breslow depth, a patient’s risk for metastasis to the SLN is as follows: 

- ≤ 1 mm: 4%; 1-2 mm: 12%; 2-4 mm: 28%; and ≥ 4 mm: 44%.33 However, the more controversial issue is whether or not SLNB should be recommended for patients with either thin melanomas (≤ 1 mm) or thick melanomas (≥ 4 mm).

SLNB for patients with thin melanomas (≤ 1 mm)

Patients with thin melanomas generally have an excellent long-term prognosis. In addition, they rarely have nodal metastases,38 and therefore SLNB is not routinely recommended in this group of patients unless they have other adverse prognostic features. In general, the incidence of nodal metastasis in patients with thin melanoma (≤ 1 mm in thickness) has been shown to be ≤ 5%, and more specifically <2% with lesions <0.76 mm.37-42 A recent metaanalysis of 34 studies, comprising 3651 patients with thin melanomas, found a pooled SLN positivity rate of 5.6%, although significant heterogeneity among studies was detected.43 In fact, most of the patients with thin melanomas enrolled in these
studies had tumors with more aggressive characteristics, such as the presence of tumor ulceration, tumor regression, and a Clark anatomic level higher than IV, indicating that the SLN positivity rate in these patients is likely higher than would be expected if SLNB was more broadly applied to all patients with thin melanoma.

Attempts have been made to identify patients with a ≤ 1 mm primary melanoma who might have a higher risk for nodal metastasis by finding other prognostic factors that might predict outcome. Mitotic rate (MR) has emerged as a predictor of sentinel lymph node positivity in patients with thin melanomas.

A recent study investigated the role of MR as a predictor of SLN positivity in patients with thin melanomas. They revealed that although the overall SLN positivity rate is about 5% in patients with a primary melanoma ≤ 1 mm, those patients who had an MR > 0 had an SLN positivity rate of 8.7% and as high as 12.3% for tumors ≥ 0.76 mm. Therefore, they concluded that MR could be used for risk stratifying of patients with thin melanomas and in selecting patients for SLNB. Other studies have identified MR—as especially in younger patients—as an independent predictor of SLN positivity in patients with thin tumors. The importance of MR was also highlighted by the 2009 American Joint Committee on Cancer (AJCC) guidelines in which T1 melanoma patients (patients with tumor thickness ≤ 1 mm) were reclassified as T1b by the presence of mitoses and/or ulceration (see the following section for details).

The meta-analysis by Warycha et al. mentioned above, which evaluated a total of 3651 patients with thin melanomas who had undergone SLNB, made the following important conclusions: the meta-analysis showed that mitotic rate was a negative prognostic indicator, but that the nodal status in these patients was not predictive of overall survival, as there was an equal number of melanoma-related deaths in SLN-positive and SLN-negative patients. Therefore, despite the negative prognostic significance of an elevated mitotic rate in patients with thin melanoma, their nodal status was not shown to be a reliable predictor of overall survival, making SLN status less prognostically significant than in patients with thicker (> 1 mm) melanomas.

**SLNB for patients with thick melanomas (≥ 4 mm)**

Nodal staging in patients with thick primary melanomas remains a matter of debate. Some assert that patients with thick (≥ 4 mm) melanomas have a high risk of occult distant disease at the time of initial presentation and therefore treatment of regional lymph nodes is not justified given their poor overall prognosis. While some studies have shown that SLN status is a strong independent predictor of survival, others have reached the opposite conclusion. More recently, a study by Gutzmer et al. analyzed 152 patients with primary melanoma thickness ≥ 4 mm who underwent SLNB. Sentinel node status was found to be the most important prognostic parameter in patients with thick melanomas, with an estimated 5-year OS rate of 37.5 ± 8.1% after positive SLNB, in comparison to 67.6 ± 6.7% after negative SLNB.

Despite conflicting evidence regarding the prognostic utility of SLNB in this group, the AJCC currently recommends SLNB in patients with thick primary melanomas who have clinically or radiographically uninvolved regional lymph nodes.

**2009 AMERICAN JOINT COMMITTEE ON CANCER CANCER STAGING MANUAL RECOMMENDATIONS ON PATIENT SELECTION FOR SENTINEL LYMPH NODE BIOPSY**

**Key points**

- Mitotic rate is now a required element for staging T1 tumors
- Clark level of invasion is no longer used to define T1b tumors
- Sentinel lymph node biopsy is recommended as a staging procedure for patients who have T1b, T2, T3, and T4 melanomas and clinically or radiographically uninvolved regional lymph nodes

The AJCC Melanoma Staging Committee recently revised the melanoma staging system. In this publication, they recommend that SLNB be performed as a staging procedure for patients who have T1b, T2, T3, and T4 melanomas and clinically or radiographically uninvolved regional lymph nodes.

In the 2009 AJCC Cancer Staging Manual, the AJCC Committee introduced melanoma MR as a required element for staging T1 tumors. The data from AJCC Melanoma Staging Database showed a significant inverse relationship between MR and survival. In fact, MR was found to be the second most powerful predictor of survival after tumor thickness. They strongly recommend assessment of the MR, which should be expressed as the number of mitoses per square millimeter, assessed in the most mitotically active area of the specimen.

Based on these findings, the committee made a major change in defining T1 melanomas by incorporating the presence or absence of ulceration and the MR in the definition. Previously, Clark level of
invasion was used to define T1b melanoma. However, current data analyses indicate that Clark level of invasion has a very low statistical correlation with survival rates after accounting for thickness and ulceration. Therefore, the Clark level is no longer used in the new Cancer Staging Manual to define T1b melanomas. In the current seventh edition of the Cancer Staging Manual, T1a lesions are defined as those whose tumor thickness is \( \leq 1 \text{ mm} \) with absence of ulceration and a MR of \(<1/\text{mm}^2\), and T1b melanomas as those tumors that are \( \leq 1 \text{ mm} \) thick, but have at least 1 mitosis/\(\text{mm}^2\) or tumor ulceration. Therefore, the 2009 AJCC Cancer Staging Manual recommends that SLNB to be performed as a staging procedure for patients with melanomas \( \leq 1 \text{ mm} \) in thickness if the tumor also has either ulceration or at least 1 mitosis/\(\text{mm}^2\). SLNB is also recommended for patients with T4 (>4 mm thickness) melanomas who have clinically or radiographically uninvolved regional lymph nodes.

### SHOULD COMPLETE LYMPH NODE DISSECTION BE OFFERED TO ALL PATIENTS WITH A POSITIVE SENTINEL LYMPH NODE?

**Key points**

- Some evidence exists that patients with sentinel lymph node micrometastases \( \leq 0.20 \text{ mm} \) in size may not have nonsentinel node involvement
- Current American Joint Committee on Cancer recommendations state that, given the available evidence, nodal deposits of any size should be considered clinically significant and used in staging

CLND provides useful information about the status of NSNs for staging and prognostication. It may also potentially improve OS in a subset of patients with metastases in the NSNs, a question that the ongoing MSLT-II will attempt to answer in the coming years. CLND allows defining of the N category in the staging system described by the AJCC where patients with one node involved by tumor are categorized as N1, those with two to three involved nodes as N2, and with four or more involved nodes as N3. The current and previous AJCC staging system for cutaneous melanoma publications have stated the number of nodal metastases is a significant predictor of survival in all patients with stage III disease.\(^5\) Currently, many institutions recommend CLND for patients who are found to have a positive SLN. However, should CLND be offered to patients with all variants of micrometastases?

Given that there is only 15% to 20% NSN involvement in patients with a positive SLN, many studies have attempted to identify a group of patients who could be spared CLND based on the characteristics of the primary tumor or the metastasis within the SLN. Characteristics of the primary melanoma and of the SLN metastases have been carefully studied to determine if they can be used to predict that patient’s probability of having tumor in the NSNs. Several studies have identified factors such as age, Breslow thickness, size, and histologic location of SLN metastasis as predictors of NSN involvement.\(^55-59\)

Unfortunately, despite a number of attempts, it has been difficult to identify reliably patient populations with a positive SLN who are at low enough risk of having NSN involvement to recommend against CLND. A recent publication by Roka et al\(^60\) consisting of a small sample size and univariate analysis showed that NSN metastasis cannot be reliably predicted based on either characteristics of the primary tumor or of the metastatic cells within the SLN (size and site of SLN metastasis). The authors suggest that CLND be recommended to all patients after positive SLN until the results of the second MSLT are available.\(^60\)

Recently, Govindarajan et al\(^61\) analyzed clinical features of 127 patients with a positive SLN who had undergone CLND. Patients in whom the largest tumor focus in the SLN was \( \leq 0.20 \text{ mm} \) had no NSN involvement and no recurrence of disease. In another retrospective study, van Akkooi et al\(^62\) reported that patients with SLN micrometastases of \(<0.1 \text{ mm} \) had no NSN involvement in CLND specimens. From these results, both concluded that perhaps patients with SLN metastases \(<0.2 \text{ mm} \) and \(<0.1 \text{ mm} \), respectively, may be considered SLN-negative and would probably not benefit from CLND. Although thought provoking, these studies were too small and had too short a follow-up period to be able to reliably predict NSN involvement. In addition, others have found conflicting results, showing as high as 12% incidence of NSN involvement in patients who with SLN tumor deposits \( \leq 0.20 \text{ mm} \).\(^63\) Therefore, the prognostic significance and clinical relevance of small micrometastases in sentinel nodes remains unclear.

As mentioned earlier, a number of studies have used the size of the metastatic deposit in the SLN in an attempt to stratify patients into groups of low- and high-risk of NSN involvement. Frankel et al\(^64\) evaluated histologic specimens of 144 patients with a positive SLN who had undergone CLND and found that of the 46 cases where a patient had a single positive SLN that contained a metastatic deposit of \(<1\% \) of the SLN’s surface area, the risk of a positive
NSN was 4% (2/46). This was in contrast to a 29% chance of NSN involvement for patients with either more than one positive SLN or >1% of disease within a given SLN. Gershenwald et al reported similar results using a different metric, stratifying patients based on size of largest metastatic deposit in the SLN. Patients in whom the largest deposit was <0.5 mm had a 5.3% chance of NSN involvement. Conversely, patients with a metastatic deposit >10 mm had a 45% chance of NSN involvement. Despite these differences, the authors cautioned that despite only 14% overall involvement of NSNs in their study, the decision to forego CLND even in patients at lower risk for NSN involvement should be made with caution and in the setting of a clinical trial.

Conflicting conclusions from these numerous smaller studies emphasizes the need to better identify reliable predictors of NSN involvement in patients with a positive SLN. The control arm of the MSLT-II (discussed in greater detail later) will provide the most significant information to date regarding the natural history of patients with a positive SLN who are closely observed, rather than undergoing immediate CLND. This, in turn, may help to define better the subgroup of patients with a positive SLN that can forego CLND given a remarkably low risk of further spread beyond the SLN.

The 2009 AJCC staging system for cutaneous melanoma states that there is not yet sufficient evidence to define a threshold for the amount of tumor in the SLN that should not be assigned to N+ category of disease for staging purposes. According to current AJCC recommendations, nodal deposits of any size are considered to be clinically significant and used in staging. Because accurate predictive factors of NSN involvement have not been identified, CLND continues to be recommended for patients who have positive SLN. The currently ongoing MSLT-II is evaluating the outcomes of patients with SLN metastasis, including those with occult metastases detected only by reverse transcriptase polymerase chain reaction (RT-PCR), that have been subsequently randomized to close follow-up with ultrasound versus immediate CLND. This study will hopefully provide insight into any potential benefit to OS provided by CLND and potentially define subgroups of patients that can avoid CLND when nodal metastasis is limited to submicroscopic deposits in the SLN.

**ONGOING TRIALS INVOLVING SENTINEL LYMPH NODE BIOPSY FOR MELANOMA**

*Key points*
- The Sunbelt Melanoma Trial and the second Multicenter Selective Lymphadenectomy Trials are ongoing trials aimed at answering many of the questions raised or not completely answered by other recent trials, such as the MSLT-I.
These trials will hopefully provide useful data relating to the optimal histopathologic evaluation of nodal tissue, as well as whether early CLND can, in fact, improve OS in patients with a positive SLNB.

The hope is that the results from ongoing trials outlined below will help clarify the role of SLNB in management of melanoma patients.

**Sunbelt Melanoma Trial**

The Sunbelt Melanoma Trial, currently closed to accrual, is a pharmaceutical industry-sponsored, prospective, randomized, national trial involving 3619 patients from 79 participating institutions. Dr. McMasters, from the University of Louisville, is the principal investigator. This trial focuses on patients with melanomas $\geq 1.0$ mm in thickness and clinical stage I/II disease, all of whom have undergone lymphatic mapping and SLNB (Fig 2). The study compares outcomes of patients placed in different treatment arms depending on whether their SLN(s) are positive for tumor by routine hematoxylin-eosin stain (H&E) and immunohistochemistry (IHC), negative by H&E/IHC but positive by PCR, or negative by both evaluations. The goal of the study is to attempt to establish, in a multicenter setting, the clinical relevance of potentially missed micrometastatic disease detected only by RT-PCR in patients with nodal disease limited to the SLN only (detected by H&E or IHC) versus those with a SLN positive only by RT-PCR. The initial results of this study did not find a significant difference in DFS or OS between RT-PCR-positive and RT-PCR-negative patients at 30 months of follow-up. However, as mentioned in part I of our review, a large metaanalysis that has included the results of the Sunbelt Melanoma Trial has concluded that the use of RT-PCR in detection of SLN metastases may have clinically valuable prognostic power.

**Multicenter Lymphadenectomy Trial II**

The organizers of MSLT-I designed a second MSLT (MSLT-II) to further address the importance of SLN metastases, the relevance of molecular assessment of the SLN and, most importantly, to evaluate the potential for therapeutic benefit of CLND after positive SLNB (Fig 3).
Although some progress has been made regarding the molecular genetics of melanoma and optimal surgical management of primary lesions, no effective therapy exists at this time for metastatic disease to internal organs. Until effective therapy is developed, the focus must remain on early detection and removal of the primary tumor.

CONCLUSION

In the era of evidence-based medicine, clinicians should rely on the best supporting evidence when recommending a treatment or procedure to patients. However, in an evolving world of medicine, sometimes years of research, trials, data accumulation, and analysis are required before any unequivocal conclusions can be made. At such times, optimal medical practice requires integration of the best available current and ongoing evidence, clinical expertise, and patient preferences and circumstances in order to provide optimal patient care.

Although at the current time no randomized trial exists to support the claim that removal of lymph nodes has therapeutic value in extending the OS of melanoma patients, the data support its use for purposes of more accurate staging, prognosis, and improved regional disease control as recommended by AJCC guidelines. SLN staging is also necessary for the accurate identification of patients who might be candidates for adjuvant therapy as it becomes available, and for stratification of these patients into uniform risk groups for clinical trials.

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