Anatomic location of primary melanoma: Survival differences and sun exposure

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Background: Anatomic location of melanoma has been shown to independently influence melanoma-specific survival (MSS).

Objective: We aimed to compare the MSS of specific anatomic subsites and between chronically, intermittently, and rarely sun-exposed sites.

Methods: A prospective cohort study was performed of primary invasive cutaneous melanomas with known thickness and location reviewed at a tertiary referral center over 21 years.

Results: Overall, 3570 primary cutaneous invasive melanoma cases were included. After adjustment for clinicopathologic variables (including thickness, ulceration, mitotic rate, sex, age, and subtype), posterior scalp melanoma was associated with worse MSS (hazard ratio [HR], 2.46; 95% confidence interval [CI], 1.38-4.40) compared with the upper back, whereas melanoma on the thighs, forearms/hands, and anterior upper arms had better MSS. Intermittent (HR, 0.56; 95% CI, 0.41-0.76) and chronically sun-exposed sites (HR, 0.70; 95% CI, 0.51-0.96) had improved survival compared with rarely exposed sites on multivariate analysis.

Limitations: Potential selection bias of a tertiary referral center selecting for advanced cases.

Conclusion: Altered MSS in the posterior scalp, thighs, forearms, hands, and anterior upper arms appears to be independent of clinicopathologic factors. Results were similar for both sexes and age groups. The posterior scalp should be considered a poor prognosis site. (J Am Acad Dermatol 2019;81:500-9.)

Key words: anatomic location; melanoma; subsite; sun exposed; survival; ultraviolet radiation; UV.

Anatomic location of primary cutaneous melanoma is a well-established prognostic factor. Location was incorporated into American Joint Committee on Cancer (AJCC) risk models after recognition of poorer melanoma-specific survival (MSS) and higher risk of recurrence for axial over extremity primary melanomas for Australian and US cohorts. Axial melanoma is also associated with an increased risk of nodal metastases.[1-4] Multiple models have been proposed to identify higher-risk anatomic subsites for primary melanoma. The back, posterior arms, posterior neck, posterior scalp (BANS) model, reported more than 30 years ago, suggested that upper back, posterior arms, posterior neck, and posterior scalp sites have significantly increased melanoma-specific death rates compared

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with non-BANS sites in intermediate-thickness melanoma.[5] Although several following reports were unable to confirm these findings, an ensuing meta-analysis endorsed the initial conclusion.[6-10] A subsequent German study expanded the BANS sites to include the thorax, coining the TANS (ie, thorax and back, posterior arms, posterior neck, posterior scalp) acronym.[11] Since then, multiple reports have confirmed extremity sites as having favorable MSS over axial locations.[11-14] In particular, Surveillance, Epidemiology, and End Results (ie, SEER) data have shown that the scalp, neck, and lips are at elevated risk for melanoma-specific death compared with the trunk.[15,16] Previous Australian research has also corroborated the high-risk features of scalp melanoma.[17-19] However, multiple studies have been unable to fully adjust for potential confounders given lack of information (eg, melanoma subtype, mitotic rate, or patient factors),[5,6,11-16,20-23] have found no independent association between anatomic subsites and MSS,[24-26] or have suggested contrasting findings from previous research.[27,28] Therefore, we sought to examine survival using more precise anatomic subsites to explore the association between MSS and anatomic location in greater detail than has been possible. We also aimed to account for potential confounders such as melanoma subtype, patient factors, and mitotic rate and simultaneously attempted to validate previous hypotheses such as the BANS and TANS areas in a modern cohort. Finally, given the complex relationship between sun exposure, sex, melanoma subtype, and melanoma incidence, we also assessed whether chronic versus intermittent sun-exposed sites also influenced survival.

CAPSULE SUMMARY

- Large studies have established poorer melanoma-specific survival for axial melanoma over extremities.
- Results from this study identify independent associations of subsite with survival and indicate that previous models do not discriminate variability in survival and that more chronically sun-exposed sites have favorable survival.

METHODS

Institutional ethics approval was obtained from the Alfred Hospital Human Research Ethics Committee and Monash University for this study. All invasive cutaneous primary melanoma cases reviewed at the Victorian Melanoma Service from its commencement in 1994 until January 2016 with known Breslow thickness and location were included. The Victorian Melanoma Service is a multidisciplinary, tertiary-level referral service located at the Alfred Hospital in Melbourne, Victoria, Australia. It reviews approximately one quarter of total new diagnoses of melanoma in the state of Victoria.

Clinical features of each patient collected by the reviewing clinician included age; sex; date of diagnosis (biopsy date); and tumor location, which was coded based on a body map of 232 areas, differentiating anterior from posterior and left from right and midline structures, as developed by the Pigmented Lesion Study Group.[29] Other features included clinical hypomelanosis, Fitzpatrick skin type, hair color, presence of actinic keratosis, previous history of nonmelanoma skin cancer, and family history of melanoma. Patients were examined by reviewing clinicians to determine total nevus count, quantity of dysplastic nevi, freckles, and lentigines. Independent pathology review of each melanoma was undertaken by our experienced melanoma dermatopathologists. Histologic features that were assessed included tumor subtype according to World Health Organization guidelines,[30] Breslow thickness, ulceration status, mitotic rate, neurotropism, lymphovascular invasion, satellite metastasis, regression, and tumor-invading lymphocytes. Because the mitotic rate was recorded as number per 10 high-powered fields before 2005, the reporting pathologist's conversion factors were used to convert to number per mm^2.

Survival information for all patients in the study was obtained through linkage with the Victorian Cancer Registry, a population-based cancer registry that collects data on all cancer diagnoses and mortality for residents in the state of Victoria, Australia. Patient vital status was current as of December 31, 2015. For patients diagnosed with more than 1 primary cutaneous melanoma, the melanoma with the largest Breslow thickness was retained.[31] A total of 317 cases were unable to be linked to the Victorian Cancer Registry because the date of diagnosis was too close to December 31, 2015 (the earliest diagnosis date of cases that could not be linked was October 2015) and because of migration outside of Victoria. There were 5598 melanoma records with known location, and after exclusion of in situ cases (n = 1329), non—registry-linked cases (n = 317), unknown Breslow thickness (n = 44), noncutaneous melanoma (n = 4), and multiple melanomas (n = 334), 3570 invasive cutaneous melanoma cases were available for analysis.

Abbreviations used:

AJCC: American Joint Committee on Cancer
BANS: back, posterior arms, posterior neck, posterior scalp
HR: hazard ratio
MSS: melanoma-specific survival
TANS: thorax and back, posterior arms, posterior neck, posterior scalp

Analysis of MSS for anatomic subsite and for sun-exposed sites was performed with Kaplan-Meier survival estimates and Cox proportional hazards models. Given skewed distribution for the Breslow thickness, a log transformation was applied, with the transformed variable included in models as a continuous variable. The 232 anatomic areas were collapsed into 21 distinct subsites (Fig 1). Age at diagnosis was dichotomized for analysis at the median age of 65 years. Mitotic rate was categorized into 5 strata to allow discrimination and create similar strata to observed survival differences in AJCC data.[31] The upper-back subsite was chosen as the reference site because it was the most common subsite and an intermediate MSS risk area. Sun-exposed sites were categorized into rarely exposed, intermittent, and chronically exposed, with sex differences and Australian clothing habits incorporated.[32,33] Multiple imputation with chained equations was used to impute values in place of missing data (see Table I legend for the number of missing values for each variable).[34] The calculated Nelson-Aalen estimate of cumulative hazard generated from univariate analysis and the censor indicator variable were included in the imputation model.[35] Ten sets (cycles) of imputed values were generated based on the average fraction of missing data for imputed variables being 0.12, and analysis was applied to all 10 sets, with results combined according to Rubin's rules.[36-39] All statistical analyses were performed with Stata, version 14.3 (StataCorp, College Station, TX). Multivariate results were considered statistically significant if the *P* value was less than .05. Clinicopathologic variables were included in the multivariate analysis if the overall *P* value from a univariate Cox proportional hazards model *F* statistic was less than 0.2.[40] There were approximately 9 melanoma-specific deaths per hazard ratio and 20 melanoma-specific deaths per variable included in the multivariate models.[41-43] There was no evidence of violation of proportional hazards.

RESULTS

Survival characteristics

Baseline clinical and pathologic characteristics of all patients included are detailed in Table I. There were 3570 cases available for analysis with 398 melanoma-specific deaths. A total of 944 (26.4%) melanomas occurred on the lower extremities, 800 (22.4%) on the head and neck, 585 (16.4%) on the upper back, 676 (18.9%) on the arms, 308 (8.6%) on the lower and mid back, 173 (4.8%) on the chest, 78 (2.2%) on the abdomen, and 6 (0.2%) on the groin. The median follow-up was 6.9 years (interquartile range, 2.4-13.0). Most pathologic variables were significantly associated with decreased MSS on univariate analysis (Table I). There were 2313 cases with complete data for all variables.

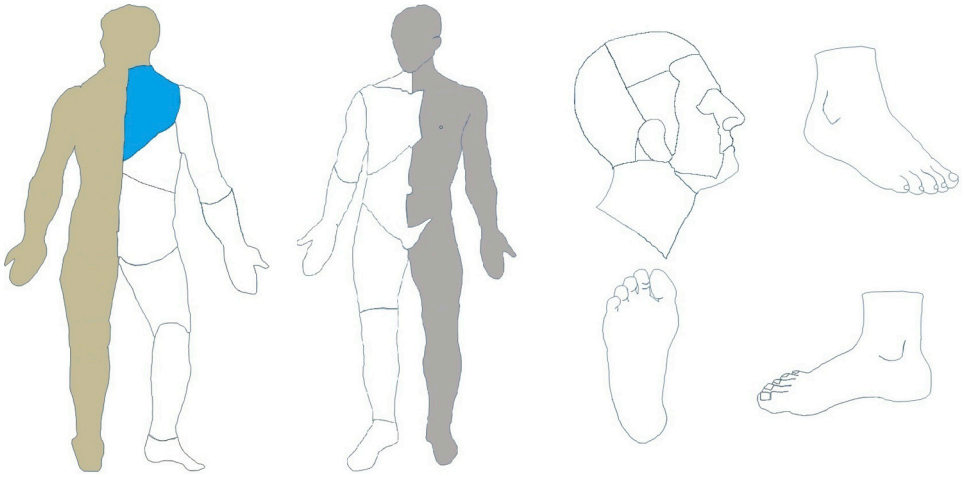

Fig 1. Anatomic subsite model: blue highlighted area indicates the reference region for the calculation of hazard ratios, and white-filled bordered regions indicate individual subsites. (Adapted from Wee et al.[65])

Table I. Baseline clinicopathologic characteristics of invasive melanoma of 3570 individuals and *P* values for univariate melanoma-specific survival associations

Clinicopathologic factor	Value	*P**
Female sex, n (%)	1715 (48.0)	<.001
Age, y, median (IQR)	65 (24.0)	.06
Breslow thickness, mm, median (IQR)†	1.1 (1.7)	<.001
Tumor subtype, n (%)		<.001
Superficial spreading	2272 (63.6)	
Nodular	578 (16.2)	
Lentigo maligna melanoma	390 (10.9)	
Pure desmoplastic	119 (3.3)	
Acral lentiginous	101 (2.8)	
Other	74 (2.1)	
Unknown	36 (1.0)	
Ulceration, n (%)*	642 (19.4)	<.001
Mitotic rate, per mm,^{2} n (%)*		<.001
<1	1,264 (42.0)	
1-4	1,142 (37.9)	
5-9	318 (10.6)	
10-19	207 (6.9)	
>20	79 (2.6)	
Regression, n (%)*	577 (19.2)	.21
Lymphovascular invasion, n (%)*	117 (3.9)	<.001
Neurotropism, n (%)*	125 (4.1)	<.001
Satellite metastases, n (%)*	52 (1.7)	<.001
Previous melanoma, n (%)		.02
0	3152 (88.3)	
1	322 (9.0)	
≥2	96 (2.7)	
Preexisting nevus, n (%)*	860 (26.7)	<.001
Number of family members with history of melanoma, n (%)*		<.01
0	2854 (80.1)	
1	550 (15.4)	
≥2	159 (4.5)	
Clinically hypomelanotic, n (%)	357 (10)	<.001
Tumor-invading lymphocytes, n (%)*		<.001
Absent	1276 (43,2)	
Minimal or mild	1062 (35.9)	
Moderate	451 (15.3)	
Severe	166 (5.6)	
Previous history of NMSC, n (%)*		
0	2342 (71.3)	
1	446 (13.6)	
2-5	335 (10.2)	
6-10	78 (2.4)	
>10	86 (2.6)	
Previous severe sunburns, n (%)*		
0	1281 (37.0)	
1-5	1510 (43.6)	
6-10	331 (9.6)	
10-20	206 (6.0)	
>20	137 (4.0)	
Total nevus count, n (%)*		
<50	1529 (47.6)	
50-100	718 (22.4)	
100-200	622 (19.4)	
>200	343 (10.7)	
Clinical dysplastic nevus count, n (%)*		
0	2273 (71.9)	
1	249 (7.9)	
2	149 (4.7)	
3	104 (3.3)	
≥4	387 (12.2)	
Fitzpatrick skin type, n (%)*		
1	1002 (28.7)	
2	1439 (41.2)	
3	843 (24.2)	
4	181 (5.2)	
5	19 (0.5)	
6	6 (0.2)	
Previous solar keratosis, n (%)	1207 (33.8)	
Eye color, n (%)*		
Blue	1881 (54.8)	
Green	403 (11.8)	
Light brown or hazel	676 (19.7)	
Brown	470 (13.7)	
Hair color, n (%)*		
Blond	733 (21.4)	
Red	400 (11.7)	
Light brown	1016 (29.6)	
Brown	1104 (32.2)	
Black	179 (5.2)	
Freckle count, n (%)*		
Few	1467 (48.9)	
Moderate	945 (31.5)	
Many	590 (19.7)	
Lentigo count, n (%)*		
Few	1325 (44.3)	
Moderate	1047 (35.0)	
Many	622 (20.8)	

IQR, Interquartile range; *NMSC*, nonmelanoma skin cancer.

**P* values are from postprocessing of analysis applied to 10 multiple imputed data sets. Imputed missing values, n (% of observed): ulceration status, 268 (8.1); mitotic rate, 560 (18.6); previous history of NMSC, 283 (8.6); severe sunburn history, 105 (3); family history of melanoma, 7 (0.2); Fitzpatrick skin type, 80 (2.3); eye color, 140 (4.1); hair color, 138 (4.0); total nevus count, 358 (11.1); dysplastic nevus count, 408 (12.9); ephelides count, 568 (18.9); lentigo count, 576 (19.2); microsatellite presence, 563 (18.7); lymphovascular invasion, 542 (17.9); tumor invading lymphocytes, 615 (20.8); regression, 561 (18.6); preexisting nevus, 352 (10.9); and neurotropism 552 (18.3).

†Logarithmic transformed continuous variable.

Table II. Univariate and multivariate melanoma-specific survival associations according to anatomic location subsite compared with upper back and according to sun exposure compared with rarely sun-exposed site category

Category	Univariate HR (95% CI)	Univariate *P* value	Multivariate* HR (95% CI)	Multivariate *P* value	Melanoma specific deaths/total melanoma
Anatomic subsite					
Posterior scalp	4.81 (2.78-8.35)	<.001†	2.46 (1.38-4.40)	<.01‡	16/45
Anterior scalp	2.55 (1.51-4.32)	<.001†	1.00 (0.57-1.78)	.99	18/104
Temporal and periauricular	2.63 (1.66-4.19)	<.001†	1.34 (0.82-2.16)	.24	25/112
Forehead and cheeks	1.13 (0.72-1.78)	.59	1.15 (0.70-1.87)	.58	27/258
Ears	1.16 (0.61-2.21)	.64	0.84 (0.43-1.63)	.61	11/95
Midline face	1.03 (0.49-2.16)	.93	0.82 (0.38-1.79)	.63	8/82
Neck	1.54 (0.89-2.67)	.12	1.53 (0.88-2.68)	.14	16/104
Upper back	Ref	Ref	Ref	Ref	62/585
Mid back	1.50 (0.95-2.37)	.08	1.23 (0.77-1.98)	.38	26/167
Lower back	1.02 (0.58-1.79)	.94	1.08 (0.61-1.93)	.79	15/141
Chest	1.23 (0.76-2.01)	.40	1.30 (0.80-2.14)	.30	22/173
Abdomen and perigenital skin	1.30 (0.67-2.54)	.44	1.31 (0.68-2.55)	.42	11/84
Anterior upper arms	0.27 (0.12-0.63)	<.01‡	0.27 (0.11-0.62)	<.01‡	6/185
Posterior upper arms	0.82 (0.50-1.33)	.42	0.93 (0.56-1.53)	.77	22/260
Forearm and hands	0.52 (0.28-0.96)	.04§	0.38 (0.20-0.75)	<.01‡	12/231
Thighs	0.57 (0.34-0.95)	.03§	0.54 (0.32-0.91)	.02§	19/285
Anterior lower legs	0.98 (0.62-1.55)	.92	1.00 (0.62-1.63)	.98	26/226
Posterior lower legs	1.10 (0.72-1.70)	.66	1.22 (0.78-1.92)	.39	31/285
Dorsal feet	1.4 (0.81-2.42)	.23	0.48 (0.22-1.05)	.07	16/108
Plantar feet	2.65 (1.32-5.33)	<.01‡	0.69 (0.27-1.80)	.45	9/40
Sun-exposure site category					
Rare	Ref	Ref	Ref	Ref	62/284
Intermittent	0.36 (0.27-0.48)	<.001‡	0.56 (0.41-0.76)	<.01‡	190/1977
Chronic	0.42 (0.31-0.56)	<.001‡	0.70 (0.51-0.96)	.02§	146/1309

Rare sites: buttocks, genitals, palms of hands, soles of feet, posterior scalp, temporal hair-bearing scalp, and periauricular skin.
Intermittent sites: chest (for males), abdomen, proximal upper/lower limb, dorsal feet, back, medial forearms.
Chronic sites: Face, neck, ears, dorsum hands, anterior scalp (categorized for males), lateral forearms, lower legs.
CI, Confidence interval; *HR*, hazard ratio derived from univariate Cox proportional hazards regression model; *Ref*, reference.
*Multivariate melanoma-specific survival model for anatomic subsite, adjusted for previous melanoma, age <65 years or ≥65 year, sex, Breslow thickness, melanoma subtype, ulceration status, mitotic rate, microsatellite presence, neurotropism, lymphovascular invasion, preexisting nevus, family history of melanoma, clinically hypomelanotic melanoma, and tumor-invading lymphocytes.
†*P* value less than .001.
‡*P* value less than .01.
§*P* value less than .05.

Anatomic subsite MSS

In unadjusted analysis, the posterior scalp, anterior scalp, temporal and periauricular, and plantar feet were all associated with decreased MSS compared with the upper back. The anterior upper arms, forearms and hands, and thighs were associated with increased MSS compared with the upper back (Table II). After adjusting for 14 clinicopathologic variables, only the posterior scalp retained decreased MSS compared with the upper back with a 2.4-fold higher hazard for melanoma-specific death. The anterior upper arms, forearm and hands, and thighs remained significantly associated with improved MSS compared with the upper back (Table II). Results were similar for both males and females and in both age groups in specific Cox proportional hazard models (Table III). BANS and TANS regions showed no evidence of differing survival in Cox proportional hazards regression models (univariate hazard ratio [HR] for BANS, 1.03; $P = .76$; HR for TANS, 0.98; $P = .86$; multivariate HR for BANS [all thickness categories], 1.19; $P = .15$; multivariate HR for BANS [intermediate thickness], 1.34; $P = .25$; multivariate HR for TANS, 1.07; $P = .55$).

MSS for sun-exposed sites

On univariate analysis, both intermittent and chronically exposed subsites had significantly improved survival compared with rarely sun-exposed sites (HR, 0.36 and 0.42, respectively; $P < .001$) (Table II). After adjustment for

Table III. Multivariate* postimputation sex- and age-specific melanoma-specific survival associations according to anatomic location subsite compared with upper back and according to sun exposure compared with rarely sun-exposed sites

Subsite	Male HR	Male *P* value	Female HR	Female *P* value
Posterior scalp	2.23	.02	3.92	.04
Anterior scalp	1.06	.87	0.56	.38
Temporal and periauricular	1.76	.03	0.28	.23
Forehead and cheeks	1.67	.08	0.40	.08
Ears	1.14	.72	0.18	.11
Midline face	0.93	.89	0.51	.39
Neck	1.56	.22	1.31	.59
Upper back			Reference	
Mid back	1.10	.74	1.05	.92
Lower back	1.32	.40	0.39	.21
Chest	1.43	.22	0.82	.70
Abdomen and perigenital skin	1.33	.51	1.21	.74
Anterior upper arms	0.28	.03	0.19	<.01
Posterior upper arms	0.73	.44	0.75	.46
Forearm and hands	0.36	.03	0.21	.02
Thighs	0.36	.02	0.54	.11
Anterior lower legs	0.90	.81	0.86	.67
Posterior lower legs	1.59	.15	0.77	.46
Dorsal feet	0.29	.05	0.51	.18
Plantar feet	0.43	.19	1.08	.92

Subsite	<65 years HR	<65 years *P* value	≥65 years HR	≥65 years *P* value
Posterior scalp	3.25	.02	1.99	.07
Anterior scalp	1.96	.14	0.80	.57
Temporal and periauricular	2.01	.07	1.10	.78
Forehead and cheeks	1.39	.47	1.09	.79
Ears	1.48	.41	0.59	.29
Face	1.18	.77	0.68	.54
Neck	1.51	.29	1.19	.70
Upper back			Reference	
Mid back	1.21	.61	1.32	.43
Lower back	1.26	.53	0.85	.76
Chest	0.95	.90	1.93	.05
Abdomen and perigenital skin	1.60	.26	0.98	.98
Anterior upper arms	0.23	.02	0.30	.05
Posterior upper arms	0.96	.91	1.04	.90
Forearm and hands	0.32	.05	0.42	.06
Thighs	0.49	.06	0.62	.22
Anterior lower legs	1.05	.90	1.08	.81
Posterior lower legs	1.17	.67	1.43	.27
Dorsal feet	0.27	.08	0.81	.66
Plantar feet	0.35	.19	1.69	.47

Site exposure category	Male HR	Male *P* value	Female HR	Female *P* value
Rare			Reference	
Intermittent	0.56	.002	0.60	.07
Chronic	0.70	.06	0.59	.07

Site exposure category	<65 years HR	<65 years *P* value	≥65 years HR	≥65 years *P* value
Rare			Reference	
Intermittent	0.48	.003	0.65	.05
Chronic	0.65	.07	0.66	.06

HR, Hazard ratio derived from multivariate Cox proportional hazards regression model.

*Multivariate melanoma-specific survival model for anatomic subsite adjusted for previous melanoma, age younger or older than 65 years or sex (dependent on specific analysis), years, Breslow thickness, melanoma subtype, ulceration status, mitotic rate, microsatellite presence, neurotropism, lymphovascular invasion, preexisting nevus, family history of melanoma, clinically hypomelanotic melanoma, and tumor-invading lymphocytes.

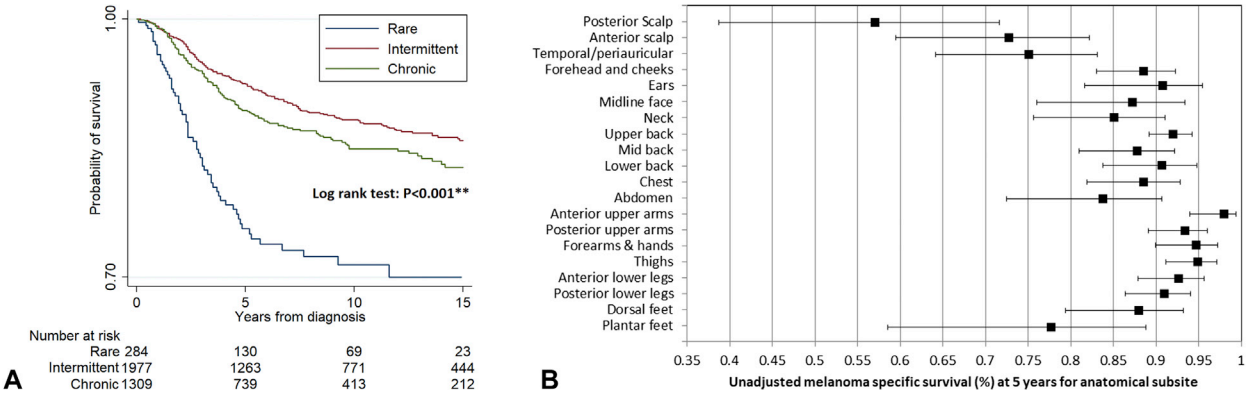

Fig 2. A, Kaplan-Meier estimates of melanoma-specific survival in sun-exposed sites for cutaneous invasive melanoma. **B**, Melanoma-specific survival (%) at 5 years for anatomic subsite (n = 3570).

clinicopathologic factors, these HR estimates were similar in magnitude for intermittent and chronic sites (0.56 and 0.70, respectively), with survival remaining improved compared with rarely exposed sites ($P < .01$ and $P = .02$, respectively) (Table II). Survival differed significantly between sun-exposed categories, with divergent unadjusted estimated MSS at 5 and 10 years ($P < .001$) (Fig 2). Results were similar for both males and females and in both age groups (Table III).

DISCUSSION

This study describes survival outcomes of a large, prospectively collected Australian melanoma cohort with respect to anatomic location and sun-exposed sites. Patients whose melanoma originated in the posterior scalp had significantly higher hazards of melanoma-specific death than those whose melanoma originated in the upper back. Poorer survival was not explained despite adjustment for Breslow thickness, melanoma subtype, ulceration, age, sex, and mitotic rate, among other clinicopathologic factors. This finding is consistent with several previous articles that described the scalp or the scalp and neck as a distinct subsite at higher risk of melanoma-specific death.[14,15,23,44] Notably, these studies lacked adjustment for potential confounders in melanoma subtype, satellite metastases, and mitotic rate. The scalp has been shown to have higher rates of satellite metastasis, increased mitotic rate, and greater proportion of nodular melanoma, all of which have been previously associated with increased univariate risk of death.[31,45,46] Our multivariate model reduced the potential of these confounding associations to affect the subsite association with MSS.

It is challenging to explain the observed survival differences within the scalp. Sentinel lymph node biopsy has known challenges in the head and neck given complex lymph drainage; however, persistent increased risk of death for the scalp has remained after adjustment for sentinel node status in another large study.[15,47,48] Despite the influences of androgenic alopecia, the posterior scalp is largely hair bearing, and given that there was little influence on the HR after accounting for Breslow thickness, it is unlikely that hair coverage influenced survival through delayed melanoma detection.[49,50] Head and neck melanoma cases also have increased tendency to develop brain metastases compared with the rest of the body, but there are no data available on whether this preferential metastasis can be extrapolated to be scalp specific.[51,52] It is clear, therefore, that further research is required to provide an adequate explanation for the posterior scalp results.

Independently decreased survival of the posterior scalp is a novel finding, with previous studies unable to discriminate between anterior and posterior scalp or scalp and neck.[11,12,14-16,23,44] Moreover, our HR estimate for the posterior scalp was substantially higher than previous findings for the entire scalp (published HR ranges, 1.2-1.84),[12,14-16,23] Independent increased MSS for our subsites differed from the only published specific subsite model for the extremities.[28] Previous research identified the calves, forehead, upper arms, cheeks, face, and temples as lower-risk sites but did not identify the thigh or forearm as having favorable survival.[28] In our study, MSS was different between the posterior and anterior upper arms, with the former similar to the upper back and the latter similar to the forearm. The forehead and cheeks had similar risks to each other, as did the anterior and posterior lower legs. Given their similarity to the upper back, these sites appeared to be intermediate in risk. Despite limited

power, there was some suggestion of higher risk for the neck and lower risk for the dorsal feet, but neither of these sites attained statistical significance in multivariate analysis. Due to lack of melanoma-specific deaths and melanoma cases, the lips were not found to be independently associated with MSS and were included as part of the face, despite previous suggestion that they may be a high-risk site.[16] Despite anecdotally poor outcomes with ear melanoma, the absence of poorer MSS in our study agreed with other reports.[15,17,44,53] Poorer survival in difficult—to—self-examine areas (scalp, postauricular, back, posterior upper arms, and thighs and buttocks) independent of sex, age, ulceration, and thickness appears to align with subsite-related survival differences observed in our data, with these being intermediate to poor survival locations.[27] Owing to the independent poor prognosis of posterior scalp melanoma, more frequent clinical or radiologic surveillance may be warranted to detect earlier recurrence, given the belief of improved response to systemic treatment and easier surgical access.[54,55]

We also tested previously stated hypotheses in the BANS and TANS areas. Differences in subsite survival that comprise the BANS and TANS areas may have accounted for the lack of survival difference between BANS and TANS and non-BANS and non-TANS sites. Our attempt to reproduce BANS findings mirrored the inability of another subsite study to do so.[28] One additional study to date has re-examined the TANS model,[56] showing independent poorer survival; however, their classification did not exactly align with the initial report.

Our multivariate results examining sun-exposed sites were similar to those of a single published study.[27] In our study, we included the lower legs and forearms in the chronic sun-exposed category, because they are frequently exposed by clothing such as T-shirts, dresses, or shorts in the Australian climate. We also included implications for androgenetic alopecia for male anterior scalp hair density in our model, with the anterior scalp included in our chronic sun-exposure category.[40] This may explain our findings of adjusted chronically sun-exposed sites having a slightly increased hazard ratio over intermittently exposed sites. Non-subsite observational studies have also suggested a similar relationship between chronic sun exposure and improved melanoma survival, examining solar elastosis, sunburn within 10 years of diagnosis, and recreational sun-exposure indices.[57-60] Although sun-exposed sites have high incidence of melanoma, it appears that their melanoma-specific mortality may be lower than that of nonexposed sites.[33,61,62]

There were limitations to our study, which included the potential for referral bias given the nature of our service. This implies that patients in our study were more likely to have advanced disease or aggressive subtypes compared with the overall melanoma caseload in Victoria, Australia. Sentinel lymph node status and distant metastatic disease status were incomplete because of insufficient follow-up periods for some patients and, therefore, were not included. Mutational status was incomplete for earlier cases because molecular testing was introduced only relatively recently and, therefore, was not assessed. Finally, there was the potential for loss to follow-up with patients moving interstate or overseas, leading to delay or loss of registry linkage, although this would have been a small proportion of the study population.

CONCLUSION

Although traditionally overlooked as an independent melanoma prognostic factor, anatomic location of the primary tumor has a significant impact on melanoma survival. In our study, particularly poor melanoma survival was observed in the posterior scalp as distinct from the anterior scalp. Although several extremity subsites showed improved MSS, there was some suggestion that not all extremity subsites do. These regional differences in survival have yet to be explained, but they likely involve a complex interplay of sun-exposure patterns, regional lymph and vascular drainage, whether the site is difficult to self-examine for patients,[53,63,64] host response factors, and downstream effects on tumor biology.[40,59,60] It is important for clinicians to be aware of the potential poor prognostic nature of posterior scalp melanoma for heightened surveillance of recurrence.

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