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ORIGINAL ARTICLE – MELANOMA

Subungual Melanoma of the Hand

Annette H. Chakera, MD[1], Michael J. Quinn, MBBS[1], Serigne Lo, PhD[1,2], Martin Drummond, MBiostat[1,2], Lauren E. Haydu, PhD[1,2], Jeremy S. Bond, MBChB[1], Jonathan R. Stretch, MBBS, DPhil(Oxon)[1,2,3], Robyn P. M. Saw, MBMS[1,2,3], Ken J. Lee, MBBS[1,2,3], W. H. McCarthy, MBBS[1,2,3], Richard A. Scolyer, MD[1,2,4], and John F. Thompson, MD[1,2,3]

[1]Melanoma Institute Australia, Sydney, NSW, Australia; [2]Sydney Medical School, The University of Sydney, Sydney, NSW, Australia; [3]Department of Melanoma and Surgical Oncology, Royal Prince Alfred Hospital, Sydney, NSW, Australia; [4]Department of Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Sydney, NSW, Australia

ABSTRACT

Background. The diagnosis of subungual melanoma (SUM) can be challenging and SUMs generally have a worse prognosis than melanomas arising elsewhere. Due to their rarity, the evidence to guide management is limited. This study sought to identify clinicopathological features predictive of outcome and to provide guidelines for management.

Methods. From a large, single-institution database, 103 patients with in situ (n = 9) or invasive (n = 94) SUMs of the hand treated between 1953 and 2014 were identified and their features analyzed.

Results. The most common site of hand SUMs was the thumb (53%). Median tumor thickness was 3.1 mm, and SUMs were commonly of the acral subtype (57%), ulcerated (58%), amelanotic (32%), and had mitoses (73%). Twenty-one patients reported prior trauma to the tumor site. Twenty-two patients were stage III at diagnosis; 7 underwent therapeutic lymph node dissection and 22 underwent elective lymph node dissection (5 positive), while 36 had sentinel node biopsy (SNB), 28% of which were positive. Forty percent of SNB-positive patients had involved non-sentinel nodes (SNs) in their completion lymph node dissection. Five-year melanoma-specific survival (MSS) and disease-free survival (DFS) rates were 70% and 52%, respectively. On multivariate analysis, regional node metastasis and right-hand tumor location were significant predictors of shorter DFS and MSS, whereas mitoses negatively impacted DFS only and increasing Breslow thickness impacted MSS only.

Conclusions. This study confirms that SUMs on the hand usually present at an advanced stage. Distal amputation appears safe for invasive SUMs, and SNB should be considered as these patients have a high risk of both SN and non-SN metastasis.

Subungual melanoma (SUM) is an uncommon tumor of the nail apparatus perceived to have a worse prognosis than cutaneous melanomas located elsewhere. This is principally related to a more advanced stage at diagnosis. Also, SUMs have poorer responses to immunotherapies and BRAF mutations are infrequent, therefore targeted therapies are uncommonly an option.[1,2] SUMs are more common on the feet than on the hands. The percentage of melanomas that arise in a subungual location varies inversely with the incidence of melanoma in the population; SUMs account for only approximately 1% of cutaneous melanomas in Caucasians,[3] however they comprised 23% in a Japanese study.[4] Moreover, the incidence of SUMs is similar between racial groups, with an annual incidence rate estimated to be 0.1 per 100,000.[4,5] At Melanoma Institute Australia (MIA), SUMs of the hand comprise 0.3% of cutaneous melanomas recorded in the database.

Annette H. Chakera and Michael J. Quinn have contributed equally to this work.

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J. F. Thompson, MD
e-mail: john.thompson@melanoma.org.au

SUM seems to not be associated with excessive sun exposure, and the nail plate has been shown to protect against ultraviolet (UV) B irradiation;[3,5,6] however, this protection may only be partial as occasionally SUMs show evidence of a UV radiation mutation signature.[7] A correlation with trauma has been noted and has been proposed as a potential etiological factor.[8,9] SUMs are often difficult to diagnose clinically and pathologically and may mimic numerous other conditions. Therefore, diagnosis is often delayed, and is also compounded by the difficulty and specialized techniques required for performing nailbed biopsies. Historically, proximal amputation of the digit was the standard treatment, but in recent years a more conservative strategy has been applied, with distal amputation and even wide local excision (WLE) for very thin tumors. However, there is no definitive evidence to support treatment recommendations.[10]

This study sought to describe the clinicopathological features, management, and follow-up of a large series of patients with SUMs of the hand, to identify predictors of outcome and provide recommendations for their management.

MATERIALS AND METHODS

Prospectively collected clinicopathological information on 103 patients with SUMs of the hand treated between 1953 and 2014 was extracted from the MIA research database. MIA-affiliated specialist pathologists reviewed all pathology specimens and patients were staged according to the 8th Edition of the American Joint Committee on Cancer (AJCC) staging system[11] (Table 1).

The length of follow-up was calculated from the date of primary diagnosis to last follow-up or death, while disease-free survival (DFS) was calculated as the time from the date of primary diagnosis to first recurrence. The site of first recurrence was recorded, however subsequent recurrences were not analyzed. Melanoma-specific survival (MSS) was calculated as the time from the date of primary diagnosis to death caused by melanoma.

Statistics

The effects of treatment and clinicopathologic variables on patient outcomes were compared in univariate and multivariate analyses, with the latter using the Cox proportional hazards model. DFS and MSS curves were plotted using the Kaplan–Meier product limit method, and the difference in survival curves was tested using the log-rank test. Univariate analysis was performed using the Wald test to identify potentially significant variables for the multivariate model, whereas multivariate analysis was performed using the purposeful selection of covariates method, with variables initially entered into the model if the variable's significance by univariate analysis was $p < 0.20$ and did not have more than 10% missing data. The final models were assessed for validity of the proportional hazards assumption using Schoenfeld residual plots and corresponding test statistics. Data management and statistical analyses were performed using Intercooled Stata version 13.1 for Windows (Statacorp LLC, College Station, TX, USA).

RESULTS

Most patients were male (61%), with a median age of 58 years, and the most common primary melanoma site was the thumb (53%) (Fig. 1), with a slight preponderance of left-hand tumors (53%). All except two patients were Caucasian (one had Australian aboriginal heritage and one was of Asian descent).

Clinicopathological Characteristics

Fifty-eight percent of the SUMs were ulcerated, 32% were amelanotic, and 73% had a mitotic rate $\geq 1/mm^2$. Right-sided tumors tended to be thicker than left-sided tumors (median 3.0 vs. 2.0 mm, $p = 0.520$). Acral lentiginous was the most frequent melanoma subtype (57%). Twenty-one patients (28%) had a history of trauma to the affected digit; however, for 29 patients, trauma history was not recorded.

Nine patients had in situ SUMs. In patients with invasive SUMs, median Breslow thickness was 3.1 mm. Males generally presented with thicker tumors than females (median 3.0 vs. 2.0 mm, $p = 0.158$), and patients diagnosed after 1993 [i.e. in the sentinel node biopsy (SNB) era] generally presented with thinner tumors than patients diagnosed earlier (median 1.8 vs. 3.3 mm, $p = 0.023$). Clark level IV invasion was present in 43% of patients, and in 30% of patients there was invasion of the periosteum or bone of the distal phalanx; however, Clark level of invasion was removed from the AJCC staging system in 2009 and is particularly difficult to measure in SUMs.

Primary Site Treatment

Distal amputation was performed at the neck of the proximal phalanx/interphalangeal joint for the thumb, and at the neck of the middle phalanx/distal interphalangeal joint for the other digits. Proximal amputation was defined as any level proximal to this, usually at the metacarpophalangeal joint or as a ray amputation.

Among the patients with in situ melanomas, three had WLE and skin grafting, five had a distal amputation, and

TABLE 1 Patient and disease characteristics for the overall SUM cohort

Feature	Value	*N*	%
Sex	Female	40	39
	Male	63	61
Age at diagnosis (years)	Median	58	–
	Range	6–93	–
	≤ 60	59	57
	> 60	44	43
Primary site	Thumb	54	53
	Other digits	48	47
	Unknown digit	1	–
	Right	48	47
	Left	55	53
Primary treatment	Distal amputation	77	75
	Proximal amputation	21	21
	Amputation level unknown	1	–
	Wide excision and skin graft	3	3
	Local excision only	1	1
Stage at primary diagnosis [AJCC 8th edition] (n = 103)	Tis	9	9
	IA	8	8
	IB	15	15
	IB/II	6	6
	IIA	15	15
	IIB	18	18
	IIC	10	10
	IIIA	2	2
	IIIB	2	2
	IIIC	17	17
	IIIB/C	1	1
Breslow thickness, mm (n = 90)[a]	Median	3.1	–
	Range	0.2–13.0	–
	≤ 1	18	20
	> 1.0–2	20	22
	> 2.0–4	30	33
	> 4	22	24
	Missing	4	–
Ulceration (n = 93)[a]	Absent	39	42
	Present	54	58
	Missing	10	–
Mitotic rate, per mm^2 (n = 97)[a]	Median	4	–
	Range	0–80	–
	0	26	27
	≥ 1	71	73
	Missing	6	–
Melanoma subtype	Acral lentiginous[b]	59	57
	Nodular	17	16
	Desmoplastic[c]	7	7
	SSM	4	4
	Unclassified	16	16
Pigmentation (n = 74)	Absent	24	32
	Present	50	68
	Missing	29	–
History of trauma (n = 75)	Yes	21	28
	No	54	72
	Missing	28	–
Site of first recurrence (n = 44)	Local	5	11
	In transit	8	18
	Regional	17	39
	Distant	14	32

SUM subungual melanoma, *AJCC* American Joint Committee on Cancer, *SSM* superficial spreading melanoma

[a]Excluding in situ melanoma (n = 9)

[b]Four mixed acral lentiginous-desmoplastic

[c]Two neurotropic

one chose no further excision after biopsy. The majority of patients with invasive SUMs had a distal amputation (75%), while only 21% had a proximal amputation and none had WLE.

Treatment of Regional Nodes

Twenty-two patients were stage III at diagnosis; 7 with clinically/radiologically detected metastasis had a therapeutic lymph node dissection, and 22 had an elective

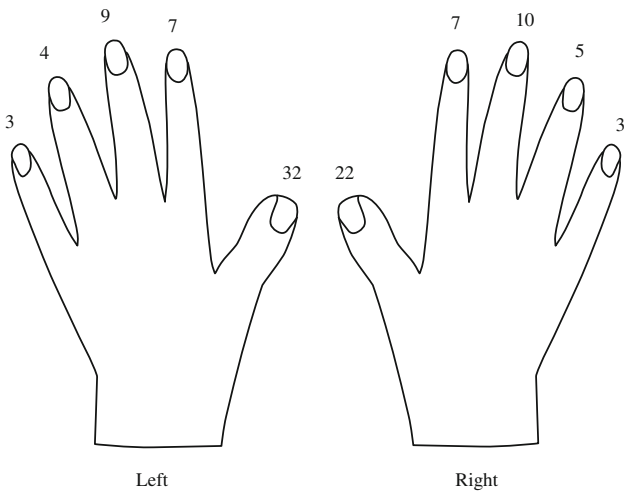

FIG. 1 Distribution of subungual melanomas per digit (n = 102)

lymph node dissection (ELND), 23% of which contained metastatic lymph nodes. Five of the ELNDs were performed at the same time as a prophylactic isolated limb perfusion/infusion; these procedures were later abandoned as they did not improve survival.[12]

Treatment of the regional lymph node field after 1993 included SNB for T1b-4 melanomas with no evidence of nodal metastasis. SNB was performed in 36 patients, 28% of whom were sentinel node (SN)-positive. Six had lymphatic drainage to both the axillary and epitrochlear nodes; one had metastasis in the axilla but not the epitrochlear region. The median number of SNs removed was two (range 1–6). All SN-positive patients subsequently underwent axillary level I–III completion lymph node dissection (CLND), except for one patient who declined and later recurred in the same axilla. Forty percent of patients had metastasis in non-SNs in the CLND specimen (Table 2).

Recurrence

Long-term follow-up was available for 93% of patients, with a median follow-up of 105 months. Forty-four patients recurred, with a median DFS of 70 months [95% confidence interval (CI) 44–435]; 5- and 10-year DFS was 52% (95% CI 42–65%) and 46% (95% CI 35–60%), respectively. There were no differences in DFS or MSS for patients treated pre/post the introduction of SNB ($p = 0.168$ and 0.277, respectively).

None of the patients with in situ melanomas recurred; five patients with invasive melanomas developed local recurrence, three after distal amputation and two after proximal amputation. The most common site of first recurrence was in the regional lymph nodes (39%). Two SN-negative patients had regional node recurrence after 11 and 58 months, respectively, which represents a failure rate of 6% and a false-negative rate of 17%. Twenty-five patients who would have met the current criteria for being offered SNB did not have their lymph nodes assessed pathologically at diagnosis. Most of these were treated in the pre-SNB era, except for five subjects who did not have SNB due to significant comorbidity or because they were stage IA according to the staging system applicable at the time of their diagnosis, but would have been upstaged to IB in the current version. Ten of these patients (40%) later developed regional metastasis as a first site of recurrence. DFS and MSS were better for patients with microscopic compared with macroscopic lymph node metastases ($p = 0.01$ and $p < 0.01$, respectively).

TABLE 2 Summary of lymph node procedures conducted at the time of primary presentation

Lymph node procedure at primary presentation		*N*	Result	
			Positive (%)	Negative (%)
Sentinel lymph node biopsy		36	10 (28)	26 (72)
Regional lymph node dissection	Completion (positive sentinel node)	10[a]	4 (40)	6 (60)
	Therapeutic (clinical metastasis)	7	7 (100)	0
	Elective (no clinical metastasis)	22[b]	5 (23)	17 (77)

[a]One patient declined completion lymph node dissection but recurred in the same axilla and was therefore included

[b]Five were performed concurrently with elective isolated limb perfusion/infusion

Survival

During follow-up, 30% of patients died of melanoma. Median MSS was 181 months and 5- and 10-year MSS was 70% (95% CI 60–83%) and 55% (95% CI 43–70%), respectively.

On multivariate analysis, regional lymph node metastasis and right-hand tumor location were significant predictors of shorter DFS and MSS. Increasing Breslow thickness was a negative predictor of MSS, whereas elevated mitotic rate was a negative predictor of DFS (Table 3 and Fig. 2).

DISCUSSION

This retrospective analysis of 103 mainly Caucasian patients with SUM of the hand, treated over a 62-year period, confirmed many findings highlighted in previous smaller reports, namely that SUMs are rare tumors that usually present at an advanced stage with thicker primaries, commonly with adverse prognostic features and involvement of regional lymph nodes. This suggests delayed diagnosis and a more aggressive tumor biology than melanomas arising in cutaneous sites elsewhere. The substantial proportion of amelanotic SUMs (32%) may have contributed to diagnostic delay due to the lack of clinical suspicion of melanoma.

Surprisingly, patients with right-hand SUMs performed significantly worse than patients with left-hand SUMs, even when controlling for pathological factors. There is no obvious clinical explanation for this difference, but it induces speculation that (micro)trauma-induced inflammation to the right hand, which is most often the dominant hand and therefore more prone to injury, may play a role in pathogenesis, as previously suggested;[8,9,13] however, the possible role of trauma should be interpreted with caution

TABLE 3 Univariate and multivariate analysis for predictors of DFS and MSS for patients with invasive SUM ($n = 90$)

Variable	DFS						MSS					
	N	Median time (95% CI)	Univariate		Multivariate		*N*	Median time (95% CI)	Univariate		Multivariate	
			HR (95% CI)	*p* value*	HR (95% CI)	*p* value*			HR (95% CI)	*p* value*	HR (95% CI)	*p* value*
Age primary (years)												
≤ 60	51	70.14 (38.74, 505.6)	1				51	(78.85, NR)	1			
> 60	39	58.94 (20.17, NR)	1.39 (0.74, 2.60)	0.3071			39	181.2 (58.18, NR)	1.60 (0.76, 3.38)	0.2135		
Sex												
Female	33	96.16 (25.92, NR)	1				33	181.2 (62.92, NR)	1			
Male	57	70.14 (35.52, 505.6)	0.99 (0.51, 1.89)	0.9643			57	223.5 (70.01, NR)	1.10 (0.51, 2.34)	0.8095		
Primary site												
Thumb	47	239.2 (24.44, 505.6)	1				47	235.6 (70.01, NR)	1			
Other fingers	42	58.81 (30.09, 202.2)	1.25 (0.66, 2.36)	0.4881			42	223.5 (78.85, NR)	1.00 (0.48, 2.08)	0.9954		
Right/left primary												
Right	43	58.81 (26.22, 202.2)	1		1		43	102.7 (58.18, NR)	1		1	
Left	47	239.2 (38.74, NR)	0.58 (0.31, 1.11)	0.1003	0.42 (0.21, 0.85)	0.0163	47	(114.8, NR)	0.48 (0.22, 1.02)	0.0571	0.29 (0.12, 0.68)	0.0045
Breslow[a] (mm)												
≤ 2	38	239.2 (58.81, 239.2)	1		1		38	(114.8, NR)	1		1	
> 2–4	30	64.59 (27.66, 202.2)	2.15 (0.96, 4.79)	0.0308	1.49 (0.58, 3.80)	0.0669	30	223.5 (62.92, NR)	2.19 (0.77, 6.26)	0.0218	1.84 (0.64, 5.28)	0.0143
> 4	22	24.44 (12.81, 43.60)	3.11 (1.33, 7.24)		2.79 (1.09, 7.15)		22	51.25 (26.87, NR)	4.22 (1.48, 12.01)		4.48 (1.52, 13.17)	
Ulceration												
Absent	31	70.14 (36.01, NR)	1				31	181.2 (78.85, NR)	1			
Present	51	56.77 (24.44, 239.2)	1.44 (0.73, 2.84)	0.2995			51	223.5 (43.99, NR)	1.64 (0.72, 3.74)	0.2357		
Mitosis												
Absent	18	(58.81, NR)	1		1		18	(78.85, NR)	1			
Present	68	58.94 (26.22, 202.2)	3.20 (1.13, 9.08)	0.0290	2.97 (0.98, 8.95)	0.0534	68	181.2 (67.48, NR)	1.87 (0.64, 5.41)	0.2511		
Subtype												
Non-acral	25	202.2 (24.44, NR)	1				25	223.5 (43.99, 235.6)	1			
Acral lentiginous	53	64.59 (35.52, 505.6)	1.02 (0.48, 2.13)	0.9672			53	(80.95, NR)	0.67 (0.29, 1.52)	0.3381		

TABLE 3 continued

Variable	DFS						MSS					
	N	Median time (95% CI)	Univariate		Multivariate		*N*	Median time (95% CI)	Univariate		Multivariate	
			HR (95% CI)	*p* value*	HR (95% CI)	*p* value*			HR (95% CI)	*p* value*	HR (95% CI)	*p* value*
Trauma												
No	47	202.2 (24.44, 505.6)	1				47	223.5 (78.85, NR)	1			
Yes	20	56.77 (27.66, NR)	1.12 (0.56, 2.26)	0.7472			20	102.7 (43.99, NR)	1.14 (0.51, 2.57)	0.7489		
Pigmentation												
No	23	38.74 (25.92, 64.59)	1				23	70.01 (42.22, NR)	1			
Yes	46	202.2 (58.81, 505.6)	0.56 (0.27, 1.14)	0.1118			46	223.5 (102.7, NR)	0.60 (0.27, 1.33)	0.2076		
Stage[b]												
I	23	(58.81, NR)	1				23	(78.85, NR)	1			
II	46	70.14 (35.52, 239.2)	2.55 (0.88, 7.41)	0.0077			46	223.5 (102.7, NR)	6.18 (0.82, 46.74)	0.0050		
III	21	20.17 (14.92, 64.59)	5.43 (1.76, 16.81)				21	53.91 (38.41, NR)	16.31 (2.09, 127.0)			
Primary treatment												
Distal amputation	67	(35.52, NR)	1				67	181.2 (80.95, NR)	1			
Proximal amputation	20	63.46 (17.02, 239.2)	1.26 (0.63, 2.50)	0.5110			20	102.7 (32.46, NR)	1.51 (0.69, 3.31)	0.2991		
Lymph node status												
Negative	70	202.2 (55.46, 505.6)	1		1		70	235.6 (181.2, NR)	1		1	
Micro/macro positive	20	25.92 (14.92, NR)	2.10 (1.04, 4.25)	0.0393	2.55 (1.20, 5.43)	0.0147	20	58.18 (24.05, NR)	3.22 (1.47, 7.05)	0.0036	3.78 (1.63, 8.74)	0.0019

DFS disease-free survival, *MSS* melanoma-specific survival, *SUM* subungual melanoma, *CI* confidence interval, *HR* hazard ratio, *NR* not reached

[a]Patients with unknown Breslow thickness were excluded

[b]Stage was not included in the multivariate analysis as it is collinear with other variables in the model

*Based on Wald statistics to test the global effect of the covariate

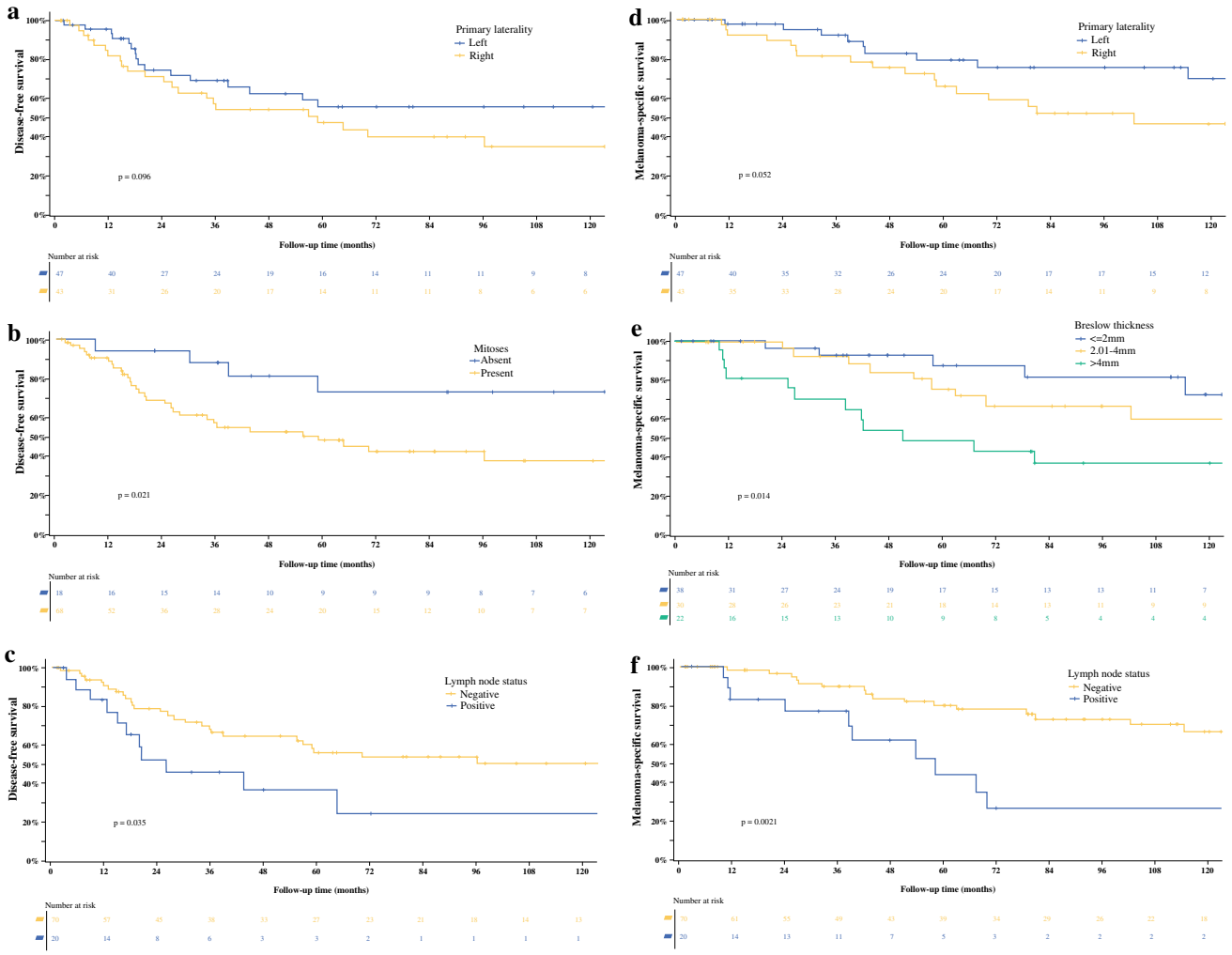

FIG. 2 Disease-free and melanoma-specific survival curves according to significant prognostic factors

due to the risk of recall bias. Trauma is common on hands and feet, while SUMs are rare, and trauma may simply draw attention to a lesion on the digit without explaining causality. The literature mostly consists of case reports of SUMs appearing after trauma such as burns, penetrating injuries, or irradiation,[14–16] but one case-control study reported a fivefold increase in the risk of acral melanoma of hands or feet in patients who recalled a serious penetrating injury compared with those who did not.[17] There was no association with having a chronic skin condition on the soles or palms, and the authors speculated that local penetrative injury may induce acral melanoma through stimulation of melanocytes by fibroblast growth factor abundant in healing wounds.[17] This theory is supported by a study showing that melanocytic nevi, when subjected to trauma such as dermabrasion, show histologic features 4 weeks after the injury similar to alterations occurring after UV exposure.[18]

Local recurrence rates in cutaneous melanoma in general are positively correlated with Breslow thickness and the width of the WLE, with the clearance margins influencing local recurrence but not overall survival.[19] Level of amputation can be regarded as a surrogate of width of excision, and, historically, proximal amputation was advocated to treat this aggressive disease, based on the results of small studies.[20] Proximal amputation often has psychological, functional, cosmetic, and socioeconomic implications for the patient, and the choice of amputation level is therefore very important. Nevertheless, there is a lack of definitive evidence to guide extent and there have been no randomized trials evaluating surgical margins for SUMs. In recent years, a number of authors have advocated a more conservative approach and, in small series, distal amputation appeared to be as safe as proximal amputation.[10] This is supported by the results of the present larger study. Nguyen et al.[21] advocated distal amputation with

resection through the distal interphalangeal joint for fingers, and distal to the interphalangeal joint for the thumb. This maximizes hand function, with preservation of flexor digitorum superficialis/flexor pollicis longus and the central slip of extensor digitorum longus/extensor pollicis longus.[22] Thumb length is maintained, allowing two and three finger pinch. This relative preservation of function is particularly important as the thumb is the most commonly involved digit.[3,23–25]

For in situ SUMs, WLE has been increasingly used, with varying results.[24,26] Three patients in our study had WLE, and none developed recurrence during follow-up. However, in another study, a similar approach eventually led to amputation for persistent positive margins or local recurrence in many patients.[24] Others have even used WLE for early invasive melanomas and reported good results.[26,27] A recent review showed a tendency towards more frequent local recurrence but similar frequencies of regional and distant recurrence after WLE instead of amputation. Nevertheless, these studies were again small and suboptimally designed, precluding definitive conclusions.[10] Due to the anatomy of the nail matrix, with close proximity to the periosteum, bone and tendon apparatus, application of minimal margins, in our view, is potentially risky for invasive SUMs. Because of this concern, none of our patients had WLE of invasive SUMs. This issue was highlighted in a study by Kim et al.[28] in which the distance from the deep surface of the nail matrix to the periosteum was measured in 15 cadavers; the mean distance for all digits was 0.90 mm, with the shortest being only 0.27 mm. A natural barrier may exist between the nail matrix and underlying periosteum, making a wide margin unnecessary. However, nearly one-third of the SUMs in our study (30%) showed invasion into the periosteum or bone, which suggests that clearance of the deep margin would have been compromised by any procedure other than amputation. Thus, WLE does not seem to provide an adequate deep margin for assured local eradication of deeply invasive SUMs.

The median Breslow thickness in our study (3.1 mm) is similar to that in other SUM studies,[21] and the SN positivity rate of 28%, which is higher than reported for melanomas located elsewhere, probably reflects the locally advanced nature of most SUMs at presentation.[29] The non-SN positivity rate of 40% in the CLND specimens is higher than reported in the first Multicenter Selective Lymphadenectomy Trial.[30] Our SNB failure rate of 6% is identical to the rate in a previous report on SUMs, whereas our false-negative rate was lower (17% vs. 29%).[24]

A previous study of 281 acral melanomas (defined as acral or subungual location) that were compared with non-acral cutaneous extremity melanomas showed that acral melanomas had an inferior survival when stage matched.[31] A possible explanation is the spectrum of mutations; while BRAF mutations are relatively uncommon in acral melanomas (approximately 10%), KIT mutations are more common (approximately 10%) than in other cutaneous melanomas.[1,2,32,33] In addition, a more widespread field change, with atypical melanocytes as far as 3 cm away from the clinically apparent primary tumor, has been shown for acral compared with superficial spreading melanomas, theoretically increasing the risk of local recurrence.[33] However, when looking specifically at the acral lentiginous melanoma subtype, we were not able to demonstrate a significant difference in survival for these SUMs compared with other subtypes, perhaps due to the small patient number.

Limitations of the present study include its retrospective nature, the modest sample size, and the inclusion of patients treated over a 62-year period. The patient group is heterogeneous, however this enabled us to analyze differing treatment modalities and assess survival with prolonged follow-up.

CONCLUSIONS

This study of hand SUMs, one of the largest to date, demonstrates that this diagnosis carries serious adverse prognostic implications. SUMs have a worse prognosis than melanomas occurring at other cutaneous sites, possibly related to delays in diagnosis and more aggressive tumor biology. While challenges remain in diagnosing SUMs, including difficulties in performing and interpreting biopsies, there is a need for greater awareness and earlier diagnosis to improve clinical outcomes. Distal amputation, maximizing residual function, seems safe as definitive treatment of invasive SUMs, and SNB should be considered for prognostic information as these patients have a high risk of both SN and non-SN metastasis.

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