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ORIGINAL ARTICLE – MELANOMA

Postbiopsy Pigmentation is Prognostic in Head and Neck Melanoma

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ABSTRACT

Purpose. To assess postbiopsy pigmentation (PBP) as a prognostic feature in patients with cutaneous head and neck (H&N) melanoma.

Methods. Retrospective review of patients undergoing sentinel lymph node biopsy (SLNB) for H&N melanoma (1998–2018). PBP was defined as visible remaining pigment at the scar or biopsy site that was documented on physical exam by both a medical oncologist and a surgeon at initial consultation. Variables associated with disease-free survival (DFS) and overall survival (OS) were analyzed using multivariable Cox proportional hazards models.

Results. Among 300 patients, 34.3% (n = 103) had PBP and 44.7% (n = 134) had microscopic residual disease on final pathology after wide local excision. Prognostic factors associated with DFS included advanced age, tumor depth, ulceration, PBP, and positive SLNB ($p < 0.05$). Patients with PBP fared worse than their counterparts without PBP in 5-year DFS [44.1% (31.1–56.3%) vs. 73.0% (64.1–80.0%); $p < 0.001$] and 5-year OS [65.0% (50.0–76.6%) vs. 83.6% (75.7–89.2%); $p = 0.005$]. After multivariable adjustment, PBP remained associated with shorter DFS [hazard ratio (HR) 1.72, 95% confidence interval (CI) 1.01–2.93; $p = 0.047$], but was not prognostic of OS.

Conclusions. In patients with H&N melanoma, PBP is associated with significantly shorter DFS. Patients with PBP may warrant greater consideration for SLNB and closer postoperative surveillance.

In the USA, it is estimated that 87,000 patients were diagnosed with cutaneous melanoma and more than 9000 patients died of this disease in 2017.[1] Head and neck (H&N) melanomas account for 15%[2,3] to 18%[4] of all primary melanomas diagnosed and are associated with inferior survival outcomes compared with extremity melanomas.[5,6] Reasons for differences in oncologic outcomes among these patients are unclear, though several explanations have been proposed. Patients tend to be older and present at a more advanced stage compared with other primary tumor locations.[3,4,12] Melanomas of the scalp are difficult to visualize, leading to delayed diagnosis, and often are detected at greater depth.[7,8] The less predictable lymphatic drainage of H&N melanomas leads to higher false-negative rates for sentinel lymph node (SLN) biopsies and higher local recurrence rates.[9–11] Adequate margins are also more difficult to achieve due to cosmetic or functional concerns.

The objective of the present study is to identify and assess novel prognostic features in patients with cutaneous melanoma of the H&N. We hypothesized that postbiopsy pigmentation (PBP) was of prognostic significance and would correlate with disease-free survival (DFS) and overall survival (OS).

METHODS

We performed a retrospective review of a prospectively maintained database of patients undergoing SLN biopsy for cutaneous melanoma between 1998 and 2018 at our

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institution. Only patients with H&N melanoma were included in the analysis. Patients with ophthalmic melanoma and mucosal melanoma were excluded. Many patients underwent initial tumor biopsy at an outside hospital and were subsequently referred to our institution for surgical management. The study was approved by the Colorado Multiple Institutional Review Board.

Medical records were reviewed for presence of PBP, defined as visible remaining pigment at the scar or biopsy site that was documented by both the medical oncologist and surgeon evaluating the patient at initial consultation. This was routinely documented as "present" or "absent," and patients missing these data were excluded. Further descriptors including dimensions of PBP were not routinely described and thus not assessed in the study. Both the diagnostic biopsy and wide local excision (WLE) pathology reports were reviewed for positive deep and/or lateral margin on initial biopsy, tumor type, location, Breslow thickness, ulceration, mitotic rate (≥ 1 per high-power field), lymphovascular invasion, width of surgical margin, residual microscopic tumor on WLE specimen, SLN status, and if indicated, complete lymph node dissection (CLND). The margins described are surgical, rather than pathologic, as the latter are rarely reported. The use of adjuvant therapy was noted as well as the therapeutic modality following detection of recurrence. SLNs were detected using both blue dye and radioactive colloid lymph node mapping. SLNs were defined as nodes that stained blue or had radioactive counts that were at least $\geq 10\%$ of the lymph node with the greatest radioactivity. A positive SLN was defined as one with any degree of metastatic disease.

Long-term outcomes including follow-up duration, locoregional recurrence, distant recurrence, DFS, and OS were recorded. Follow-up duration was defined as the time among all patients—those who died and survived. Locoregional recurrence was defined as recurrence in the skin or lymph nodes, or in-transit metastases. DFS was defined as the duration from the date of WLE until the date of locoregional or distant recurrence, whichever was shorter. OS was defined as the duration from the date of WLE until the date of death from any cause.

Statistical Analysis

Data were analyzed using Stata 14.1 (Stata Corp, College Station, TX). Baseline and tumor characteristics were compared using a Wilcoxon rank-sum (Mann–Whitney) test or Student's t test for continuous variables where appropriate and the Chi square test for categorical variables. DFS and OS estimates were calculated with the Kaplan–Meier method and compared with a log-rank test. A multivariable Cox proportional hazards model was applied to estimate hazard ratios (HR) of predictors of locoregional recurrence, distant recurrence, any recurrence, DFS, and OS. All variables with p-value of 0.10 or less on univariable analysis were utilized in multivariable analysis. Statistical significance was defined as $p < 0.05$.

RESULTS

A total of 300 patients were diagnosed with H&N melanoma and underwent SLN biospy at our institution (Table 1). The mean age was 56.6 years, and 74.7% were male ($n = 224$). The most common location was the face ($n = 121$, 40.3%), followed by the scalp ($n = 99$, 33.0%). Median tumor depth was 1.7 mm (range 0.22–19 mm). Ulceration and mitsoses were present in 24.7% ($n = 74$) and 61.7% ($n = 185$) of patients, respectively. The median width of the surgical margin for all patients was 1.0 cm. In 57 patients (19.0%), the surgical margin was less than 1.0 cm; in 164 patients (54.7%), the margin was 1.0–1.9 cm; in 67 patients (22.3%), the margin was 2.0 cm or greater. Following initial diagnositic biopsy, 34.3% ($n = 103$) had PBP, 58.7% ($n = 176$) had a positive deep histologic margin, and 62.0% ($n = 186$) had a positive lateral margin. Positive lateral margins included invasive disease ($n = 160$) and melanoma in situ ($n = 23$). Among patients with a deep positive margin, 102/176 (58.0%) had microscopic residual disease on final WLE pathology. Among patients with a positive lateral margin, 102/186 (54.8%) had microscopic residual disease on the final WLE pathology. Overall, 134/300 (44.7%) patients had microscopic residual disease on the WLE specimen. Nearly 40% of patients in the series had both deep and lateral margins positive on biopsy (118/200). Forty-nine (16.3%) patients had a positive SLN, and 27 patients subsequently underwent CLND. The remaining patients with a positive SLN did not undergo CLND due to patient refusal, unrespectable location, or comorbid conditions precluding surgical resection. Thirty-seven patients (12.3%) received adjuvant therapy. Of the 86 patients who developed recurrent disease, 75 (87.2%) received further therapy: immunotherapy in 26 patients, biochemotherapy in 5, molecular targeted agents in 10, radiation in 12, and surgery in 8 patients. The median follow-up time among all patients was 2.1 years (interquartile range, IQR 0.5–4.7 years).

Median DFS was 12.5 years; factors associated with DFS on univariable analysis included age, tumor location, tumor depth, ulceration, microscopic residual tumor on WLE, PBP, and lymph node status (all $p < 0.001$) (Table 2). After multivariable adjustment, advanced age, tumor depth, ulceration, PBP, and positive SLN were associated with shorter DFS (all $p < 0.05$). Median OS was 13.8 years; factors associated with OS on univariable

TABLE 1 Patient demographics, pathologic characteristics, and oncologic outcomes in patients with head and neck melanoma

Variable	All patients (n = 300)
Age (years)	56.5 ± 15.7
Male gender	224 (74.7)
Type	
Melanoma	267 (89.0)
Pure DM	20 (6.7)
Mixed DM	12 (4.0)
Unknown DM type	1 (0.3)
Location	
Scalp	99 (33.0)
Ear	49 (16.3)
Face	121 (40.3)
Neck	31 (10.3)
Tumor depth, median (range), in mm	1.7 (0.22–19)
Ulceration	74 (24.7)
Mitosis	
None	54 (18.0)
≥ 1	185 (61.7)
Unknown	61 (20.3)
Surgical margins, median (range), in cm[a]	1.0 (0.3–2.0)
< 1.0 cm	57 (19.0)
1.0–1.9 cm	164 (54.7)
≥ 2.0 cm	67 (22.3)
Unknown	12 (4.0)
Postbiopsy pigmentation	103 (34.3)
Positive deep margin on diagnostic biopsy	
No	107 (35.7)
Yes	176 (58.7)
Unknown	17 (5.7)
Positive lateral margin on diagnostic biopsy	
No	82 (27.3)
Yes	186 (62.0)
Unknown	32 (10.7)
Positive lateral (invasive only) and deep margin on diagnostic biopsy	118 (39.3)
Microscopic residual tumor on final pathology	134 (44.7)
Positive SLN	49 (16.3)
Lymph node status	
Negative SLND	251 (83.7)
+ SLN, CLND	27 (9.0)
+ SLN, no CLND	22 (7.3)
Adjuvant therapy	37 (12.3)
Locoregional recurrence	59 (19.7)
Skin	17 (5.7)
In transit	25 (8.3)
Regional LN	27 (9.0)
Distant recurrence	60 (20.0)
Any recurrence	86 (28.7)
Therapy after recurrence	75/86 (87.2)
Immunotherapy	26
Biochemotherapy	5
Molecular targeted agents	10
Radiation therapy	12
Surgery	8
Deaths	61 (20.3)
Follow-up time, median (IQR), in years	2.1 (0.5–4.7)
Disease-free survival	
1-Year (95% CI)	83.2% (77.9–87.3%)
3-Year (95% CI)	70.5% (63.9–76.1%)
5-Year (95% CI)	63.6% (56.2–70.1%)
Overall survival	
1-Year (95% CI)	96.9% (93.8–98.4%)
3-Year (95% CI)	87.2% (81.9–91.0%)
5-Year (95% CI)	78.1% (71.1–83.6%)

All values listed as mean ± standard deviation and number (percent) unless otherwise indicated

DM desmoplastic melanoma, *MIS* melanoma in situ, *WLE* wide local excision, *SLN* sentinel lymph node, *SLND* sentinel lymph node dissection, *CLND* completion lymph node dissection, *IQR* interquartile range, *CI* confidence interval

[a]Missing n = 12

analysis included age, tumor location, tumor depth, ulceration, PBP, and lymph node status (all $p < 0.01$) (Table 3). After multivariable adjustment, advanced age, increasing tumor depth, ulceration, and positive SLN were associated with worse OS (all $p < 0.05$). DFS and OS are longer than our follow-up interval because the follow-up takes into account both patients who died and those who survived.

Additional analyses to identify differences in patient and tumor characteristics, as well as survival outcomes in patients with (n = 103, 34.3%) and without PBP (n = 197, 65.7%) are presented in Table 4. Patients with PBP were older than patients without PBP (62.4 ± 14.8 vs. 53.4 ± 15.4 years; $p < 0.001$). Furthermore, patients in the PBP group were more likely to have lesions located on the scalp (44.7% vs. 26.9%; p = 0.004) and have a positive SLN (25.2% vs. 11.7%; p = 0.003) compared with patients without PBP. The median Breslow depth of primary lesion was deeper in patients with PBP compared with patients without (2.0 vs. 1.6 mm), and this trended toward significance (p = 0.077). There was no difference in melanoma type, ulceration, mitosis, surgical margin, or use of adjuvant therapy between the two groups (all $p > 0.05$). Patients with PBP were significantly more likely to have a positive deep margin on biopsy (77.7% vs. 48.7%; $p < 0.001$), have a positive lateral margin on biopsy

TABLE 2 Hazard ratios of variables associated with disease-free survival in univariable and multivariable Cox proportional hazard models

Variable	Univariable HR (95% CI)	*p*	Multivariable HR (95% CI)	*p*
Age (years)	1.02 (1.01–1.04)	**0.003**	1.02 (1.01–1.04)	**0.006**
Male gender	1.33 (0.80–2.22)	0.268	–	
Location			–	
Face	1.0 (reference)	< **0.000**	1.0 (reference)	0.269
Ear	0.89 (0.43–1.86)		0.77 (0.36–1.61)	
Scalp	2.53 (1.55–4.13)		1.45 (0.86–2.45)	
Neck	0.94 (0.36–2.46)		1.10 (0.42–2.90)	
Type			–	
Melanoma	1.0 (reference)	0.465	–	
Pure DM	0.73 (0.27–2.01)		–	
Mixed DM	1.62 (0.66–4.02)		–	
Unknown	1.45 (0.20–10.54)			
Tumor depth (mm)	1.16 (1.09–1.23)	< **0.001**	1.08 (1.01–1.16)	**0.024**
Ulceration	2.43 (1.58–3.74)	< **0.001**	2.31 (1.46–3.65)	< **0.001**
Mitosis ≥ 1			–	
No	1.0 (reference)	0.192	–	
Yes	1.84 (0.94–3.61)		–	
Unknown	1.53 (0.70–3.36)		–	
Positive deep margin on initial biopsy			–	
No	1.0 (reference)	0.359	–	
Yes	1.33 (0.82–2.13)		–	
Unknown	1.66 (0.74–3.69)		–	
Positive lateral margin on initial biopsy			–	
No	1.0 (reference)	0.656	–	
Yes	1.04 (0.63–1.73)		–	
Unknown	1.34 (0.69–2.62)		–	
Microscopic residual tumor on final pathology	2.67 (1.71–4.16)	< **0.001**	1.39 (0.80–2.41)	0.248
Postbiopsy pigmentation	2.56 (1.66–3.93)	< **0.001**	1.72 (1.01–2.93)	**0.047**
Adjuvant therapy	1.98 (1.18–3.33)	**0.010**	1.01 (0.40–2.05)	0.969
Lymph node status				
Negative SLND	1.0 (reference)	< **0.001**	1.0 (reference)	< **0.001**
+ SLN, CLND	2.41 (1.30–4.50)		3.00 (1.33–6.74)	
+ SLN, no CLND	4.60 (2.50–8.45)		2.57 (1.26–5.22)	

Bold values indicate statistical significance ($p < 0.05$)

DM desmoplastic melanoma, *SLN* sentinel lymph node, *SLND* sentinel lymph node dissection, *CLND* completion lymph node dissection, *HR* hazard ratio, *CI* confidence interval

(84.5% vs. 50.3%; $p < 0.001$), and have microscopic residual disease on final WLE (84.5% vs. 23.9%; $p < 0.001$).

Patients in the PBP group were more likely to develop locoregional recurrence (32.0% vs. 13.2%), distant recurrence (26.2% vs. 16.8%), and any recurrence (39.8% vs. 22.8%), and were more likely to die during the study period (25.2% vs. 17.8%). One-, 3-, and 5-year DFS were significantly shorter in the PBP group (70.6% vs. 89.6%, 49.3% vs. 80.7%, and 44.1% vs. 73.0%) ($p < 0.001$) (Table 4; Fig. 1a). Similarly, OS at 1, 3, and 5 years was shorter in the PBP group (96.7% vs. 97.6%, 77.7% vs. 91.3%, and 65.0% vs. 83.6%) ($p = 0.005$) (Table 4; Fig. 1b).

DISCUSSION

In this single-institution retrospective study of 300 patients with cutaneous H&N melanoma, PBP was present in 34.3% of patients and was associated with other known adverse prognostic factors including advanced age, scalp tumors, microscopic residual tumor, depth of residual tumor on final biopsy, and positive SLN. After controlling

TABLE 3 Hazard ratios of variables associated with overall survival in univariable and multivariable Cox proportional hazard models

Variable	Univariable HR (95% CI)	*p*	Multivariable HR (95% CI)	*p*
Age (years)	1.04 (1.02–1.06)	< **0.001**	1.03 (1.01–1.05)	**0.002**
Male gender	1.44 (0.77–2.71)	0.257	–	
Location			–	
Face	1.0 (reference)	**0.002**	1.0 (reference)	0.146
Ear	0.75 (0.30–1.91)		0.72 (0.28–1.87)	
Scalp	2.62 (1.46–4.70)		1.76 (0.91–3.41)	
Neck	1.21 (0.41–3.60)		2.07 (0.64–6.64)	
Type			–	
Melanoma	1.0 (reference)	0.957	–	
Pure DM	1.09 (0.40–3.03)		–	
Mixed DM	0.85 (0.21–3.47)		–	
Unknown	1.55 (0.21–11.44)			
Tumor depth (mm)	1.18 (1.09–1.27)	< **0.001**	1.15 (1.04–1.27)	**0.009**
Ulceration	2.61 (1.56–4.36)	< **0.001**	2.74 (1.57–4.77)	< **0.001**
Mitosis ≥ 1			–	
No	1.0 (reference)	0.673	–	
Yes	1.01 (0.51–2.00)		–	
Unknown	1.30 (0.61–2.77)		–	
Positive deep margin on initial biopsy			–	
No	1.0 (reference)	0.224	–	
Yes	1.51 (0.83–2.75)		–	
Unknown	2.04 (0.86–4.83)		–	
Positive lateral margin on initial biopsy			–	
No	1.0 (reference)	0.454	–	
Yes	0.88 (0.48–1.63)		–	
Unknown	1.33 (0.64–2.73)		–	
Microscopic residual tumor on final pathology	1.67 (0.99–2.78)	0.056	0.80 (0.41–1.56)	0.517
Postbiopsy pigmentation	2.01 (1.01–2.78)	**0.044**	1.51 (0.78–2.91)	0.222
Adjuvant therapy	1.54 (0.78–3.04)	0.213		
Lymph node status				
Negative SLND	1.0 (reference)	**0.005**	1.0 (reference)	**0.024**
+ SLN, CLND	2.80 (1.41–5.58)		2.96 (1.36–6.45)	
+ SLN, no CLND	2.42 (0.95–6.17)		1.42 (0.52–3.87)	

Bold values indicate statistical significance ($p < 0.05$)

DM desmoplastic melanoma, *SLN* sentinel lymph node, *SLND* sentinel lymph node dissection, *CLND* completion lymph node dissection, *HR* hazard ratio, *CI* confidence interval

for these poor prognostic factors, however, PBP remained associated with significantly worse DFS. This is the first description of PBP as a prognostic feature in melanoma.

Several clinical and histological factors have been associated with poor prognosis in patients with cutaneous H&N melanoma, including advanced age, male gender, increasing Breslow thickness, ulceration, mitosis, and lymph node involvement.[13–16] In agreement with this literature, we found that increasing age, ulceration, tumor depth, and positive SLN significantly decreased both DFS and OS. However, male gender and presence of mitoses were not associated with DFS or OS.

Recent evidence suggests that there may also be a correlation between prognosis and anatomic location of melanoma confined to the H&N. In a study of 27,097 patients with cutaneous H&N melanoma using the Surveillance, Epidemiology, and End Results (SEER) database, the most common location was the face (48%), followed by the scalp/neck (34%) and ear (15%).[15] Those authors also concluded that melanomas located on the scalp/neck were associated with worse overall (HR 1.20, 95% CI 1.14–1.26) and melanoma-specific survival (HR 1.64, 95% CI 1.49–1.80) compared with melanomas of the face. Xie et al.[8] concluded that scalp melanoma was

TABLE 4 Patient demographics, pathologic characteristics, and survival outcomes in patients with head and neck melanoma stratified by postbiopsy pigmentation

	No postbiopsy pigmentation (n = 197)	With postbiopsy pigmentation (n = 103)	p values
Age (years)	53.4 ± 15.4	62.4 ± 14.8	< **0.001**
Male gender	146 (74.1)	78 (75.7)	0.760
Type			
Melanoma	175 (88.8)	92 (89.3)	0.911
Pure DM	13 (6.6)	7 (6.8)	
Mixed DM	8 (4.1)	4 (3.9)	
Unknown	1 (0.5)	0 (0)	
Location			
Scalp	53 (26.9)	46 (44.7)	**0.004**
Ear	37 (18.8)	12 (11.7)	
Face	81 (41.1)	40 (38.8)	
Neck	26 (13.2)	5 (4.9)	
Tumor depth, median (range), mm	1.6 (0.3–10)	2.0 (0.2–19)	0.077
Ulceration	46 (23.4)	28 (27.2)	0.464
Mitosis			
None	37 (18.8)	17 (16.5)	0.520
≥ 1	117 (59.4)	68 (66.0)	
Unknown	43 (21.8)	18 (17.5)	
Surgical margins, median (range), in cm[a]	1.0 (0.5–2.0)	1.0 (0.3–2.0)	0.088
< 1.0 cm	43 (21.8)	14 (13.6)	0.139
1.0–1.9 cm	104 (52.8)	60 (58.3)	
≥ 2.0 cm	40 (20.3)	27 (26.2)	
Unknown	10 (5.1)	2 (1.9)	
Positive deep margin on diagnostic biopsy			
No	87 (44.2)	20 (19.4)	< **0.001**
Yes	96 (48.7)	80 (77.7)	
Unknown	14 (7.1)	3 (2.9)	
Positive lateral margin on diagnostic biopsy			
No	73 (37.1)	9 (8.7)	< **0.001**
Yes	99 (50.3)	87 (84.5)	
Unknown	25 (12.7)	7 (6.8)	
Microscopic residual tumor on final pathology	47 (23.9)	87 (84.5)	< **0.001**
Depth of microscopic residual tumor on final pathology (median, range mm)	1.1 (0.1–7.0)	1.7 (0.1–19.0)	< **0.001**
SLN positive	23 (11.7)	26 (25.2)	**0.003**
Lymph node status			
Negative SLND	174 (88.3)	77 (74.8)	**0.004**
+ SLN, CLND	15 (7.6)	12 (11.7)	
+ SLN, no CLND	8 (4.1)	14 (13.6)	
Adjuvant therapy	20 (10.2)	17 (16.5)	0.112
Locoregional recurrence	26 (13.2)	33 (32.0)	
Skin	6 (3.1)	11 (10.7)	
In transit	10 (5.1)	15 (14.6)	
Regional LN	12 (6.1)	15 (14.6)	
Locoregional DFS			
1-Year (95% CI)	93.2% (88.1–96.2%)	71.9% (61.0–80.3%)	< **0.001**

TABLE 4 continued

	No postbiopsy pigmentation (n = 197)	With postbiopsy pigmentation (n = 103)	p values
3-Year (95% CI)	88.1% (81.6–92.3%	59.4% (46.6–70.1%)	
5-Year (95% CI)	81.1% (72.6–78.2%)	53.2% (39.0–65.5%)	
Distant recurrence	33 (16.8)	27 (26.2)	
Distant DFS			
1-Year (95% CI)	95.0% (90.2–97.5%)	90.4% (81.6–95.1%)	< **0.001**
3-Year (95% CI)	86.0% (79.1–90.8%)	65.7% (52.5–76.0%)	
5-Year (95% CI)	80.1% (71.6–86.4%)	56.1% (40.0–69.4%)	
Any recurrence	45 (22.8)	41 (39.8)	
Therapy after recurrence	40 (20.3)	35 (34.0)	**0.009**
Immunotherapy	17	9	
Biochemotherapy	3	2	
Molecular targeted agents	3	7	
Radiation therapy	9	3	
Surgery	12	8	
Deaths	35 (17.8)	26 (25.2)	
Follow-up time, median (IQR), in years	3.5 (1.80–6.63)	2.2 (0.93–4.41)	**0.023**
Any recurrence disease-free survival			
1-Year (95% CI)	89.6% (83.8–93.4%)	70.6% (59.5–79.2%)	< **0.001**
3-Year (95% CI)	80.7% (73.3–86.2%)	49.3% (36.8–60.6%)	
5-Year (95% CI)	73.0% (64.1–80.0%)	44.1% (31.1–56.3%)	
Overall survival			
1-Year (95% CI)	97.0% (93.0–98/7%)	96.7% (90.1–98.9%)	**0.005**
3-Year (95% CI)	91.3% (85.5–95.0%)	77.7% (65.4–86.0%)	
5-Year (95% CI)	83.6% (75.7–89.2%)	65.0% (50.0–76.6%)	

Bold values indicate statistical significance ($p < 0.05$)

All values listed as mean ± standard deviation and number (percent) unless otherwise indicated

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associated with shorter melanoma-specific survival only among patients with tumors 0.76–1.50 mm thick. In the present study, tumors on the scalp were associated with worse DFS (HR 2.53, 95% CI 1.55–4.13) and worse OS (HR 2.62, 95% CI 1.46–4.70) on univariate analysis only.

Prior studies have evaluated the impact of residual tumor cells after WLE on outcomes. In a prospectively collected database, Mills et al. determined that 43% of all cases had residual disease in the WLE specimen, but this was not associated with melanoma-specific survival or OS on multivariable analysis.[17] Similarly, both Molenkamp et al. and Egnatios et al. concluded that presence of residual tumor cells on the WLE was not associated with DFS or OS on multivariable analysis.[18,19] Hocevar et al.[20] found in their study of 692 patients that there was increased local recurrence and poorer 5-year overall survival in those with residual melanoma. In the present study, residual tumor cells on WLE was associated with DFS on univariable analysis and trended toward significance on OS, but after controlling for other factors, this was no longer statistically significant. This suggests that, in concordance with previous studies, residual microscopic disease on WLE acts as a surrogate for thicker and more aggressive melanomas.

A novel finding of the present study is the poor prognosis associated with the presence of PBP. Patients with PBP were older and had primary locations on the scalp; nearly half of all scalp lesions were diagnosed with PBP. They also were more likely to have positive deep and lateral margins on initial biopsy, residual tumor on final pathology, increased depth of residual tumor on final pathology, and nodal involvement. Tumor depth on initial biopsy was greater in PBP patients, but this did not reach significance (p = 0.077). Furthermore, after adjusting for these factors, PBP remained statistically significant with worse DFS. Interestingly, 16 of 103 (15.5%) of patients with PBP did not have evidence of microscopic residual

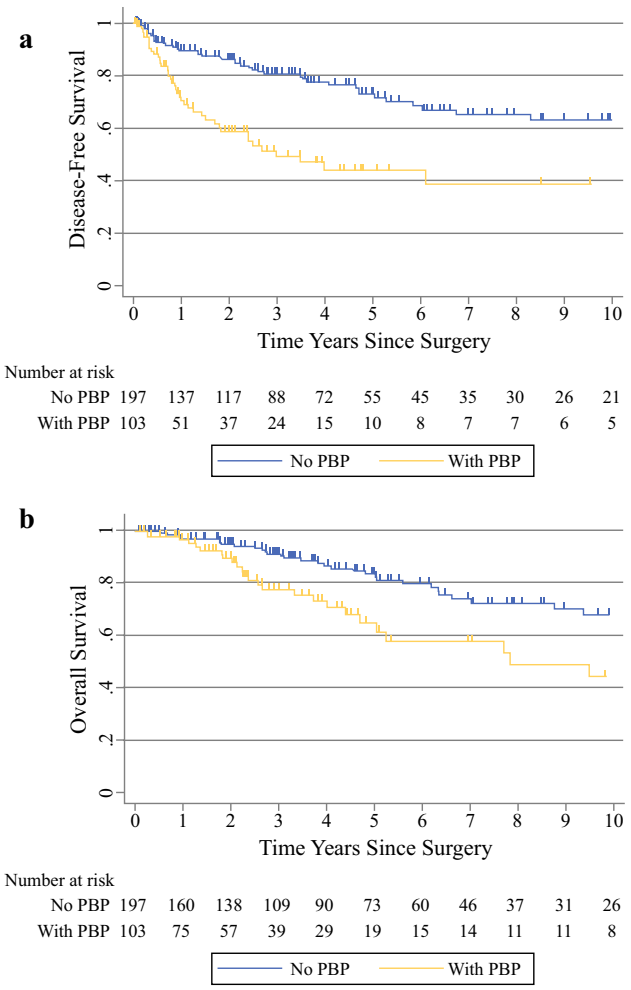

FIG. 1 Kaplan–Meier curve demonstrating disease-free survival (**a**) and overall survival (**b**) in patients with head and neck melanoma stratified by postbiopsy pigmentation (PBP)

tumor cells on the WLE specimen. On final pathology, 2 patients had a benign nevus, 13 patients had melanoma in situ (MIS), and 1 patient had no findings.

In some patients, PBP can be an indication for SLNB. National Comprehensive Cancer Network (NCCN) guidelines state that SLNB is not recommended in melanomas < 0.8 mm without ulceration (T1a) unless there is significant concern for understaging, for example, positive biopsy margins.[21] Koshenkov et al.[22] showed that melanomas < 0.76 mm deep, but with a positive deep biopsy margin, had the same risk of a positive SLN as thicker lesions. Some clinicians consider PBP to be a concerning feature because depth is underestimated or unknown. Is PBP a clinical factor that should be better quantified when describing melanomas? Currently it is merely a correlative finding, usually found in a specific type of high-risk patient—older age, scalp melanomas, greater Breslow depth, with positive biopsy margins. Patients with PBP in this study tended to have increased residual disease in WLE, suggesting that perhaps T is being understaged. Thus, a patient with PBP is more likely to have a positive SLN and, consequently, increased risk of recurrence.

These patients may have clinically and radiographically occult metastatic disease. Supporting this hypothesis, we found that our patients with PBP were more likely to develop locoregional recurrence and distant metastases. Additionally, PBP was significantly associated with shorter distant DFS ($p < 0.001$) after adjusting for age, location, ulceration, tumor depth, and lymph node involvement.

Our data increase support for performing SLNB when PBP is seen in H&N melanoma given the association with age, positive margins on initial biopsy, and SLN positivity. However, we cannot currently comment on whether increased margins on WLE are necessary. Perhaps patients with a constellation of high-risk features—increased age, scalp location, PBP, residual tumor on WLE—should be surveilled more closely due to increased risk of recurrence and/or considered for systemic therapy.

This study does have limitations. Medical records were reviewed retrospectively and may limit the accuracy of the data documented. We did not record the type of diagnostic biopsy performed (excisional, shave, punch, incisional) or its impact on survival outcomes. However, both Mills et al. and Egnatios et al. concluded that the method of diagnostic biopsy was not associated with DFS or OS.[17,19] The radial dimension of the initial tumor is unknown, as are dimensions of PBP. In the future, our medical and surgical oncologists can be more detailed in reporting PBP by including the dimensions to better quantify its effect. On final pathology of the WLE specimen, the closest margin to the tumor was not routinely described. Our median follow-up duration is short, but is sufficient to capture locoregional recurrences. Lastly, to our knowledge, there are no studies on PBP in cutaneous melanoma in the H&N or other locations. We hypothesize that its presence is greater in the H&N due to the difficulty in biopsying H&N melanoma. Scalp lesions in particular can be difficult to detect and thus develop greater symptoms and pigment prior to biopsy.[4]

CONCLUSIONS

In patients with cutaneous H&N melanoma, presence of postbiopsy pigmentation was associated with significantly shorter DFS after controlling for other prognostic factors. Further studies are required to better understand the etiology and pathogenesis of PBP on survival outcomes. However, these findings may help guide patient management and identify patients with H&N melanoma who should further be considered for sentinel lymph node biopsy or may require more intensive surveillance after treatment.

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