A Selective Approach to Regional Lymphatics in Melanoma

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The management of regional lymphatics in patients with melanoma has evolved over the past several decades from delayed lymphadenectomy, to elective resection, to the current approach which utilizes sentinel lymph node mapping to accomplish a selective approach to performing lymphadenectomy. Sentinel lymphatic mapping allows for an opportunity to demonstrate regional lymphatic disease prior to the development of lymphadenopathy. Complete resection of a nodal basin can be reserved for patients with documented disease in a sentinel node while patients with a negative sentinel node can avoid an unnecessary and potentially morbid surgery. The preliminary results of sentinel node mapping at Ochsner Medical Institutions reflect an outstanding ability to demonstrate the sentinel node in patients with trunk and extremity melanoma when radioactive colloid is used in combination with a vital blue dye. The results of sentinel node mapping in patients with head and neck melanoma have not been as reliable and require additional refinements of technique.

Surgeons have debated the optimal management of regional lymphatics in patients with malignant melanoma for the last several decades while fundamentally agreeing that when melanoma metastasizes to lymph nodes, complete excision of the entire lymphatic drainage basin is an important component of therapy. The controversy surrounds the optimal management of patients with clinically uninvolved lymph nodes. Supporters of an aggressive surgical approach claim that lymphadenectomy for high-risk patients with clinically negative nodes can maximize cure rates. A high-risk designation is based on known prognostic factors with the most important being tumor thickness. The main criticism of this aggressive surgical approach is that the majority of patients without palpable lymphadenopathy and treated by lymphadenectomy will not have disease and will therefore suffer the potential morbidity of surgery without deriving any therapeutic benefit. The debate appears to be over, however, thanks to the development of a new technique of excising and evaluating a single node to determine if melanoma has spread to a lymphatic basin. This node is considered sentinel, or representative of the entire lymph node basin, in that if melanoma is not found in the sentinel node it is not present in the remaining lymph nodes. The sentinel node biopsy technique identifies patients with lymph node disease by removing a single lymph node, a procedure with minimal associated morbidity, and allows for aggressive therapy for patients with regional metastases, while sparing patients without lymph node disease from unnecessary therapy. This report examines the evolution of lymph node surgery in the management of melanoma patients and discusses the current state-of-the-art therapy.

In 1967 the World Health Organization (WHO), a cooperative group of European and South American centers, began a randomized prospective trial designed to compare the survival of radical regional lymph node dissection with the survival of patients with extremity melanoma and no clinically apparent regional nodal disease (1). The trial was designed to evaluate the potential impact of performing radical lymphadenectomy prior to the development of clinically apparent lymph node disease compared with the standard of care which at the time called for lymphadenectomy to only be performed when palpable lymphadenopathy developed. Patients were treated by wide resection of their primary melanoma and then randomized to immediate (prophylactic) lymph node dissection, or observation of the nodal basin at risk. Radical resection was reserved only for patients who went on to demonstrate clinically apparent nodal disease (therapeutic). Proponents of the prophylactic approach to regional lymphadenectomy argued that melanoma demonstrated an orderly progression from primary site to a regional basin before becoming a systemic problem. Supporters of the therapeutic approach maintained that disease could be resected and potentially cured when it became clinically apparent in a regional basin and that most patients would never manifest nodal disease and could therefore be spared the morbidity of surgery. Patients in the study have been followed for beyond 10 years, and survival curves for these 2 groups overlap, demonstrating no advantage for prophylactic lymph node dissection (Fig 1).

The therapeutic approach to the management of lymph node disease in melanoma patients was supported by the findings of the WHO trial. Surgeons supporting a prophylactic approach reasoned that disease could be "caught" while still in regional lymphatics, before involving distant sites, and complete resection could maximize cure rates. Based on retrospective data, and intense statistical scrutiny, however, it was demonstrated that patients with intermediate-thickness melanoma were a subgroup of patients for whom a prophylactic node dissection could indeed improve cure rates (2). It was reasoned that intermediate-thickness melanoma patients were most likely to have microscopic lymph node disease that could escape clinical detection and could therefore benefit from resection (Fig 2). Patients with thinner melanomas would be unlikely to benefit from prophylactic dissection because they were unlikely to have regional microscopic disease. Patients with thicker melanomas were also unlikely to benefit from prophylactic node dissection because they were likely to harbor distant metastatic disease at the time of diagnosis and any intervention designed to treat regional disease would be ineffective. Proponents of a prophylactic approach to regional lymphadenectomy also argued that the WHO trial was flawed in its design because a survival advantage for the prophylactic approach could have been missed due to the following:

- The patients were poorly distributed with respect to ulceration of their primary lesion, an important prognostic factor that was not appreciated at the time of the study's design.
- A disproportionate percentage of women with thin extremity melanomas entered in the trial: a subgroup of patients with an improved prognosis that might not be at a sufficient survival disadvantage to demonstrate a benefit from prophylactic lymph node dissection (3).

The Intergroup trial of prophylactic lymphadenectomy versus therapeutic lymphadenectomy was designed to include only those patients considered at risk for harboring regional microscopic lymph node disease and at low risk for having distant metastatic disease (4). The Intergroup trial selected only patients with 1-4 mm melanomas. Patients with trunk melanomas had their regional lymph node basin at-risk identified preoperatively by cutaneous lymphoscintigraphy. Patients were stratified according to tumor thickness, location of primary (trunk vs. extremity vs. head and neck), and ulceration. Nearly 800 patients were entered in the study. The results of the trial were disappointing in that no survival advantage could be demonstrated for the prophylactic lymphadenectomy group. Extensive subgroup analysis revealed that patients less than 60 years of age with thinner lesions (1-2 mm) and no evidence of ulceration were the patients most likely to derive a survival benefit from prophylactic lymph node dissection.

Any further efforts to advance the cause of prophylactic lymphadenectomy were derailed by the development of sentinel lymph node mapping. This selective approach, initially described by Morton et al. in 1992, seemed to satisfy proponents of both delayed and prophylactic lymphadenectomy (5). The selective technique avoided performing potentially morbid lymphadenectomy on patients without regional disease but also allowed for an opportunity to identify patients with subclinical disease that could benefit from radical lymph node surgery. The initial description of lymphatic mapping called for an injection of vital blue dye at the primary site of a melanoma. An incision was made over the lymphatic nodal basin responsible for drainage of the injected area. The blue stained lymphatic channels could then be identified and followed to a blue stained node that theoretically would be primarily responsible, or "sentinel," for the melanoma involved skin. The technique was ideal for lesions on the extremities when the lymphatic basin at-risk (axilla or groin) was obvious. Cutaneous lymphoscintigraphy studies demonstrated that the lymphatic basin at-risk for patients with trunk melanoma (40% of melanoma patients) could not be reliably predicted without a radioscopic means of detection (6). The cutaneous injection of radioactive material also afforded an opportunity to make the sentinel node radioactive. A hand-held gamma probe could then be used in the operating room to identify the sentinel node for patients with ambiguous lymphatic drainage. The radioactive node could also be localized in a lymphatic basin with the gamma probe prior to surgery so that a small precise incision could be made directly overlying the sentinel node, further limiting morbidity. The combination of blue dye and radioactive injection allowed for a 99% ability to identify sentinel nodes (7). An initial report of 618

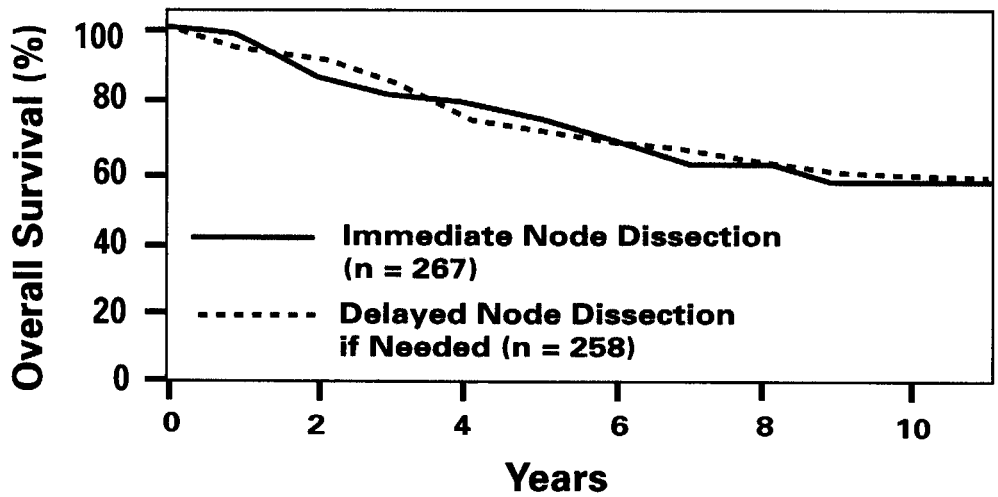

Figure 1. Overall survival in 553 Stage 1 patients according to treatment (Adapted with permission from: CANCER, 49:2424, 1982. Copyright 1982 American Cancer Society. Reprinted by permission of Wiley-Liss, Inc., a subsidary of John Wiley & Sons, Inc.)

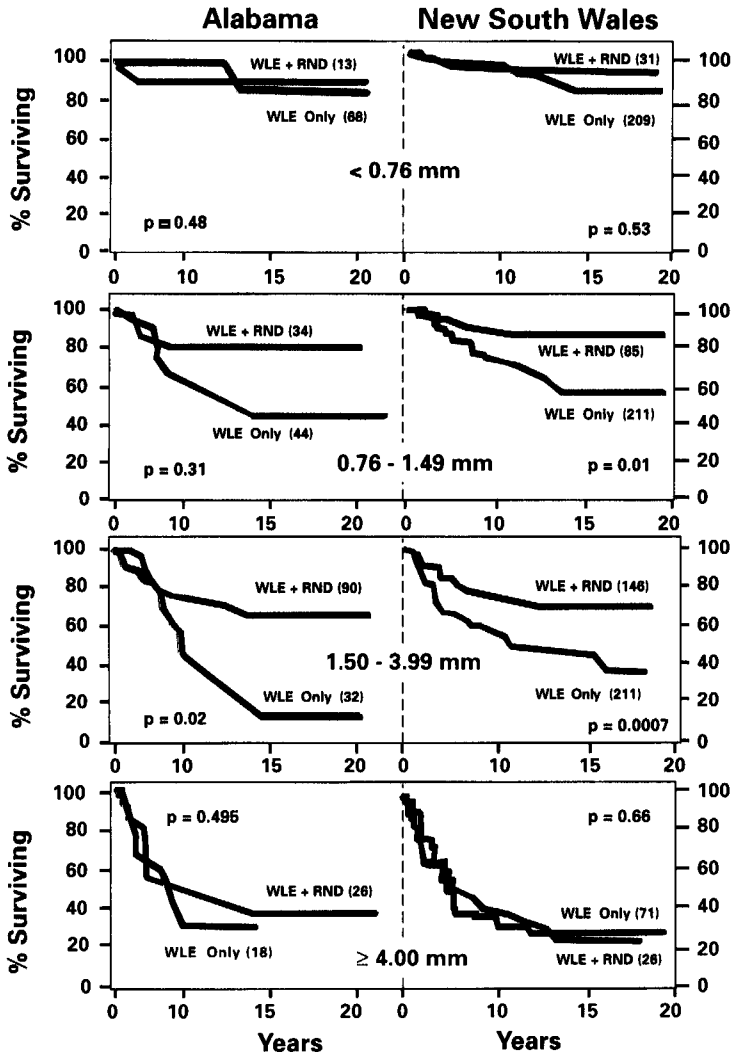

Figure 2. Actuarial survival curves calculated over 20 years for clinical stage 1 melanoma patients subdivided by thickness subgroups and their initial surgical management (WLE ± ELND). The number of patients in each group is shown in parenthesis. P values were calculated for differences between each pair of survival curves. The benefit of ELND was greatest in patients with 1.50 to 3.99 mm lesions. For 0.76- to 1.49-mm melanomas, the differences were significant only for the Australian patients. Note that the survival curves did not begin to diverge significantly until the fifth to eight postoperative years. Patients with thin melanomas (< .76 mm) and thick melanomas (4.00 mm) did not benefit from an ELND. (Reprinted with permission from: ANNALS OF SURGERY, 196:680, 1982. Copyright 1982 Lippincott, Williams & Wilkins.)

patients evaluated by sentinel node mapping, published in abstract form only, demonstrated the accuracy of the technique, specifically the ability of the sentinel node to reliably predict the presence of disease in a regional basin (8). A recent detailed evaluation of a large subgroup of these 618 patients, treated at M.D. Anderson Cancer Center, documents the accuracy of the technique and the prognosis associated with a positive sentinel node (9). The identification of a single node also afforded the pathologist an opportunity to extensively study a single node with more sensitive techniques than in a routine histologic examination, which is all that is practical in a complete lymphadenectomy specimen containing dozens of nodes. The sentinel node mapping technique therefore allowed for a very sensitive ability to stage melanoma patients.

The staging of melanoma patients took on new importance with the result of the Eastern Cooperative Oncology Group (ECOG) 1684 trial, which demonstrated that the prognosis of node-positive melanoma patients could be improved by adding interferon therapy to lymphadenectomy (10). This trial has altered the standard of care for patients with regional nodal disease and magnifies the importance of accurate staging. The ECOG 1684 trial was conducted prior to the widespread employment of sentinel node mapping, and the overwhelming majority of patients evaluated in the trial had clinically obvious regional nodal disease.

Current adjuvant trials should incorporate sentinel node mapping into their design. A new cooperative group of surgical oncologists, the Sunbelt Melanoma Trial Group, has organized a trial designed to confirm the results of ECOG 1684 and also evaluate whether patients with subclinical (non-palpable) nodal disease confined to the sentinel node will benefit from adjuvant therapy. Another question that begs to be answered is whether a sentinel node biopsy that demonstrates melanoma requires a complete lymphadenectomy. An unpublished observation from investigators involved in the Sunbelt trial is that, in the absence of palpable nodal disease, it is extremely rare to encounter nodal disease beyond the sentinel node. Therefore, sentinel nodal excision may provide the necessary staging information, and complete excision of regional disease, for patients with non-palpable nodal disease.

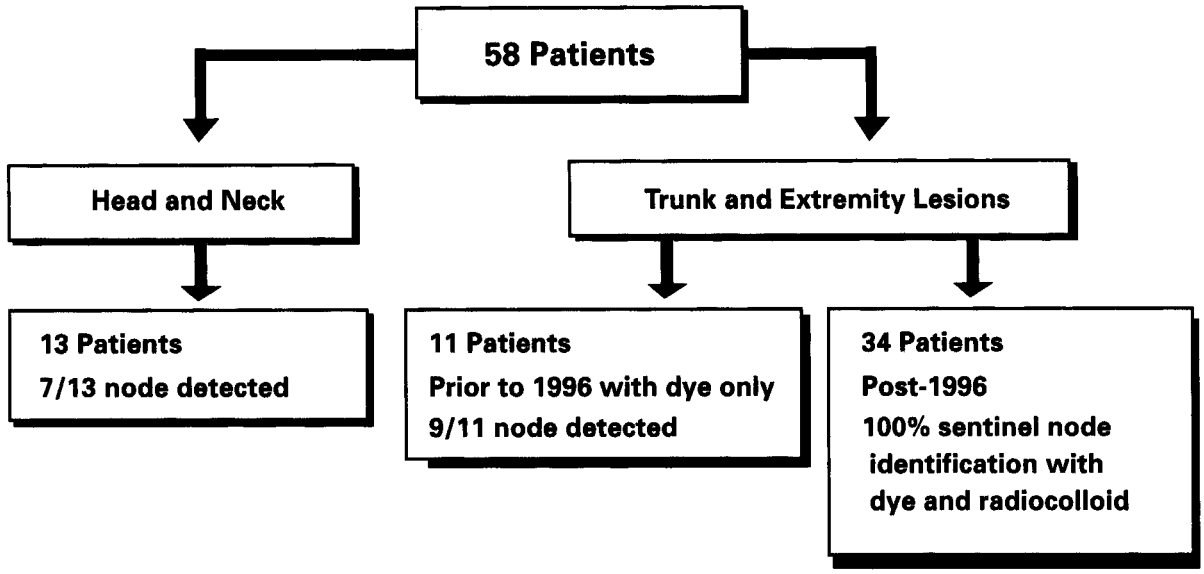

Figure 3. Summary of Ochsner experience with sentinel node mapping

At Ochsner Clinic, sentinel node mapping has been employed as the standard approach to patients with melanomas of greater than 0.76 mm thickness or Clark's level III invasion, or in cases where the depth of invasion cannot be determined. Mapping is only employed in patients without palpable node disease. From 1994 to 1998, 58 patients have been evaluated with sentinel node mapping (Figure 3). Patients can be divided into 3 groups: those with head and neck lesions (n=13), those with trunk and extremity lesions evaluated prior to 1996 (n=11), and those with trunk and extremity lesions evaluated after 1996 (n=34).

Patients with head and neck primary melanomas present a unique challenge for surgeons who perform lymphatic mapping. The rich lymphatic drainage of the head and neck results in rapid and diffuse drainage of radioactivity and dye after injection, making precise identification of the node more difficult. The experience at Ochsner with lymphatic mapping for head and neck melanoma demonstrates that a sentinel node could only be detected in 7 of 13 patients. New unpublished information from the Moffitt Cancer Center has called for the use of a lower dose of radioactivity and blue dye in the evaluation of head and neck melanoma patients. Hopefully, the use of the lower dose injection will improve our ability to provide sentinel node mapping for patients with head and neck lesions.

From 1994 to 1996, only blue dye was used to perform lymphatic mappings. Of the 11 patients evaluated during this time period with trunk or extremity lesions, 9 had successful identification of a sentinel node. Since 1996 all 34 patients with trunk and extremity lesions have had successful identification of a sentinel node by combining blue dye and a radiolabeled colloid injection.

Combining all 3 groups of patients, 50 successful sentinel node mappings have been performed at Ochsner. Ten patients have demonstrated a postive sentinel node and 2 of these patients have developed systemic recurrences. Only one patient in the group of 40 with negative mapped sentinel nodes has had a recurrence in the evaluated regional basin. In the 8 patients in whom a sentinel node could not be detected, 3 have developed systemic recurrences.

We have demonstrated an ability to reliably perform sentinel node mapping for patients with trunk and extremity lesions and will continue to attempt to improve our technique for patients with head and neck lesions. We are committed to continuing to enter our patients on cooperative group trials to generate new knowledge in the evaluation and management of melanoma patients.

The controversy regarding the management of regional lymphatics in malignant melanoma has been settled due to the development of sentinel node mapping. Advocates of prophylactic and therapeutic node dissection can be satisfied with the selective approach of sentinel node mapping because there is an opportunity for early surgical resection of subclinical regional lymph node disease and patients without lymph node involvement can be spared unnecessary potentially morbid surgery. The sentinel node provides the most powerful prognostic indicator yet for melanoma patients and will allow for selection of the most appropriate patients for future adjuvant therapy trials. The continued support for cooperative clinical trials is essential as new adjuvant therapeutic strategies are developed and tested.

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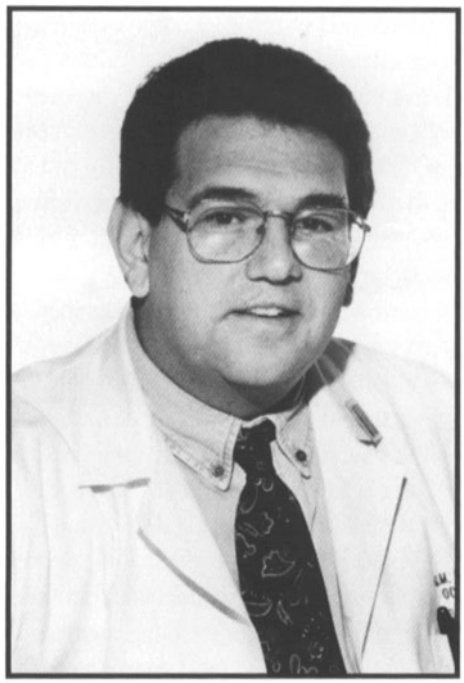

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