

Survival and the Sentinel Lymph Node in Melanoma

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Lymphatic mapping with sentinel lymphadenectomy (SLND) has become the standard approach to intermediate thickness melanoma at most melanoma centers worldwide. The procedure has yielded numerous, unquestioned benefits for patients with melanoma, including providing vital prognostic information and improving disease-free survival with reduction of morbid regional nodal recurrences. However, some uncertainty regarding the impact of the procedure on overall survival persists.^{1,2}

Leiter and colleagues provide additional data to examine SLND in this issue of the *Annals of Surgical Oncology*. They present a retrospective series of the 879 patients with intermediate thickness melanoma treated at the University of Tuebingen from 1991 to 2005, half of whom had undergone SLND (439) and half of whom did not (440). These investigators were not participants in the Multicenter Selective Lymphadenectomy Trial (MSLT1), and so their data are independent of those of the randomized, prospective trial.³ One of their stated goals was to contribute to the evaluation of the procedure's impact on survival. Their analysis demonstrates remarkable consistency with the findings of MSLT1 (Table 1).

Once again, the dominant prognostic importance of sentinel node status is confirmed, as is the impact on disease-free survival, and they confirm an identical risk of in-transit recurrences with or without SLND.^{3–6} As with MSLT1 thus far, definitive evidence of an overall survival benefit among all patients was not found. At the third interim analysis of MSLT1, there was an absolute 3% improvement in 3-year melanoma-specific survival, which was not statistically superior and vanished into wide confidence intervals by 5 years. In the current study, the

nonsignificant difference was 4%, although multivariate analysis demonstrated a stronger trend toward benefit in the SLND group ($p = 0.09$). Earlier elective lymph node dissection results are nearly identical (4% at 5 years).⁷

Why was there no difference in the overall group comparisons? The most important reason is the absence of nodal disease in the majority of patients. As with any targeted therapy, if over 80% of patients do not demonstrate the responding phenotype, it is extremely difficult to demonstrate an overall survival improvement. For example, a trial of the monoclonal antibody trastuzumab would not be likely to show an overall survival benefit if subjects' expression of the target antigen is unknown at the time of randomization. The predictive biomarker here for response to nodal surgery is within the node itself. Unfortunately, as yet there is no way to accurately know the status of the sentinel node until it is on the pathologist's microscope.

This brings us to the final group of striking similarities of Leiter et al. and MSLT1: comparisons of the node-positive patients. These comparisons have been approached with marked statistical trepidation because patients were not directly randomized into the node-positive groups, which results in the possibility of bias by chance or through an unidentified confounder. The statistically ideal trial, one which randomizes patients with clinically occult nodal metastases to immediate removal or to removal after the disease has become clinically apparent, would clearly be unethical. The debate in melanoma lymph node management has never been about *whether* to removed diseased lymph nodes, only *when* to do it.

How comparable are the two groups with lymph node involvement in this study and MSLT1? Again the similarities are striking. The fraction of patients with nodal disease in each treatment group, demonstrated by either positive sentinel node or by clinical nodal recurrence, are identical in the Leiter study and within 1% of each other in MSLT1, when projected to 8 years of follow-up. There does not appear to be an excess of positive nodes in the SLND groups,

TABLE 1 Comparison of Leiter et al. and MSLT1 findings

Finding	Leiter et al.	MSLT 1
Multivariate OS hazard ratio (HR) of positive SLN	3.4 (1.8–6.4) $p < 0.001$	2.48 (1.54–3.98) $p < 0.001$
% Positive SLN versus control nodal recurrence	16.4% versus 16.4%	19.4% versus 18.5% ^a
DFS benefit in SLN groups	9.1% (76.9% versus 67.8%)	5.2% (78.3% versus 73.1%)
In-transit metastasis (SLN versus control)	9.2% versus 10.1% ($p = 0.655$)	7.7% versus 8.4% ($p = 0.38$)
HR for melanoma death: overall analysis	0.74 (0.52–1.05, $p = 0.09$)	0.92 (0.67–1.25, $p = 0.58$)
HR for melanoma death node +: SLN versus Control	0.45 (0.25–0.71, $p = 0.002$) ^b	0.62 (0.4–0.95, $p = 0.02$)

^a Projected at 8 years

^b Reported in the current article as the inverse: control versus SLN

which suggests that virtually all positive sentinel nodes are clinically significant. Recent data from The Netherlands suggest that isolated melanoma cells (<0.1 mm) in sentinel nodes do not impart a worse prognosis than completely negative nodes.⁸ However, patients with such minimal disease are also the most likely to have their disease progression arrested by the SLND itself. Absence of recurrence among these patients may be evidence of therapeutic efficacy, rather than clinical insignificance.

In addition, comparisons of known prognostic variables within the node-positive groups of both the Tuebingen cohorts and MSLT1 show no indication of biologically favorable characteristics in the SLND groups. In fact, what differences there are tend to favor the nodal observation groups. These include gender, ulceration, and level of invasion in the Tuebingen series, and age in MSLT1. Overall, it seems a survival bias in favor of the SLND groups is unlikely.

When survival comparisons of node-positive patients are made in the two studies, the results are remarkably similar and are not subtle. In each study, the risk of melanoma death is cut approximately in half by the early removal of nodal disease. This magnitude of difference would be difficult to explain through an unidentified, uncontrolled bias in the two cohorts and clearly has major clinical implications for those patients who harbor micrometastases at the time of presentation. If we accept that SLND improves survival in node-positive patients, and with no operative mortality reported in major trials, overall survival must be improved, though it might require a trial of several thousand patients to prove it.⁹

What then should we tell our patients with newly diagnosed, intermediate thickness melanoma about SLND? First, for those without life-limiting comorbidities, it is an essential part of their evaluation and treatment. Second, since a false-negative SLND is at least as bad as no SLND at all, the procedure should be done at institutions with adequate experience and expertise. Finally, if the patient harbors a lymph node metastasis, removing it while it is clinically undetectable will markedly reduce the risk of dying from melanoma.

Whether this last assertion has been proven beyond a reasonable doubt depends on one's definition of reasonable. Perhaps additional follow-up in MSLT 1 will yield a statistically significant answer in the fourth interim or final analyses yet to come, but since the procedure is essential to accurate staging, decreases disease recurrence, and can be done with minimal morbidity, that particular question is essentially moot. The important remaining question is whether, in the setting of a positive sentinel node, there is a benefit to completion nodal dissection.

While current data demonstrate the benefit of early removal of micrometastases, the majority of patients with positive sentinel nodes will not have pathologically detected melanoma in the completion dissection specimen.¹⁰ Furthermore, those patients who do have positive nonsentinel nodes have a markedly higher risk of distant metastases and may be beyond the reach of further preventative surgery.¹¹ Finally, the morbidity associated with completion dissection is significantly greater than that of SLND for melanoma, so that the clinical cost of a negative procedure is greater than with SLND alone. These factors make completion of MSLT2, which randomizes patients with positive sentinel nodes to completion lymph node dissection or clinical observation with nodal ultrasound, critical to rational management of regional lymph nodes in melanoma.

Leiter and colleagues should be congratulated for their analysis of SLND at Tuebingen. The close reproduction of the MSLT1 results at this independent institution further substantiates the findings of other retrospective series and of the prospective trial. Observational studies such as theirs add weight to the measured value of SLND and improve the resolution of our picture of its survival impact.

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