Annals of Surgical Oncology, 4(1):13–18
Published by Lippincott-Raven Publishers

Metastasis of Primary Melanoma to Two Separate Lymph Node Basins: Prognostic Significance

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Background and Methods: Depending on the location of the primary lesion, melanoma patients may develop metastases in more than one regional lymph node basin. To determine whether this is prognostically significant, we reviewed our experience with melanoma patients who had undergone regional lymphadenectomy (RLND) in two separate basins.

Results: Of 3,603 patients who underwent RLND between April 1971 and January 1993, 406 underwent procedures in two separate basins; of these, 120 (30%) had metastases in both basins and 124 (30%) had metastases in one basin. When calculated from the first positive RLND, 1-year, 3-year, and 5-year survival rates were 82%, 48%, and 33%, respectively, for patients with dual-basin involvement and 88%, 59%, and 48%, respectively, for patients with single-basin involvement ($p = 0.0173$). Median survival from the first positive RLND was 33.5 months for dual-basin involvement and 56.6 months for single-basin involvement. Univariate analysis demonstrated that Breslow thickness of the primary melanoma, clinical status of the regional lymph nodes, number of positive RLNDs, and tumor burden (total number of positive lymph nodes) were significant indicators of survival. The patient's age and gender, the anatomic location and Clark level of the primary melanoma, the disease-free interval before regional metastasis, and the site and timing of RLNDs were not significant by univariate analysis. Multivariate analysis demonstrated significance for Breslow thickness, number of positive RLNDs, and tumor burden.

Conclusions: The survival rate of melanoma patients with regional metastases in two lymph node basins is lower than that of patients with an equal tumor burden confined to a single basin. This suggests that primary melanomas metastasizing to more than one lymph node basin may have a higher metastatic potential, or that dual-basin involvement may increase the risk of systemic spread. We advocate lymphatic mapping, sentinel node biopsy, and selective lymphadenectomy as a cost-effective technique with little morbidity to identify and manage occult metastases in patients who have two lymph basins at risk.

Key Words: Melanoma—Prognosis—Lymph nodes—Lymphadenectomy.

The first site of metastasis from a primary cutaneous melanoma is most often the regional lymph nodes. Melanoma patients with regional lymph node metastasis (American Joint Committee on Cancer [AJCC] stage III) usually present with single-basin involvement, and their prognosis is significantly worse than that of melanoma patients with nonmetastatic primary disease (AJCC stage I/II). Depending on the primary melanoma's anatomic site, some patients may be at risk for metastasis to more than one lymph node basin. Ambiguous or dual-basin drainage patterns, especially from primary tumors on the head, neck, or trunk, have been documented in lymphoscintigraphic studies (1–3). Two previous reports estimate the incidence of dual-basin metastasis at 5–12% (4,5). The prognostic significance of this phenomenon and its impact on survival have not been adequately studied and are therefore the subject of this report.

Received June 20, 1995; accepted February 27, 1996.
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Presented at the 47th Annual Cancer Symposium of The Society of Surgical Oncology, Houston, Texas, March 17–20, 1994.

PATIENTS AND METHODS

The computerized melanoma database at the John Wayne Cancer Institute contains the clinical records of 6,129 patients treated between April 1971 and January 1993. All patients with melanoma undergoing regional lymphadenectomy (RLND) were identified. RLND was defined as inguinal (superficial and/or deep), axillary, or cervical. Dissection of each basin was considered a separate procedure, even if more than one RLND was performed during the same operation. Patients with evidence of distant metastatic disease (AJCC stage IV melanoma) at the time of RLND were excluded from the study. The period of observation ranged from 6 months to 22 years, with <1% lost to follow-up.

We recorded each patient's age at the time of RLND, gender, characteristics of the primary melanoma (anatomic location, Clark level of invasion, Breslow thickness), clinical status of the regional nodes, site of each RLND, status of excised nodes, number of involved lymph node basins, disease-free interval before diagnosis of regional metastasis, tumor burden, and duration of survival after the first RLND. Tumor burden was evaluated as the total number of pathologically positive lymph nodes. A low tumor burden was defined as two to four positive lymph nodes and a high tumor burden as ≥5 positive nodes. In the multivariate model, tumor burden was used as a continuous variable. Complete data were available for >80% of all patients.

Statistical Analysis

Survival rates, standard errors, and median survival in months were estimated using the Kaplan-Meier method. Univariate comparison of survival curves was performed using the log-rank statistic. Survival was defined as the interval between the first RLND or the first positive RLND and the patient's death from melanoma or the last follow-up date. Multivariate analysis used only those patients with at least one positive RLND and only those factors identified by univariate analysis as significant predictors of survival. Cox regression analysis was used to calculate multivariate probability values; patients with missing or unknown data were deleted. The statistical package of SAS procedures LIFETEST and PHREG was used to provide Kaplan-Meier, log-rank, and Cox regression data. Procedure FREQ cross-tabulated the data.

TABLE 1. *Summary of data for groups A, B, and C*

	Group A (n = 120)	Group B (n = 124)	Group C (n = 162)
Median age (yr)	44	46	44
Gender (M:F)	1:1.9	1:2.5	1:1.8
Location of primary tumor			
Trunk	75%	80%	80%
Head/neck	7%	9%	12%
Extremity	18%	11%	8%
Clark level			
I–II	11%	5%	5%
III–IV	84%	88%	90%
V	5%	7%	5%
Breslow thickness			
<0.75 mm	10%	8%	7%
0.76–4.0 mm	73%	75%	83%
>4.0 mm	17%	17%	10%

RESULTS

A total of 3,603 patients underwent at least one RLND. Of these, 406 (11%) underwent RLND of two separate lymph node basins: 120 (30%) had two pathologically positive dissections (group A), 124 (30%) had one pathologically positive dissection (group B), and 162 (40%) had no pathologically positive dissections (group C). The median age of all patients was 45.2 years (range 15–82). Each group had a similar age distribution; median age was 44, 46, and 44 years for groups A, B, and C, respectively. Gender distribution was also similar for each group; the male:female ratio was 1:1.9, 1:1.25, and 1:1.8 for groups A, B, and C, respectively. The anatomic site of the primary melanoma was evenly distributed among the three groups, and ~80% of all lesions were on the trunk. Clark level III–IV accounted for 84%, 88%, and 90% of groups A, B, and C, respectively; Breslow thickness of 0.76–4.0 mm represented 73%, 75%, and 83% of each group. These data are summarized in Table 1.

The median disease-free interval before diagnosis of regional node metastasis was 4.3 months in group A and 1.3 months in group B. The tumor burden of groups A and B is shown in Table 2. The median number of positive nodes was five in group A and one in group B. In group A, 75% of all patients undergoing a first RLND and 43% of all patients undergoing a second RLND had clinically positive lymph nodes preoperatively (Table 3). In group B, the first RLND specimen was clinically positive in 40% and pathologically positive in 45%; in the same group, the second RLND specimen was clinically positive in 27% and pathologically positive in 55%. The time between the first and second RLNDs was

TABLE 2. *Tumor burden in groups A and B*

	No. of Positive Nodes				
	1	2–4	≥5	Unknown	Total
Group A	—	50	62	8	120
Group B	68	33	18	5	124

similar in each group; median intervals were 8.7, 10, and 9.7 months for groups A, B, and C, respectively. There were 257 synchronous same-day RLNDs: 46 (38%) in group A, 64 (52%) in group B, and 147 (91%) in group C (Table 4).

In each group, survival rates were determined from the first RLND, independent of the pathologic status of excised lymph nodes (Fig. 1). Patients with dual-basin metastasis (group A) had poorer 1-year, 3-year, and 5-year survival rates (82%, 48%, and 33%, respectively) than did patients with single-basin involvement (85%, 66%, and 53%, respectively). As expected, patients with no evidence of regional lymph node metastasis (group C) had the highest 1-year, 3-year, and 5-year survival rates (95%, 84%, and 78%, respectively). When calculated from the first positive RLND, the 1-, 3-, and 5-year survival rates were 82%, 48%, and 33%, respectively, for group A and 88%, 59%, and 48%, respectively, for group B; this difference was significant ($p = 0.0173$, log rank analysis) (Fig. 2). The median survival time after the first positive RLND was 56.6 months for group B versus 33.5 months for group A.

Statistical analyses were performed for each of the following prognostic variables: patient's age and gender; primary melanoma's site, Breslow thickness, and Clark level; clinical status of regional lymph nodes; site and timing of RLNDs; number of pathologically positive RLND specimens; disease-free interval; and tumor burden. As indicated in Table 5, univariate analysis showed that Breslow

TABLE 3. *Clinical status of regional drainage basins and pathologic status of corresponding RLND specimens*

Patient group	Pathologically positive	Clinically positive	Clinically negative	Unknown
First RLND				
A (n = 120)	120 (100%)	90 (75%)	13 (11%)	17 (14%)
B (n = 124)	56 (45%)	49 (40%)	60 (48%)	15 (12%)
C (n = 162)	—	13 (8%)	142 (88%)	7 (4%)
Second RLND				
A	120 (100%)	52 (43%)	4 (4%)	64 (53%)
B	68 (55%)	34 (27%)	28 (23%)	62 (50%)
C	—	17 (10%)	128 (79%)	17 (11%)

TABLE 4. *Timing of RLNDs*

	Group A	Group B	Group C
Synchronous	46 (38%)	64 (52%)	147 (91%)
Asynchronous	74 (62%)	60 (48%)	15 (9%)[a]
Median Interval between RLNDs	8.7 mo	10 mo	9.7 mo

[a] These patients all had clinically palpable nodes.

thickness ($p = 0.0007$), clinical status of the regional lymph nodes ($p = 0.022$), number of positive RLND specimens ($p = 0.0214$), and tumor burden ($p = 0.009$) were indicators of survival. When multivariate analysis was performed, only Breslow thickness ($p = 0.0001$), number of involved basins ($p = 0.0477$), and tumor burden ($p = 0.0043$) remained significant.

When the tumor burden was two to four nodes, group A patients had a significantly poorer survival than did group B patients ($p = 0.019$; Fig. 3, top). There was no significant difference in survival between groups A and B when tumor burden exceeded five nodes ($p = 0.705$; Fig. 3, bottom). As shown in Table 6, these findings could not be explained by variance in the number of patients in each group with two versus three versus four positive nodes. Our analysis of tumor burden and survival excluded the 68 patients with only one positive lymph node. These patients tended to have higher 1-year, 3-year, and 5-year survival rates

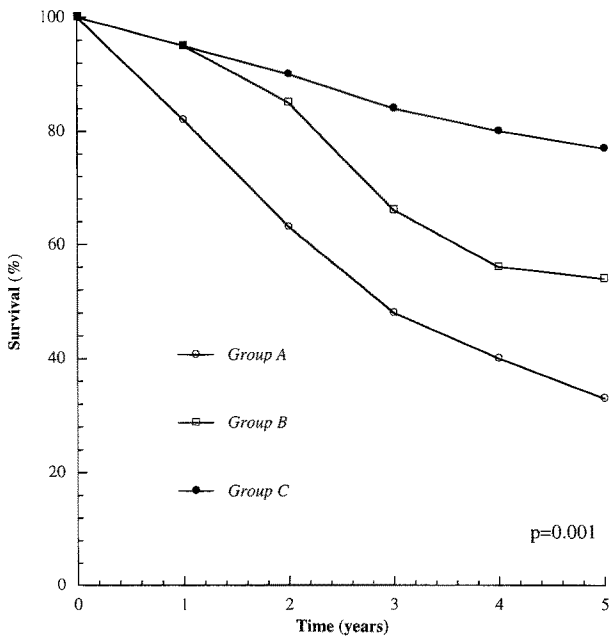

FIG. 1. Five-year survival after the first RLND.

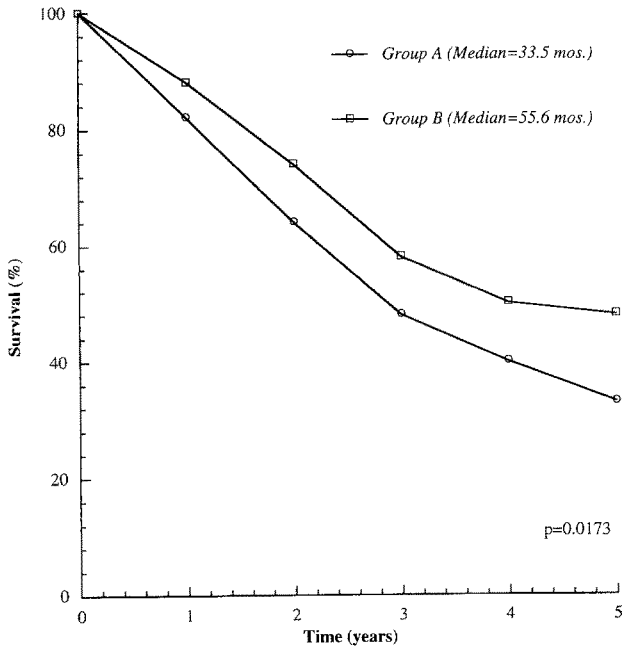

FIG. 2. Five-year survival in groups A and B after the first positive RLND. (Note that the curve for group A is the same as that shown in Fig. 1 because the first RLND was always positive.)

(88%, 63%, and 47%, respectively) than did other patients in group A or B.

DISCUSSION

Patients whose primary melanoma has spread to more than one regional lymph node basin are a poorly studied subgroup of AJCC stage III patients. In our study, 406 patients with melanoma had or were at high risk for metastasis to two separate lymph node basins; of these, 120 (30%) had pathologically identified dual-basin metastases. Therefore, our overall incidence of dual-basin metastasis for all patients undergoing RLND was 3% (120 of 3,603). Coit et al. (4) reported a similar result: 5% (51 of 1,019) of their patients with melanoma undergoing RLND had at least two positive lymph node basins. Barth et al. (5) found that 12% (21 of 175) of patients with melanoma undergoing RLND had metastases in two or more separate lymph node basins. This comparatively high percentage might reflect more patients with clinically palpable lymph nodes and a smaller overall number of patients. We believe that the actual rate of dual-basin metastasis from primary melanomas probably exceeds 3–5%, especially among patients whose primary tumors are on the head, neck, or trunk, because some lymphatic basins contain subclinical (occult) metastases.

TABLE 5. *Factors affecting survival of groups A and B after the first positive RLND*

Variable	Univariate analysis	Multivariate analysis
Age	0.8103	—
Gender	0.1890	—
Primary site (extremity/ trunk/head and neck)	0.1536	—
Breslow thickness	0.0007	0.0001
Clark level	0.1694	—
RLND site	0.5041	—
Clinical status of regional nodes	0.0220	—
Synchronous/asynchronous RLND	0.6830	—
Number of positive RLNDs	0.0214	0.0477
Tumor burden[a]	0.0090	0.0043

[a] Defined as a continuous variable.

AJCC stage III patients treated at John Wayne Cancer Institute have 1-year, 3-year, and 5-year survival rates of 84%, 55%, and 46%, respectively (6). Because most have only one tumor-positive lymphatic basin, these rates are comparable with those for group B patients in our study. One-year, 3-year, and 5-year survival rates in group A patients were 82%, 48%, and 33%, respectively, lower than those in group B but similar to the rates reported by Barth et al. (5) for patients with dual-basin involvement (80%, 50%, and 25%, respectively). The worse prognosis for patients with melanoma with dual-basin metastases involves multiple factors. Although these patients often have a higher tumor burden, even when tumor burden is a constant, the presence of metastases in more than one lymph node basin significantly reduces survival. Dual-basin involvement might indicate a tumor with higher metastatic potential, i.e., a more aggressive tumor with a poorer prognosis. It is possible that drainage to secondary basins reflects development of collateral lymphatics due to local tumor growth, congestion of the primary drainage pathway by tumor cells, and/or postoperative development of new lymphatic channels around the resected primary drainage basin.

Lymphatic drainage of primary melanomas varies according to the anatomic location of the primary lesion. The original description of lymphatic drainage by Sappey (7) identified a line just above the level of the umbilicus above which lymph drains superiorly to the ipsilateral axilla and below which lymph drains inferiorly to the ipsilateral groin. The midline is generally considered the demarcation between right-sided and left-sided drainage, and for

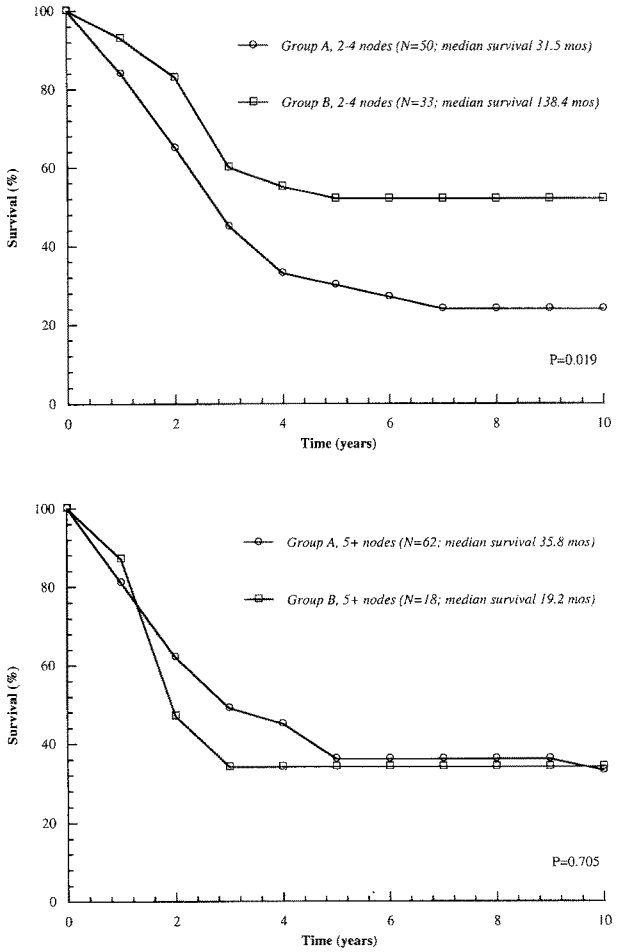

FIG. 3. Five-year survival in groups A and B after the first positive RLND, according to low (two to four positive nodes, top) or high (five or more positive nodes, bottom) tumor burden.

over a century this system of cutaneous lymphatic drainage seldom has been challenged. In the 1970s, we introduced cutaneous lymphoscintigraphy using colloidal gold and other agents to demonstrate the actual and often ambiguous drainage regions of the trunk, especially in the region of Sappey's line (1–3). Continued experience with lymphoscintigraphy has further expanded our knowledge of lymphatic drainage from cutaneous sites (8). Lamki and Logic (9) reported bidirectional or multidirectional lymphatic drainage in 49% of patients with truncal melanomas. In our study, ~80% of all patients with dual-basin drainage had primary melanomas on the trunk. These percentages are similar to those reported by Barth's group (5).

Extremity lesions generally drain to the ipsilateral axilla or groin, although this pattern may become more obscure as a lesion becomes more proximal on the extremity. Thus, upper-extremity lesions near the shoulder may drain to the axilla or neck, and lower-extremity lesions may have crossover metastasis to the contralateral groin. In our study, almost 20% of the patients with dual-basin metastasis had primary melanomas on an extremity.

TABLE 6. *Distribution of positive nodes among patients with a low tumor burden*[a]

	2+	3+	4+	Total
Group A	20	7	6	33
Group B	22	14	14	50

[a] No significant difference between groups A and B.

The actual incidence of dual-basin drainage for primary melanomas cannot be determined unless all patients undergo preoperative lymphoscintigraphy at the time of wide local excision. After lymphoscintigraphy, the actual incidence of dual-basin metastasis cannot be determined unless the high-risk nodes in each drainage basin are excised for histologic evaluation (10,11). This can be accomplished via RLND or with much lower morbidity via intraoperative lymphatic mapping with selective lymphadenectomy (10,12). Intraoperative mapping is based on the premise that tumor cells from a primary cutaneous melanoma pass through subdermal lymphatics to the regional lymphatic basin and then sequentially through the nodes in this basin. Thus, the first evidence of regional node metastasis most likely is found in the node at the entrance to the basin, the so-called sentinel node. Immunohistopathologic examination of sentinel nodes removed during selective lymphadenectomy can more accurately determine which patients have regional node metastasis and therefore should undergo therapeutic RLND. If lymphoscintigraphy identifies more than two regional lymphatic drainage basins, then selective lymphadenectomy of each basin should be undertaken for confirmation of metastases. This aggressive approach to identify occult nodal disease may give patients with melanoma with dual-basin metastases the same chance of survival as those with involvement of only one lymph node basin.

CONCLUSIONS

Patients whose primary melanoma has metastasized to two separate lymph node basins represent a small but prognostically distinct subgroup of AJCC stage III patients. Breslow thickness of the primary tumor, number of involved regional drainage ba-

sins, and tumor burden are independent predictors of survival in this AJCC stage III subgroup. These patients have a less favorable prognosis than the overall group of AJCC stage III patients.

The actual incidence of dual-basin drainage is not known. Routine preoperative lymphoscintigraphy in patients with head, neck, or truncal primaries can identify all lymph node basins at risk for metastasis. Selective lymphadenectomy followed by immunohistochemical analysis should then be used to determine the pathology of sentinel nodes in each drainage basin (10). Therapeutic (complete) RLND can subsequently be undertaken in all nodal basins containing histologic evidence of metastasis.

Acknowledgment: This study was supported by grants from the National Cancer Institute (CA 12582 and CA 29605) and by funding from the Joyce and Ben Eisenberg Foundation, the Steele Foundation, and the Wrather Family Foundation.

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