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Is Pregnancy-Associated Melanoma Associated with Adverse Outcomes?

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Abstract

Background—Melanoma is the most common malignancy encountered during pregnancy. Conflicting data have led to ongoing confusion regarding pregnancy associated melanoma (PAM) in the media and among the public. The objective of this study was to better characterize both the clinical presentation of PAM and its prognostic implications.

Study Design—Female patients of reproductive age with stage 0-IV cutaneous melanoma were identified from our prospectively maintained database. Clinical and histopathologic factors were analyzed with appropriate statistical methods. Univariable and then multivariable analysis were utilized on matched data to compare disease free survival (DFS), overall survival (OS) and melanoma specific survival (MSS) for stage 0-III PAMs vs non-PAMs. Kaplan-Meier survival curves were then plotted for OS and MSS and compared using the log-rank test.

Results—Clinical presentation of melanoma was similar for PAM and non-PAM patients. There was no significant difference in recurrence between the two groups; for PAMs, 38.5% of patients recurred as compared to 36.6% of non-PAMs (p=0.641). For PAMs, median follow up was 14.6 years (range 0–42.6 years) and 11.1 years (0 – 48.5 years) for the non-PAMs. No significant differences in DFS, MSS, or OS were identified on univariable or multivariable analysis for PAM vs non-PAMs in stage 0/I/II and stage III cutaneous melanoma respectively (p=0.880 DFS, p=0.219 OS and p=0.670 MSS).

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Conclusions—We observed no difference in DFS, OS or MSS between the two groups. Pregnant patients should be screened for melanoma in a similar manner to non-pregnant patients and should be counseled that their survival is not adversely affected by their pregnancy.

Keywords

Melanoma; Pregnancy; overall survival; melanoma specific survival; disease free survival

Introduction

Melanoma is the most common malignancy encountered during pregnancy, accounting for 31% of all malignancies in the intrapartum period. (1, 2) For many years, pregnancy has been thought to have an adverse effect on the course of melanoma. Reports beginning in the 1950s suggested pregnancy increased the risk of melanoma development, metastasis and recurrence. (3–6) Many hypotheses since then have been formulated, linking worsened outcomes to hyperpigmentation, relative immunosuppression, and hormone binding of melanocytes. (7–10) Given the overall increase in melanoma incidence in women of childbearing age in the US, this topic has become even more pertinent. (11, 12) Editorials, systemic reviews, and media coverage of PAM persist but fail to draw definitive conclusions despite many years of attention and underpowered studies. (13–21) Many of the adequately powered studies that do exist come from large, non-US based registries, with a resultant lack of granular detail and reliability. (22–25) The primary objective of this study was to query our large, single institution melanoma database to better characterize PAM with particular attention to overall survival (OS) and melanoma specific survival (MSS). Secondarily, we examined other clinical factors with regard to melanoma mortality and such as parity and gravidity, in addition to known prognostic factors such as age, stage, histologic type, Breslow thickness, and ulceration.

Methods

Female patients of reproductive age (18–50) with American Joint Committee on Cancer (AJCC) stage 0-IV cutaneous melanoma were identified from the prospectively maintained John Wayne Cancer Institute melanoma database between January 1971 and May 2016. All patient data were de-identified, and this study was independently confirmed to be exempt from Institutional Review Board review. Melanomas were staged by seventh edition AJCC criteria. (26–28) In order to ensure adequate staging, patients without lymph node staging for melanomas with Breslow thickness ≥0.75 mm were excluded from analysis (n=540 non-PAM, n=43 PAM). Pregnancy associated melanoma is a field derived either from patient questionnaire responses (self reported) or direct physician queries (physician reported). The JWCI melanoma database defines PAMs by an affirmative response to “did melanoma develop during pregnancy.” This includes cases that developed de novo during pregnancy or melanomas that arose from pre-existing lesions that changed during pregnancy. We cannot exclude the possibility that some of these lesions were identified incidentally during prenatal visits. Laboratory pregnancy confirmation is incomplete in this data set as patients receiving office based excisions would not have routinely received urine or serum pregnancy evaluations. For this reason, we are not able to comment on the women who were deemed

pregnant based on preoperative bHCG alone. Clinical and histopathologic factors were examined between PAM and non-PAM groups. T-test was used to analyze age at diagnosis, parity, gravidity, and Breslow thickness. Chi-square test was used for Clark level, anatomic site, ulceration, sentinel lymph node examination status, recurrence status, type of first recurrence, stage at diagnosis, and stage first seen at JWCI. A 1:1 matched pair sample was then created using pairs of PAM and non-PAM patients who were matched for Breslow thickness, age, stage and ulceration status. With respect to age, we matched utilizing the following categories: <25, 25 – =35, ≥3. With respect to Breslow thickness, we matched for categories: ≤ 0.75, 0.75 – <2.00, 2.00 – ≤4.00, > 4.00 and unknown. For stage at diagnosis, we matched using categories: 0, I/II, and III. Finally, for ulceration, we matched using categories: yes, no and unknown. These details have been incorporated in to the manuscript on page 4. Univariable and then multivariable analyses were conducted with the matched data to analyze DFS, OS and MSS for patients with stage 0/I/II and stage III cutaneous melanoma at diagnosis. Due to the paucity of PAM patients with Stage IV disease at diagnosis (n=1), those patients were excluded from this analysis. Kaplan-Meier survival curves were then plotted for OS and MSS and compared using the log-rank test. SAS software, version 9.3 (SAS Institute) was used for all analyses. A two-sided p-value of 0.05 or lower was considered to indicate statistical significance.

Results

Of the entire patient cohort (n=2025), 156 women (7.7%) with PAM were identified after selection criteria applied. No cases of transplacental transfer of melanoma were identified. Clinical presentation of melanoma was similar for PAM and non-PAM patients with no significant differences in Breslow thickness (1.30 mm vs. 1.34 mm, p=0.737), histologic type, or primary tumor site (see Table 1). Age was greater in the non-PAM patients (36.8 vs 31.7 years, p<0.001). There was also no significant difference in stage at diagnosis. (Table 1) Parity was significantly increased in the PAM group, p=0.010, as was gravidity, p<0.001 At 10-years; disease-free survival was 65.7% and 62.3% for the non-PAM and PAM groups, respectively (p=0.8934). Mean disease-free survival was also similar at 24.48 years in the non-PAM group and 20.65 years in the PAM group.

Matched Pair Sample

In an attempt to decrease potential biases associated with delay in diagnosis of PAMs, we created a matched pair sample. Each PAM patient was matched with a non-PAM patient by Breslow thickness, age, stage and ulceration status. In this group of 310 patients (155 matched pairs), PAMs had a median follow-up of 14.6 years (range 0–42.6 years), and non-PAMs had a median follow-up of 11.1 years (0 – 48.5 years). When comparing the PAM and non-PAM matched pairs, clinical features were similar (see Table 2) except for histologic type (p=0.046), primary site (p=0.040), gravidity and parity (p<0.001, p<0.001). There were also no differences in recurrence between the PAM and non-PAM group (Table 2).

Univariable Survival Analysis by Stage

For matched patients with stage 0/I/II melanoma at diagnosis, there were no differences identified in DFS (p=0.880, HR 0.97, 95% CI 0.62–1.5), OS (p=0.219, HR 0.73, 95% CI

0.44–1.21) or MSS (p=0.670, HR 0.89, 95% CI 0.51–1.53) for PAMs. For those patients with stage III melanoma at diagnosis, there were no differences in DFS (p=0.858, HR 0.94, 95% CI 0.46–1.93) OS (p=0.365, HR 0.64 95% CI 0.24–1.69) or MSS (p=0.595, HR 0.75, 95% CI 0.26–2.17) for PAMs. Concordant results were obtained when Kaplan-Meier curves were plotted and compared using log-rank test for OS and MSS for both stage 0/I/II at diagnosis (Figure 1) and stage III at diagnosis (data not shown).

Expected differences in DFS, OS and MSS with regard to increasing Breslow thickness, stage first seen, ulceration, Clark level, histologic type and recurrence data (Tables 3–5) were identified for patients with stage 0/I/II melanoma at diagnosis. For patients with stage III melanoma at diagnosis, none of the clinicopathologic factors assessed were significantly associated with significant DFS, OS or MSS differences except for ulceration.

Univariable Reproductive History and Survival Differences

Interestingly, increasing gravidity was associated with worse DFS (p=0.026, HR 1.18, 95% CI 1.02–1.36), OS (p=0.042 HR 1.19 95% CI 1.01–1.40) and MSS (p=0.034, HR 1.21 95% CI 1.02–1.44) for stage 0/I/II melanomas, but these differences were not seen for stage III patients. Conversely, when parity was examined, there were no significant differences in DFS (p=0.330, HR 1.07, 95% CI 0.93–1.24), OS (p=0.562, HR 1.05 95% CI 0.88–1.26) or MSS (p=0.556 HR 1.06 95% CI 0.88–1.28) for stage 0/I/II melanomas. There were also no significant differences in OS or MSS for stage III patients with respect to parity as an independent prognostic factor.

Multivariable Survival Analysis by Stage

For patients with stage 0/I/II or stage III melanoma at diagnosis, there were no significant differences identified in DFS, OS or MSS for PAMs in the model (Tables 3–5, not shown). The only factors associated with significant differences in OS were ulceration (yes or unknown) and increasing Breslow thickness for stage 0/I/II melanoma. (Table 3) For MSS, factors associated with significant differences in OS were trunk as primary site (p=0.016, HR 2.22, 95% CI 1.16–4.23), Breslow thickness 2-≤4 and >4 (p<0.001 HR 5.62, 2.05–15.35, and p<0.001, HR141.76, 95% CI 21.47–936.05), ulceration (yes: p<0.001, HR 6.83 95% CI 2.38–9.96; unknown: p<0.01, HR 4.87, 95% CI 1.27–5.15) and increasing gravidity (p=0.027, HR 1.24, 95% CI 1.03–1.51). For DFS, the only factors associated with significant differences on multivariable analysis were also expected: increasing Breslow thickness, trunk as the primary site (p=0.007, HR 1.91, 95% CI 1.19–3.06) and histologic type (SSM, In situ, and other) for stage 0/I/II melanoma. (See Table 5) There were no factors associated with significant differences in Stage III patients with respect to DFS, OS and MSS on multivariable analysis.

Discussion

Despite previous study, controversy remains for women of childbearing age at risk for or diagnosed with cutaneous melanoma. In our institutional analysis, the incidence of PAM was 7.7%, congruent with previous work from this institution identifying a 8.7 percent incidence of PAM. (29) In early 2016, Tellez and colleagues reported that women with melanoma

arising during or within one year of childbirth had a significantly worse prognosis when compared to their non-pregnant counterparts. (30) This study was limited by its small, retrospective nature; additionally, only 19 of 41 patients in the study had melanoma diagnosed during pregnancy. Based on multivariable analysis of this limited sample, the authors reported a 9-fold increase in recurrence (odds ratio (OR) 9.30, p=0.01), a 7-fold increase in metastasis (OR 6.70, p=0.01) and a 5-fold increase in mortality (OR 5.10, p=0.03). (30)

Larger studies have been published, however, that refute this notion of diminished survival for PAMs. In 2004, O'Meara et al. evaluated 412 women with PAM from California maternal and neonatal discharge records linked to California Cancer Registry data. After controlling for age, race, stage, and tumor thickness, pregnancy had no impact on survival in women with melanoma. This held true for those during pregnancy (p=0.570) or in the postpartum period (p=0.162). (23) Johansson and colleagues used Swedish Cancer and Multi-Generation Registers to conduct a population-based cohort study examining 1019 PAMs. However, the definition of PAM in this study was broad, including patients with melanoma arising during pregnancy or up to two years following delivery. (24) This group showed no significant difference in survival (p=0.47) for PAMs vs non-PAMs in this study of women aged 15–44. (24) Similarly, in 2004, Lens et al. examined 185 PAMs using data from the Swedish National and Regional Registries. This group also found no significant difference in overall survival between PAMs and non-PAMs (p=0.84, log rank test). At multivariable cox regression, pregnancy at the time of melanoma diagnosis was not related to increased risk of death (p=0.804, HR 1.08, 95% CI 0.60–1.93). Prognostic factors for these women were Breslow thickness (p<0.001, HR 2.16 95% CI 1.80–2.58) and axial vs limb site of the primary melanoma (p<0.001, HR 2.51 95% CI 1.78–3.56). (22)

In this study, as expected, Breslow thickness was associated with worsened OS and MSS in Stage 0/I/II patients. (Tables 3 and 4) A criticism of previous studies linking melanoma with abject survival outcomes was the preponderance of thicker tumors in PAM patients, possibly due to delay in diagnosis. Travers et al., in 1995, queried patient records from the Massachusetts General Hospital and identified 45 women with PAM. This group reported significantly greater mean tumor thickness in PAMs than non-PAMs (2.28 vs 1.22 mm, p<0.007). (31) While the authors stated that "the mechanisms by which pregnancy may lead to increased thickness of melanoma remain unclear…" they do acknowledge that a delay in diagnosis may have led to the thicker lesions identified in PAM cases. (31) When examining incidence and outcomes of 577 PAMs from registry data in New South Wales, Bannister-Tyrrell and colleagues showed that melanomas diagnosed in pregnancy were thicker (median = 0.75 mm) than melanomas diagnosed postpartum (median = 0.60 mm, p = 0.002). (25) When we controlled for this potential confounder by matching for Breslow thickness, no difference in survival outcomes were identified for PAMs as compared to non-PAMs. Additionally, by excluding patients without lymph node staging for lesions ≥ 0.75 mm in Breslow thickness, our group limited the proportion of patients receiving non-standard care. Mackie et al. reported similar findings with regard to Breslow thickness in a study of 388 women of childbearing age with melanoma (92 treated during pregnancy) from the World Health Organization melanoma programme. These authors concluded that Breslow thickness

was greater in women who were diagnosed while pregnant (p=0.002), however once Breslow thickness was controlled for, survival rates did not differ (p=0.1). (32)

To our knowledge, this is the first study associating increased gravidity to worsened survival outcomes in women of childbearing age with stage 0/I/II melanoma. Mechanisms underlying this finding could be associated with hormonal differences or other un-characterized risk factors associated with gravidity. Future study will be needed to fully examine this association in a prospective manner. Also of note, while we do not have consistent or reliably documented follow up for babies born to these mothers with PAM, no cases of transplacental melanoma have been identified in the JWCI melanoma database comprising approximately 15,600 patients to date. Compared to larger registry-based studies, our data comes from a well-maintained and reliable single institution database with extensive follow up. Additionally, we excluded patients with melanomas ≥ 0.75 mm thick who did not receive nodal staging, thereby limiting non-standard care and inaccurately staged lesions. In contrast to previous studies that were not matched for pertinent factors such as Breslow thickness, age, and stage; our study was not clouded by these known prognostic factors.

Limitations of this study include its retrospective nature and treatment-related biases inherent to our referral center. Additionally, the majority of patients evaluated exhibited favorable prognostic factors and few PAMs had stage III disease or thick primary tumors (n=17 and n=5 respectively). Finally, due to the time period over which this data was collected, some subjects did not have complete data with regard to histology, ulceration and lymph node staging exam, which introduces some amount of uncertainty with regards to their initial prognosis. Despite these limitations, we believe this work accurately reflects PAM incidence and outcomes.

Conclusions

This, the largest, single-institution study examining the characteristics and outcomes associated with melanoma arising during pregnancy demonstrates no significant difference in DFS, OS or MSS. Pregnant patients should be screened for melanoma in a similar manner to non-pregnant patients and should be counseled that their prognosis is not adversely affected by pregnancy.

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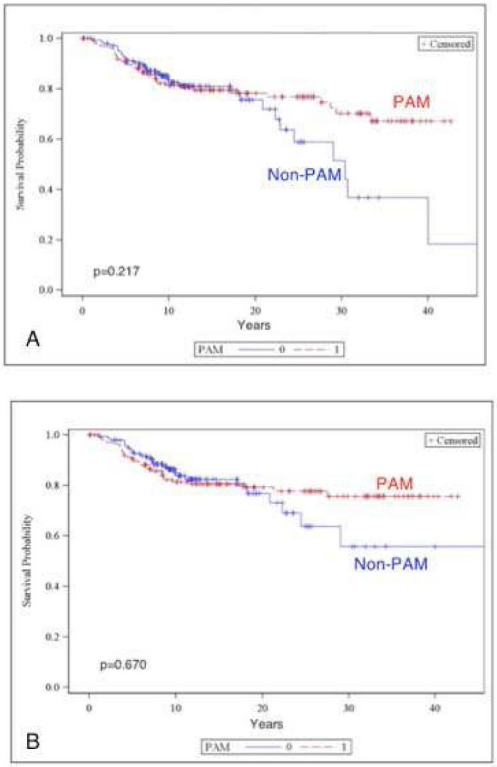

Figure 1.

Kaplan-Meier survival curves from stage 0, I, and II matched date, for (A) overall survival and (B) melanoma specific survival. p Values calculated by log rank test. PAM, pregnancy-associated melanoma.

Table 1

Whole Group Frequency

	Non-PAM	PAM	p Value
n	2,025	156	
Age at diagnosis, y, mean ± SD	36.76 ± 8.43	31.69 ± 8.69	<0.001
Age, n (%)			<0.001
<25 y	215 (10.62)	20 (12.82)	
25 – ≤35 y	611 (30.17)	101 (64.74)	
≥35 y	1199 (59.21)	35 (22.44)	
Stage at diagnosis, n (%)			0.186
0	138 (6.81)	5 (3.21)	
I/II	1647 (81.33)	134 (85.90)	
III	240 (11.85)	17 (10.90)	
Primary site, n (%)			0.100
Head/neck	193 (9.53)	8 (5.13)	
Trunk	733 (36.20)	66 (42.31)	
Extremity	1099 (54.27)	82 (52.56)	
Breslow thickness, mm, n (%)			0.311
≤ 0.75	711 (35.11)	55 (35.26)	
0.75 – <2.00	518 (25.58)	43 (27.56)	
2.00 – ≤4.00	177 (8.74)	20 (12.82)	
> 4.00	75 (3.70)	5 (3.21)	
Unknown	544 (26.86)	33 (21.15)	
Breslow thickness (mm), continuous, mean ± SD	1.34 ± 1.58	1.30 ± 1.21	0.737
Para, mean ± SD	1.36 ± 1.46	1.68 ± 1.44	<0.001
Gravida, mean ± SD	1.78 ± 1.71	2.29 ± 1.51	<0.001
Ulceration, n (%)			0.849
Yes	173 (8.54)	12 (7.69)	
No	1381 (68.20)	105 (67.31)	
Unknown	471 (23.26)	39 (25.00)	
Clark level, n (%)			0.025
I	183 (9.04)	9 (5.77)	
II	546 (26.96)	43 (27.56)	
III	493 (24.35)	37 (23.72)	
IV	495 (24.44)	54 (34.62)	
V	51 (2.52)	1 (0.64)	
Unknown	257 (12.69)	12 (7.69)	
Histologic type, n (%)			0.228
ALM/LMM	38 (1.88)	1 (0.64)	
In situ	138 (6.81)	5 (3.21)	

	Non-PAM	PAM	p Value
NM	241 (11.90)	21 (13.46)	
SSM	972 (48.00)	84 (53.85)	
Others	78 (3.85)	3 (1.92)	
Unknown	558 (27.56)	42 (26.92)	
Lymph nodes examined, n (%)			0.540
Positive	248 (12.25)	18 (11.54)	
Negative	830 (40.99)	71 (45.51)	
Not done	947 (46.77)	67 (42.95)	
Type of first recurrence, n (%)			0.656
None	1284 (63.47)	96 (61.54)	
Nodal	412 (20.37)	38 (24.36)	
Local/in-transit	125 (6.18)	8 (5.13)	
Distant	202 (9.99)	14 (8.97)	

PAM, pregnancy associated melanoma; ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma

Table 2

Matched Sample Frequency

	Non-PAM	PAM	p Value
n	155	155	
Age,y, n (%)			
<25	20 (12.90)	20 (12.90)	
25 – ≤35	100 (64.52)	100 (64.52)	
≥35	35 (22.58)	35 (22.58)	
Stage at diagnosis, n (%)			
0/I/II	139 (89.68)	139 (89.68)	
III	16 (10.32)	16 (10.32)	
Breslow thickness, mm, n (%)			
≤ 0.75	55 (35.48)	55 (35.48)	
0.75 – <2.00	43 (27.74)	43 (27.74)	
2.00 – ≤4.00	20 (12.90)	20 (12.90)	
> 4.00	5 (3.23)	5 (3.23)	
Ulceration, n (%)			
Yes	12 (7.74)	12 (7.74)	
No	104 (67.10)	104 (67.10)	
Unknown	39 (25.16)	39 (25.16)	
Age at diagnosis , y, mean ± SD	32.17 ± 6.79	31.72 ±8.71	0.616
Stage first seen, n (%)			0.137
0	14 (9.09)	5 (3.25)	
I/II	94 (61.04)	108 (70.13)	
III	31 (20.13)	28 (18.18)	
IV	15 (9.74)	13 (8.44)	
Unknown	1 (0.01)	1 (0.01)	
Primary site, n (%)			0.040
Head/neck	21 (13.55)	8 (5.16)	
Trunk	61 (39.35)	66 (42.58)	
Extremity	73 (47.10)	81 (52.26)	
Breslow thickness, mm, continuous, mean ± SD	1.48 ± 1.94	1.30 ± 1.21	0.389
Para, mean ± SD	0.89 ± 1.22	1.68 ± 1.45	<0.001
Gravida, mean ± SD	1.24 ± 1.45	2.30 ± 1.52	<0.001
Clark level, n (%)			0.258
I	11 (7.10)	9 (5.81)	
II	43 (27.74)	43 (27.74)	
III	39 (25.16)	37 (23.87)	
IV	38 (24.52)	53 (34.19)	
V	4 (2.58)	1 (0.65)	

	Non-PAM	PAM	p Value
Unknown	20 (12.90)	12 (7.74)	
Histologic type, n (%)			0.046
ALM/LMM	2 (1.29)	1 (0.65)	
In situ	14 (9.03)	5 (3.32)	
NM	23 (14.84)	21 (13.55)	
SSM	59 (38.06)	84 (54.19)	
Others	2 (1.29)	3 (1.94)	
Unknown	55 (35.48)	41 (26.45)	
Lymph nodes examined, n (%)			0.627
Positive	17 (10.97)	17 (10.97)	
Negative	79 (50.97)	71 (45.81)	
Not done	59 (38.06)	67 (43.23)	

PAM, pregnancy associated melanoma; ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma

Table 3

Overall Survival Stage 0/I/II at diagnosis: Matched Data

	Univariable		Multivariable	
	p Value	**Hazard ratio (95% CI)**	**p Value**	**Hazard ratio (95% CI)**
Age in years (increasing)	0.103	1.03 (0.99, 1.06)		
Location				
Extremity (Reference)				
Head/Neck	0.440	1.52 (0.53, 4.37)		
Trunk	0.215	1.43 (0.81, 2.50)		
Breslow thickness (mm) ≤ 0.75 (Reference)				
0.75 – <2.00	0.020	2.68 (1.17, 6.14)	0.067	2.05 (0.95, 4.39)
2.00 – ≤4.00	<0.001	7.59 (3.23, 17.83)	<0.001	4.73 (2.10, 10.66)
>4.00	<0.001	40.03 (8.2,4 194.46)	<0.001	49.20 (10.24, 236.39)
Unknown	0.018	2.75 (1.19, 6.36)	0.067	1.98 (0.95, 4.12)
Breslow thickness (mm), continuous	<0.001	1.74 (1.40, 2.18)		
Para	0.562	1.05 (0.88, 1.26)		
Gravida	0.042	1.19 (1.01, 1.40)		
PAM	0.219	0.73 (0.44, 1.21)		
Stage first seen				
0	NA*	NA*		
I/II (Reference)				
III	<0.001	4.91 (2.53, 9.56)		
IV	<0.001	17.45 (9.05, 33.62)		
Ulceration				
Yes	<0.001	8.49 (3.79, 19.02)	<0.001	5.19 (2.18, 12.34)
No (Reference)				
Unknown	0.009	2.20 (1.22, 3.97)	<0.001	3.18 (1.82, 5.55)
Clark Level				
I (Reference)				
II	0.113	5.23 (0.68, 40.50)		
III	0.018	11.26 (1.50, 84.28)		
IV	0.007	16.50 (2.17, 125.44)		
V	NA*			
Unknown	<0.001	45.88 (5.74, 366.92)		
Histologic type				
ALM/LMM	0.86	0.83 (0.11, 6.54)		
In Situ	NA*			
NM (Reference)				
SSM	0.003	0.32 (0.15, 0.67)		

	Univariable		Multivariable	
	p Value	**Hazard ratio (95% CI)**	**p Value**	**Hazard ratio (95% CI)**
Others	0.448	0.45 (0.06, 3.53)		
Unknown	0.413	0.73 (0.34, 1.56)		

*NA, Not applicable: analysis not available due to small sample size.

PAM, pregnancy associated melanoma; ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma

Table 4

Melanoma-Specific Survival Stage 0/I/II at Diagnosis: Matched Data

	Univariable		Multivariable	
	p Value	**Hazard ratio (95% CI)**	**p Value**	**Hazard ratio (95% CI)**
Age in years (increasing)	0.189	1.03 (0.99, 1.06)		
Location				
Extremity (Reference)				
Head/neck	0.261	1.85 (0.63, 5.42)		
Trunk	0.157	1.54 (0.85, 2.81)	0.016	2.22 (1.16, 4.23)
Breslow thickness (mm), continuous	<0.001	1.77 (1.39, 2.24)		
Breslow category (mm)				
≤ 0.75 (Reference)				
0.75 – <2.00	0.015	3.07 (1.24, 7.62)		
2.00 – ≤4.00	<0.001	8.45 (3.32, 21.49)	<0.001	5.62 (2.05, 15.38)
> 4.00	<0.001	44.69 (8.89, 224.68)	<0.001	141.76 (21.47, 936.05)
Unknown	0.015	3.20 (1.26, 8.13)		
Para	0.556	1.06 (0.88, 1.28)		
Gravida	0.034	1.21 (1.02, 1.44)	0.027	1.24 (1.03, 1.51)
PAM	0.670	0.89 (0.51, 1.53)		
Stage first seen				
0	NA*			
I/II (Reference)				
III	<0.001	6.63 (3.27, 13.48)		
IV	<0.001	21.18 (10.59, 42.36)		
Ulceration				
Yes	<0.001	10.12 (4.42, 23.17)	<0.001	6.83 (2.38 9.96)
No (Reference)				
Unknown	0.007	2.38 (1.26, 4.47)	<0.001	4.87 (1.27, 5.15)
Clark Level				
I	NA*			
II (Reference)				
III	0.040	2.35 (1.04, 5.32)		
IV	0.003	3.56 (1.52, 8.34)		
V	NA*			
Unknown	<0.001	11.30 (4.35, 29.34)		
Histologic type				
NM (Reference)				
SSM	0.004	0.31 (0.14, 0.68)		
Others	0.534	0.52 (0.07, 4.10)		
Unknown	0.487	0.76 (0.34, 1.68)		

PAM, pregnancy associated melanoma; ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma

Table 5

Disease-Free Survival Stage 0/II/II at Diagnosis: Matched Data

	Univariable		Multivariable	
	p Value	**Hazard ratio (95% CI)**	**p Value**	**Hazard ratio (95% CI)**
Age in years (increasing)	0.739	1.01 (0.97 – 1.04)		
Location				
Extremity (Reference)				
Head/neck	0.007	2.57 (1.30–5.09)		
Trunk	0.027	1.69 (1.06–2.70)	0.007	1.91 (1.19–3.06)
Breslow thickness (mm) (continuous)	<0.001	1.74 (1.43–2.13)		
Breslow category (mm)				
≤ 0.75 (Reference)				
0.75 – <2.00	0.021	2.18 (1.12–4.23)	0.009	2.47 (1.25–4.89)
2.00 – ≤4.00	<0.001	5.51 (2.72–11.15)	<0.001	4.28 (1.87–9.85)
> 4.00	<0.001	18.60 (4.17–82.85)	<0.001	22.50 (4.86–104.21)
Unknown	<0.001	4.22 (2.26–7.87)	<0.001	3.95 (2.01–7.74)
Para	0.330	1.07 (0.931–1.24)		
Gravida	0.026	1.18 (1.02–1.36)		
PAM	0.880	0.97 (0.62–1.50)		
Stage first seen				
0	0.500	0.50 (0.07–3.71)		
I/II (Reference)				
III	<0.001	12.78 (7.5–21.77)		
IV	<0.001	12.15 (7.00–21.11)		
Ulceration				
Yes	<0.001	4.19 (1.86–9.45)		
No (Reference)				
Unknown	<0.001	2.92 (1.86–4.60)		
Clark Level				
I	NA *			
II (Reference)				
III	0.068	2.01 (0.95–4.26)		
IV	<0.001	3.90 (1.95–7.82)		
V	0.176	4.12 (0.53–32.08)		
Unknown	<0.001	8.88 (4.34–18.15)		
Histologic type				
ALM/LMM	NA *			
NM (Reference)				
In Situ	0.022	0.09 (0.01–0.71)		

	Univariable		Multivariable	
	p Value	**Hazard ratio (95% CI)**	**p Value**	**Hazard ratio (95% CI)**
SSM	<0.001	0.22 (0.12–0.43)		
Others	0.070	3.15 (0.91–10.82)		
Unknown	0.619	0.87 (0.49–1.53)		

*NA, sample size too small for comparison.

PAM, pregnancy associated melanoma; ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma