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ORIGINAL ARTICLE – MELANOMAS

In-transit Melanoma Metastases: Incidence, Prognosis, and the Role of Lymphadenectomy

Rebecca L. Read, MBBS, DPhil[1,2], Lauren Haydu, BSCHE, MIPH[1], Robyn P. M. Saw, MBMS[1,2,3], Michael J. Quinn, MBBS[1,2,3], Kerwin Shannon, MBBS[1,2,3], Andrew J. Spillane, MD[1,2,3], Jonathan R. Stretch, MBBS, DPhil[1,2,3], Richard A. Scolyer, MD[1,2,4], and John F. Thompson, MD[1,2,3]

[1]Melanoma Institute Australia, Sydney, NSW, Australia; [2]Royal Prince Alfred Hospital, Sydney, NSW, Australia; [3]Discipline of Surgery, Sydney Medical School, The University of Sydney, Sydney, NSW, Australia; [4]Discipline of Pathology, Sydney Medical School, The University of Sydney, Sydney, NSW, Australia

ABSTRACT

Purpose. To analyze a large, single-institution database to further understanding of melanoma in-transit metastases (ITM) with regard to incidence, prognosis, and the role of lymphadenectomy.

Methods. A total of 11,614 patients with single primary cutaneous melanomas were treated at Melanoma Institute Australia between January 1994 and December 2009. Of these, 505 developed ITM. Clinicopathologic characteristics, sentinel node (SN) status, patterns of disease progression, and outcomes were analyzed.

Results. In the 505 patients with ITM, the median primary tumor thickness was 2.95 mm, and 39.4 % were ulcerated. The ITM rates for patients with primary melanomas <1 or ≥ 1 mm in size and in those who underwent sentinel node biopsy were 0.4, 7.8, and 7.2 %, respectively. The ITM rates for SN-positive and SN-negative patients were 21.6 and 4.7 %, respectively. The median time from primary diagnosis to the development of ITM was 17.9 months. After ITM diagnosis, the median survival time was 19.9 months, 5-year survival was 32.8 %, and 10-year survival was 27.5 %. After ITM diagnosis, primary tumor site (head/neck, trunk) and ulceration were predictors of poorer survival. Five-year survival from the time of ITM ranged from 47.9 % for nonulcerated limb primary lesions to only 13.6 % for ulcerated trunk primary lesions. Elective lymph node dissection in clinically node-negative patients with ITM did not significantly alter overall survival.

Conclusions. This large study demonstrates that the diagnosis of melanoma ITM carries serious adverse prognostic implications and will assist in improving the accuracy of staging and prognostic estimates as well as treatment in these patients.

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J. F. Thompson, MD
e-mail: john.thompson@melanoma.org.au

The development of in-transit metastases (ITM) in melanoma patients has serious prognostic implications, as it often heralds progression to regional and systemic disease. The phenomenon of ITM is almost unique to melanoma. ITM are thought to be due to the entrapment of tumor cells within dermal and subdermal lymphatics between the site of the primary tumor and the draining regional lymph nodes,[1] but the mechanisms responsible for the development of ITM are not completely understood.[2,3] Other possible explanations include tumor cell dispersion through tissue fluid,[4] spread of tumor cells around the abluminal surface of lymphatics and blood vessels in a pericytic location (termed angiotropism[5]), and implantation of tumor cells after spread via the bloodstream.[6]

The 7th edition of the American Joint Committee on Cancer (AJCC) staging system for melanoma uses the term "intralymphatic metastases" (satellitosis and ITM) and includes patients with stage IIIB or IIIC disease. In the database analysis undertaken by the AJCC Melanoma Staging Committee, patients with intralymphatic metastases but not regional node involvement (stage IIIB disease) had a 5-year survival of 69 %, while patients with intralymphatic metastases and regional node metastases (stage IIIC disease) had a 5-year survival of 46 %.[7] A study reported the 5-year survival for patients with ITM (including satellitosis) was 60.1 % for skin metastasis only and 36.3 % for skin and regional node metastases.[8]

The ITM literature is limited, but in large contemporary studies, including the First Multicenter Selective Lymphadenectomy Trial (MSLT-I), in which the primary study group had melanomas 1.2 to 3.5 mm in Breslow thickness, the incidence of ITM ranged from 3.6 to 7.0 % and was not affected by utilization of SNB.[9–11]

The aim of the present study was to determine the incidence of ITM, disease characteristics, the role of elective lymph node dissection (ELND), and survival outcomes to allow patients with ITM to be more appropriately staged and treated.

PATIENTS AND METHODS

Patients with ITM who underwent definitive treatment for a single primary cutaneous melanoma at Melanoma Institute Australia (MIA) between January 1994 and December 2009 were identified from the MIA database. Patients with multiple primary melanomas and occult, ocular, mucosal, or other noncutaneous primary melanomas and patients whose initial definitive surgical treatment was performed elsewhere were excluded.

The management of primary melanoma at MIA evolved over the study period. Between April 1994 and October 2000, SNB was offered to selected patients (with primary melanomas of Breslow thickness ≥1 mm and Clark level III or higher, or any Breslow thickness but with Clark level IV/V invasion) as part of MSLT-I in the great majority of cases.[9,10] Discussion of SNB has since become part of the standard management for patients treated at MIA for selected primary cutaneous melanomas (≥1 or <1 mm but with adverse features including ulceration, mitotic rate >1/mm^2, and lymphatic invasion) in the absence of clinical evidence of nodal or other metastases.

The MIA database definitions of local recurrence, ITM, regional metastasis, and distant metastasis were used. Local recurrences were those <5 cm from the original primary melanoma (including satellitosis). ITM were cutaneous, intradermal, and subcutaneous metastases occurring ≥5 cm from the primary site but before the regional node field. Regional node metastases occurred within the regional node field (including SNB-positive patients). Distant metastases were beyond the regional node field, including in visceral organs.

Univariate survival analysis of categorical variables was carried out by the Kaplan–Meier method with the log-rank (Mantel–Cox) test to calculate statistical significance. Univariate survival analyses of continuous variables and multivariate survival analyses used the Cox proportional hazard model. Two-tailed p-values of <0.05 were considered statistically significant. The IBM SPSS Statistic 19.0 software package was used. Factors with limited sample size (microsatellites, lymphatic invasion, and vascular invasion) were excluded from the multivariate analysis. Disease-free survival was not assessed because many patients with ITM were not rendered disease-free by treatments aimed at maintaining local control. Melanoma-specific survival (MSS) was calculated from the date of primary melanoma diagnosis and/or date of ITM diagnosis to the date of last follow-up or death from melanoma.

RESULTS

Presentation with ITM

The Breslow thickness was <1 mm in 5,288 patients, ≥1 mm in 6,211 patients, and not recorded in 115 patients. ITM (as defined for this study) occurred in 505 patients, and 22 had primary melanomas <1 mm thick. Overall 4.3 % of patients developed ITM. The rate of ITM was 0.4 % in patients with primary disease <1 mm and 7.8 % in patients with primary disease ≥1 mm. An additional 536 patients (4.6 %) with primary melanomas ≥1 mm thick developed recurrences <5 cm from the primary melanoma site.

The clinical and pathologic characteristics of patients with ITM ($n = 505$) are shown in Table 1. The median follow-up was 40.6 months (range 1.8–186.4 months) from the date of primary diagnosis and 14.5 months (range 0–179.8 months) from ITM diagnosis.

The median interval between primary melanoma diagnosis and ITM was 17.9 months. Only 42 patients had ITM at the time of initial primary melanoma diagnosis, and seven of these had stage IV disease. Patients with a head or neck primary site progressed to ITM more quickly (median 11.2 months) than those with limb (median 19.2 months, $p < 0.001$) or trunk (median 18.6 months, $p = 0.005$) primary lesions. At ITM presentation, the disease of patients was restaged and was found to be stage IIIB ($n = 274$), stage IIIC ($n = 183$), and stage IV ($n = 48$).

Implications for SNB

SNB was performed in 3,642 of the 11,614 patients (511 were SN positive and 3,091 were SN negative). Of the 505 patients who developed ITM, 264 had previously had a SNB; 119 were SN positive and 145 were SN negative. The rate of ITM in all patients undergoing SNB was 7.2 %. The rate was 4.7 % in SN-negative patients but 21.6 % in SN-positive patients.

TABLE 1 Patient and primary melanoma characteristics

Characteristic	Value
Total	505 (100.0 %)
Gender	
Male	309 (61.2 %)
Female	196 (38.8 %)
Age, yr	
Mean	63.6
Median	65.9
Range	16.7–92.7
Breslow thickness	
≤1.0 mm	27 (5.3 %)
1.01–2.0 mm	110 (21.8 %)
2.01–4.0 mm	195 (38.6 %)
≥4.01 mm	164 (32.5 %)
Unknown	9 (1.8 %)
Mean (mm)	3.86
Median (mm)	2.95
Range (mm)	0.32–35.0
Clark level	
I	2 (0.4 %)
II	8 (1.6 %)
III	74 (14.7 %)
IV	304 (60.2 %)
V	99 (19.6 %)
Unknown	18 (3.5 %)
Ulceration	
Absent	257 (50.9 %)
Present	199 (39.4 %)
Unknown	49 (9.7 %)
Mitoses	
0 /mm^2	22 (4.2 %)
1–2 /mm^2	109 (21.6 %)
3–5 /mm^2	120 (23.7 %)
6–10 /mm^2	108 (21.4 %)
>10 /mm^2	110 (21.8 %)
Unknown	37 (7.3 %)
Histologic subgroup	
SSM	101 (20.0 %)
NM	215 (42.6 %)
SSM with NM	25 (4.9 %)
MIS/HMF	8 (1.6 %)
Desmoplastic	32 (6.3 %)
Acral lentiginous	21 (4.2 %)
Unknown	103 (20.4 %)
Location of primary lesion	
Head and neck	104 (20.6 %)
Trunk	131 (25.9 %)
Upper limb	59 (11.7 %)
Lower limb	211 (41.8 %)
Lymphatic invasion	
Absent	257 (50.9 %)
Present	39 (7.7 %)
Unknown	209 (41.4 %)
Vascular invasion	
Absent	310 (61.4 %)
Present	36 (7.1 %)
Unknown	159 (31.5 %)
Microsatellites	
Absent	201 (39.8 %)
Present	43 (8.5 %)
Unknown	261 (51.6 %)
AJCC stage at primary diagnosis	
I	54 (10.7 %)
II	262 (51.9 %)
III	174 (34.5 %)
IV	11 (2.2 %)
Unknown	4 (0.1 %)
AJCC stage at time of ITM	
IIIB	274 (54.3 %)
IIIC	183 (36.2 %)
IV	48 (9.5 %)

AJCC American Joint Committee on Cancer, *ITM* in-transit metastases, *SSM* Superficial spreading melanoma, *NM* nodular melanoma, *MIS* melanoma in situ, *HMF* Hutchinson's melanotic freckle

At the time of primary melanoma treatment, 145 patients with ITM were SN negative; however, 45 (31 %) subsequently developed clinical regional node disease. Hence, using the broadest definition, the false-negative (FN) SNB rate [FN/(truly positive + FN) = 45/(119 + 45)] was 27.4 %. However, the 45 patients can be divided into two groups. Clinical node metastases occurred in 24 patients before they presented with ITM. The remaining 21 patients only developed regional node metastases after they developed ITM. If the FN SNB rate is considered to include only regional metastases that occur before any other metastases become apparent (including locoregional recurrences such as ITM), the FN SNB rate was 16.8 %, or 24/(119 + 24).

Melanoma-Specific Survival in ITM Patients

MSS was first considered in patients with ITM whose disease was staged as IIIB or IIIC at the time of their primary melanoma presentation (35 patients). This group can be directly compared to the AJCC stage groupings. Thirty-one had no regional node involvement, and their 5-year survival was 43 %. Only 4 of 35 presented with a

TABLE 2 Comparison of reported 5YS in ITM patients

ITM status	AJCC stage groups[a]	AJCC ITM[a]	This study		
			ITM at primary diagnosis[b] ($n = 35$)	Stage III ITM patients[c] ($n = 457$)	All ITM patients[c] ($n = 505$)
ITM with no regional node metastases	59 % (IIIB)	69 %	43 %	47 %	40 %
ITM with regional node metastases	40 % (IIIC)	46 %	–	19 %	19 %

ITM in-transit metastases, *AJCC* American Joint Committee on Cancer

[a] From Balch et al.[7]

[b] Patients with stage III disease with ITM at initial presentation ($n = 35$) can be compared directly to the AJCC data; the dash indicates that there were insufficient numbers for accurate calculation of 5-year survival

[c] These groups include all patients with ITM, not only those with ITM at initial presentation. Reported 4-year survival is from the time of ITM in patients with stage III disease ($n = 457$) and in all patients with ITM (stage III and IV disease) ($n = 505$)

primary melanoma, ITM, and regional node metastasis—a group too small to allow accurate calculation of 5-year survival (Table 2).

The second group (457 patients) had no evidence of distant metastatic disease either at primary diagnosis or before ITM (stage IIIB/IIIC). Median MSS from time of ITM diagnosis was 24.7 months (95 % confidence interval [CI] 17.9–31.4). The overall 5-year survival from ITM diagnosis was 36 %, and the 10-year survival was 30 %. Univariate analysis showed MSS from ITM diagnosis was significantly better when patients had no regional node involvement before ITM diagnosis or within 4 weeks from the time of ITM diagnosis ($n = 274$, 5-year survival 47 %, median 46.3 months, 95 % CI 23.4–69.3), compared with those who had been diagnosed with regional node metastases before the development of ITM or within 4 weeks of their ITM diagnosis ($n = 183$, 5-year survival 19 %, median 16.3 months, 95 % CI 13.0–19.5, $p < 0.001$) (Table 2, Fig. 1a). Ulceration status also significantly influenced MSS from the time of ITM diagnosis (5-year survival 44.2 % not ulcerated, 5-year survival 23.0 % ulcerated, $p = 0.001$) (Fig. 1b). SNB did not affect survival from primary diagnosis ($p = 0.373$) or from the diagnosis of ITM ($p = 0.789$). Multivariate analysis confirmed the prognostic significance of regional node metastases ($p < 0.001$, hazard ratio [HR] 1.818, CI 1.379–2.398) and ulceration status ($p = 0.009$, HR 0.681, 95 % CI 0.512–0.908).

For all 505 patients with ITM who had stage IIIB, IIIC, and IV disease at ITM diagnosis, the median survival was 19.9 months; 5-year survival was 32.8 % and 10-year survival was 27.5 %. Univariate analysis showed that increased Breslow thickness, ulceration, higher stage at primary melanoma diagnosis, nodular subtype and primary site (head and neck, trunk) and prior or concurrent regional node metastases were associated with shorter survival (Table 2; Online Supplementary Information). Performing a SNB did not affect survival from the time of primary diagnosis ($p = 0.272$) or from ITM diagnosis ($p = 0.453$). After multivariate analysis, the only statistically significant prognostic factor was prior or concurrent regional node metastases ($p = 0.011$, HR 1.388, 95 % CI 1.077–1.788). Ulceration status tended toward significance (5-year survival 39.2 % not ulcerated, 21.4 % ulcerated, $p = 0.051$) (Fig. 1c). Five-year survival varied with site of primary tumor, but this was not significant on multivariate analysis (5-year survival limb 38.7 %, head and neck 32.2 %, trunk 21.8 %) (Fig. 1d). The 5-year survival from time of ITM ranged from 47.9 % in patients with a nonulcerated limb primary lesion to only 13.6 % in patients with ulcerated trunk primary lesions (Table 3).

Recurrence and Disease Progression

ITM was the first recurrence in 190 (37.6 %) of 505 patients. The 190 patients with ITM as a first site of recurrence had an overall median survival of 107.7 months and an overall 5-year survival of 61.1 % Local recurrence or satellitosis (defined in the study as recurrence <5 cm from the primary site) occurred before ITM in 54 patients (10.7 %). Regional disease was the first site of metastasis, before or concurrently with ITM in 213 patients (42.2 %). Distant metastatic disease was the first site of metastasis, before or concurrently with ITM, in 48 patients (9.5 %). Of the 190 patients with ITM as a first site of recurrence the disease was limited to ITM in 35.9 %, progressed next to regional node metastasis in 21.5 %, and to distant metastasis without intervening regional node metastasis in 42.5 %.

Elective Lymph Node Dissection

Of the 190 patients who had ITM as their first site of metastatic disease, 31 patients (16.3 %) underwent ELND, and 6 of 31 had regional node metastases identified in their

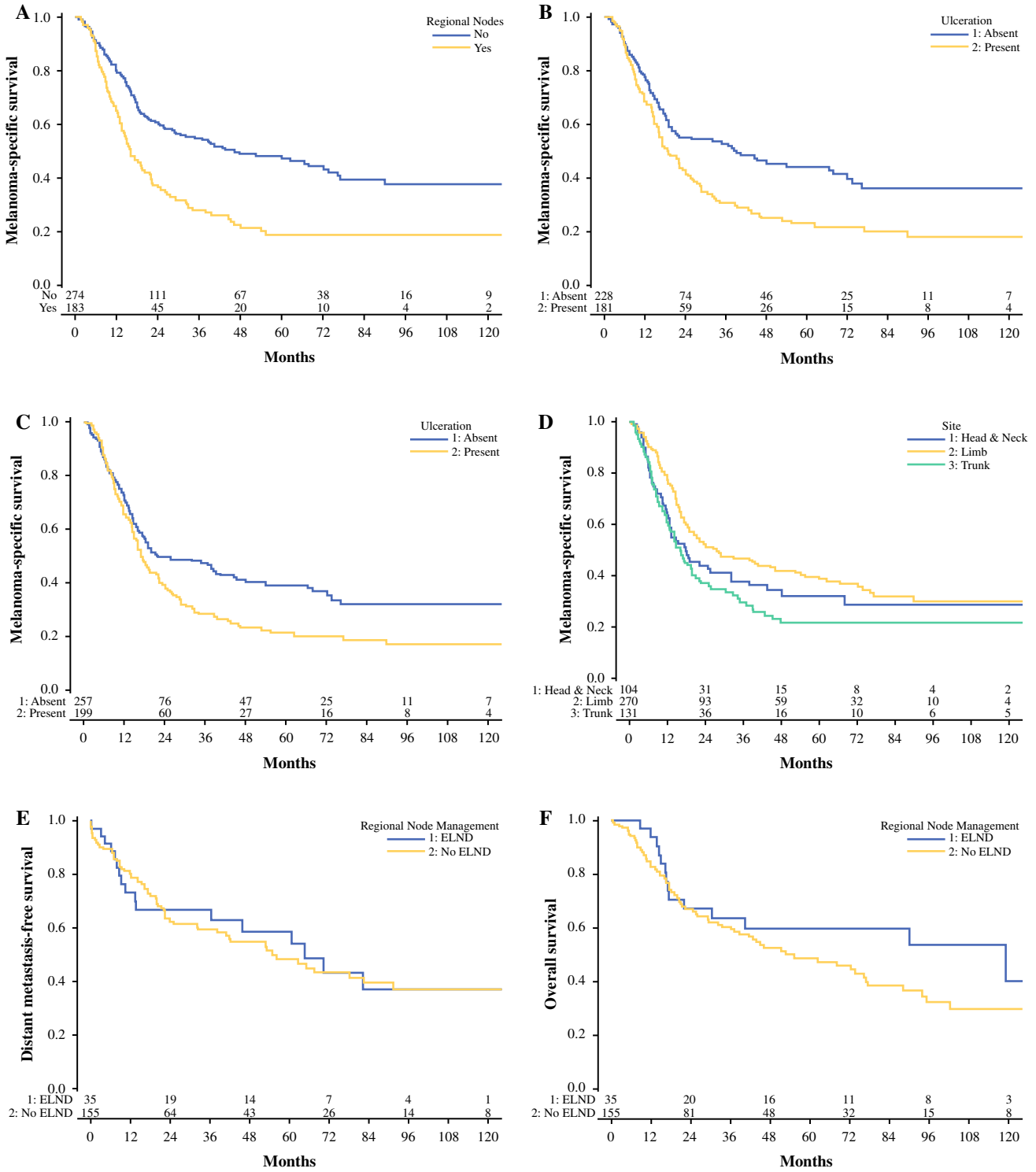

FIG. 1 Survival curves from the time of diagnosis of ITM demonstrating **a** MSS for patients with stage III melanoma ($n = 457$) based on regional node status, **b** MSS for patients with stage III disease stratified by the absence or presence of ulceration, **c** MSS for all patients stratified by the absence or presence of ulceration, and **d** MSS of all patients stratified by primary site (limb, head and neck, trunk). **e** Distant metastasis-free survival for patients with ITM as a first site of recurrence ($n = 190$) stratified by ELND. **f** Overall survival for patients with ITM as a first site of recurrence ($n = 190$) stratified by ELND

TABLE 3 Five-year survival after ITM diagnosis according to primary site and ulceration status for all patients with ITM ($n = 505$)

Ulceration status of primary lesion	Site of primary lesion		
	Limb ($n = 247$)	Head and neck ($n = 90$)	Trunk ($n = 119$)
Nonulcerated	47.9 %	30.8 %	28.6 %
Ulcerated	24.1 %	25.4 %	13.6 %

ITM in-transit metastases

operative pathology specimen. A total of 159 patients did not undergo ELND at the time of ITM diagnosis. Regional recurrence subsequently occurred in 35 (22.2 %) of 159 patients in the absence of distant metastases, and 34 of these underwent therapeutic lymphadenectomy. There was no difference in distant metastasis-free 5-year survival (59 % ELND, 48 % no ELND, $p = 0.934$) or overall 5-year survival (60 % ELND, 49 % no ELND, $p = 0.172$) based on performing an ELND at the time of ITM presentation (Fig. 1e,f).

DISCUSSION

In this study, ITM occurred in 7.8 % of patients with primary melanomas ≥1 mm thick. This is slightly higher than the rates reported in other recent studies in similar patients.[9,11] The true rate of ITM in our patient population may have been even higher (up to 12.4 %) because patients with recurrences <5 cm from the primary site were excluded because they were recorded in our database together with patients with true local recurrence who have a better prognosis.[12] Although true local recurrence is likely to be a rare event, retrospective separation of these groups was not possible.[13]

Regional node metastases are confirmed as a negative prognostic factor in patients with ITM. Primary melanoma ulceration also had negative prognostic implications after ITM diagnosis in patients with stage III disease. This has varied in other studies of ITM and satellitosis.[8,14] In our study, survival varied from 47.9 % (nonulcerated limb primary lesion) to 13.6 % (ulcerated trunk primary lesion) (Table 3). Survival estimates are worse than those reported by the AJCC and other studies.[8] This may be due to the inclusion in those studies of patients with local recurrence/satellitosis, who may have a better prognosis as a result of lesser extent of disease. Tumor burden (ITM number and size) could not be assessed because this information was not routinely recorded in the MIA database.

MIA performs over 500 SNB procedures annually. The theoretical concern that surgical removal of lymph nodes during SNB could cause an increased rate of ITM by disrupting lymphatic drainage has been extensively addressed and is unfounded.[11,15–17] At 7.2 %, the rate of ITM in patients undergoing a SNB procedure is slightly lower than the rate in our overall population of patients with melanomas ≥1 mm in thickness, corroborating previous studies.[9,11] Patients who were SN positive developed ITM at an increased rate (21.6 %), probably reflecting the underlying biology of metastasis[17]; this finding is consistent with other studies.[11,16,18]

We hypothesized that occult ITM may explain the occurrence of some FN SNBs, with melanoma cells traveling from the ITM to the regional node field. A SNB is FN when lymph node metastases develop in a previously mapped regional node field from which a tumor-negative SN has been removed.[19] This is a broad definition, and in some centers, including our own, a SNB is considered FN only when regional recurrence is the first site of recurrence after a previous tumor-negative SNB procedure.[20]

Melanoma FN SNB rates have been reported to be as low as 5.7 % [21] but up to 32.1 % for head and neck primary melanomas.[22] In a previous MIA study of 836 patients, the FN SNB rate was 13.2 % at a median follow-up of 42.1 months.[23] In the present study, the incidence of FN SNB was 16.8 % when patients with ITM before regional node disease were excluded from the false-negative group, but it was 27.4 % when all patients with recurrence in a SNB-negative regional node field were included. A previous analysis of the Sunbelt Melanoma Trial data set also demonstrated a high incidence of ITM (32.5 %) in the cohort of patients who had FN SNBs.[19] This high incidence of FN SNBs probably reflects dissemination from tumor cells trapped in the lymphatic system. Regional recurrence may occur even when the SN or SNs have been accurately identified, removed, and evaluated pathologically. However, only 7.2 % of patients undergoing SNB developed ITM, so their contribution to the overall FN SNB rate is likely to have been small. Other factors, including deficiencies in nuclear medicine, surgery, and pathology, remain important possible determinants of the FN SNB rate.[20]

The role of ELND in patients with ITM is not well defined. Patients with ITM as a first recurrence are twice as likely to next experience progression to distant metastatic disease rather than to regional metastasis. From this retrospective study, there is no evidence that ELND, which can cause long-term morbidity, provides a survival benefit in patients with ITM. A prospective trial of ELND in patients with ITM with a clinically negative regional node field would be required to definitively answer this question, but it is unlikely that such a trial will ever be performed. Regional node failure can cause significant morbidity. Regular clinical examination and ultrasound of the relevant node field or fields should enable early identification of subsequent regional metastases, enabling timely lymphadenectomy when appropriate. SNB is feasible and may

contribute to assessment of the regional node field in patients with an isolated ITM.[24]

Multiple modalities are used to treat ITM, with the choice dependent on their number, site, and size.[24] Definitive surgical excision remains the treatment of choice when possible. Sometimes other local treatments more are appropriate, including intralesional injection (e.g., Rose Bengal), electrochemotherapy, carbon dioxide laser ablation, diathermy fulguration, topical agents (e.g., diphencyprone), radiotherapy, and isolated limb perfusion or infusion.[25]

Targeted inhibitors of *BRAF* and other MAP kinase pathway proteins, as well as immune modifying agents (e.g., anti-CTLA4 and anti-PD1/anti-PDL1 antibodies) have been shown to be effective in the treatment of patients with stage IV and unresectable stage III melanoma.[26] These agents are the subjects of trials in the adjuvant setting, and the identification of patients with poor prognostic features is becoming increasingly important in determining eligibility for these trials and is likely to be important in the future in selecting patients for adjuvant treatment.

This study should assist the Melanoma Staging Committee of the AJCC to assign melanoma patients with ITM appropriately in the next AJCC staging manual and will provide better prognostic estimates and guide treatment choices.

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