VIEWPOINT

Sentinel Lymph Node Biopsy in Cutaneous Melanoma—Where Do We Stand?

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There are few procedures as controversial as the sentinel lymph node biopsy (SLNB) in the treatment of cutaneous melanoma. Early proponents hypothesized it would improve patient outcomes and provide valuable prognostic information. The Multicenter Selective Lymphadenectomy Trial (MSLT-1),[1] however, demonstrated that addition of SLNB to wide excision did not improve melanoma-specific survival (MSS). The MSLT-2 trial and the German Dermatologic Cooperative Oncology Group trials[1] further showed that among patients with a positive SLNB, completion lymph node dissection (CLND) did not improve MSS or overall survival (OS), respectively. Although controversy persists regarding a potential reduction in MSS in selected subgroup analyses of patients with intermediate-thickness melanoma, the findings from these trials redefined the primary role of SLNB to that of a prognostic test, which subsequent adjuvant therapy trials have used as eligibility criteria for systemic therapy.

In MSLT-1, the SLNB was interpreted as the strongest predictor of disease recurrence or death from melanoma.[1] Bigby et al,[2] however, questioned the contemporary role of the SLNB, noting that the added prognostic value of SLNB status to standard clinicopathological factors remains unproven. To address this need, El Sharouni et al[3] recently characterized the added prognostic utility of SLNB. The authors created clinicopathological only (CP) (based on tumor thickness, sex, age, anatomical site, mitoses, ulceration, regression, and subtype) and clinicopathological plus SLNB (CP-SLN) prediction models from a cohort of 9272 Dutch patients and validated the models' performance in 5644 Australian patients. Similar to MSLT-1,[4] SLNB status was a robust predictor of recurrence-free survival (hazard ratio, 2.7). In addition, the CP-SLN model had higher discrimination (area under the curve) than the CP model for prediction of all survival outcomes, underscoring the prognostic validity of SLNB.

However, these data do not tell us whether the information gained from SLNB leads to better treatment choices. For this, decision curve analysis was used by El Sharouni et al[3] to investigate SLNB's clinical utility. To interpret a decision curve, one needs to specify a risk threshold for a particular melanoma treatment. Although risk thresholds are poorly quantified, some US clinicians would obtain cross-sectional imaging (eg, computed tomographic scan) for a patient with *American Joint Committee on Cancer Staging Manual, 8th Edition*, stage IIB-positive disease (approximately 87% MSS), as National Comprehensive Care Network (NCCN) guidelines state to consider imaging in this population for occult metastatic disease. This suggests that an approximately 15% 5-year risk of melanoma death is a clinically significant threshold.

At the 15% risk threshold for imaging, the CP-SLN model had an approximate 0.7% net benefit over the CP model for prediction of melanoma death—demonstrating potential for utility.[3] However, unlike the CP model, use of the CP-SLN model requires a "fee"—the SLNB procedure—which was not considered. The fee of the SLNB includes expenditures of time, effort, and money, as well as potential surgical adverse effects like infection, pain, seroma, and lymphedema. An advantage of decision curve analysis is that these parameters do not need to be explicitly defined. Instead, the fee can holistically be estimated by considering the maximum number of patients one would subject to an SLNB procedure to find 1 patient destined to die of melanoma.[5] To directly compare the CP-SLN model to the CP model, this fee must be subtracted from the CP-SLN benefit. Given the 0.7% net benefit identified for the CP-SLN model, a clinician would have to be willing to perform more than 142 SLNB procedures to identify 1 patient destined to die of melanoma to maintain a positive net benefit after accounting for this fee. Otherwise, use of the CP-SLN model could lead to net harm if used to select patients for imaging. The net benefit between the models at higher thresholds—such as those that might theoretically be used for selection of adjuvant therapy (approximately 20%-40% risk of melanoma death)—showed differences in net benefit of up to approximately 1.0% for the CP-SLN model, suggesting greater potential for clinical utility.[3]

There are limitations to the data published by El Sharouni et al.[3] The CP model is not available to clinicians. Many of the histopathologic variables in the CP model may not be as reliably measured outside of academic centers, necessitating further validation of its generalizability and transportability. The added prognostic value of SLNB to clinicopathologic factors used in guidelines—thickness and ulceration—is likely substantially greater. The SLNB is not a binary measure because the metastatic burden provides additional prognostic information not accounted for in this study design. It must also be emphasized that the 5-year risk of recurrence, which may be the most clinically useful outcome for making decisions about follow-up, imaging, or adjuvant therapy, is directly reduced 5% to 13% by the SLNB (and, if positive, CLND).[4] Thus, the CP model's prediction of disease recurrence would deteriorate if SLNB were not actually performed. Finally, the net benefit of the CP and CP-SLN models were not compared with the net benefit of a treat-all approach (ie, performing an SLNB on all patients), which could be equivalent or even superior at some risk thresholds. Nonetheless, these analyses highlight the need to carefully consider the potential benefits and harms of each new predictor added to melanoma prognostic tools.

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The Road Ahead

If ongoing trials demonstrate that adjuvant therapy is efficacious in patients with high-risk localized disease (stages IIB/C), SLNB could have a diminished role in patients diagnosed with T3b-positive primary tumors, who may have systemic therapy recommended regardless of SLNB status. For this population, the prognostic tool that simply provides the highest net benefit across the range of risk thresholds relevant for choosing systemic therapy should be employed. A model that provides individualized absolute risk estimates of disease recurrence would be anticipated to be more clinically useful than a high- vs low-risk marker, as an appropriate treatment threshold may vary based on individual patient preferences and characteristics. Among patients with lower- and intermediate-risk disease who may be eligible for SLNB (T1b-T3a) and, if positive, potential adjuvant therapy, efforts should initially focus on mitigating harms by using emerging prediction tools, including gene expression profiling (GEP), combined CP-GEP models, and clinicopathologic nomograms, to improve selection for SLNB given the well-defined risk thresholds that already exist for this procedure.

As long as SLNB is valued by patients and surgeons due to its potential therapeutic effect on disease recurrence (improved locoregional control) and used by oncologists for eligibility into standard of care-defining trials of systemic therapy, SLNB will, and should, continue to be employed. However, the improvement of prediction models and identification of novel noninvasive prognostic factors, such as GEP, T-cell fraction,[6] and/or circulating tumor DNA, raise the possibility that SLNB could be applied much more selectively. Better and unbiased prognostic models have the potential to provide improved risk predictions and improve patient outcomes, but numerous models have been developed,[7] and none have yet been routinely incorporated into guidelines or clinical practice. This may be partially owing to the absence of defined risk thresholds for most melanoma treatment decisions. What use is it knowing that a patient has a 22% chance of recurrence? Should this patient be imaged? How often? Should they be considered for adjuvant therapy? Without risk-based treatment recommendations, estimates are not actionable. Definition of consensus risk thresholds would also allow assessment of the relative clinical value of competing prognostic models and tests, as well as characterization of the added utility of novel prognostic factors, using measures like net benefit and decision curve analysis. Tools with the most potential to improve patient and physician decision-making must then be validated prospectively in clinical studies.

Conclusions

For a prognostic tool to fully displace SLNB, however, adjuvant systemic therapy will need to be demonstrated efficacious in a randomized clinical trial using patients risk stratified with prediction tools other than SLNB. Only then will the field be able to truly move beyond the modestly invasive, clearly prognostic, potentially therapeutic, and always controversial test that is SLNB.

ARTICLE INFORMATION

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