Identification, Clinical Significance, and Management of Very Small Melanoma Metastases in Sentinel Lymph Nodes

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Early treatment of metastatic melanoma remains appealing. In the 1980s Morton et al. evaluated whether they could identify, without complete lymphadenectomy, the individual regional nodes most susceptible to early metastases.¹ These studies developed S-100 protein as the first immunohistochemical marker for melanocyte-derived cells,^{2,3} established that preoperative lymphoscintigraphy identified the regional lymph nodes that received lymph from the site of a primary melanoma, and that intradermally injected marker dyes identified the actual lymph node(s) [sentinel nodes (SNs)] that received lymph from a primary melanoma.¹ Animal studies demonstrated the predictability and reliability of lymph drainage from specific anatomical sites.⁴ These techniques were applied to melanoma patients. After identification by isotope and marker dye, the SN was evaluated for melanoma. Complete lymphadenectomy (completion lymphadenectomy) was then performed and the non-SNs (NSNs) were evaluated for metastases. In most patients, metastases were exclusive to the SNs; in a small minority, tumor was present in one or more NSNs. Patients with tumor-negative SNs very rarely had tumor in NSNs. These extended studies were the basis of our initial report regarding the novel techniques of lymphatic mapping and SN biopsy.¹ A multicenter trial [Multicenter Selective Lymphadenectomy Trial 1 (MSLT-1)] was initiated to compare wide excision followed by observation with wide excision/lymphatic mapping and SN

biopsy, with immediate completion lymphadenectomy if the SN contained tumor. The final results of MSLT-1 (with 10-year survival data) were published in 2014.⁵ These approaches are widely used in melanoma management and have been adapted to the treatment of breast cancer and other cancers.

In MSLT-1, melanoma patients were randomly assigned to wide excision/nodal observation, with lymphadenectomy for nodal relapse, or to wide excision/SN biopsy, with immediate completion lymphadenectomy if the biopsied node contained micrometastases. Among 1269 patients with intermediate-thickness primary melanoma, 5-year disease-free survival was higher with nodal biopsy than nodal observation [78.3 vs. 73.1 %; hazard ratio (HR) 0.74; 95 % confidence interval (CI) 0.59–0.93; $p = 0.009$]. Five-year melanoma-specific survival in the study groups was not different (87.1 vs. 86.6 %). In the nodal biopsy arm, SN tumor status was the most important prognostic factor; 5-year survival was 72.3 % for tumor-positive SNs and 90.2 % for tumor-negative SNs (HR 2.48; 95 % CI 1.54–3.98; $p < 0.001$). Sixteen percent of SNs contained metastases (122/764 patients), and the rate of nodal relapse during observation was 15.6 % (78/500 patients). Corresponding mean numbers of tumor-involved nodes were 1.4 and 3.3 ($p < 0.001$), indicating substantial disease progression during observation. Patients with nodal metastases had better survival when a positive SN biopsy was followed by immediate lymphadenectomy relative to individuals observed after wide excision, with lymphadenectomy delayed until clinically detected nodal relapse (5-year survival, 72.3 vs. 52.4 %; HR 0.51; 95 % CI 0.32–0.81; $p = 0.004$). Staging of intermediate-thickness primary melanomas (1.2–3.5 mm) by SN biopsy provides important prognostic information and identifies patients with early nodal metastases, whose survival may be enhanced by immediate completion lymphadenectomy.

The role of completion lymphadenectomy following a positive SN is being evaluated in a separate trial (MSLT-2) that is fully accrued and in the follow-up phase.

Despite truly widespread use of lymphatic mapping and SN biopsy, aspects of the techniques require further study to confirm that the techniques and approaches in use are best practice. One such area of interest is the use of nodal tumor burden to indicate likely prognosis and the need for additional surgery.⁶⁻¹¹ It has been proposed that patients with very small SN metastases (<0.1 mm diameter) have a favorable outcome and may not need completion lymphadenectomy.¹²⁻¹⁴ Others have not been able to confirm these claims^{10,15} which are, in any case, weakened by the fact that follow-up in the reported studies was initially short and that, predictably, recurrences and deaths have accumulated in this 'favorable' group as follow-up periods have increased. Coupled with this dilemma are concerns about the extent of nodal sampling required to accurately determine that NSNs are truly metastasis-free. Because of cost and workload concerns, NSNs are currently evaluated by examining hematoxylin and eosin (H&E)-stained sections. Studies of regional lymph nodes by immunohistochemistry^{1,16} show that most patients with tumor-positive SNs have tumor-free NSNs. Only a minority of patients have a few tumor cells in one or two NSNs. In such cases, tumor in NSNs is less than that in the SNs.

This issue of *Annals of Surgical Oncology* contains an instructive report of the outcomes of 20 patients with low-volume SN melanoma metastases.¹⁷ This study is enhanced by extended sampling of all 343 NSNs, using multiple sections and immunohistology (S-100, HMB-45 and Melan-A), a major commitment of time and resources. Metastases were detected in only 1 of 343 NSNs (0.003 %) from 20 patients (21 nodal sites)—a minute (0.18 mm diameter) subcapsular tumor. Disappointingly, outcomes for patients in this putatively favorable study group were relatively poor. At 4 years of follow-up, six patients (30 %) had developed recurrent melanoma, five (25 %) had died of melanoma, and the estimated 5-year melanoma-specific survival was 64 %. These dismal figures were reported after a relatively short period of follow-up. From the MSLT-1 experience, at least 10 years of follow-up are required to accurately determine survival/recurrence figures (and some observed patients reportedly recur nodally after 10 years). The techniques of lymphatic mapping and SN biopsy permit identification of very early metastases at a stage of tumor evolution that we have not seen previously. The corollary for that is that such metastases need considerable time to evolve to clinical detectability. Within MSLT-1, patients with minimal disease in the SNs were few, but recurrences and deaths were observed in such individuals (unpublished data). The Australian data thus provide no support for claims that patients with low-volume disease can be spared completion lymphadenectomy.

Definitive guidance on possible selective application of completion lymphadenectomy must await final analysis of MSLT-2, expected around 2019–2020.

Should we be examining all NSNs by immunohistochemistry? The data from Holtkamp et al.¹⁷ suggest that the return from such a demanding and expensive approach is likely to be very small, although they do point out that even their extended sampling of NSNs leaves most of the nodal tissue unsampled and that it is possible that more exhaustive evaluation of NSNs might identify greater numbers of undetected metastases. Molecular and/or genetic approaches may eventually resolve this dilemma and allow the identification of patients with melanoma likely to progress beyond the lymph nodes, permitting a desirably tailored approach to management.

For the present, pathologists need to determine the manner and extent of nodal sampling in consultation with their surgical colleagues. Most will likely settle for careful examination of the NSNs in well-fixed H&E-stained sections, using immunohistochemistry only where there is suspicion of micrometastases. Surgeons must decide whether it is in their patients' interests to withhold completion lymphadenectomy if the SN harbors very small melanoma metastases, knowing that data on the clinical significance of low-volume metastases are limited and conflicting.

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