JAMA Dermatology | Original Investigation

Risk of Melanoma Recurrence After Diagnosis of a High-Risk Primary Tumor

Lena A. von Schuckmann, MBBS, MPH; Maria Celia B. Hughes, MMedSci; Reza Ghiasvand, PhD; Maryrose Malt, BBus; Jolieke C. van der Pols, PhD; Vanessa L. Beesley, PhD; Kiarash Khosrotehrani, MD, PhD; B. Mark Smithers, MBBS; Adele C. Green, MBBS, PhD

IMPORTANCE With emerging new systemic treatments for metastatic melanoma, early detection of disease recurrence is increasingly important.

OBJECTIVE To investigate the risk of melanoma recurrence in patients with a localized melanoma at a high risk of metastasis.

DESIGN, SETTING, AND PARTICIPANTS A total of 1254 patients with newly diagnosed, histologically confirmed tumor category T1b to T4b melanoma in Queensland, Australia, were recruited prospectively between October 1, 2010, and October 1, 2014, for participation in a cohort study. Data analysis was conducted from February 8, 2018, to February 20, 2019. We used Cox proportional hazards regression analysis to examine associations between patient and tumor factors and melanoma recurrence.

EXPOSURES Disease-free survival (DFS) by melanoma tumor category defined by the 7th vs 8th editions of the *AJCC Cancer Staging Manual* (*AJCC 7* vs *AJCC 8*).

MAIN OUTCOMES AND MEASURES Melanoma recurrences were self-reported through follow-up questionnaires administered every 6 months and confirmed by histologic or imaging findings.

RESULTS Of 1254 patients recruited, 825 individuals (65.8%) agreed to participate. Thirty-six were found to be ineligible after providing consent and a further 89 patients were excluded after reclassifying tumors using *AJCC 8*, leaving 700 participants with high-risk primary melanoma (mean [SD] age, 62.2 [13.5] years; 410 [58.6%] men). Independent predictors of recurrence were head or neck site of primary tumor, ulceration, thickness, and mitotic rate greater than 3/mm^2 (hazard ratio, 2.36; 95% CI, 1.19-4.71). Ninety-four patients (13.4%) developed a recurrence within 2 years of diagnosis: 66 tumors (70.2%) were locoregional, and 28 tumors (29.8%) developed at distant sites. After surgery for locoregional disease, 37 of 64 patients (57.8%) remained disease free at 2 years, 7 patients (10.9%) developed new locoregional recurrence, and 20 patients (31.3%), developed distant disease. Two-year DFS was similar when comparing *AJCC 7* and *AJCC 8*, for T1b (AJCC 7, 253 [93.3% DFS]; AJCC 8, 242 [93.0% DFS]) and T4b (AJCC 7 and AJCC 8, 50 [68.0% DFS] category tumors in both editions. Patients with T2a to T4a tumors who did not have a sentinel lymph node biopsy (SLNB) at diagnosis had lower DFS than patients with the same tumor category and a negative SLNB (T2a: 136 [91.1%; 95% CI, 86.4-95.9] vs 96 [96.9%; 95 % CI, 93.4-100.0]; T4a: 33 [78.8%; 95% CI, 64.8-92.7] vs 6 [83.3; 95% CI, 53.5-100.0]).

CONCLUSIONS AND RELEVANCE These findings suggest that 13.4% of patients with a high-risk primary melanoma will experience disease recurrence within 2 years. Head or neck location of initial tumor, SLNB positivity, and signs of rapid tumor growth may be associated with primary melanoma recurrence.

Editorial

Related articles

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Lena A. von Schuckmann, MBBS, MPH, Population Health Department, QIMR Berghofer Medical Research Institute, 300 Herston Rd, 4006 Herston, Australia (lena.vonschuckmann@uqconnect.edu.au).

JAMA Dermatol. doi:10.1001/jamadermatol.2019.0440
Published online May 1, 2019.

The incidence of melanoma continues to increase in most white populations worldwide,[1,2] with the greatest burden associated with melanoma occurring in Australasian, North American, and European populations.[3] The prognosis of primary cutaneous melanoma is largely dependent on tumor characteristics such that 10-year survival rates are 98% for thin (<0.8 mm), nonulcerated primary melanomas and 75% for thick (>4 mm), ulcerated tumors.[4] Historically, the prognosis of metastatic disease has been less than 10% survival,[4] although recent advances in systemic therapies have led to significant improvements in patient outcomes.[5]

To guide diagnostic and treatment decisions, it is necessary to accurately classify the stage of a patient's melanoma at the time of diagnosis. The *AJCC Cancer Staging Manual* on melanoma staging is updated regularly based on emerging evidence, and in the 8th edition (*AJCC 8*) implemented in January 2018,[4] mitosis was removed as a staging criterion, the thickness cut point for thin invasive melanomas was reduced from 1.0 to 0.8 mm, and thickness measurements were rounded to the nearest 0.1 mm across all tumor categories.[4] Survival estimates for tumor category T2 to T4 melanomas are now based on a cohort of patients with negative sentinel lymph node biopsy (SLNB) in contrast to the previous *AJCC 7*, in which SLNB was not required. Spread of disease to lymph nodes, lungs, and central nervous system is now differentiated from "all other viscera" to provide better prognostic information for patients and clinicians.

Although there are no universal follow-up guidelines for primary melanoma survivors, the general consensus is that regular examinations of skin and lymph nodes are required for early detection of disease recurrence or subsequent new primary tumors.[6-8] With the introduction of targeted and immune therapies for treatment of metastatic melanoma, including possible adjuvant therapy, a detailed understanding of the risk of melanoma recurrence may assist clinicians to advise patients with a primary tumor at high risk of disease metastasis.

Using data from a large, prospective cohort of patients with localized cutaneous melanomas at high risk of disease recurrence, we examined the frequency, timing, and sites of predilection of melanoma recurrence in the 2 years following treatment and the associated clinical and histologic factors. We also compared disease-free survival (DFS) using *AJCC 8* vs the seventh edition (*AJCC 7*) to assess prognostic implications of the new staging guideline.

Key Points

Question What is the risk of recurrence after diagnosis of a localized melanoma at high risk of disease metastasis?

Findings In this cohort study of 700 patients with high-risk primary melanoma, 94 individuals (13.4%) developed a recurrence within 2 years of diagnosis at locoregional sites (70.2%) and distant sites (29.8%). After surgery for locoregional disease, 57.8% of the patients remained disease free at 2 years, 10.9% developed new locoregional recurrence, and 31.3% developed distant disease; 2-year disease-free survival was 95% for category T1b melanomas and 67% for category T4b melanomas.

Meaning Understanding the patterns of melanoma recurrence can inform clinical follow-up recommendations.

Methods

Study Population

Participants were recruited between October 1, 2010, and October 1, 2014, from various public specialist hospital clinics in Queensland, Australia; private practices of collaborating surgeons; and through private pathology laboratories. Patients were invited to participate and signed informed consent forms if they had a histologically confirmed new diagnosis of tumor category 1b to 4b cutaneous melanoma with no clinical or radiographic evidence of metastases at time of diagnosis, were older than 16 years, and could complete the study questionnaire. Details have been described elsewhere.[9] The study was approved by the human research ethics committees of the Metro South Health Service and the QIMR Berghofer Medical Research Institute, Brisbane, Australia. Participants did not receive financial compensation.

Data Collection

All participants completed a self-administered questionnaire at baseline giving personal details, including sex, age, and history of melanoma (later confirmed by obtaining reports on histologic findings). Histologic details of all index primary melanomas were extracted from diagnostic reports of pathologic findings, including thickness (millimeters), presence of ulceration (yes/no), regression (yes/no) or mitoses (per square millimeter or high-power field) as well as site (head or neck, trunk, upper limb, lower limb) and subtype. Results from SLNB (if performed) were collected from clinical notes and pathologic test reports.

Melanoma recurrences (yes/no) were reported via 6-monthly, self-completed follow-up questionnaires. Numbers and sites of reported recurrences were then verified based on histologic, imaging, and clinic reports. We defined a recurrence as histologic or radiologic evidence of a metastatic melanoma deposit diagnosed at least 1 month after diagnosis of the primary tumor. Hospital records and the Queensland Cancer Registry were also searched every 6 months for any information about melanoma recurrences or deaths in patients lost to follow-up. Metastatic sites were categorized as local (within 5 cm of primary scar) or regional (regional lymph nodes, intransit, and subcutaneous tissue of draining lymph node), which were collectively termed locoregional, and distant (distant lymph node, lung, central nervous system, or other viscera) in accordance with the *AJCC 8*.[4] If multiple recurrences occurred within 30 days of each other, they were counted as the same event and assigned the date of the earliest recurrence; the recurrence site was classified as distant when any distant metastasis occurred.

Statistical Analysis

Patient and tumor characteristics were assessed in association with recurrence status by using frequencies and proportions, and differences between groups were assessed using

Pearson χ^2 tests. Melanomas were staged using both the *AJCC 7* and *AJCC 8*.[4,10] Clinical stage but not tumor (T) category classification included information from SLNB when performed. Statistical methods were prespecified. The primary outcome of interest was first melanoma recurrence, and patients who did not experience a recurrence or who died within 2 years were censored. To identify clinical and histologic associations with first recurrence, we conducted univariate, age- and sex- adjusted, and multivariate Cox proportional hazards regression analyses, adjusting in turn for variables significantly associated in univariate analyses (age, sex, thickness, ulceration, melanoma subtype, and site of primary tumor). Hazard ratios (HRs) with 95% CIs were obtained for each factor: patient-related (age, sex, skin type, previous occurrence of melanoma, and SLNB) and tumor-related (thickness, ulceration, regression, mitotic rate, subtype, T category, clinical stage, and body site). The final model was examined for effect modification, and proportionality was assessed using time-dependent covariates.

For sensitivity evaluation, we repeated the Cox proportional hazards regression analyses excluding patients with a previous diagnosis of melanoma. We obtained 2-year DFS estimates according to each AJCC guideline edition using Kaplan-Meier analyses, comparing results from the entire cohort with results from those who did not receive an SLNB and from those who had a negative SLNB result. To evaluate the rates of disease recurrence by site, we categorized all first recurrences occurring within 2 years of diagnosis as local, regional, or distant. We also assessed rates of subsequent recurrence for patients who achieved remission after surgical treatment of their first recurrence. Data analysis was conducted from February 8, 2018, to February 20, 2019. Findings were considered significant at $P < .05$. All analyses were performed using SAS, version 9.4 (SAS Institute Inc).

Results

Recurrence Risk

Of 1254 patients with primary melanoma invited to participate, 825 individuals (66%) consented to take part. A further 36 patients (4%) were found to be ineligible after providing informed consent, leaving 789 and, ultimately, 700 patients with T1b to T4b melanomas according to *AJCC 7* and *AJCC 8*, respectively, surgically treated with wide local excision[9] (89 further patients were ineligible under *AJCC 8*). Mean (SD) age at diagnosis was 62.2 (13.5) years, and 410 patients (58.6%) were men. Among the patients meeting the *AJCC 8* criteria for T1b to T4b categorization, 94 individuals (13.4%) developed at least 1 recurrence within 2 years of diagnosis. Tumor factors significantly associated with 2-year recurrence in adjusted analyses were the presence of ulceration (HR, 1.55; 95% CI, 1.00-2.41), more than 3/mm^2 mitotic figures (HR, 2.36; 95% CI, 1.19-4.71), more advanced disease stage (clinical stage IIC: HR, 2.52; 95% CI, 1.08-5.87), and an unclassified histologic subtype (HR, 1.84; 95% CI, 1.04-3.25) (**Table 1**). Head or neck tumors were more likely to recur than those on the trunk or lower limbs (HR, 1.67; 95% CI, 1.01-2.76), while those on the upper limbs were less likely to recur (HR, 0.42; 95% CI, 0.18-0.97). Patients' age, sex, or previous melanoma were not associated with recurrence, and sensitivity analyses excluding the latter showed no change in adjusted HRs.

Disease-Free Survival

Considering the entire cohort and regardless of whether SLNB was performed, 2-year DFS was 95% for T1b tumors and decreased similarly with increasing T stage to 67% for T4b tumors when *AJCC 7* and *AJCC 8* were used for staging (**Table 2**). Disease-free survival decreased with increasing tumor thickness and when ulceration was present. Among patients with T2a-T4a tumors, those who did not have an SLNB at diagnosis had significantly lower 2-year DFS compared with patients with a negative SLNB result of the same tumor stage (all $P < .05$) (Table 2).

Patterns of Recurrence

Of the 94 patients whose melanoma progressed within 2 years, 66 individuals (70.2%) had locoregional disease and 28 individuals (29.8%) had distant disease as the site of first recurrence (14 patients had involvement of multiple sites) (**Figure**). First recurrences that presented as a distant metastasis most commonly occurred in the lungs (9 [47.4%]) or central nervous system (6 [31.6%]). Median time to first recurrence was 40 weeks (Figure). Of 64 patients whose locoregional disease was excised (2 did not have surgery owing to comorbidities), 37 patients (57.8%) remained in remission 2 years post diagnosis, whereas 7 patients (10.9%) developed new locoregional recurrence and 20 patients (31.3%) developed distant disease. Median (SD) time from diagnosis to second recurrence was 57 (22) weeks. Second recurrences at distant sites more often occurred simultaneously in multiple organs (17 [77.3%]) compared with first recurrences at distant sites (3 [15.8%]) ($P < .05$). Second recurrences were found in a variety of sites, including bone (10 [12.2%]), abdominal organs (18 [24.4%]), and thyroid (2 [2.7%]) and parotid glands (2 [2.7%]).

Among the 94 patients with recurrence within 2 years of diagnosis, the number of metastatic sites per patient ranged from 1 to 11, with the most commonly affected sites overall being regional lymph nodes (95 [38.0%]), lung (35 [14.0%]), local sites (23 [9.2%]), distant lymph nodes (23 [9.2%]), and central nervous system (23 [9.2%]).

Discussion

In this cohort of patients with high-risk primary melanoma treated by wide local excision with or without SLNB, 2-year DFS was 95% for T1b tumors and 67% for T4b tumors. Patients who did not undergo an SLNB had a significantly lower 2-year DFS compared with patients with a melanoma of the same tumor category and a negative SLNB result. Presence of ulceration significantly decreased survival across all tumor thicknesses. Other factors associated with poorer 2-year prognosis included mitotic rate greater than 3/mm^2 and head or neck location of the primary tumor. Most first recurrences occurred at locoregional sites (70.2%). Thirty-seven patients (57.8%) who

Table 1. Patient and Tumor Risk Factors for 2-Year Melanoma Recurrence

Variable	Total	No Recurrence	Recurrence	HR (95% CI)[a]
Patient Factors				
Total, No. (%)	700 (100)	606 (86.6)	94 (13.4)	
Sex				
Men	410 (58.6)	345 (56.9)	65 (69.1)	1.10 (0.67-1.75)
Women	290 (41.4)	261 (43.1)	29 (30.9)	1 [Reference]
Age, No. (%), y				
<55	189 (27.0)	170 (28.1)	19 (20.2)	0.92 (0.52-1.63)
55-70	309 (44.1)	270 (44.6)	39 (41.5)	1 [Reference]
>70	202 (28.8)	166 (27.4)	36 (38.3)	1.12 (0.70-1.78)
Previous melanoma				
No	563 (80.4)	488 (80.5)	75 (79.8)	1 [Reference]
Yes	137 (19.6)	118 (19.5)	19 (20.2)	0.91 (0.53-1.56)
SLNB				
No	442 (63.1)	377 (62.2)	65 (69.1)	1 [Reference]
Yes	258 (36.9)	228 (37.6)	30 (31.9)	0.98 (0.60-1.60)
SLNB positive result				
No	220 (85.3)	208 (91.2)	12 (40.0)	
Yes	38 (14.7)	20 (8.8)	18 (60.0)	NA[b]
Tumor Factors				
Body site				
Trunk	247 (35.3)	217 (35.8)	30 (31.9)	1 [Reference]
Head/neck	154 (22.0)	116 (19.1)	38 (40.4)	1.67 (1.01-2.76)[c]
Upper limbs	143 (20.4)	136 (22.4)	7 (7.4)	0.42 (0.18-0.97)[c]
Lower limbs	156 (22.2)	137 (22.6)	19 (20.2)	0.84 (0.46-1.54)
Thickness, mm				
≤1	121 (17.3)	115 (19.0)	6 (6.4)	1 [Reference]
>1-2	312 (44.6)	281 (43.4)	31 (33.0)	1.41 (0.58-3.42)
>2-4	178 (25.4)	145 (23.9)	33 (35.1)	1.94 (0.78-4.85)
>4	89 (12.7)	65 (10.7)	24 (25.5)	2.20 (0.83-5.83)
Ulceration				
No	504 (72.0)	454 (74.9)	50 (53.2)	1 [Reference]
Yes	196 (28.0)	152 (25.1)	44 (46.8)	1.55 (1.00-2.41)[c]
Mitotic rate[d]				
<1	109 (16.0)	99 (16.8)	10 (11.0)	1 [Reference]
1-3	300 (44.0)	280 (47.4)	20 (22.0)	0.88 (0.38-2.02)
>3	273 (40.0)	212 (35.9)	61 (67.0)	2.40 (1.10-5.24)[c]
Regression				
No	457 (65.3)	389 (64.2)	68 (72.3)	1 [Reference]
Yes	243 (34.7)	217 (35.8)	26 (27.7)	0.92 (0.56-1.50)
Subtype				
SSM	278 (39.7)	253 (41.7)	25 (26.6)	1 [Reference]
Nodular	172 (24.6)	145 (23.9)	27 (28.7)	1.08 (0.60-1.95)
Other[e]	118 (16.9)	103 (17.0)	15 (16.0)	1.37 (0.69-2.69)
Not classified[f]	132 (18.9)	105 (17.4)	27 (28.7)	1.84 (1.04-3.25)[c]
T category				
T1b	121 (17.3)	115 (19.0)	6 (6.4)	1 [Reference]
T2a	242 (34.6)	225 (37.1)	17 (18.1)	1.16 (0.45-2.97)
T2b	70 (10.0)	56 (9.2)	14 (14.9)	2.55 (0.95-6.83)
T3a	121 (17.3)	100 (16.5)	21 (22.3)	2.49 (0.98-6.32)
T3b	57 (8.1)	45 (7.4)	12 (12.8)	1.85 (0.65-5.23)
T4a	40 (5.7)	32 (5.3)	8 (8.5)	1.48 (0.48-4.59)

(continued)

Table 1. Patient and Tumor Risk Factors for 2-Year Melanoma Recurrence (continued)

Variable	Total	No Recurrence	Recurrence	HR (95% CI)[a]
T4b	49 (7.0)	33 (5.4)	16 (17.0)	3.86 (1.40-10.64)[c]
Clinical stage[g]				
IB	352 (53.2)	332 (56.7)	20 (26.0)	1 [Reference]
IIA	176 (26.6)	147 (25.1)	29 (37.7)	2.19 (1.22-3.93)[c]
IIB	93 (14.0)	75 (12.8)	18 (23.4)	1.38 (0.67-2.84)
IIC	41 (6.2)	31 (5.3)	10 (13.0)	2.52 (1.08-5.87)[c]

Abbreviations: HR, hazard ratio; SLNB, sentinel lymph node biopsy; SSM, superficial spreading melanoma.

[a] Adjusted for age, sex, thickness, ulceration, mitotic rate, subtype, and body site.

[b] Too few participants.

[c] Statistically significant.

[d] Missing data (n = 18).

[e] Other: lentigo maligna (17.8%), desmoplastic (36.4%), naevoid (21.2%), spitzoid (4.2%), lentiginous (2.5%), acral lentiginous (3.8%), mixed (11.0%).

[f] Not classified: unable to classify (15.2%), not stated (84.1%), and other (0.8%).

[g] Excludes patients with a positive SLNB result (n = 38).

Table 2. Two-Year DFS by Tumor Category and Clinical Stage Comparing *AJCC 7* vs *AJCC 8*, With and Without Information From SLNB

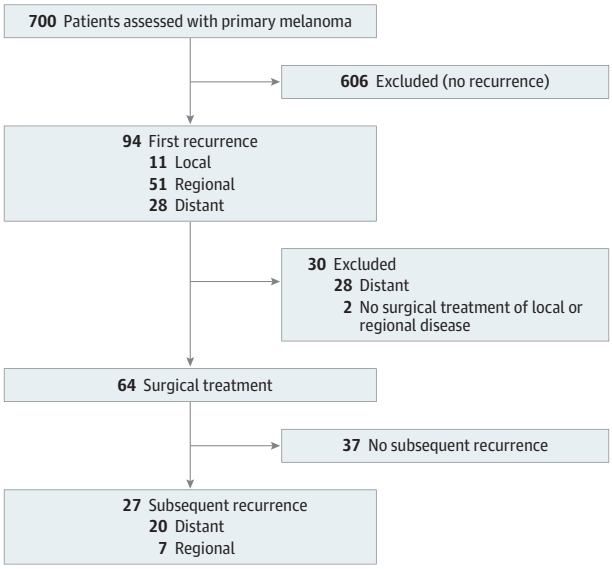
	AJCC 7			*AJCC 8*				
						DFS		
Tumor Status	Total, No. (n = 789)	Recurrence, No. (%) (n = 99)	DFS: All Patients, % (95% CI)	Total, No. (n = 799)	Recurrence, No. (%) (n = 94)	All Patients, % (95% CI)	Without SLNB, % (95% CI) (n = 442)	With Negative SLNB Result, % (95% CI) (n = 220)
T category								
T1b	195	10 (5.1)	94.9 (91.8-98.0)	121	6 (5.0)	95.0 (91.2-98.9)	96.5 (92.6-100.0)	94.1 (86.2-100.0)
T2a	253	17 (6.7)	93.3 (90.2-96.4)	242	17 (7.0)	93.0 (89.8-96.2)	91.1 (86.4-95.9)	96.9 (93.4-100.0)
T2b	71	14 (17.7)	80.3 (71.0-89.5)	70	14 (20.0)	80.0 (71.0-89.0)	76.9 (63.7-90.1)	91.7 (80.6-100.0)
T3a	122	22 (18.0)	82.0 (75.1-88.8)	121	21 (17.4)	82.6 (75.9-89.4)	77.5 (68.3-86.7)	100.0 (100.0-100.0)
T3b	57	12 (21.1)	78.9 (68.4-89.5)	57	12 (21.1)	78.9 (68.4-89.5)	77.8 (64.2-91.4)	88.2 (72.9-100.0)
T4a	40	8 (20.0)	80.0 (67.6-92.4)	39	8 (20.0)	79.5 (66.8-92.2)	78.8 (64.8-92.7)	83.3 (53.5-100.0)
T4b	50	16 (32.7)	68.0 (55.1-80.9)	50	16 (32.7)	68.0 (55.1-80.9)	75.0 (60.0-90.0)	80.0 (55.2-100.0)
Clinical stage								
IB	437	24 (5.5)	94.5 (92.4-96.6)	352	20 (5.7)	94.3 (89.9-96.5)	n = 209; 93.8 (90.5-97.1)	n = 130; 96.2 (92.8-96.2)
IIA	178	30 (16.9)	83.1 (77.6-88.6)	176	29 (16.5)	83.5 (78.0-89.0)	n = 116; 77.6 (70.0-85.2)	n = 57; 96.5 91.7-100.0)
IIB	93	18 (19.1)	80.6 (72.6-88.7)	93	18 (19.4)	80.4 (72.3-88.5)	n = 67; 79.1 (69.4-88.8)	n = 23; 87.0 (73.2-100.0)
IIC	42	10 (24.4)	76.2 (63.3-89.1)	41	10 (24.4)	76.2 (63.3-89.1)	n = 31; 74.0 (58.8-89.6)	n = 10; 80.0 (55.2-100.0)

Abbreviations: AJCC, American Joint Committee on Cancer; *AJCC 7*, 7th edition of the *AJCC Cancer Staging Manual*; *AJCC 8*, 8th edition of the *AJCC Cancer Staging Manual*; DFS, disease-free survival; SLNB, sentinel lymph node biopsy.

had surgical resection of their locoregional recurrence remained disease free 2 years after diagnosis of the index melanoma, whereas 31.3% developed a subsequent recurrence at a distant site.

Tumor thickness has been recognized as the single most important criterion for staging localized tumors since the 1st AJCC guideline edition was published in 1977.[11] Since then, the AJCC melanoma stage classification has been revised 7 times as the understanding of melanoma has evolved. Changes to *AJCC 8* were based on consistent evidence that sentinel lymph node biopsy positivity is negligible in melanomas thinner than 0.75 mm[12,13] and thickness measurements are impractical and imprecise.[4,14] Our findings reported herein demonstrate that the outcome of rounding on T1b to T4b tumors is minimal, as DFS by tumor stage did not differ significantly between *AJCC 7* and *AJCC 8*. In contrast, 2-year DFS was significantly affected by information obtained from SLNB as recommended in *AJCC 8*. Two-year DFS was significantly lower in patients who did not have an SLNB at diagnosis compared with pa-

Figure. Proportion of Local, Regional, and Distant Recurrences Within 2 Years



Median time to first recurrence, 40 weeks; median time to second recurrence, 57 weeks.

tients with a negative SLNB result, suggesting that SLNB should be considered routinely for use in high-risk patients.

Our findings that ulceration and many mitoses are important histopathologic features associated with higher rates of recurrence are consistent with other evidence.[15,16] Ulceration and mitoses indicate rapid tumor growth; hence, they were incorporated into the AJCC melanoma staging criteria in the 6th and 7th editions, respectively.[10] The removal of mitosis in the latest staging classification may have a detrimental effect on assessing some patients' prognosis.[17] It is likely that future melanoma staging will integrate clinicopathologic, molecular, and other correlates of tumor biological factors to help streamline treatment and more accurately advise on likely prognosis.[4]

The benefit of detecting distant unresectable disease at an early stage is becoming an important question with the evolution of effective systemic therapies.[18] Understanding the patterns of disease recurrence may assist clinicians in counseling patients about self-examinations and symptoms of melanoma recurrence.[8] A total of 70.2% of first recurrences occurred locoregionally; hence, our data appear to support the recommendation for careful scar and regional skin and lymph node examination during patient follow-up.[19] Subsequent recurrences occurring at distant sites were more likely to involve multiple organs, which is consistent with other studies.[20]

Strengths and Limitations

Strengths of this study are its prospective design and well-characterized clinical cohort reflecting the demographics of the high-risk primary melanoma population in the state at large.[9] Primary melanoma recurrence was confirmed with histologic and/or radiologic analysis. Detailed tumor characteristics were obtained from histologic findings, and interobserver agreement in reporting melanoma features is high in Australia.[21] Limitations of the study include the lack of information regarding the method of recurrence detection and the relatively short follow-up time, although our rates of first recurrence are robust and consistent with reports from other population cohorts.[22,23]

Conclusions

The findings of this study suggest that approximately 13% of patients with a high-risk primary melanoma may develop recurrence within 2 years, and SLNB should be considered to improve prognostic accuracy. Understanding the patterns and risk factors of melanoma recurrence can inform clinical follow-up recommendations.

ARTICLE INFORMATION

Accepted for Publication: February 21, 2019.

Published Online: May 1, 2019. doi:10.1001/jamadermatol.2019.0440

Author Affiliations: Population Health Department, QIMR Berghofer Medical Research Institute, Brisbane, Australia (von Schuckmann, Hughes, Malt, Beesley, Green); School of Public Health, The University of Queensland, Brisbane, Australia (von Schuckmann); Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway (Ghiasvand); School of Exercise and Nutrition Sciences, Queensland University of Technology, Brisbane, Australia (van der Pols); Experimental Dermatology Group, The University of Queensland Diamantina Institute, Translational Research Institute, Brisbane, Australia (Khosrotehrani); Department of Dermatology, Princess Alexandra Hospital, Brisbane, Australia (Khosrotehrani); Queensland Melanoma Project, Princess Alexandra Hospital, The University of Queensland, Brisbane, Australia (Smithers); Cancer Research UK Manchester, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom (Green).

Author Contributions: Mss von Schuckmann and Hughes had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: von Schuckmann, Beesley, Khosrotehrani, Smithers, Green.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: von Schuckmann, van der Pols, Green.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: von Schuckmann, Hughes, Ghiasvand.
Obtained funding: Green.
Administrative, technical, or material support: Hughes, Malt, Beesley, Khosrotehrani, Smithers, Green.
Supervision: van der Pols, Khosrotehrani, Smithers, Green.

Conflict of Interest Disclosures: None reported.

Funding/Support: The study is supported by National Health and Medical Research Council (NHMRC) Program grants 1073898 and 552429. Ms von Schuckmann is funded by NHMRC Postgraduate Scholarship 1133317, Dr Ghiasvand is funded by Norwegian Cancer Society project 6823329, and Dr Khosrotehrani is funded by a NHMRC Career Development Fellowship.

Role of the Funder/Sponsor: The funding bodies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Guy GP Jr, Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and costs of skin cancer treatment in the US, 2002-2006 and 2007-2011. *Am J Prev Med*. 2015;48(2):183-187. doi:10.1016/j.amepre.2014.08.036

2. Whiteman DC, Green AC, Olsen CM. The growing burden of invasive melanoma: projections of incidence rates and numbers of new cases in six susceptible populations through 2031. *J Invest Dermatol*. 2016;136(6):1161-1171. doi:10.1016/j.jid.2016.01.035

3. Karimkhani C, Green AC, Nijsten T, et al. The global burden of melanoma: results from the Global Burden of Disease Study 2015. *Br J Dermatol*. 2017;177(1):134-140. doi:10.1111/bjd.15510

4. Gershenwald JE, Scolyer RA, Hess KR, et al; for members of the American Joint Committee on Cancer Melanoma Expert Panel and the International Melanoma Database and Discovery Platform. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67(6):472-492. doi:10.3322/caac.21409

5. Bhatia S, Tykodi SS, Lee SM, Thompson JA. Systemic therapy of metastatic melanoma: on the road to cure. *Oncology (Williston Park)*. 2015;29(2):126-135.

6. Trotter SC, Sroa N, Winkelmann RR, Olencki T, Bechtel M. A global review of melanoma follow-up guidelines. *J Clin Aesthet Dermatol*. 2013;6(9):18-26.

7. Gutiérrez García-Rodrigo C, Antonini A, Rocco T, Pellegrini C, Micantonio T, Fargnoli MC. Staging and follow-up of cutaneous melanoma patients. *G Ital Dermatol Venereol*. 2017;152(3):231-240. doi:10.23736/S0392-0488.17.05581-X

8. Turner RM, Bell KJ, Morton RL, et al. Optimizing the frequency of follow-up visits for patients treated for localized primary cutaneous melanoma. *J Clin Oncol*. 2011;29(35):4641-4646. doi:10.1200/JCO.2010.34.2956

9. Smithers BM, Hughes MCB, Beesley VL, et al. Prospective study of patterns of surgical management in adults with primary cutaneous melanoma at high risk of spread, in Queensland, Australia. *J Surg Oncol*. 2015;112(4):359-365. doi:10.1002/jso.24013

10. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol*. 2009;27(36):6199-6206. doi:10.1200/JCO.2009.23.4799

11. American Joint Committee for Cancer. *Manual for Staging of Cancer—1977*. Chicago, Illinois: American Joint Committee for Cancer; 1977.

12. Han D, Zager JS, Shyr Y, et al. Clinicopathologic predictors of sentinel lymph node metastasis in thin melanoma. *J Clin Oncol*. 2013;31(35):4387-4393. doi:10.1200/JCO.2013.50.1114

13. Murali R, Haydu LE, Quinn MJ, et al. Sentinel lymph node biopsy in patients with thin primary cutaneous melanoma. *Ann Surg*. 2012;255(1):128-133. doi:10.1097/SLA.0b013e3182306c72

14. Veierød MB, Page CM, Aaserud S, et al. Melanoma staging: varying precision and terminal digit clustering in Breslow thickness data is evident in a population-based study. *J Am Acad Dermatol*. 2018;79(1):118-125. doi:10.1016/j.jaad.2018.03.023

15. Thompson JF, Soong SJ, Balch CM, et al. Prognostic significance of mitotic rate in localized primary cutaneous melanoma: an analysis of patients in the multi-institutional American Joint Committee on Cancer melanoma staging database. *J Clin Oncol*. 2011;29(16):2199-2205. doi:10.1200/JCO.2010.31.5812

16. Azzola MF, Shaw HM, Thompson JF, et al. Tumor mitotic rate is a more powerful prognostic indicator than ulceration in patients with primary cutaneous melanoma: an analysis of 3661 patients from a single center. *Cancer*. 2003;97(6):1488-1498. doi:10.1002/cncr.11196

17. von Schuckmann LA, Celia B, Hughes M, et al. Survival of patients with early invasive melanoma down-staged under the new eighth edition of the American Joint Committee on Cancer staging system. *J Am Acad Dermatol*. 2019;80(1):272-274. doi:10.1016/j.jaad.2018.04.017

18. Tsao H, Feldman M, Fullerton JE, Sober AJ, Rosenthal D, Goggins W. Early detection of asymptomatic pulmonary melanoma metastases by routine chest radiographs is not associated with improved survival. *Arch Dermatol*. 2004;140(1):67-70. doi:10.1001/archderm.140.1.67

19. Francken AB, Bastiaannet E, Hoekstra HJ. Follow-up in patients with localised primary cutaneous melanoma. *Lancet Oncol*. 2005;6(8):608-621. doi:10.1016/S1470-2045(05)70283-7

20. Patel JK, Didolkar MS, Pickren JW, Moore RH. Metastatic pattern of malignant melanoma: a study of 216 autopsy cases. *Am J Surg*. 1978;135(6):807-810. doi:10.1016/0002-9610(78)90171-X

21. Murali R, Cochran AJ, Cook MG, et al. Interobserver reproducibility of histologic parameters of melanoma deposits in sentinel lymph nodes: implications for management of patients with melanoma. *Cancer*. 2009;115(21):5026-5037. doi:10.1002/cncr.24298

22. Hafez KK, MacCormick R. Malignant melanoma, with emphasis on first relapse cases. *Taibah Univ Med Sci*. 2012;7(2):81-86. doi:10.1016/j.jtumed.2012.11.005

23. Leiter U, Meier F, Schittek B, Garbe C. The natural course of cutaneous melanoma. *J Surg Oncol*. 2004;86(4):172-178. doi:10.1002/jso.20079