Second Primary Melanoma: Risk Factors, Histopathologic Features, Survival, and Implications for Follow-Up

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Abstract

The impact on survival of a second primary melanoma (SPM) is unclear. We used our melanoma center's database to examine clinicopathologic risk factors and outcomes of stage 0 to IV cutaneous melanoma in patients with one *versus* two primaries. Among 12,325 patients with primary melanoma, 969 (7.86%) developed SPM. SPMs were significantly thinner than autologous primary melanomas ($P = 0.01$), and 451 SPM patients had better overall and melanoma-specific survival than 451 prognostically matched non-SPM patients ($P < 0.0001$ and 0.0001, respectively) at a median follow-up of 142.37 months. Patients with cutaneous melanoma are at high risk for development of SPM, but the development of SPM does not seem to impair survival.

A previous retrospective review from our institution found that patients who develop one primary melanoma have a 25-fold increased risk of developing a second primary melanoma (SPM) as compared with the general population.[1] However, it is not well established that PM patients are at greatest risk for SPM, and what effect SPM has on their outcome. This study examines a large population of melanoma patients with long-term follow-up to address these questions.

Materials and Methods

All patient data were deidentified, and this study was independently reviewed and confirmed to be exempt from Institutional Review Board review. A review of our institution's prospectively collected melanoma database identified all patients diagnosed with American

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Joint Committee on Cancer (AJCC) stages 0 to Iv cutaneous melanoma between January 1971 and August 2015.[2, 3] Melanomas were staged by seventh edition AJCC criteria,[4] with two modifications based on data availability: inclusion of Clark level and exclusion of mitotic rate. SPM was defined as a cutaneous melanoma detected at least two months after diagnosis of the first melanoma, and determined by a John Wayne Cancer Institute treating physician to be a SPM. Patients with synchronous nonmelanoma primary malignancies, unknown primary melanoma, or other noncutaneous melanomas were excluded.

The interval between first and second melanomas was examined by patient age (55 *vs* >55 years). Chi-squared test was used for analysis of clinicopathologic factors-associated development of one *versus* two primaries. Annual and cumulative risks of developing SPM were determined using life table methodology, as was the interval from first to second primary. McNemar's test was used to analyze histopathologic differences between autologous PM and SPM lesions. univariate and multivariate Cox regression analysis examined clinically relevant risk factors. Kaplan- Meier curves for overall and melanoma-specific survival were plotted from diagnosis of PM and compared using the log-rank test. Survival analysis used pairs of PM-only and SPM patients who were matched for Breslow thickness, primary site, histologic type, ulceration status of the first primary, sex, age (55 or >55), calendar year of first primary melanoma diagnosis, and pathologic lymph node status. All statistical tests were two sided, and $P < 0.05$ was considered to be statistically significant.

Results

Among 12,325 patients with AJCC stages 0 to IV cutaneous melanoma, 969 (7.86%) developed SPM. The cumulative risk of developing SPM was 5.58 per cent at 5 years, 8.04 per cent at 10 years, and 43.95 per cent at 49 years of follow-up. The median time to the development of SPM was 8.39 years [interquartile range (IQR): 3.5–16.2]. The cumulative risk of developing SPM was always significantly higher for patients older than 55 years at first diagnosis of PM ($P < 0.0001$). Median follow-up was 17.2 years (IQR: 10.3–28.2) for the 581 patients aged 55 years, and 9.9 years (IQR: 5.8–15.1) for the 386 older patients. Younger patients developed SPM at a mean $\pm$ SD of 9.1 $\pm$ 9.6 years, whereas older patients developed a SPM at 4.2 $\pm$ 4.9 years ($P < 0.001$).

As compared with PM-only patients, SPM patients were more likely to be older, male, fair skinned, have fair/blonde hair, with head/neck primaries, and lower-stage disease (Table 1). As compared with autologous PMs, SPMs were more likely to be thin, not invasive, not ulcerated and *in situ*. Age above 55 years at diagnosis of PM and male sex significantly increased risk for SPM, whereas PM truncal/extremity location, Breslow thickness of 2.01 to 4.0 mm, or Clark level II to V decreased risk of SPM (Table 2). Multivariate analysis revealed an inverse relationship between the melanoma-free interval after PM and the likelihood of developing SPM. Patients with *in situ* melanoma and lentigo maligna melanoma (LMM) were more likely to develop SPM.

Of 969 SPM patients, 354 had complete records to examine the changes in histopathological characteristics from the first primary to SPM. The most common histopathological subtypes

were superficial spreading melanoma (SSM) and melanoma *in situ* in both PM and SPM, but no significant correlation was seen between the histopathologic subtypes of PM and SPM. In 384 patients with complete Breslow thickness records, SPM was found to be significantly thinner than the PM. The mean ± SE Breslow thickness was 0.4 ± 0.1 mm thinner in SPM compared with PM (P 0.0001). Because Breslow thickness is only recorded in invasive melanoma, the significance of this finding may actually be higher, given that the frequency of *in situ* disease was higher in SPM than the first primary. In 636 patients with complete records; 41.5 per cent of first primaries were Clark levels I or II, compared with 61.3 per cent in SPMs ($P < 0.001$). To investigate the relationship between SPM development and patient survival, the interval of time between first and SPMs on survival was analyzed. Increasing time from the first to the SPM was found to significantly decrease the risk of death from melanoma [hazard ratio (HR): 0.80, 95% confidence interval (CI): 0.80–0.81, $P < 0.0001$]. Kaplan-Meier survival curves were plotted for 50 years of follow-up. To attempt to decrease bias from the length of follow-up time, we performed a matched pair analysis of SPM and PM patients. Each SPM patient was matched with a single primary patient by the same calendar year of first primary melanoma diagnosis, along with other clinical and histopathological factors. In this group of 451 matched pairs, SPM patients had a median follow-up of 156.8 months (range 2.0–586.6 months), and PM patients had a median follow-up of 124.6 months (range 0.4–503.0 months). When single and SPM patients were matched, patients with a SPM had significantly better overall survival (OS; $P < 0.0001$) and melanoma specific survival (MSS; $P < 0.0001$). Breslow thickness of the PM was thinner in SPM patients than in PM-alone patients.

Discussion

Risk factors for the development of SPM have been previously examined with variation in the reported incidence of SPM.[5–11] In a prospective cohort study, Siskind et al. examined the incidence of SPM in 1083 patients with PM and found 20.4 per cent developed SPM, whereas Levi et al. noted the incidence of SPM to be 1.3 per cent.[6, 7] In a more recent study, Jung et al. queried the Surveillance, Epidemiology and End Results database from 1973 to 2008; 3.3 per cent patients with PM developed SPM.[8] Hwa et al. reviewed 788 patients and identified an 8.7 per cent cumulative incidence of developing a SPM five years after the initial PM diagnosis with 4.1 per cent of that risk accumulating within the first year after diagnosis.[11] Youlden et al. noted an elevated standardized incidence ratio of 5.4 for the development of a SPM after the diagnosis of an invasive PM.[9] In our institutional analysis, a 7.86 per cent incidence of SPM was found among 12,325 patients who were initially diagnosed with AJCC stage 0 to IV cutaneous melanoma with a median follow-up time of 109.68 months. Follow-up time for the >55- year age group was likely shorter due to competing risks associated with older age, making the increased likelihood of SPM development in this group even more meaningful. Krajewski et al., in a retrospective study of 222 elderly melanoma patients, describe a 10 per cent incidence of SPM, akin to what we have seen in our review.[12] Increasing time from diagnosis is recognized as a risk factor for the development of a SPM. We have shown that subsequent SPM lesions, when found, are thinner. In our study, the increased risk of developing SPM during the 49 years after first primary diagnosis likely reflects increased skin scrutiny by physicians as well as increased

awareness and alertness to new skin lesions by patients. It remains to be seen if clinical or histopathological characteristics can predict SPM development. In this study, increasing patient age from the time of the PM and male sex were significantly associated with increased risk for SPM. SPM was significantly thinner than the PM, with a significantly increased proportion of *in situ* disease. Diagnosis of thinner SPM lesions has previously been noted by other groups, as well as an increased incidence of *in situ* lesions.[10,12–17] Siskind et al. also reported that SPM were associated with high nevus count, high familial melanoma risk, fair skin, inability to tan, *in situ* first primary melanoma, and male sex.[6] Predicting the development of SPM by histopathologic subtype is controversial. This group also noted that LMM or nodular melanoma as the PM had higher risk of SPM than patients whose PM was SSM. Bower et al. alternatively reported SSM as significantly associated with SPM on multivariate analysis.[6, 18] In our study, consistent with the findings of Siskind et al., LMM as the PM led to SPM more commonly.

The impact of SPM on patient survival has also been an area of controversy.[19–22] Doubrovsky et al. reported increased survival in patients whose stage I or II melanoma was associated with three versus one SPM. investigated the survival of stages I and II melanoma patients and found that in those with three primary melanomas, there was a significant increase in survival.[19] In contrast, Kricker et al. investigated all stages of melanoma and reported no OS difference between PM patients and multiple primary melanoma patients (n = 1206).[22] Burden et al. also reported in two separate studies that the development of multiple primary melanomas was not an independent prognostic factor of melanoma.[20, 21]

In our study, SPM patients had significantly better OS and MSS than did patients with a PM alone. This may be because patients who developed SPM had favorable prognostic factors associated with the PM; therefore, these patients lived long enough to develop the SPM. Increased Breslow thickness (up to 4.0 mm) decreased the risk of developing a SPM in this study; however, this is likely because patients with thicker lesions do not live long enough to develop a SPM. These survival data emphasize the importance of patient and physician education such that first primary melanomas are detected and treated at an early stage.

The retrospective nature of our study limited analyses to patients with complete clinicopathologic data. Differences in follow-up time between the PM and SPM groups also limit this work. Finally, our study was subject to treatment-related biases at our referral center. Despite these limitations, we believe that our results accurately reflect patterns of SPM development.

Conclusions

Although the risk of melanoma-associated death in SPM patients decreases with increased interval after PM diagnosis, follow-up surveillance should be lifelong. The risk for SPM seems to be continuous, and persists for decades after the initial diagnosis. All patients, especially those older than 55 years, should be educated on the importance of regular self-examination and features to look for regarding pigmented skin lesions.

Acknowledgments

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Table 1

Clinical and Histopathological Features of the PM and SPM

	PM	SPM	P Value[*]
Number of patients	11,356	969	
Age at diagnosis, mean ± SD	49.73 ± 16.69	51.12 ± 16.05	0.0128
Sex			0.0130
Female	4885 (43.02%)	377 (38.91%)	
Male	6471 (56.98%)	592 (61.09%)	
Stage at initial diagnosis			<0.0001
0/I/II	6752 (59.46%)	638 (65.84%)	
III	2836 (24.97%)	206 (21.26%)	
IV	1594 (14.04%)	99 (10.22%)	
Unknown	174 (1.53%)	26 (2.68%)	
Primary site			<0.0001
Head/neck	2887 (25.42%)	273 (28.17%)	
Trunk	4611 (40.60%)	368 (37.98%)	
Lower extremity	2576 (22.68%)	185 (19.09%)	
Upper extremity	1264 (11.13%)	119 (12.28%)	
Unknown	18 (0.16%)	24 (2.48%)	
Breslow thickness (mm)			<0.0001
1.0	3768 (33.18%)	348 (35.91%)	
1.01–2.00	2519 (22.18%)	173 (17.85%)	
2.01–4.00	1697 (14.94%)	85 (8.77%)	
>4.00	845 (7.44%)	34 (3.51%)	
Unknown	2527 (22.25%)	329 (33.95%)	
Ulceration			<0.0001
Yes	1529 (13.46%)	80 (8.26%)	
No	6902 (60.78%)	589 (60.78%)	
Unknown	2925 (25.76%)	300 (30.96%)	
Clark level			<0.0001
I	803 (7.07%)	121 (12.49%)	
II	1934 (17.03%)	191 (19.71%)	
III	2837 (24.98%)	209 (21.57%)	
IV	3610 (31.79%)	224 (23.12%)	
V	565 (4.98%)	25 (2.58%)	
Unknown	1607 (14.15%)	199 (20.54%)	
Histological type			<0.0001
ALM	113 (1.01%)	1 (0.10%)	
In situ	634 (5.67%)	102 (10.65%)	
LMM	345 (3.09%)	44 (4.59%)	
NM	1853 (16.58%)	91 (9.5%)	
SSM	4466 (39.96%)	313 (32.67%)	

	PM	SPM	P Value[*]
Others	520 (4.65%)	21 (2.19%)	
Unknown	3245 (29.04%)	386 (40.29%)	
Eye color			0.0010
Blue/grey	2393 (21.07%)	252 (26.01%)	
Brown/black	1398 (12.31%)	114 (11.76%)	
Green/hazel	1741 (15.33%)	159 (16.41%)	
Unknown	5824 (51.29%)	444 (45.82%)	
Early adult hair color			0.0013
Black	117 (1.03%)	13 (1.34%)	
Dark brown	1671 (14.71%)	130 (13.42%)	
Light brown	806 (7.1%)	99 (10.22%)	
Dark red/auburn	568 (5.0%)	56 (5.78%)	
Light red/ginger	52 (0.46%)	4 (0.41%)	
Fair/blonde	2243 (19.75%)	214 (22.08%)	
Unknown	5899 (51.95%)	453 (46.75%)	
Skin color			0.0005
Dark/medium	926 (8.15%)	65 (6.71%)	
Fair	4467 (39.34%)	442 (45.61%)	
Unknown	5936 (52.51%)	462 (47.68%)	

ALM, acral lentiginous melanoma; NM, nodular melanoma; SD, standard deviation.

[*] *P* values were obtained after excluding unknown or missing data.

Table 2

Univariate and Multivariate Cox Regression of Clinical and Histopathological Risk Factors for SPM

	Univariate		Multivariate	
	P Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)
Increasing age from first primary	<0.0001	1.019 (1.019–1.023)	<0.0001	1.017 (1.01–1.02)
Age at first primary [*] (>55 *vs* 55)	<0.0001	1.66 (1.45–1.89)		
Sex (male *vs* female)	<0.0001	1.368 (1.20–1.56)	0.0003	1.286 (1.12–1.48)
First primary site (reference: head/neck)			0.3056	0.918 (0.78–1.08)
Lower extremity	<0.0001	0.64 (0.53–0.77)		
Trunk	0.0015	0.776 (0.66–0.91)		
Upper extremity	0.1724	0.86 (0.66–0.91)		
First primary ulceration (yes *vs* no)	0.1247	0.833 (0.66–1.05)		
First primary Breslow (reference: 1.0)				
1.01–2.0	0.0518	0.834 (0.70–1.00)		
2.01–4.0	0.0217	0.757 (0.60–0.96)	0.0303	0.812 (0.67–0.98)
>4.0	0.0931	0.739 (0.52–1.05)	0.0289	0.754 (0.59–0.97)
First primary Clark level (reference: Clark I)				
II	<0.0001	0.480 (0.38–0.60)		
III	<0.0001	0.400 (0.32–0.50)		
IV	<0.0001	0.433 (0.35–0.54)		
V	<0.0001	0.400 (0.26–0.62)		
First primary histological type (reference: NMM)				
In situ	<0.001	10.93 (1.52–78.66)	<0.0001	2.718 (1.96–3.78)
LMM	<0.001	5.96 (0.82–43.53)		
ALM	0.2083	0.282 (0.04–2.03)		
SSM	0.2556	1.145 (0.91–1.45)		
Others	0.9813	1.005 (0.67–1.50)		
Unknown	<0.0001	2.200 (1.75–2.77)	<0.0001	1.832 (1.43–2.34)
Eye color (reference: brown/black)				
Blue/grey	0.0510	1.247 (1.00–1.56)		
Green/hazel	0.7182	1.045 (0.82–1.33)		
Unknown	0.4677	1.079 (0.88–1.33)		
Hair color (reference: black)				
Dark brown	0.0873	0.608 (0.34–1.08)		
Light brown	0.6376	1.149 (0.64–2.05)		
Dark red/auburn	0.2400	0.696 (0.38–1.27)		
Light red/ginger	0.1668	0.453 (0.15–1.39)		
Fair/blonde	0.1228	0.643 (0.37–1.13)		
Unknown	0.1931	0.693 (0.40–1.20)		
Skin color (reference: dark/medium)				
Fair	0.0494	1.298 (1.00–1.69)		
Unknown	0.0976	1.246 (0.96–1.62)		

NMM, nodular malignant melanoma.

*
 Increasing age from first primary is a continuous variable, and age at first primary is dichotomized variable. Continuous variables were used because they give more complete information than dichotomized variables.