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Surgical Management of Regional Lymph Nodes in Patients with Melanoma

Experience with 4682 Patients

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Objective

The purpose of this study was to evaluate a large number of patients with cutaneous melanoma who had or who were at risk for lymph node metastases to contribute to the understanding of the behavior of and appropriate management of draining nodes. A major goal of the study was to reassess the clinical impact of elective lymph node dissections (ELND) in a large patient population.

Summary Background Data

Large retrospective studies suggest that ELND may improve the prognosis of patients with intermediate-thickness melanomas; however, that improvement has not been observed in two randomized prospective controlled trials.

Methods

The charts of 4682 patients treated at a single institution for localized or regional disease were reviewed individually. The median follow-up was 4.7 years, with 814 patients followed more than 10 years. The data were tabulated and evaluated with the aid of a computer data base system.

Results

Among patients with nodal metastases, 10% of nodal metastases were to contralateral nodes, and 6% were to nodal basins that would not be predicted by classic models of lymphatic drainage; in 13% of patients, nodal metastases occurred to greater than one nodal basin (3% of the entire study group). For all thickness ranges, the incidence of nodal metastases was comparable to the incidence of distant metastases; intermediate-thickness lesions had no relative predilection for nodal metastases. At the initial evaluation, regional nodal basins were clinically negative in 3550 patients, of whom 911 (25.7%) underwent ELND. Stratified into five thickness groups (< 0.76 mm, 0.76 to 1.5 mm, 1.5 to 2.5 mm, 2.5 to 4 mm, and > 4 mm), pathologically positive nodes were identified in 0%, 5%, 16%, 24%, and 36%, respectively (16% overall). Among the 911 patients who underwent ELND, 214 (23%) had nodal metastases, 143 at the time of ELND and 71 at a later date. Of these 71 patients, 31 (44%) had nodal metastases in a previously dissected nodal basin, and 40 (56%) had them in basins not previously dissected. The survival of patients with clinically negative nodes treated with and without ELND were compared. The two groups were well matched for major prognostic factors. Stratified by Breslow thickness and primary site, no significant improvement in survival was observed with ELND.

Conclusions

Because of the significant incidence of metastases to contralateral and atypical nodal basins, lymphoscintigraphy may be justified for the preoperative evaluation of patients for ELND. However, the therapeutic value of ELND is questionable as a result of (1) the finding that the risk of nodal metastases is not relatively more common than is that of distant metastases among patients with intermediate-thickness melanomas, (2) the fact that only 16% of ELND were positive, (3) the finding that ELND may not prevent recurrent nodal disease in the dissected basin, and (4) the absence of any apparent impact on survival among patients who underwent ELND.

The most common first site of metastasis among patients with melanoma is the regional nodal basin.[1] In the majority of these patients, the nodes are clinically negative at the time of initial diagnosis but harbor occult metastases. The high likelihood of occult nodal metastases at the time of initial diagnosis has prompted the use of elective lymph node dissection (ELND) as a therapeutic modality intended to prevent subsequent regional and distant dissemination. Despite the frequent use of ELND, however, its therapeutic value is unconfirmed.

The argument for ELND depends on assumptions that (1) micrometastases to regional nodes may exist in the absence of systemic micrometastases, (2) removal of nodal metastases while they are microscopic prevents subsequent distant metastases,[2] and (3) ELND prevents subsequent nodal metastases in the dissected basin. If those assumptions are valid, the therapeutic value of ELND also depends on proper patient selection and accurate identification of draining nodal basins. Large retrospective studies suggest that ELND may improve the prognosis of patients with intermediate-thickness melanomas,[3–5] but that improvement has not been observed in two randomized prospective controlled trials.[6–8] The prospective trials have been faulted for their inclusion of disproportionate numbers of certain subgroups of patients. A third prospective controlled trial is being coordinated through the Intergroup Melanoma Committee of the National Cancer Institute.[2] At the time of writing, the results of that trial are pending. A major goal of the present study was to reassess the clinical impact of ELND in a large patient population.

In support of the belief that regional nodal metastases may exist in the absence of systemic metastases, it was reported that patients with intermediate-thickness melanomas have a high probability of regional nodal metastases developing within 3 years but a low risk of distant metastases within 5 years.[9] In light of the long interval to distant metastases in a large subset of patients,[10,11] re-evaluation of this observation with a large patient group and longer follow-up is in order. The present work will address this issue in the interest of re-evaluating the validity of the rationale for ELND.

A goal of ELND is the removal of nodal tissue at risk for metastasis; however, we have observed that patients, after ELND, may have clinical nodal metastases in the same basin. The risk of recurrent disease in a microscopically involved basin after ELND has not been well defined but has a bearing on our understanding of the effectiveness of ELND in the removal of tumor-involved nodes. The incidence and prognostic implication of recurrence in a previously dissected nodal basin will be examined in this report.

The identification of nodal basins at risk has attracted attention recently; there has been a resurgence of interest in preoperative lymphoscintigraphy in several major centers. Since Sappey's[12] description of the classic patterns of cutaneous lymphatic drainage, it has widely been held that the lymphatic drainage of cutaneous lesions followed clinically predictable patterns, except for small areas of ambiguous drainage within 5 cm of the midline and within 5 cm of Sappey's line across the lower trunk. The recent experience with lymphoscintigraphy suggests that the areas of ambiguous drainage are more extensive that previously suspected[13] and that 57% of patients with primary melanomas on the trunk or head and neck will have two or more draining nodal basins.[14] However, clinical experience suggests that, before the development of widely disseminated disease, it is uncommon for a patient to have regional nodal disease in more than one basin. To provide a background against which to judge lymphoscintigraphy's clinical relevance, the present report endeavors to define the frequency of metastases to unanticipated nodal basins and to define the incidence of nodal metastases to more than one nodal basin.

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Any retrospective study of ELND is subject to criticism. However, a retrospective study of several thousand patients, as in the present study, has the advantage of permitting the evaluation of multiple subgroups, each of which includes a large number of patients, with similar clinical characteristics. Although this study, at the outset, is not presented as a substitute for well-controlled randomized data, it is presented in the context of existing data in the hope that it may contribute to a resolution of the controversy regarding ELND for melanoma and that it may contribute to a broader understanding of the natural history of lymph node metastases.

In summary, the purpose of the present study was to evaluate a large number of patients who had or were at risk for lymph node metastases to contribute to our understanding of the behavior and appropriate management of draining nodes. Those questions on which the present study focused were those in which the least data and/or the least consensus existed. The specific questions addressed were (1) do these data confirm previous observations that patients with intermediate-thickness melanomas are at greater risk of nodal metastases than of distant metastases, (2) how accurate is the clinical impression in identifying nodal basins at risk, (3) how often was more than one regional nodal basin involved with tumor before there was evident distant dissemination, (4) what is the risk of recurrent nodal metastases after lymphadenectomy and what is its prognostic implication, and (5) what is the impact of ELND on the survival of patients with clinically negative nodes.

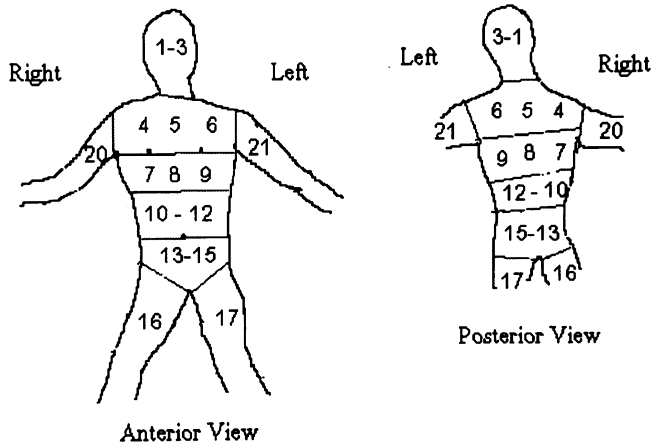

Figure 1. Somatic regions of primary melanomas. The primary sites of melanomas were grouped into the regions shown: regions 1 to 3 are the head and neck, 4 to 6 are the shoulders and upper chest, 7 to 9 are the upper trunk, 10 to 12 are the lower to middle trunk, and 13 to 15 are the pelvis. In each case, these three numbers represent right-sided, midline, and left-sided lesions, respectively. The right lower, left lower, right upper, and left upper extremities are regions 16, 17, 20, and 21, respectively. The division between regions 10 to 12 and regions 13 to 15 is Sappey's line. Lesions whose location could not be ascertained clearly from the patient records were not included in this classification scheme.

METHODS

Subjects

The patients treated for melanoma at Duke University were evaluated, and their characteristics were recorded prospectively in the Duke Cancer Center Data Management Unit (Morris Building, Duke University Medical Center, Durham, NC). The primary lesions were managed with wide excision. ELND was principally reserved for patients with intermediate-thickness melanomas; however, some patients in all thickness ranges underwent ELND. Regional nodes were often managed by the patient's local surgeon, which resulted in a variety of management approaches. Lymphoscintigraphy was performed only in a small minority of patients, and it was not specifically evaluated for this report. A majority of patients underwent adjuvant specific active immunotherapy.[15] In patients in whom metastatic disease developed, limited metastases were surgically extirpated, and disseminated disease was managed with multidrug chemotherapy. The patients were followed regularly after the diagnosis was made, and their outcomes were recorded in the data base.

From a data base of more than 8000 patients, exclusions were made for multiple, mucosal, ocular, or unknown primary lesions; unknown thickness of the primary lesion; presentation with distant metastases; initially incorrect histologic diagnoses; and insufficient data. After these exclusions, 4682 patients with localized or regional disease were included in the study. Their charts were reviewed individually. Clinical data were confirmed, corrected, or added to the existing data base. Particular attention was paid to the clinical status of the draining nodes. There were a number of patients for whom the records did not clearly document that the nodes were clinically positive or negative, and these were recorded as clinically unknown. Others were recorded as clinically suspicious, possibly reactive, or possibly malignant. Only those that were clearly negative by clinical examination were included in the evaluation of ELND. Particular attention was paid also to the site of the primary lesion; these were grouped into regions (Fig. 1) based on the expected nodal drainage patterns. Every intervention regarding regional nodes was recorded, including complete node dissections, fine-needle aspirations, and excisional biopsies. The management of nodal basins was recorded in a format that permitted us to group together distinct procedures that were linked to the definitive management of a specific clinical situation. As an example, a patient had a palpable axillary node

Table 1. CHARACTERISTICS OF THE PATIENT POPULATION

Number	4,682
Mean age at diagnosis	47.7 yrs.
Male:female ratio	1.14
Race: caucasian	99.2%
Primary site	
Trunk	43%
Extremity	37%
Head and neck	17%
Acral	3%
Breslow thickness	
<0.76 mm	16%
.76–1.5 mm	34%
1.5–2.5 mm	23%
2.5–4 mm	14%
>4 mm	11%
Ulceration present	24%
Median followup (yrs.)	4.7 yrs.
No. of patients followed >10 yrs.	814
Recurrent disease	41%
Mortality	27%

Table 2. SEQUENCE OF THERAPEUTIC AND DIAGNOSTIC PROCEDURES PERFORMED ON REGIONAL NODES AFTER EXCISION OF THE PRIMARY MELANOMA

	Number Performed*					
Procedure	**1st**	**2nd**	**3rd**	**4th**	**5th**	**6th**
Complete LND	2074	128	17	0	0	1
Excisional biopsy only	174	183	44	7	2	0
Biopsy, followed by complete LND†	116	13	3	0	0	0
FNA only	42	60	11	8	1	0
FNA followed by complete LND†	64	10	1	0	0	0
Unclear or other‡	31	11	0	0	0	0
Total procedures	2501	405	76	15	3	1
Total no. of patients	2411	395	70	15	3	1

* Therapeutic and diagnostic procedures performed on regional nodes are recorded in the order they were performed. For 101 patients, there were two or more procedures performed simultaneously on more than one nodal basin.

† When a complete LND was performed as a result of an initial biopsy or FNA, the sequence of procedures is recorded as a single event. When they were performed as independent events in response to distinct clinical situations, they were recorded as two events.

‡ This includes patients in which the extent of LND was partial or unclear from the patient record.

that underwent biopsy and was found to be metastatic; the surgeon decided, as a result, to perform a complete node dissection of the same basin. This was considered one management scenario; two separate clinical management events were recorded when a patient had a negative excisional biopsy result of a reactive node and, then, years later, had a therapeutic node dissection of the same basin for metastatic disease. The details of each management scenario were recorded.

Statistical Evaluation

Survival curves were constructed using Kaplan–Meier estimates.[16] Differences in survival distributions were tested with the Cox–Mantel (log-rank) statistic.[17]

RESULTS

The study population included 4682 patients with a mean age of 48 years at diagnosis, followed for a median of 4.7 years. The median follow-up of living patients was 5.5 years. Eight hundred fourteen patients were followed more than 10 years. There was recurrent disease in 41%, and the overall mortality rate was 27%. The details of the patient population are listed in Table 1.

Management of Regional Nodes

The management of regional nodes took several forms, ranging from a clinical examination only to full lymph node dissection. Almost one half of patients (2271 of 4682) never had any surgical or cytologic evaluation of regional nodes. The first procedures performed on lymph nodes in this population amounted to 2501 procedures in 2411 patients. Ninety percent (90%) were complete LND, including 7% who had fine-needle aspiration or excisional biopsies as a preliminary diagnostic step before LND. An additional 9% had either fine-needle aspiration or excisional biopsies only, without complete LND. Among the 2411 patients who had a first lymph node procedure, only 395 (16%) had a subsequent lymph node operation. Subsequent nodal management was progressively less likely to involve complete nodal dissections. These observations are summarized in Table 2.

ELND

Among the 4682 patients in the study population, the regional nodes were clinically negative in 76% (3550 patients). Of these, 911 (26%) had ELND, whereas the remainder did not. The initial clinical status and surgical management of these nodal basins is defined in Table 3. Among the 911 patients, 929 ELND were performed. ELND was performed on 1 nodal basin for 894 patients,

Table 3. INITIAL LYMPH NODE EVALUATION AND SURGICAL MANAGEMENT

Initial Assessment	No. of Patients
Clinically negative	3550
No LND	2639
ELND done*	911
Clinically palp, uncertain significance	112
No LND	83
LND done	29
Clinically positive	295
No LND	0
Therapeutic LND	295
Clinical status unknown	719
No LND	402
LND done	317

* 929 ELND performed in 911 patients included full LND in 899 patients (97%), and partial LND or excisional biopsy of nodes in 25 patients (3%).

2 basins for 16 patients, and 3 basins for 1 patient. Of these, 899 (97%) were complete LND, and 25 (3%) were partial node dissections or excisional biopsies. The extent of the ELND was undefined for five patients.

The 929 ELND were evaluated for the yield of positive nodes in each. Stratified by the thickness of the primary lesion, the percent positive nodes was 0% for those less than 0.76 mm and 36% for melanomas greater than 4 mm in thickness. These data are presented in Figure 2.

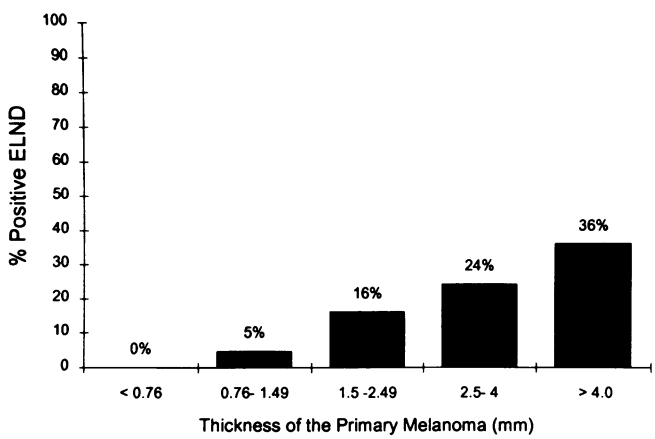

Figure 2. The results of ELND. For melanomas < 0.76-mm thick, 0 of 43 ELND performed in 43 patients were positive. For melanomas 0.76 to 1.49 mm in thickness, 14 of 298 ELND performed in 295 patients were positive. For melanomas 1.5 to 2.49 mm in thickness, 47 of 291 ELND performed in 284 patients were positive. For melanomas 2.5- to 4.0-mm thick, 45 of 186 ELND performed in 182 patients were positive. For melanomas > 4-mm thick, 40 of 111 ELND performed in 107 patients were positive. The total results were 146 of 929 ELND (16%) performed in 911 patients were positive.

Table 4. SITES OF FIRST AND SECOND METASTASES

	First (%)	Second (%)
Local skin	15	19
Nodes	60	25
Distant skin	5	12
Lung	8	15
Liver	3	7
CNS	3	10
Bone	1	4
GI	1	2
Other	4	6

The overall yield of positive nodes in ELND was less than 16%.

Metastatic Patterns

The sites of first and second metastases are listed in Table 4. Sixty percent of first metastases were to regional nodes, whereas only 25% of second metastases were to regional nodes. Local and distant skin, regional nodes, and the lung, together, accounted for 88% of first metastases and 71% of second metastases.

Stratified by the thickness of the primary lesion, the percentages of patients in whom regional nodal metasta-

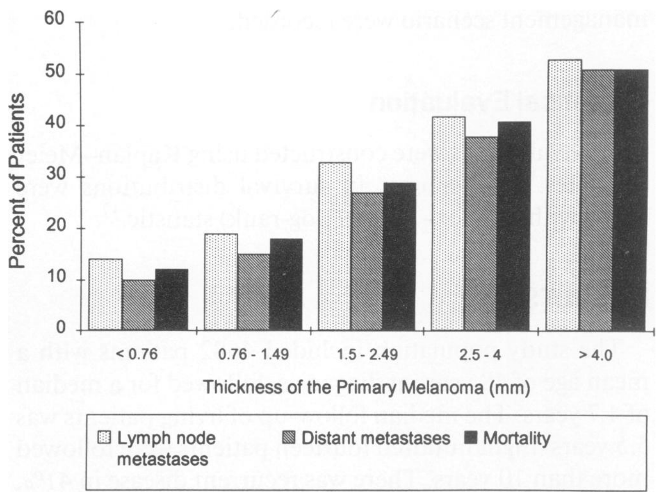

Figure 3. Risk of regional and distant failure by thickness. The percentage of patients in whom lymph node metastases developed during the follow-up period is shown for each of five thickness ranges. These closely match the percentage of patients with distant metastases and the mortality rate. For the five thickness ranges (< 0.76, 0.76 to 1.49, 1.5 to 2.49, 2.5 to 4, and > 4 mm, respectively), the numbers of patients were 769, 1612, 1091, 676, and 534, and the median follow-up periods were 5.0, 5.4, 4.8, 3.8, and 3.2 years.

Table 5. NUMBER OF NODAL BASINS INVOLVED PRIOR TO DISTANT METASTASES

No. of Nodal Basins Involved Prior to Distant Metastases	No. of Patients (%)
0	3410 (73%)
1	1106 (24%)
2	154 (3%)
3	12 (0.3%)
4	1 (<0.1%)

ses and distant metastases developed throughout their clinical course were recorded. These data are presented in Figure 3. These data reflect the experience in all 4682 patients, during a median follow-up of 4.7 years, including 814 patients followed for more than 10 years. The incidence of distant metastases closely mirrored the incidence of regional metastases. The mortality rate paralleled the metastatic rate. For no thickness range was there a disproportionately higher incidence of regional metastases as opposed to distant metastases.

The Incidence of Metastases to Two or More Nodal Basins

To assess the number of regional nodal basins in which metastatic disease might need to be addressed by surgical extirpation, those nodal metastases that appeared before distant dissemination were determined. Among the 4682 patients, only 3% had involvement of more than one nodal basin before distant dissemination (Table 5). Subdividing by site, the incidence of metastatic disease to more than one nodal basin was 2.5%, 4.3%, and 10.8%, respectively, for extremity, lateral axial, and midline lesions. As the proportion of those patients in whom nodal metastases developed, those with metastases to two or more basins amounted to 10%, 16%, and 34%, respectively.

Identification of the Nodes Draining Each Cutaneous Region

The somatic sites in which melanomas arose included all cutaneous areas. The recorded data on the majority of these sites was adequate to identify a specific region of origin. These are illustrated in Figure 1 and are listed in Table 6, along with the number of positive nodal sites and the percentage of positive basins that were contralateral or that were atypical for those sites. In calculating the percentage of contralateral nodal metastases, it should be acknowledged that many lesions were at or near the midline (within approximately 5 cm). They were recorded as midline lesions; metastases were considered contralateral only if the primary was clearly not a midline lesion. The overall rate of contralateral nodes was 10.5%. For extremity lesions, it was approximately 5%. Six percent (6%) of nodal metastases were to sites considered atypical. Examples include axillary metastases from the pelvis and inguinal metastases from an upper extremity.

The specific sites of lymph node metastases from melanomas of each cutaneous region are defined in Table 7. The majority of nodal metastases were to major draining basins, but metastases to other basins were identified in a significant proportion of cases. As detailed in Table 6, a small but significant percentage (6%) of patients had nodal metastases in sites that might not be predicted, usually, to have any role in draining the tumor site.

Recurrent Disease After Lymph Node Dissection

Among the 911 patients who underwent ELND, 214 (23%) developed nodal metastases: 143 (16%) at the time

Table 6. SUMMARY OF METASTATIC NODAL INVOLVEMENT

Region	No. of Patients	No. of Positive Nodal Sites	Percent Contralateral	Percent in Atypical Nodal Basins	Atypical Sites of Tumor-Involved Nodes
Head and neck	656	216 in 169 pts. (26%)	8	4	Axilla
Shoulders	1380	536 in 415 pts. (30%)	18	7	Inguinal, iliac, breast
Upper trunk	369	166 in 130 pts. (35%)	7	9	Epitrochlear, inguinal
Lower-mid trunk	261	132 in 98 pts. (38%)	12	2	Neck, breast, submandibular
Pelvis	78	46 in 35 pts. (45%)	7	17	Axilla
Lower extremity	1112	389 in 311 pts. (28%)	6	5	Axilla, neck, supraclavicular
Upper extremity	737	184 in 147 pts. (20%)	3	4	Neck, inguinal
Total	4593	1669 in 1305 pts. (28%)	176 (10.5%)	93 (6%)	

Table 7. NODAL METASTASES OF MELANOMA FROM EACH CUTANEOUS REGION

Nodal Basin Involved	No. of Patients	Percent
Head and neck		
Anterior Neck or Neck, NOS	143	66
Posterior Neck	24	11
Supraclavicular	4	2
Axilla	8	4
Intransit	4	2
Parotid (2 include neck dissection)	25	12
Submandibular	1	<0.1
Submental	7	3
Total	216	100
Shoulders		
Neck	54	10
Supraclavicular	36	7
Axilla	409	76
Inguinal/Iliac	33	6
Breast	1	<1
Other	3	1
Total	536	100
Upper to mid trunk		
Neck	1	1
Supraclavicular	2	1
Axilla	134	81
Epitrochlear	2	1
Inguinal	13	8
Intransit	14	8
Total	166	100
Lower mid trunk		
Supraclavicular	1	<1
Axilla	75	57
Inguinal	46	35
Iliac	2	2
Intransit	5	4
Neck	1	<1
Submandibular	1	<1
Breast	1	<1
Total	132	100
Pelvis		
Axilla	8	17
Inguinal	34	74
Iliac	4	9
Total	46	100
Lower extremity		
Neck	4	1
Supraclavicular	2	<1
Axilla	12	3
Inguinal	322	83
Iliac	39	10
Popliteal	2	<1
Intransit	7	2
Obturator	1	<1
Total	389	100
Upper extremity		
Neck	6	3
Supraclavicular	3	2
Axilla	154	84
Epitrochlear	8	4
Inguinal	1	<1
Intransit	10	5
Breast	1	<1
Subclavian	1	<1
Total	184	100

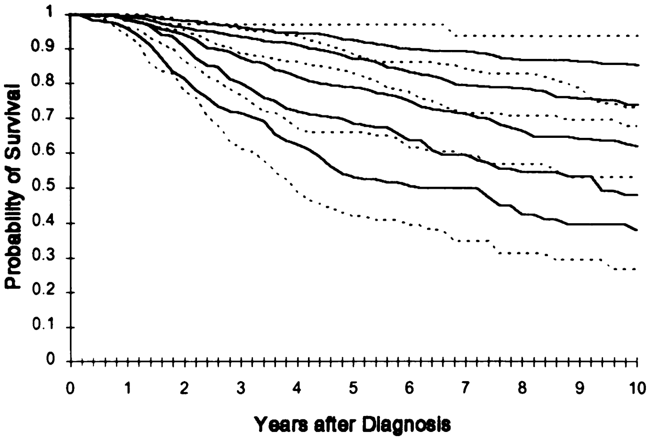

Figure 4. Kaplan-Meier survival curves for five thickness ranges, with and without ELND. Kaplan-Meier estimates of the survival rates of patients with melanoma are plotted for the first 10 years after the diagnosis. The five solid lines represent the survival rates of patients with tumors in the five thickness ranges treated with wide local excision only; the five dotted lines represent the survival rates of the patients in the same five thickness ranges treated with wide local excision and ELND. The five thickness ranges are < 0.76 mm, 0.76 to 1.49 mm, 1.5 to 2.49 mm, 2.5 to 4 mm, and > 4.0 mm. With increasing thickness, there was a progressively poorer prognosis. In no thickness range was ELND associated with significantly improved survival rates. Five-year survival estimates for wide local excision only and ELND only, respectively, were: for lesions < 0.76 mm, 92% and 94%; for lesions 0.76 to 1.49 mm, 87% and 89%; for lesions 1.5 to 2.49 mm, 79% and 83%; for lesions 2.5 to 4 mm, 69% and 65%; for lesions > 4 mm, 53% and 42%. The probability values comparing the Kaplan-Meier curves for these five thickness ranges were 0.116, 0.576, 0.098, 0.972, and 0.050, respectively. Note that the only difference with a probability value of 0.05 or less was for melanomas more than 4-mm thick, for which the outcome was worse for those patients who underwent ELND.

of ELND, and 71 (8%) at a later date. Of these 71 patients, 31 (44%) developed metastases in a nodal basin that was histologically negative at the time of ELND, and 40 (56%) developed them in basins not dissected previously. An additional 13 patients developed recurrent nodal metastases in basins that were histologically positive at initial ELND. Therefore, among the 911 patients with ELND, 44 (5%) developed clinically evident nodal metastases in an ELND basin, subsequent to the ELND. Among the thirty-one (70%) of these that developed in a basin that was histologically negative at the time of ELND, 84% occurred after complete ELND. The remainder occurred after node biopsies (3 of 15), or partial LND (2 of 6). Overall, of 747 patients with negative complete ELND, 26 subsequently developed positive nodes in those basins (3.5%).

Among the entire study population of 4,682 patients, 137 patients (3%) developed nodal metastases to the *same* basin as two or more separate clinical events. Considering the sum of all positive ELND and all positive TLND as a denominator, this amounts to a 10% recur-

Table 8. COMPARISON OF PROGNOSTIC FACTORS AMONG MELANOMA PATIENTS TREATED WITH OR WITHOUT ELND

Factor	Thickness (mm)	% Ulcer	% Axial	% Male	Mean Age (yrs)
<0.76 mm No LND	0.53	5	59	44	45
<0.76 mm ELND	0.61	7	35	43	46
0.76–1.5 No LND	1.08	11	63	49	47
0.76–1.5 ELND	1.13	12	49	50	45
1.5–2.5 No LND	1.90	27	66	55	50
1.5–2.5 ELND	1.94	26	49	51	47
2.5–4.0 No LND	3.10	40	70	64	50
2.5–4.0 ELND	3.10	47	42	63	50
>4.0 No LND	6.01	50	69	59	53
>4.0 ELND	6.20	59	51	54	52

rence rate after positive node dissections. The mortality among these 137 patients was 74%, with a median survival of 434 days (1.2 years) after the recurrent nodes, and a 23% survival estimate at 3 years.

Therapeutic Impact of ELND

The impact of ELND in patients with clinically negative nodes was evaluated by comparing Kaplan–Meier survival curves for each thickness range. As shown in Figure 4, the overall survival rate of the patients who underwent ELND was no better than the outcome of those with comparably sized lesions who did not. The major prognostic variables for each patient subset are listed in Table 8; the groups were well matched for these variables.

The potential therapeutic value of ELND was further assessed by comparing the outcome of patients stratified, not only by thickness, but also by primary site. These data are presented in Table 9. Five-year survival rate estimates were compared. The probability values reflect the comparisons of the Kaplan–Meier survival curves, not just the survival rate at a specific time interval. The only differences for which the probability values were less than 0.05 were (1) among patients with thin melanomas on the extremity and (2) among patients with thick melanomas on the head and neck. In the former, there was a slight survival advantage among those patients who had ELND; in the latter, there was a survival disadvantage associated with ELND. Among the patients with thin extremity melanomas, the probability value was 0.048. A substantial proportion of the patients with thin melanomas that were followed in the Duke Melanoma Clinic were those referred after the development of metastatic disease. Therefore, there may be a referral bias in this study against patients with melanomas less than 0.76 mm thick, and this may have had an effect on the small difference in outcome observed among patients with thin extremity melanomas. There was a slight difference in the outcome among patients with extremity lesions 1.5 to 2.5 mm thick, but the probability value slightly exceeded 0.05. These patients appeared to be well matched, except that those who did not undergo ELND had a higher incidence of ulceration (28% *vs.* 22%).

In summary, this report reviewed a 20-year experience with 4682 patients with melanoma from the standpoint of regional nodal disease and the impact of surgical management on its progression and its effect on patient survival.

Table 9. SURVIVAL WITH OR WITHOUT ELECTIVE LYMPH NODE DISSECTION

Thickness	No LND (n)	ELND (n)	p Value
	5-year survival estimates*		
Extremity			
<0.76 mm	90% (233)	100% (28)	0.048
0.76–1.5 mm	90% (363)	91% (139)	0.234
1.5–2.5 mm	81% (168)	88% (131)	0.053
2.5–4.0 mm	68% (74)	66% (87)	0.695
>4.0 mm	62% (63)	59% (48)	0.274
Trunk			
<0.76 mm	94% (260)	86% (13)	0.813
0.76–1.5 mm	87% (467)	86% (96)	0.120
1.5–2.5 mm	75% (261)	80% (85)	0.492
2.5–4.0 mm	70% (147)	64% (43)	0.871
>4.0 mm	49% (108)	36% (38)	0.149
Head/Neck			
<0.76 mm	92% (83)	<100 (2)	0.660
0.76–1.5 mm	81% (164)	85% (48)	0.401
1.5–2.5 mm	81% (87)	71% (53)	0.832
2.5–4.0 mm	66% (51)	56% (33)	0.929
>4.0 mm	51% (54)	20% (16)	0.017

* Kaplan-Meier survival estimates.

DISCUSSION

In patients with malignant melanoma, the issue on which there is the least agreement is the surgical management of clinically negative draining lymph nodes. ELND have been proposed as a means of removing micrometastatic disease before it metastasizes more systemically. The putative benefit of ELND depends on (1) the presence of lymph node metastases in the absence of distant disease, (2) an increased metastatic risk as the amount of tumor in the nodes increases, and (3) the absence of a significant immunologic benefit from keeping draining nodes in place.

Because micrometastatic disease cannot be identified *in situ* with current diagnostic tests, it is not possible in a given patient to verify the absence of distant micrometastatic disease. Several recent studies suggest[18-20] that metastatic risk depends more on the characteristics of the malignant cell than a function of the number of malignant cells present. Finally, there is evidence that lymphocytes from draining lymph nodes have the ability to recognize autologous tumor and to lyse it.[21] However, there is also some suggestive evidence that suppression of the immune response may be found in draining nodes proximal to the tumor.[22] The effects of removing regional nodes may be complex; until the host–tumor interaction is better understood, the immunologic effects of removing the nodes will remain to be elucidated.

The present report provides evidence that a small but measurable proportion of patients have nodal metastases in basins previously dissected. This amounts to approximately 3% of patients with negative ELND and 3% of all patients with a prior positive nodal basin. These observations suggest that LND does not guarantee the removal of all metastatic disease from the nodal basin site; an implication is that survival after LND may depend on factors other than the surgical management. The host–tumor interaction and specific characteristics of the tumor may cause the tumor to behave aggressively or not, despite the surgical management. The poor prognosis after recurrence of nodal metastases in a previously dissected basin (1.2-year median survival) suggests that the presence of recurrence in this setting is a marker for aggressive disease.

Clinical experience with ELND is mixed. The major institutions that manage melanoma have reported, retrospectively, in nonrandomized fashion, that ELND has a therapeutic impact limited to those patients with intermediate-thickness primary lesions.[3-5] The explanation provided is that thin melanomas rarely metastasize (so such affected patients do not benefit from ELND) and that thick melanomas are likely to seed micrometastatic disease to visceral or distant sites (so that removal of the nodes is too late to have an impact on survival). The present report evaluated the incidence of regional metastases *versus* distant metastases in patients with varied thicknesses of melanomas (Fig. 3). The incidence rates of regional metastases, distant metastases, and death paralleled each other closely, suggesting that there is no special predilection for regional metastases over distant metastases in any thickness range. These data did not corroborate the previously reported findings of a difference among patients with intermediate-thickness melanomas.[9] The reasons may include a larger patient population or longer follow-up in the present group.

By contrast with prior retrospective experience, two randomized prospective trials did not show any survival benefit of ELND. These include the World Health Organization trial[6,7] and the Mayo Clinic trial.[8] Both studies included large numbers of patients and were, for the most part, well controlled. The survival curves are virtually superimposable. It has been argued that the validity of the World Health Organization's conclusion was compromised by a maldistribution of ulcerated lesions between the two study populations, a low percentage of male patients, variations in the results from different treatment centers and from different countries, and some deviations of World Health Organization outcomes from expected outcomes.[2,23] The Mayo clinic trial has been faulted for having too few patients with intermediate-thickness lesions and for not including ulceration as a stratification criterion. Despite these criticisms, no survival benefit for ELND has yet been reported from a prospective randomized trial.

In a brief report evaluating the outcome after ELND in a slightly different subset of patients from the Duke data base, no therapeutic effect for ELND was found.[24] The present report differs from that report by (1) evaluating several aspects of nodal metastases in addition to the specific question of the outcome of patients with ELND, (2) collecting information on the specific nodal basins treated for metastatic disease, and (3) verifying and correcting recorded data on the clinical status of regional nodes by our individual chart review of all 4682 patients. Based on this chart review, more than 1000 patient records were corrected or clarified with regard to the clinical status of the regional nodes.

In the present report, well-matched cohorts of patients with clinically negative nodes and with or without ELND were compared. Survival rates were not improved for patients with primary melanomas in any of the five thickness ranges (Fig. 4). Stratification by primary site and by thickness yielded 15 patient subsets, within which those with ELND were compared with those without ELND (Table 9). In two of these subsets, differences in survival on the basis of ELND were associated with probability values between 0.016 and 0.05. In a third subset, the probability value was 0.053. The small differences in outcome in these subgroups included both poorer outcomes after ELND and improved outcomes after ELND. An interpretation of the statistical significance of differences within multiple subgroups requires special consideration. The probability that a random distribution would produce a probability value less than 0.05 in at least one of these fifteen subsets was $[1 - (0.95)^{15}]$, which equals 54%. A probability value less than

0.003 is required for a difference in one of the 15 subsets to be considered meaningful. Tukey[25] suggested that, in the analysis of multiple subgroups, the probability value required for significance should be 0.05 divided by k, where k is the number of subgroups or 0.05/15 = 0.003. Even if only three subgroups were considered relevant (*e.g.*, 1.5- to 2.5-mm lesions from the extremity, head and neck, or trunk), the probability value required for statistical significance would be 0.016. Among intermediate-thickness melanomas (0.76 to 4 mm), no probability value less than 0.05 was observed, and in none of the 15 subgroups was a probability value less than 0.016 observed.

The weaknesses of a retrospective study are acknowledged. It is hoped, however, that, by meticulously verifying the data on which the report is based, this report may make a meaningful contribution toward understanding the proper management of regional lymph nodes. In addition to finding no difference in outcome among patients treated with ELND, the data in this report constitute evidence that some of the arguments used to justify ELND may be questioned. Specifically, the recurrence of metastatic melanoma in 3% of nodal basins after complete ELND would not be expected if ELND effectively removed all occult regional nodal metastases. The low yield of positive nodes in ELND (16%, Fig. 2) was consistent with the findings of prior reports[7] and suggests that, at best, no more than a minority of patients could be expected to benefit from ELND. More than 80% should have no realistic expectation of benefit. Finally, the data in this report do not show any difference, among patients with intermediate-thickness melanoma, in the relative risk of regional nodal metastases over the risk of distant metastases. It is likely that, as in breast cancer and other malignancies, the appearance of the tumor in the regional nodes may be more a marker of aggressive disease than a cause of subsequent systemic dissemination of disease.

The morbidity rate of ELND is not insignificant. The operative mortality rate after node dissections should be minimal, but postoperative deaths have occurred.[26] The postoperative complications reported include wound infection, skin edge necrosis, lymphocele, and lymphedema, and they may occur in up to 67% of patients.[26–28] Persistent edema may cause disability in a small percentage (1% to 2%) of patients.[29] The present report adds to a growing sentiment that ELND does not have enough potential therapeutic benefit to warrant its routine use.[30,31]

Until there is more definitive proof that ELND is or is not therapeutic, however, there will be surgeons who recommend it to their patients. In those cases, it is important to identify the draining nodal basins accurately. Identification of the draining basin for extremity lesions is relatively straightforward; however, the basins draining axial sites are far more ambiguous. Head and neck primaries may drain to the anterior or posterior cervical nodes, supraclavicular nodes, major salivary glands, occipital nodes, or contralateral neck nodes. Sappey's original description of a line that divides the trunk into regions drained by axillary nodes and regions drained by inguinal nodes, recently was re-evaluated using routine lymphoscintigraphy, which has resulted in defining much larger areas of ambiguous drainage than were previously suspected.[13] In particular, the head and neck area has large amounts of ambiguity, and lesions as far as 11 cm from the midline may drain to contralateral nodes. It has been suggested that the management of regional nodes by ELND may be altered in up to 59% of patients by the use of lymphoscintigraphy rather than by the use of classic anatomic considerations. In many cases, drainage to more than one basin is found. The present report includes data that only 3% of patients with positive nodes have metastases before distant dissemination in more than one nodal basin. Even among patients with midline lesions in whom nodal metastases developed, the majority of patients had metastases in only one basin.

Although lymphoscintigraphy is probably the best way to identify basins draining a specific area of skin, we believe the number of basins identified by lymphoscintigraphy may overestimate the number of basins in which nodal metastases acquire clinical relevance. It was significant that 80% to 90% of basins (Tables 6 and 7) involved with melanoma during 5 years of follow-up were the major draining basins that would routinely be identified based on the clinical impression of an experienced surgeon.

The 6% incidence of nodal metastases to atypical basins and the 10.5% incidence of contralateral nodal metastases may reflect the variability of lymphatic drainage patterns among individuals, a hematogenous origin of some lymph node metastases, or metastases from a second unknown primary. Lymphatic drainage from the lower extremities and lower torso could proceed to cervical nodes through retroperitoneal and mediastinal lymphatic channels. Patients who present with metastatic nodal disease have unknown primaries in up to 9% of cases,[32,33] and the likelihood of a second primary melanoma is 5% in 10 years.[34] By this assessment, a crude estimate of the number of unknown primaries presenting as second primaries may be approximately 0.5%. Presumably, the majority of lymph node metastases to atypical or contralateral sites are caused by variability in lymphatic drainage patterns.

In summary, it is hoped that the data in the present report might contribute to an improved understanding of the natural history and management of regional nodes in patients with melanoma. These data were consistent with a diminished enthusiasm for ELND as a therapeutic measure in melanoma, and they provide quantitative information from a large series of patients in regard to the typical and atypical patterns of nodal metastases. Future progress depends on the results of the ongoing clinical trial of ELND being conducted through the Intergroup Melanoma Committee[2] and on a better understanding of the physiology of lymph nodes in the control of metastatic melanoma.

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