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The rationale for sentinel-node biopsy in primary melanoma

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Recent articles published in this journal have questioned the value of sentinel-node biopsy (SNB) for the management of clinically localized primary melanoma.[1,2] In this Viewpoint, we discuss data that support routine SNB, an approach now widely adopted worldwide. SNB is a minimally invasive staging procedure performed at the same time as wide excision to identify the first (sentinel) melanoma-draining lymph node(s) for focused pathologic study. The SNB procedure is associated with minor morbidity.[3]

One of five patients with intermediate-thickness primary melanoma has metastases in regional lymph nodes. These small tumor foci are seldom detectable by clinical or radiologic examination. Prior to SNB there were two management alternatives, neither of which was satisfactory. Elective immediate complete lymph-node dissection (CLND) exposed all patients to morbidity but could only benefit the 20% of patients with nodal metastases. Nodal observation after wide excision avoided unnecessary CLND (i.e. for patients without nodal metastases) but committed all patients to the possibility of delayed CLND (dCLND) if nodal micrometastases became clinically detectable, sometimes 8 to 10 years later. As the sentinel node (SN) tumor status predicts nodal basin status, only patients with SN metastases need undergo therapeutic immediate CLND (iCLND); patients with tumor-negative SNs require no further nodal surgery, have prolonged survival[4] and require fewer follow-up visits.

The first Multicenter Selective Lymphadenectomy Trial (MSLT-I) randomized 1,347 patients with intermediate-thickness (1.2 to 3.5 mm) melanomas to the primary study group; 1,269 of these patients were evaluable because they accepted the assigned treatment: either wide excision plus postoperative observation, with dCLND for clinically detectable nodal recurrence; or wide excision plus SNB, with iCLND for SN metastases.[4] An additional 654 patients with lesions thinner than 1.2 mm (low risk of nodal metastases) and thicker than 3.5 mm (high risk of distant metastases at initial diagnosis) were enrolled to evaluate surgical morbidity and accuracy of the procedure,[3,4] but these patients were considered unlikely to exhibit survival differences based on modeling from the John Wayne Cancer Institute's database.

In 2006, the MSLT-I data safety and monitoring board reviewed the results of the third interim analysis and recommended publication of findings with potential significance for management decisions. Although SNB did not improve overall survival, it reduced the relative risk of recurrence at any site by 26% (hazard ratio [HR], 0.74; $P = 0.009$).[4] Particularly dramatic was the lower rate of regional nodal relapse in the SNB group (3.4%) versus the observation group (15.6%); in addition, there were fewer recurrences overall in the SNB group (20.7% versus 26.8%).[4] A recent update also shows a lower rate of distant metastases in the SNB group (18.1% versus 21.2%).[5]

Among patients with nodal metastases in the MSLT-I trial, the mean number of tumor-involved nodes was 1.4 and 3.3 for SNB and observation groups, respectively ($P = 0.001$).[4] Therefore

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the observation period allows extension of metastases within the nodal basin,[4] which correlates with increased risk of death.[6] MSLT-I demonstrated 5-year survival rates of 72.3 ± 4.6% versus 52.4 ± 5.9% when nodal metastases were managed by SNB/iCLND versus observation/dCLND (HR for death, 0.51; $P = 0.004$).[4] Among subgroups of all patients who had nodal metastases but were balanced for other prognostic factors,[4] the corresponding survival rates were 66.2% versus 52.4% (HR, 0.60; 95% CI, 0.40–0.95; $P = 0.02$) after inclusion of patients undergoing dCLND for falsely negative SNs, a group whose survival approximated that of patients undergoing dCLND after observation. By comparison, 5-year survival rates for patients without nodal metastases were 93% in SNB and 92% in observation arms; these similar rates confirm the favorable prognostic significance of tumor-negative SNs.[4]

Thomas claims a 3.8% rate of SN false-positivity in MSLT-I, based on the difference between a 19.4% rate of nodal metastasis in the SNB group (16% positive plus 3.4% false negative SNBs) and a 15.6% rate of clinical recurrence during nodal observation.[1] This comparison is inappropriate. Most metastases in the SNB group were detected by SNB at wide excision, whereas metastases in the observation group occurred during follow-up (median 48 months). As follow-up lengthens, the number of nodal relapses increases, from 78 at the third interim analysis[4] to 84 most recently.[5,7] Also, the calculation by Thomas does not consider 10% of patients who dropped out or were lost to follow-up[4] and therefore cannot be observed for evidence of nodal metastasis. The correct calculation requires Kaplan–Meier methodology, which adjusts for censored patients: the actuarial rate of nodal metastases in the SNB arm versus the observation arm was 19.4% versus 18.5% at 8 years,[4] and 20.8% versus 20.5% at 10 years.[4,7] The equivalent incidence of occult metastases in these two groups of patients who were balanced for other prognostic features[4] indicates that virtually all unresected SN metastases eventually progress and become detectable.[8]

It is not customary to expect survival benefits from a staging procedure, but Thomas[1] and Rosenberg[2] discount SNB because the third interim analysis of MSLT-I data showed no significant overall survival benefit. Survival benefits from SNB were limited to the 16% of patients with SN micrometastases who underwent a therapeutic iCLND because iCLND is performed only for SN metastases. Therefore, any overall survival benefit was likely obscured by the 84% of patients whose SNs were truly (80.6%) or falsely (3.4%) negative and who only underwent a staging SNB.[4]

Overall disease-free survival was significantly better in patients assigned to SNB versus observation (72.5% versus 64.2% at 10 years; $P = 0.005$). The possibility of recurrence is a source of great anxiety for patients,[4] and recurrence is an accepted endpoint for FDA approval of new drugs.[7,9] Also, surgical morbidity such as chronic lymphedema is substantially higher after dCLND for clinically evident nodal disease.[3,5,10]

Thomas[1] asserts that SN metastases not identified by preoperative ultrasonography are prognostically insignificant. He advocates nodal surgery only when ultrasound monitoring identifies metastases. Investigators from the Sydney Melanoma Unit and other teams report that ultrasonography rarely detects metastases smaller than 4–5 mm in diameter;[11] 64% of SN metastases in MSLT-I were less than 4 mm and 88% were less than 5 mm.[5,12] Metastases smaller than 4–5 mm are associated with favorable survival relative to larger metastases, but even tiny micrometastases can progress if unresected.[12,13] In MSLT-II, routine preoperative ultrasonography in 893 patients identified only 8 of 193 (4.2%) patients with SN micrometastases.[5] Therefore, ultrasonography as presently practiced cannot replace SNB for management of intermediate-thickness melanomas.

Most patients informed about nodal management options for intermediate-thickness melanoma select SNB, a low-risk, minimally morbid operative procedure that yields accurate staging/

prognostic information and is valuable for treatment planning. Few choose long-term nodal observation with its attendant anxiety and uncertain outcome. MSLT-I data indicate that iCLND for SN metastases improves overall disease-free survival of patients with intermediate-thickness melanoma and improves disease-specific survival of patients with nodal metastases. This highly accurate technique correctly stages the regional nodes in at least 96.6% of patients,[4] causes minimal morbidity, and well deserves its current status as the gold standard for staging patients with clinically localized, intermediate-thickness melanoma.[8,9]

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Biography

Author print biographies. DL Morton is Chief of the Melanoma Program and Director of the Surgical Oncology Fellowship Program, at the John Wayne Cancer Institute at Saint John's Health Center Professor of Surgery Emeritus, School of Medicine of the University of California at Los Angeles (UCLA). AJ Cochran is Distinguished Professor of Pathology and Laboratory Medicine and Surgery, at the UCLA School of Medicine. JF Thompson is Director of The Sydney Melanoma Unit and Professor of Surgery (Melanoma and Surgical Oncology) at the University of Sydney.

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