Prognostic Usefulness of Sentinel Lymph Node Biopsy for Patients Who Have Clinically Node Negative, Localized, Primary Invasive Cutaneous Melanoma

A Bayesian Analysis Using Informative Published Reports

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Objective: To assess the prognostic value of sentinel lymph node biopsy status for patients with localized, clinically node-negative, primary invasive cutaneous melanoma.

Design: Predictive value of positive or negative sentinel lymph node biopsy (SLNB) results for melanoma-related death, using raw numbers from informative publications.

Setting and Participants: Reports comprising 50 patients with cutaneous melanoma who had undergone SLNB, based on PubMed search (January 1, 1993, through June 3, 2010).

Main Outcome Measure: Melanoma-related death.

Results: For the 2 informative reports of patients with tumors of intermediate thickness (1-4 mm), risk of melanoma-related death ranged from 26.2% to 31.6% for node-positive cases and from 9.7% to 15.6% for node-negative cases. Based on 4 informative reports of patients with thin tumors (≤1 mm), risk of melanoma-related death ranged from 0% to 0.6% for both node-positive and node-negative cases. For the single informative report of patients with thick tumors (≥4 mm), risk of melanoma-related death was 32.5% for node-positive cases and 30.1% for node-negative cases. For 19 informative case series with any tumor thickness, risk of melanoma-related death ranged from 0% to 47.8% for node-positive cases and from 0% to 13.3% for node-negative cases.

Conclusion: Prognostic information provided by SLNB status may be variably useful for patients who have tumors of intermediate thickness (1-4 mm) and not very useful for patients who have thin (≤1 mm) or thick (≥4 mm) tumors.


See Practice Gaps at end of article
subset analyses conducted by the authors of the MSLT. The goal of the present analysis was to assess the usefulness of SLNB status in providing clinically relevant prognostic information for asymptomatic patients with CM, relying on raw numbers obtained from informative published reports and using CM-related death as the outcome.

METHODS

LITERATURE SEARCH

The English-language Medline database was searched electronically using PubMed for original reports containing the terms cutaneous melanoma and sentinel lymph node biopsy, published between January 1, 1993, and June 3, 2010. Abstracts were searched for indications of CM-related prognosis based on SLNB results, and potentially informative publications were reviewed in their entirety. For a report to be included, the following information was required: inclusion of at least 50 patients with invasive melanoma, distribution of tumor thickness, raw numbers of patients who had undergone lymphatic mapping plus SLNB, number of patients who had a negative or positive SLNB result, numbers of SLNB-negative and SLNB-positive patients who died from CM, and stated follow-up. Studies could include invasive tumors of any thickness.

DEFINITIONS

For purposes of this analysis, SLNB is regarded as a diagnostic and prognostic test, and risk of CM-related death based on SLNB status was assessed in terms of sensitivity and specificity of the test and positive and negative predictive value (PV), where the chance that a positive or negative result predicts CM-related death or no CM-related death, respectively.

For CM-related death, PV positive (PV+) is defined as the ratio of the number of patients who have a positive SLNB result and who ultimately die from CM (true positives), to the total number of patients who have a positive SLNB result whether or not they die from CM (true positives plus false positives). Predictive value negative (PV−) is defined as the ratio of the number of patients who have a negative SLNB result and who do not die from CM (true negatives), to the total number of patients who have a negative SLNB result whether or not they die from CM (true negatives plus false negatives). Estimates of PV+ and PV− are dependent on disease prevalence (prior probability) in the population tested. For this analysis, disease prevalence represents CM-related death within a stated follow-up interval for patients with CM who had undergone SLNB. Cutaneous melanoma–related death rate is defined as the number of SLNB patients who died from CM divided by the total number of SLNB patients within a given cohort, multiplied by 100%.

Sensitivity of SLNB for CM-related death is defined as the number of patients who had a positive SLNB result and who died from CM (true positives), divided by the total number of patients who ultimately died from CM whether the SLNB result was positive or negative (true positives plus false negatives). Specificity of SLNB for CM-related death is defined as the number of patients who had a negative SLNB result and who did not die from CM (true negatives), divided by the total number of patients who did not die from CM whether the SLNB result was negative or positive (true negatives plus false positives). Equations for PV+ and PV− are derived using these definitions for sensitivity and specificity of SLNB for CM-related death and disease prevalence (ie, CM-related death rate).15

RISK OF CM-RELATED DEATH BASED ON RESULTS OF SLNB

Raw numbers were gleaned from informative reports to calculate CM-related death rate, sensitivity, and specificity of SLNB for CM-related death and risk of CM-related death based on SLNB status. Sample calculations are described in the eAppendix (http://www.archdermatol.com).

RESULTS

The search yielded 480 publications. Eliminations included 104 reviews, 27 articles whose main focus was not CM, 13 reports that included individual cases or small case series, and 19 letters and commentaries. Of the remaining 317 reports, available abstracts provided an indication of prognosis based on SLNB status in 145. These 145 reports were reviewed in their entirety and were included for analysis if at least 50 patients with CM with invasive tumors were available in the cohort, clinically evident regional lymph nodes or distant metastases were absent at the time of CM diagnosis, and the required raw numbers were available for calculations. Of these 145 reports, 25 provided numbers for calculations of sensitivity and specificity of SLNB for CM-related death. Numbers in the report by Gomez-Rivera et al.16 which comprised 113 patients whose tumors were thicker than 1 mm (or less if Clark level IV or V or ulceration was present), were also used for calculations of PV+ and PV− for a subset of 83 patients who had tumors of intermediate thickness (1-4 mm). Informative reports were segregated into limited tumor thickness (thin [≤1 mm], intermediate [1-4 mm], and thick [≥4 mm]) (eTable 1) and any thickness (eTable 2). It is noted that the tumor thickness ranges are overlapping at 1 mm and 4 mm, a limitation of available data and the manner that tumor thickness ranges are displayed in the informative reports used for analysis.

DERIVED ESTIMATES OF PV

Patients With Tumors of Intermediate Thickness

For the single informative prospective case series of patients with tumors of intermediate thickness (1.2-3.5 mm) on any anatomic site reported by Morton et al, the CM-related death rate was 12.3%, sensitivity and specificity of SLNB for CM-related death were 34.0% and 86.6%, respectively, and risk of CM-related death was 26.2% for cases with a positive SLNB result and 9.7% for cases with...
a negative SLNB result. For a retrospective case series of tumors of intermediate thickness (1-4 mm) only on head and neck sites reported by Gomez-Rivera et al,16 the CM-related death rate was 19.3%, sensitivity and specificity of SLNB for CM-related death were 37.5% and 80.6%, respectively, and risk of CM-related death was 31.6% for cases with a positive SLNB result and 15.6% for cases with a negative SLNB result. Follow-up was a median of 48.4 months in the report by Morton et al,5 and a median of 34 months in the report by Gomez-Rivera et al.16 To summarize findings for patients with tumors of intermediate thickness based on 2 informative reports,3,10 risk of CM-related death ranged from 26.2% to 31.6% for cases with a positive SLNB result, and 9.7% to 15.6% for cases with a negative SLNB result (eTable 1).

Patients With Thin Tumors

For patients with thin tumors (eTable 1), the CM-related death rate ranged from 0% to 1.1%, sensitivity of SLNB for CM-related death was 0% in 3 studies17-19 and 50% in 1 study,10 and specificity of SLNB for CM-related death ranged from 88.5% to 96.8%. The risk of CM-related death ranged from 0% to 0.6% for both SLNB-positive and SLNB-negative cases. Follow-up for these latter 4 studies ranged from a median of 26.3 to 74 months for 3 studies17,19,20 and a mean of 27 months in 1 study.10 The range of follow-up was stated for 3 studies: 15 to 84 months,17 6 to 60 months,19 and 12 to 108 months.10 Tumor location included any cutaneous site for all 4 studies. To summarize findings for patients who have a thin primary CM, the risk of CM-related death was less than 1% for both SLNB-positive and SLNB-negative cases.

Patients With Thick Tumors

For the single informative report of patients with a 4-mm tumor thickness, a median and mean follow-up for these 4 studies ranged from a median of 26.3 to 74 months for 3 studies17,19,20 and a mean of 27 months in 1 study.10 The range of follow-up was stated for 3 studies: 15 to 84 months,17 6 to 60 months,19 and 12 to 108 months.10 Tumor location included any cutaneous site for all 4 studies. To summarize findings for patients who have a thick primary CM, the risk of CM-related death was approximately 1 in 3 for both SLNB-positive and SLNB-negative cases.

Patients With Any Tumor Thickness

eTable 2 presents 19 case series16,22-39 of patients with any tumor thickness. The risk of CM-related death ranged from 0% to 47.8% for cases with a positive SLNB result and 0% to 11.9% for cases with a negative SLNB result. Median and mean follow-up for these 19 studies ranged from 13.2 to 72 months and 22 to 42 months, respectively. The range of follow-up was available for 13 studies. Distribution of tumors according to cutaneous site was variable among the 25 studies (data not shown), unavailable for 2 studies,36,39 and available only for cases with a positive SLNB result (any cutaneous site) in 1 study.20 Tumors were confined to head and neck sites in 2 studies.16,30

DISTRIBUTION OF TUMOR THICKNESS

eTable 3 gives the distribution of tumor thickness for informative case series of patients with invasive CM that included any tumor thickness. The proportion of thin tumors ranged from a low of 1.1%24 to a high of 30.4%.20 The proportion of thick tumors ranged from a low of 5.3%25 to a high of 30.3%.24 In 3 reports,34,36,39 distribution of tumor thickness was not provided.

DISTRIBUTION OF PATIENT SEX AND AGE

Patient sex was included in all but 2 reports.37,20 Age range was available for all but 7 reports. Ethnicity was stated for only 1 report (eTable 4).20

COMMENT

A clinical test40 that accurately predicts patient outcome for localized primary invasive CM would be invaluable. In practice, SLNB is being used worldwide for this purpose. According to numerous studies,22,41-44 overall survival, disease-free survival, and disease-specific survival are significantly worse for patients with a positive SLNB result compared with those with a negative SLNB result. However, patients may survive or die from CM regardless of SLNB status. The goal of the present study was to assess the prognostic usefulness of SLNB status in predicting CM-related death.

In the assessment of any diagnostic or prognostic test for CM, choices of patient outcome may include disease-specific survival (ie, CM-related death), overall survival, and disease-free survival. In the analysis herein, CM-related death rather than recurrence (disease-free and recurrence-free survival) was used to assess prognostic usefulness of SLNB status. The prognostic usefulness of SLNB status in predicting CM-related death is dependent on the CM-related death rate in the cohort being studied and sensitivity and specificity of SLNB for CM-related death. Therefore, a Bayesian approach15,40 was used to attach a probability value for CM-related death according to SLNB status. This probability value becomes a useful measure of validity of SLNB as a diagnostic and prognostic test. Had disease-free survival been used instead of CM-related death, SLNB status as a predictive test would have been obfuscated by sites of recurrence, ie, local, in-transit, regional node, or distant. If regional node recurrence is included in disease-free survival, then surgical removal of regional nodes will strongly influence sites of recurrence and thus rates of disease-free survival. Disease-free survival will be worse in patients whose tumors recur in regional nodes compared with patients who have had TLND for microscopic disease. Reliance on CM-related death rate according SLNB status instead of disease-free survival eliminates this potential bias and will more likely permit replication in validation studies.
USEFULNESS OF SLNB IN PREDICTING CM-RELATED DEATH

For tumors of intermediate thickness, only 2 informative reports were found with available raw numbers for risk of CM-related death calculations based on SLNB status, one a prospective randomized controlled trial and the other a retrospective series. Based on raw data from the Multicenter Selective Lymphadenectomy Trial for patients who had undergone an SLNB for a primary localized CM of intermediate thickness (range, 1.2-3.5 mm) (eTable 1) on any cutaneous site and were followed up for a median of 48.9 months, risk of CM-related death was 26.2% for cases with a positive SLNB result and 9.7% for cases with a negative SLNB result. For a subset of 83 patients reported by Gomez-Rivera et al with primary CM 1 to 4 mm thick on the head or neck, risk of CM-related death was 31.6% for cases with a positive SLNB result and 15.6% for cases with a negative SLNB result, with a median follow-up of 34 months.

Based on 4 informative reports of patients with thin tumors (eTable 1), the CM-related death rate was 0% to 1.1% for follow-up intervals ranging from a median of 2 years to 6 years. The risk of CM-related death was less than 1% for both SLNB-positive and SLNB-negative cases. According to a meta-analysis of SLNB for tumors 1-mm thick or less, reported by Warycha et al for 34 studies comprising 3651 patients, the pooled rate of SLNB positivity was 5.6%, with significant heterogeneity among studies; only 4 deaths were reported, despite the fact that 6.1% of tumors were ulcerated, 31.5% demonstrated regression, and 47.5% were Clark level IV or V. According to Morris et al, even for patients whose thin primary tumors had significant histopathologic regression, rates of SLNB positivity, local recurrence, systemic recurrence, and overall survival were not significantly worse than for patients whose thin primary tumors showed no regression. In a multicenter study in Italy reported by Testori et al, the presence of regression appeared to be inversely correlated with SLNB positivity. A lack of consistent definitions further obfuscates the prognostic significance of regression. It may be concluded that for patients with thin CM, rates of SLNB positivity are approximately 6%, and SLNB status may be useless in predicting CM-related death, even in cases with adverse histopathologic features.

While clinically node-negative patients with 4-mm or thicker tumors have a 60% to 70% risk of regional micrometastatic disease and a 70% risk of occult systemic disease at the time of presentation, multiple authors make a case for SLNB in this subgroup because SLNB status is a powerful predictor of overall survival by univariate and multivariate analysis. For the single informative case series of patients with thick tumors reported by Essner et al, in which the CM-related death rate for the cohort was 31.0%, risk of CM-related death was 32.3% for cases with a positive SLNB result and 30.1% for cases with a negative SLNB result, with a median follow-up of 31 months (range, 273 months) (eTable 1). In this report, tumor status of the SLNB was predictive of disease-free survival but not overall survival. In patients with thick tumors, SLNB status is probably not useful for predicting CM-related death.

Differences in CM-related death rates for patients with thin (0%-1.1%), intermediate (12.3%-19.3%), and thick (31.0%) tumors account for striking differences in risk of CM-related death based on SLNB status, demonstrating the importance of prior probability in calculations of predictive value.

Based on informative case series composed of patients with any tumor thickness (eTable 2), CM-related death ranged from 0% to 47.8% for cases with a positive SLNB result and 0% to 13.3% for cases with a negative SLNB result. The wide range of CM-related death according to SLNB status observed for CM case series including any tumor thickness is influenced by varying composition of tumor thickness (eTable 3), patient age, distribution of tumors according to anatomic location, and duration of patient follow-up (see “Limitations” subsection). The proportion of thick tumors ranges from a low of 5.3% to a high of 30.3% (eTable 3). Tumor thickness is a prime determinant of SLNB positivity and CM-related death. Calculations of risk of CM-related death based on SLNB status for informative reports of patients with any tumor thickness (eTable 2) provide no useful conclusions.

FALSE-NEGATIVE RATE FOR SLNB

The false-negative rate for SLNB may be defined as the chance of obtaining a negative result when in fact the SLNB result is positive for tumor, for which regional lymph nodes become clinically and histopathologically tumor positive during follow-up. The false-negative rate for SLNB has been defined in various ways, likely accounting for wide variations in reported results, from 3.4% to 21.0%. A false-negative result obfuscates the prognostic usefulness of SLNB and may be due to flawed lymphatic mapping evaluation, lymphatic drainage disruption related to tumor excision, reduced sentinel lymph node detection during surgical exploration, less than optimal histopathological examination of lymph node(s), suboptimal lymphatic function (particularly in older patients), and unknown factors that influence malignant cells in lymphatic channels from reaching the sentinel lymph node.

CURRENT MANAGEMENT PRACTICES

Multiple factors influence decisions about recommending SLNB, including tumor location, economic costs, and surgical morbidity. Other factors include patient age, comorbidities, insurance availability, and ethnicity. It is not surprising that according to population-based studies, no more than half of patients with tumors at least 1-mm thick undergo SLNB. According to recent surveys of surgical units treating patients with CM, only 31% to 76% of respondents reported using SLNB in their practices. Based on results of 44,549 patients with primary CM in the US National Cancer Data Base, only 50% of 29,422 patients with a positive SLNB result underwent TLND.

COMPLICATIONS RELATED TO SLNB

According to studies by Kretschmer et al in Germany, the overall rate of at least 1 complication following SLNB...
for axillary or inguinal lymph node regions in 315 patients was 13.8%, while the rate of complications after TLND for these nodal regions was 65.5%, with a significantly higher complication rate for patients 70 years or older and inguinal lymph node involvement. According to Ling et al in Australia, the complication rate for 147 patients undergoing SLNB was 10.9% (16 of 147), related to higher body weight and body mass index and groin location. While procedures related to SLNB (and TLND) are not free of complications, it has been observed that patients who develop clinically palpable inguinal lymph node recurrence during nodal observation have a greater number of involved nodes, more often 4 or more involved nodes, and a greater incidence of extranodal extension, wound complications, and lymphedema, compared with patients with a positive SLNB result (microscopic disease) who undergo TLND. To determine the validity of this argument, it will be necessary to compare surgical morbidity rates of TLND among patients who develop advanced regional node disease during routine nodal observation compared with patients in whom regional node disease is discovered based on frequent clinical examinations with the use of ultrasonography.

**ECONOMIC CONSIDERATIONS**

Additional costs related to SLNB for a patient undergoing SLNB in England, reported in the year 2000 by Hettiarchey et al, was £1420. For 138 patients with a primary CM less than 1.2-mm thick undergoing SLNB at Ohio State University between 1994 and 2002, physician and hospital charges per patient for SLNB procedures ranged from $10,096 to $15,223 (mean, $12,193), compared with $1000 to $1740 (mean, $1466) for outpatient wide excision alone performed at the same institution. Only 2 of the 138 patients were identified as having tumor in the SLNB, resulting in an estimated cost to identify a single patient with a positive SLNB result ranging from $696 600 to $1 051 100. The 2007 Medicare reimbursement rate for SLNB procedures was reported to be $19,000. Costs related to TLND are considerably more than for SLNB, with longer hospital stays, more complications, higher physician charges, and greater lost patient income and patient downtime.

**LIMITATIONS**

The present analysis relied on available informative English-language reports in which raw numbers were available for risk of CM-related death calculations based on SLNB status. Dozens of otherwise useful reports were excluded because raw numbers were not provided. Additional informative reports, in English and other languages, may have been missed in the literature search.

The informative studies reported herein were not uniform with regard to interpretation of histopathologic features of primary tumors and lymph nodes. There were wide variations in CM-related death rate, duration of follow-up, distribution of tumors according to thickness and anatomic site, and distribution of patient age. Cutaneous melanoma–related death rate is dependent on tumor thickness and length of patient follow-up, and SLNB positivity is dependent on tumor thickness and patient age. Gutierrez et al found that among patients with primary CM at least 4-mm thick undergoing SLNB, patients with a positive SLNB result had a median age 7 years younger than patients with a negative SLNB result. Vuylsteke et al reported that patients younger than 20 years usually had a very good prognosis despite having a 30% to 80% positive SLNB rate. According to an analysis of 3076 patients enrolled in the Sunbelt Melanoma Trial and followed for a median of 19 months, a worse prognosis was associated with increased patient age, increased tumor thickness, and increased incidence of ulceration despite a lower incidence of SLNB positivity; risk of a positive SLNB result was 23% in patients younger than 30 years, compared with 12% in patients aged 61 to 70 years. According to Statius Muller et al, a positive SLNB rate was 37% for patients aged 18 to 30 years vs 17% for patients aged 71 to 84 years. Thus, SLNB status may be less useful prognostically in older (>60 years) and younger (<20 years) patients. Also, older patients are more likely to be excluded from procedures of SLNB and TLND because of increased comorbidities, thus age-biasing patient composition. Age distribution was available for only 4 of the informative reports in the present analysis (eTable 4).

Reluctance to include all patients with CM for SLNB regardless of tumor location may further bias studies. For instance, tumors on the head, neck, and mid thorax often have more than 1 lymphatic drainage site. Sentinel lymph nodes may be more difficult to locate given multiple drainage sites, and there may be reluctance to conduct multiple SLNBs in patients whose tumors have multiple drainage sites. For head and neck CM, SLNB presents unique challenges of complicated lymphatic drainage, difficulties locating the sentinel lymph node(s), radiation overlap between primary tumor and sentinel lymph node(s), less frequent visualization of the blue dye, and higher morbidity related to proximity of nodes to neurovascular structures.

In 5 of the 25 informative studies used for risk of CM-related death calculations based on SLNB status, reverse transcriptase–polymerase chain reaction (RT-PCR) was used to increase sensitivity of tumor detection. For purposes of the present analysis, SLNB cases that were histopathologically negative but RT-PCR positive were designated SLNB negative. In cases with histopathologically negative but positive RT-PCR results, capsular nevi are often found on further histopathologic investigation. Detection of tyrosinase messenger RNA by RT-PCR alone did not appear to increase the likelihood of short-term disease recurrence in one study, but was significant in predicting disease-free survival adversely in other studies. Preliminary findings of the Sunbelt Melanoma Trial revealed no difference in disease-free survival and overall survival when patients with positive RT-PCR but histopathologically negative (and immunohistochemically negative) SLNB results were randomized to observation, TLND, or TLND and 4 weeks of high-dose intravenous interferon therapy.

Patient follow-up is critical to any analysis of treatment effect on CM-related death rate. With longer follow-
up, CM-related death rate may be expected to increase regardless of SLNB status. Long-term natural history studies are useful to determine the minimum follow-up necessary for assessment of any treatment effect on CM-related death rate. Gamel et al reported on 5342 patients with localized melanoma at the Duke Comprehensive Cancer Center who underwent surgical excision between 1978 and 1996 and who had a maximum follow-up of 23 years. Of the 1486 patients who died within 23 years, 65.5% (974 of 1486) died within 5 years, 91.9% (1365 of 1486) died within 10 years, and 98.8% (1468 of 1486) died within 15 years; of the 1365 patients who died within 10 years, 43.4% (592 of 1365) died within 3 years, and 71.4% (974 of 1365) died within 5 years. For the informative reports in the analysis, only median and mean follow-up intervals were usually reported. The mean or median follow-up interval was less than 3 years in 16 reports and less than 2 years in 3 reports (eTable 1 and eTable 2). In future studies, follow-up intervals of at least 5 years for all study patients (unless death intervenes) will be required to assess the effect of SLNB (and TLND for positive cases) on CM-related death rate within well-defined age and tumor thickness groups.

In the present analysis, wide ranges in CM-related death rate and risk of CM-related death based on SLNB status were notable for informative case series including tumors of any thickness. Only 2 informative reports were available for tumors of intermediate thickness (1-4 mm),13,14 for thin tumors (≤1 mm),17,18 and only 1 for thick (≥4 mm) tumors,19 with overlap in tumor thickness limits (≤1 mm, 1-4 mm, and ≥4 mm). Additional studies with narrowly defined categories of tumor thickness and raw numbers of CM-related death according to SLNB status, including large numbers of patients pooled from multiple centers, will be required to corroborate or refute the findings presented.

CONCLUSIONS

Sentinel lymph node biopsy is being offered for not only prognostic purposes but also based on the presumption that all microscopic nodal disease progresses to bulky nodal disease. When nodal tumor burden is small, SLNB may be curative, but therapeutic usefulness may be impossible to assess, ie, the clinical equivalent of the Heisenberg principle. Nevertheless, there is no current evidence that SLNB (and TLND for positive cases) enhances disease-specific or distant disease-free survival.

Based on current practices, there may be hesitancy in exposing the majority of patients who would never progress to regional metastatic disease to the potential morbidity complications of SLNB (and TLND for positive cases) in efforts to assess prognosis and prevent bulky regional recurrence. Alternative methods of preventing bulky regional recurrence warrant further evaluation. The present analysis suggests that prognostic information provided by SLNB status may be variably useful for patients who have tumors of intermediate thickness and not very useful for patients who have thin or thick tumors. If SLNB is being offered to obtain prognostic information, patients need to be informed how SLNB status will be used to predict CM-related mortality and guide treatment options.

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REFERENCES

40. Sox HC Jr. Probability theory in the use of diagnostic tests: an introduction to
38. Gad D, Høilund-Carlsen PF, Bartram P, Clemmensen O, Bischoff-Mikkelsen M.
36. Roka F, Kittler H, Cauzig P, et al. Sentinel node status in melanoma patients is
35. Ross CR, Pasquali S, Mocellin S. Actual false-negative rate prompts the routine
34. Wells KE, Rapaport DP, Cruse CW, et al. Sentinel lymph node biopsy in thick
32. Oliveira AF, Santos ID, Tucunduva TC, et al. Sentinel lymph node biopsy in cu-
31. Tatidili C, Parkhill WS, Giacomantonio CA, Greer WL, Morris SF, Walsh NM. Detection of tyrosinase mRNA in the sentinel lymph nodes of melanoma pa-
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72. Gamel JW, George SL, Edwards MJ, Seigler HF. The long-term clinical course of melanoma overall. A review of the existing literature is possible. Recent randomized clinical trials examining SLNB in these populations, there are gaps in knowledge. This controversy highlights the major challenges facing clinicians as any new technology is adopted: should the scope of clinical indications be narrowed or broadened, and how are those decisions made? Advocating additional research in this area is important but does not inform current practice. In overcoming knowledge gaps, it is important to remember that no prognostic test should be used in isolation, and test results must be interpreted in the context of other clinical factors. In the case of SLNB for melanoma, the benefit of additional staging information must be considered with regard to characteristics of the primary tumor.

One Procedure but Many Questions

Since sentinel lymph node biopsy (SLNB) for cutaneous melanoma was developed nearly 20 years ago, there has been wide dissemination of the procedure in clinical practice, vastly changing the way patients are treated today. Although the initial Multicenter Selective Lymphadenectomy Trial,1 an international randomized clinical trial, did not clearly demonstrate a survival advantage with SLNB, the results did support its role in providing important prognostic information and improving other outcomes (eg, melanoma-specific survival rates) in patients with intermediate-thickness melanoma. The ability to accurately stage patients and offer interventions to decrease risks of regional recurrence and/or increase relapse-free survival has led to the continued use of the procedure for these patients. Ultimately, these results formed the basis of Rhodes’ analysis, and he similarly concludes that SLNB provides useful information for patients with intermediate-thickness melanoma. Despite strong scientific evidence supporting SLNB for intermediate-thickness melanoma, practice gaps exist. National practice patterns show considerable variation in the use of SLNB across the United States, indicating poor dissemination of evidence and/or slow physician uptake.

For patients with thin (≤1 mm) or thick (>4 mm) melanomas, Rhodes concludes that SLNB did not provide useful prognostic information. His method of reviewing only articles that included raw data limited his analysis to smaller studies with fewer events and excluded larger series in which multivariate analyses are reported. Nevertheless, because there are no randomized clinical trials examining SLNB in these populations, there are gaps in knowledge. This controversy highlights the major challenges facing clinicians as any new technology is adopted: should the scope of clinical indications be narrowed or broadened, and how are those decisions made? Advocating additional research in this area is important but does not inform current practice. In overcoming knowledge gaps, it is important to remember that no prognostic test should be used in isolation, and test results must be interpreted in the context of other clinical factors. In the case of SLNB for melanoma, the benefit of additional staging information must be considered with regard to characteristics of the primary tumor.

For patients with thick melanomas, expanding the use of SLNB seemed to be warranted because prognosis is heterogeneous within this group. With localized disease, many patients are actually found to have survival rates similar to patients with intermediate-thickness lesions. Rhodes examined only 1 article in this part of the analysis. The broader experience in this population is not extensive, but contemporary series have supported the prognostic importance of SLNB for thick melanomas. Our group has recently reported that patients with thick melanomas (who routinely undergo SLNB) have a markedly improved 5-year overall survival rate when the SLNB result is negative (80% vs 47%; P < .001).2 While having a thick melanoma carries a poorer prognosis because of the high risk of distant disease, not all patients have or will develop metastases. Keeping this in mind, patients with thick melanomas should be strongly considered for SLNB as an informative staging procedure.

A more difficult issue is in the utility of SLNB for thin melanomas because this population has such a good prognosis overall. A review of the existing literature is potentially much more biased because patients are only likely to be selected for the procedure when there are extenuating circumstances (eg, very high-risk features of the primary lesion). Most of these retrospective studies do not support the routine use of SLNB for thin melanomas. Even the definition of high-risk features is controversial, though ulceration and high mitotic rate are commonly cited. Expanding the use of SLNB to all patients with thin melanomas is likely to subject too many patients to the risks of the procedure without discernable benefit. The pri-