Role of Sentinel Node Biopsy in the Management of Malignant Melanoma

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The use of elective lymph node dissection for intermediate-thickness melanoma has remained controversial. The technique of sentinel node biopsy (intraoperative lymphatic mapping and selective lymphadenectomy) has been

Introduction

Malignant melanoma has been increasing in incidence at a rate of 4% to 6% per year and currently accounts for 3% of new cancer cases in both men and women. In 1996, an estimated 38,300 new cases of melanoma will be diagnosed in the United States, and 7,300 people will die of this disease [1]. Due to increased public awareness, patients with melanoma present at earlier stages than they did in the past. This may explain the steady improvement in overall 5-year survival, which now exceeds 80% [1].

Regional lymph nodes are the most frequent sites of metastasis of cutaneous melanoma, and the management of regional lymph nodes remains a subject of controversy. Morton and others [2] have proposed the technique of intraoperative lymphatic mapping and selective lymphadenectomy, also known as the "sentinel node biopsy," as a means of selecting patients with occult nodal metastases for therapeutic lymphadenectomy while avoiding the morbidity of this procedure in patients without nodal disease. In this article, we will review the basis for the need for selective lymphadenectomy, as well as technical considerations of and surgical results with this modality, in an effort to further define its role in the management of patients with malignant melanoma.

Role of Elective Lymphadenectomy

Prior to discussing the role of elective lymphadenectomy, a review of the staging system for melanoma is necessary. The 1993 American Joint Committee for Cancer (AJCC) staging system for melanoma is shown in Table 1. The presence of nodal metastases denotes stage III disease and carries a 5-year survival rate of 28% [3]. Therapeutic dissection is advocated in patients with stage III disease, as some of these patients may remain disease free if distant metastasis has not yet occurred.

The role of lymph node dissection in patients with stage I or II disease is less clear. Proponents of elective lymphadenectomy in these groups cite data showing improved survival in patients with occult nodal metastases when compared with patients with palpable disease [4]. Opponents stress that the majority of patients will be subjected to an unnecessary operation that is not without significant morbidity. Shaw and Koea reported 67% and 36% incidences of immediate and long-term complications, respectively, in a series of 101 lymphatic dissections. Complications were highest following groin dissection, with 22 of 52 patients experiencing long-term lymphedema [5]. Therefore, elective node dissection can be justified only if a survival advantage can be documented that offsets the morbidity of the dissection.

The risk of elective adenectomy may also be justified if prognostic information is gained that identifies patients who may benefit from adjuvant therapy. However, to date randomized trials have failed to support the routine use of adjuvant therapy for malignant melanoma. A prospective randomized trial conducted by Kirkwood et al [6] demonstrated a survival benefit from the use of adjuvant interferon-alfa-2b (Intron A). However, subgroup analysis failed to show a statistically significant survival advantage for patients with occult nodal disease on presentation. Therefore, the argument supporting the use of lymphadenectomy for staging purposes is not valid unless a benefit of adjuvant therapy can be demonstrated in patients with occult nodal disease.

Thickness of the Primary Tumor

The thickness of the primary tumor is an important prognostic factor and has been used to stratify
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patients in an attempt to determine which subgroup may benefit from an elective node dissection [7]. There is general agreement that the risk of occult metastases is very low in the presence of thin melanomas (thickness, less than .76 mm). In such cases, surgical resection of the primary tumor alone results in a cure rate more than 95%. On the other hand, patients with thick melanomas (equal to or more than 4.0 mm) not only have a high risk of regional node micrometastases (more than 60%) but also have a high risk (more than 70%) of occult distant disease [8]. These patients usually succumb to distant disease and have little to benefit from elective dissection of regional nodes. In patients with intermediate-thickness lesions (equal to or more than .76 to 4.0 mm), however, the risk of occult nodal metastases (up to 60%) outweighs the risk of occult distant metastases (up to 20%) [8]. In this group, elective node dissection may remove occult metastases prior to distant dissemination.

Two prospective randomized trials failed to demonstrate a survival benefit from elective node dissection in patients with malignant melanoma [9,10]. However, based on retrospective studies of large melanoma registries, as well as intensive review and reanalysis of data from both the World Health Organization and the Mayo Clinic [10] studies, advocates of elective node dissection continue to see a role for this therapy in the management of patients with intermediate-thickness melanoma [7,11,12].

The Intergroup Melanoma Trial, a prospective multicenter study sponsored by the NCI, is investigating the results of elective lymphadenectomy in patients with stage I and II disease. This trial has completed accrual, and results are anxiously awaited.

**Sentinel Node Biopsy**

Due to the controversy over the role of elective lymphadenectomy, a method was needed to identify those patients who have microscopic nodal metastases, and thus, who would benefit from elective node dissection. In 1992, Morton et al [2] reported on the use of intraoperative lymphatic mapping and selective lymphadenectomy as a means to this end. This technique, called "sentinel node biopsy," allows for the selective identification, removal, and evaluation of nodes draining the cutaneous melanoma and therapeutic dissection if microscopic metastases are detected. Thus, surgeons can rapidly identify those patients who may benefit from nodal dissection and spare those without metastases the morbidity of radical lymphadenectomy.

**Technique**

Sentinel node biopsy involves the use of cutaneous lymphoscintigraphy to identify areas of primary lymphatic drainage for ambiguous sites, such as the trunk or shoulders. For lesions on the extremity, lymphoscintigraphy is unnecessary. Previous studies by Norman et al [13], demonstrated that cutaneous drainage patterns identified by lymphoscintigraphy are discordant from predicted drainage patterns in 63% of patients with head and neck melanoma and 32% of those with primary lesions on the trunk. This series has been updated to over 500 patients with a mean follow-up of 4 years; no nodal recurrences have occurred in a lymphatic basin that was not identified by preoperative scanning [14]. If lymphoscintigraphy identifies multiple drainage basins, all should be addressed (Figure 1).

Prior to surgery, patients are asked to provide informed consent for possible radical node dissection in the event that microscopic metastases are detected. After induction of general or local anesthesia, a 25-gauge needle is used to inject 2 to 3 mL of isosulfan blue or patent blue-V dye intradermally at the site of the melanoma. If the lesion has been previously excised by excisional biopsy, the injection is made on either side of the scar. This technique cannot be applied following wide excision of the tumor, as the lymphatic drainage is altered.

An incision is made over the lymphatic basin and careful dissection is continued perpendicular to the skin until a lymphatic containing blue dye is identified. When a blue-stained lymphatic is found, it is followed to identify the blue-stained sentinel node (Figure 2). Exploration around this node may reveal other sentinel nodes. The sentinel node or nodes are sent for frozen-section and rapid immunohistochemical analysis. While these analyses are being performed, the primary melanoma may be removed.

Pathologic handling of the specimen involves bisecting the lymph node and using half for frozen section and permanent hematoxylin and eosin (H & E) staining while the other half is processed for immunohistochemical staining for S-100 protein and the melanoma-reactive monoclonal antibody NK1/C3. If metastases are detected, radical lymphadenectomy is performed. If no metastases are present, the incision is closed. If permanent specimens reveal metastases not detected on frozen section, the patient undergoes lymphadenectomy subsequently (Figure 3).
Results
The largest experience with sentinel node biopsy was reported by Morton et al [2]. In their series of 237 patients, intraoperative lymphatic mapping identified the sentinel node in 194 patients (82%). In most patients (73%), one node was identified. Two sentinel nodes were identified in 20% of the lymphadenectomy specimens, and three or more sentinel nodes were found in 8%. Success varied depending on the site of the body, with the highest success reported for the groin. The lowest success rate was reported for an arm tumor draining to the axilla and a shoulder lesion draining to the neck.

In a series of 88 patients at Roswell Park Cancer Institute, the sentinel node was identified in 90% of patients overall. Success rates for the axilla and groin were 87% and 100%, respectively [15]. There appears to be a learning curve associated with sentinel node biopsy. Morton et al [2] analyzed the success rate between the first half and second half of each surgeon's cases and noted an improvement in the more recent time period. They concluded that substantial experience is needed to develop the skills necessary to perform this technique.

In Morton's study, all patients underwent a lymphadenectomy to determine the accuracy of the sentinel node biopsy technique. As mentioned above, the sentinel node was identified in 194 of 237 lymphadenectomy specimens in this series. Metastases were noted in 40 (21%) of these specimens. For lesions less than 1.5 mm in thickness, metastases were observed in 9.7% of the specimens. This compared with an incidence of metastatic disease of 36.6% for tumors more than 1.5 mm in thickness.

Routine H & E staining detected 23 of these metastases, whereas immunohistochemical staining alone revealed metastatic tumor cells in 17. Thus, immunohistochemical staining is more sensitive than conventional histologic examination. In 30 patients, metastases were detected intraoperatively, while in 10 patients metastases did not become apparent until permanent sections were available. In only two cases were tumor cells identified in nonsentinel nodes, demonstrating that nodal metastases occur in a nonrandom manner.

In a cooperative study of 132 patients conducted at the University of South Florida, Duke, and M. D. Andersen Cancer Center, only 2 patients (1.5%) have developed recurrences following a negative sentinel node biopsy. Both H & E and immunohistochemical staining were negative in these patients. However, both of these nodes were submitted for reverse transcriptase-polymerase chain reaction (RT-PCR) for tyrosine gene products and were found to be positive, suggesting that abnormal cells were present but were missed by the conventional staining techniques. Thus, they may not have been true skip metastases [14].

Morton et al have also described the use of sentinel node biopsy for head and neck melanomas [16]. In this series of 72 patients with clinical stage I melanoma, the sentinel node was accurately identified 90% of the time. No nonsentinel nodes were the sole site of metastasis. Thus, the false-negative rate was 0. At a mean follow-up of 27 months (range, 10 to 56 months), no regional failures have been observed.

Complications associated with the lymphatic mapping technique are infrequent and minor. These consist of passage of dye in the urine for 24 hours and tattooing of the skin, which may persist for a few months.

Results With Radiolymphoscintigraphy
A more recent modification of the sentinel node biopsy technique involves the intraoperative use of a gamma probe to guide detection of the sentinel node [17]. In this modified technique, termed "radiolymphoscintigraphy," technetium-99m sulfur colloid or albumin is injected intradermally 15 minutes to 24 hours prior to surgery. A "hot spot" (defined as an area with at least 15 counts in 10 seconds and a ratio three times that of the background radiation level) signifies the site of a sentinel node. A small incision is made over the hot spot, and dissection is continued guided by the gamma probe (Figure 4).

Krag et al [18] utilized the hand-held gamma camera to identify the sentinel node in a series of 121 patients. Of these, 118 patients (98%) had successful resection of the sentinel node. Blue dye also was injected in 44 patients. In all 44 patients, the radiolabeled node was identified, and in 4 patients, blue dye was not identified in any node. All blue-stained nodes were radiolabeled. Interestingly, the sentinel node was located outside typically named nodal groups in four patients: one deep to the mid-clavicle, one within the neurovascular bundle under the 12th rib, and two in the popliteal fossa. Thus, Krag et al concluded that the gamma probe-guided technique is more sensitive than the dye technique.

Albertini et al [19] used radiolymphoscintigraphy for sentinel node identification in a series of 106 patients. These researchers injected 400 mCi of technetium-99m sulfur colloid mixed with .5 to 1.0
mL of isosulfan blue dye intradermally at the site of the primary tumor either in the operating room or 4 hours prior to the procedure. One or more sentinel nodes were identified in 96% of patients. Metastatic disease was found in 16 patients, 14 of whom underwent a lymph node dissection. Of the 25 sentinel nodes from these patients, 18 had metastatic involvement. In contrast, metastases were found in only 1 of the 228 nonsentinel nodes in these specimens. These findings confirmed the accuracy of radiolympho-scintigraphy in detecting nodes at risk for metastases. The yield was higher when the injection was performed 4 hours prior to surgery, which mirrors our experience at Roswell Park.

Albertini et al also compared the dye and radiolabeled techniques. They reported that using dye alone, an 80% success rate would have been achieved, as compared with an 84% rate for the radiolabeled technique. The methods were complementary, and a combined success rate of 96% was noted.

**Criteria for Sentinel Node Localization**

In their report on the series from the University of South Florida, Albertini et al [19] proposed criteria for sentinel lymph node localization:

1) Any node with blue-staining afferent lymphatics draining into a blue-stained node is, by definition, a sentinel node.
2) An in vivo hot spot-to-background ratio of at least 3:1 or an ex vivo ratio between a sentinel node and a nonsentinel node of at least 10:1 is a minimum acceptable criteria for sentinel node identification.
3) All attempts should be made to locate additional sentinel nodes if the hot spot-to-background ratio remains above 150%.

**Pros and Cons of the Radiolabeled Technique**

Several aspects of the radiolabeled technique have been criticized. First, not all radioactive nodes in the operative field may be sentinel nodes. Radioactive tracer passes first to sentinel nodes and then to nonsentinel nodes. Thus, the delay between injection and operation significantly affects the number of perceived sentinel nodes. Resection of multiple radiolabeled nodes may involve an extensive dissection and violate the planes of a standard lymphadenectomy. Furthermore, McCarthy et al [20] have criticized the choice of radiolabeled agent. They report that both technetium-99m sulfur colloid and albumin tend to have large particles that migrate poorly. These agents may also underestimate the number of draining nodal basins. These authors advocate the use of antimony trisulfide colloid labeled with technetium-99m, as it is smaller and allows for rapid migration through lymphatics but is still trapped within the lymph nodes. Further work is needed to identify the optimal agent.

Other practical concerns with the use of the gamma probe include the use of radioactive material in the operating room and the cost of the probe. The role of this technology is emerging. Advocates report that with the use of the gamma probe, dissections are more focused and conservative and yield an increased number of nodes. Opponents doubt the significance of these non-dye-stained but radiolabeled nodes. At Roswell Park Cancer Institute, we are currently investigating the use of radiolabeled sentinel node biopsy. Although its role remains undefined, gamma probe-guided node localization is likely to be complementary to the dye technique.

**Conclusions**

The accuracy of intraoperative lymphatic mapping in identifying the sentinel node has been demonstrated. However, the utility of this technique remains to be determined. There are obvious advantages of this technique as a staging procedure when compared with routine lymphadenectomy. The morbidity of intraoperative lymphatic mapping is low. Also, selective lymphadenectomy permits the removal of metastases at a time when the tumor is likely to be confined to the regional lymphatic basin, and thus, the systemic tumor burden is small. The 5-year survival rate of patients undergoing lymphadenectomy for gross nodal disease is 15% to 20%, while that of patients undergoing lymphatic dissection for microscopic metastases is 50% to 60% [14]. Lead time bias or an apparent increase in survival due to earlier detection of disease may account for some of this difference, however, and the benefit of elective node dissection has not been proven in prospective randomized trials. Thus, the detection of microscopic metastases in lymph nodes, especially by immunohistochemical staining, does not, by itself, justify the technique or the use of lymphatic dissection in these patients.

Currently, the application of sentinel node biopsy should be limited to clinical trials. A major
international randomized trial of lymphatic mapping and selective lymphadenectomy is underway that addresses the issues cited above. Patients in one arm will undergo sentinel node biopsy with lymphadenectomy if the sentinel node is "positive" in addition to wide excision of the melanoma, whereas patients in the control arm will undergo wide excision alone. The results of this trial, if favorable, may allow melanoma care to become more rational and conservative and spare many patients major morbidity.

References:

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