ORIGINAL ARTICLE

Ann Acad Med Singap 2021;50:456-66
https://doi.org/10.47102/annals-acadmedsg.2020535

Melanoma in Singapore: A 20-year review of disease and treatment outcomes

Pei Ming Yeo [1]*MRCP (UK)*, Ziying Vanessa Lim [1]*MRCP (UK)*, Wei Ding Virlynn Tan [1]*MSc*, Xiahong Zhao [1]*PhD*, Hui Yi Chia [1]*MRCP (UK)*, Suat Hoon Tan [1]*FAMS (Dermatology)*, Melissa Ching Ching Teo [2]*FRCSEd*, Melissa Wee Ping Tan [1]*FAMS (Dermatology)*

ABSTRACT

Introduction: Melanomas in Asians have different clinicopathological characteristics and prognosis from melanomas in Caucasians. This study reviewed the epidemiology and treatment outcomes of cutaneous melanoma diagnosed at a tertiary referral dermatology centre in Singapore, which has a multiracial population. The study also determined whether Asians had comparable relapse-free and overall survival periods to Caucasians in Singapore.

Method: This is a retrospective review of cutaneous melanoma cases in our centre between 1996 and 2015.

Results: Sixty-two cases of melanoma were diagnosed in 61 patients: 72.6% occurred in Chinese, 19.4% in Caucasians and 3.2% in Indians, with an over-representation of Caucasians. Superficial spreading melanoma, acral lentiginous melanoma and nodular melanoma comprised 37.1%, 35.5% and 22.6% of the cases, respectively. The median time interval to diagnosis was longer in Asians than Caucasians; median Breslow's thickness in Asians were significantly thicker than in Caucasians (2.6mm versus 0.9mm, *P*=0.018) and Asians tend to present at a later stage. The mortality rates for Asians and Caucasians were 52% and 0%, respectively.

Conclusion: More physician and patient education on skin cancer awareness is needed in our Asian-predominant population for better outcomes.

Ann Acad Med Singap 2021;50:456-66

Keywords: Asian, melanoma, nails, skin neoplasm, survival

INTRODUCTION

Melanoma is rare in Asians.[1] Asian studies of melanoma have reported a larger proportion of patients diagnosed with advanced melanoma (stage III or IV), and overall five-year survival rates ranging from 41.6% to 45.6%.[2] This is in contrast to the 2019 statistics from the American Cancer Society where the 5-year survival rate for all surveillance, epidemiology, and end results (SEER) stages combined was 92% for melanoma in the US. In addition, melanoma presents differently in Asian patients, with clear distinctions in the prevalent subtype, site of presentation, risk factors and tumour mutations. Our study aims to describe the clinical presentation, treatment and outcomes of cutaneous melanoma in Singapore over the last 20 years.

METHODS

We conducted a retrospective single-centre review of cutaneous invasive melanoma diagnosed at the National Skin Centre, the only tertiary referral dermatology centre in Singapore, from January 1996 to December 2015. Epidemiologic, disease, treatment and outcome data were extracted from patients' medical records from the institute. Histopathology slides of all cases of melanoma were retrieved from the institution's data bank and reviewed. For patients referred to a tertiary referral cancer centre for further management, treatment records and outcome were retrieved from that institute. Clinical or pathological staging was determined according to the 7th edition of the American Joint Committee on Cancer.[3]

Prophylactic lymph node dissection (PLND) was defined as lymph node removal without any clinical, radiological or histological evidence of lymph node involvement. Complete lymph node dissection (CLND) was defined as lymph node removal following sentinel lymph node positivity. In our institution, therapeutic lymph node dissection (TLND) involves lymph node

[1] National Skin Centre, Singapore
[2] Department of Surgical Oncology, National Cancer Centre Singapore
Correspondence: Dr Ziying Vanessa Lim, National Skin Centre, 1 Mandalay Road, Singapore 308205.
Email: vlim@nsc.com.sg

CLINICAL IMPACT

What is New

- The incidence of melanoma in Singapore has steadily increased in recent years.
- Asians have a thicker Breslow's thickness and tend to present later compared with Caucasians.

Clinical Implications

- Melanomas in Asians confer a worse prognosis than in Caucasians.
- Primary care providers should examine their patients for early lesions in the soles, palms and nails for unexplained pigmented lesions.

removal in the presence of clinical and/or histological confirmed lymph node involvement by melanoma. Locoregional relapse was defined as clinically recognisable lymph node metastases or histological relapse in the regional lymph node, satellite or in-transit lesions. Distant relapse was defined as visceral relapse.

Melanoma BRAF and c-KIT mutational analysis by Sanger sequencing started to be performed in Singapore from the year 2012. BRAF mutational analysis detects the V600E in exon 15 of BRAF gene while c-KIT 9 and 11 mutational analysis detects gene mutations in exons 9 and 11. If additional c-KIT rare mutations are requested for, they are performed for gene mutations in exons 13 and 17. NRAS mutational analysis is not routinely performed.

Median values were reported for non-normal continuous variables, and the Wilcoxon signed-rank test and Kruskal-Wallis test were performed to test for differences between 2 groups and among more than 2 groups, respectively. Counts and percentages were reported for categorical variables, and Fisher's exact test was used to test for differences in proportions between groups. Median survival time was analysed by the Kaplan-Meier method and compared using the Log-rank test between groups. Univariate analysis of the association between the prognostic factors and survival was performed using the Cox proportional hazard model. To avoid missing potential significant factors, variables with a P value<0.15 by univariate analysis were further analysed by multivariable analysis. Hazard ratios (HR) with 95% confidence intervals (CI) obtained from the multivariable Cox proportional hazard model were reported. Significance was assessed at a level of 0.05. The Stata 15 software was used for all statistical analyses.[4] This study was approved by the institutional ethics review board.

RESULTS

Epidemiological data

Sixty-two cases of invasive cutaneous melanoma were diagnosed in 61 patients at our centre (1 patient had 2 melanomas on different anatomical regions diagnosed at different time points). Cases of melanoma in situ (MIS) were excluded from the analysis. Table 1 summarises the clinical characteristics of patients with cutaneous melanoma.

There was a predominance of Chinese (72.6%), followed by Caucasians (19.4%) and Indians (3.2%), with an over-representation of Caucasians. Bangladeshi, Filipino and Nepalese constitute the other ethnicities (4.8%). There were no Malays diagnosed with cutaneous melanoma although Malays constitute the second largest group in the racial composition of the population in Singapore.

There were 39 male patients (62.9%), with a male to female ratio of 1.7 to 1, in keeping with an earlier melanoma study in Singapore.[5] The most common age of onset was in both the 6th and 7th decade and the median age at diagnosis was 64.0 years (range 27–99). Overall, there was a decreasing trend in age at the time of initial diagnosis, contributed by the younger age of presentation (65.0 years) in Asians in the last 5 years (2011–2015) compared to a median of 80.0 years in the earlier 5 years (2006–2010). The median age of Caucasians was significantly lower at 47.0 years (range 36–72 years) compared with Asians (67.0 years, range 27–99 years) during the entire study period (P=0.007).

After adjusting for population census, the incidence of cutaneous melanoma diagnosed at our centre between 2011 and 2015 was 0.13 patient per 100,000 patient-years, representing an approximately 3-fold increase compared to the period from 1996 to 2010.

Pathologic data

The most common histological subtype of cutaneous melanoma diagnosed were superficial spreading melanoma (SSM) at 37.1% and acral lentiginous melanoma (ALM) at 35.5%, followed by nodular melanoma (NM) at 22.6%. The following subtypes had one patient each: lentigo maligna melanoma, melanoma arising from a congenital melanocytic nevus, and spitzoid melanoma (Table 2). This is in

Table 1. Clinical characteristics of patients with cutaneous melanoma

Clinical characteristics	
Age, median (IQR), years	64.0 (27–99)
Sex, no. (%)	
Male	39 (62.9)
Female	23 (37.1)
Race, no. (%)	
Chinese	45 (72.6)
Caucasian	12 (19.4)
Indians	2 (3.2)
Bangladeshi	1 (1.6)
Filipino	1 (1.6)
Nepalese	1 (1.6)
Nationality, no. (%)	
Singaporeans	47 (75.8)
Foreigners	15 (24.2)
Site, no. (%)	
Limbs	15 (24.2)
Palmoplantar/ subungual	28 (45.2)
Trunk	14 (22.6)
Head and neck	4 (6.5)
Groin	1 (1.6)
Staging, no. (%)	
I	19 (30.6)
II	25 (40.3)
III	15 (24.2)
IV	1 (1.6)
Indeterminate	2 (3.2)
Primary treatment (N=47)	
Surgery, no. (%)	41 (87.2)
Wide excision only	15 (36.6)
Wide excision with SLNB in first surgery	16 (39.0)
Wide excision with LND in first surgery	10 (24.4)
Adjuvant therapy, no. (%)	2 (4.3)
Patient did not undergo surgery, no. (%)	6 (12.8)

IQR: interquartile range; LND: lymph node dissection; SLNB: sentinel lymph node biopsy

Table 2. Microtumoural characteristics of patients with cutaneous melanoma

Microtumoural characteristics	no. (%)
Histological subtype	
Superficial spreading melanoma	23 (37.1)
Acral lentiginous melanoma	22 (35.5)
Nodular melanoma	14 (22.6)
Others	
Lentigo maligna melanoma	1 (1.6)
Melanoma arising from congenital melanocytic nevus	1 (1.6)
Spitzoid melanoma with deep penetrating nevus-like features	1 (1.6)
Breslow's thickness, mm	
<1	13 (21.0)
1.01–2	10 (16.1)
2.01–4	19 (30.6)
>4	16 (25.8)
Indeterminate	4 (6.5)
Ulceration	
No	35 (56.5)
Yes	27 (43.5)
Mitotic rate	
0/mm^2	3 (4.8)
>1/mm^2	28 (45.2)
Rare	4 (6.5)
Few	1 (1.6)
Moderate	1 (1.6)
Multiple	1 (1.6)
Seen throughout	1 (1.6)
Unknown	23 (37.1)
Presence of tumour-infiltrating lymphocytes	
Absent	52 (83.9)
Non-brisk	7 (11.3)
Brisk	3 (4.8)
Presence of microsatellites	
Yes	2 (3.2)
No	60 (96.8)
Regression	
Yes	4 (6.5)
No	58 (93.5)
Lymphovascular/ perineural invasion	
Yes	6 (9.7)
No	56 (90.3)

contrast to earlier Singapore studies in which ALM[5] and NM[6] were the most common histological subtypes. Among Asians in our study, the most common subtype of melanoma was ALM (44.0%) followed by SSM (32.0%) and NM (20.0%); and among Caucasians, the most common subtype of melanoma was SSM (58.3%) followed by NM (33.3%) (P=0.005). There was no significant change in the proportion of melanoma subtypes in 2009–2015 compared to 1995–2008.

The most common site of presentation in Asians was the sole of the foot (46.0%) versus the back (33.3%) and lower limb (33.3%) in Caucasians. There were no cases of melanoma on the foot in Caucasians (Table 3).

The median Breslow's thickness was 2.5mm (range 0.2–15mm) with melanomas significantly thicker in Asians than Caucasians (median 2.6mm versus 0.9mm, P=0.02). Stratified by ethnicity, Caucasians showed a decrease in median Breslow's thickness when comparing between the periods of 1995–2008 and 2009–2015 (1.7mm versus 0.7mm, P=0.58) but this did not reach statistical significance. Asians did not show a significant change in median Breslow's thickness (2.7mm versus 2.6mm, P=0.60) over time; 38.6% of stage I and II melanoma were ulcerated at diagnosis. Asians had significantly more ulcerated

Table 3. Comparison of clinico-pathological characteristics between Asians and Caucasians

Parameters	**Asians** (n=50)	**Caucasians** (n=12)	***P* value**
Sex, no. (%)			0.508
Male	30 (60)	9 (75)	
Female	20 (40)	3 (25)	
Median age, years	67	47	0.007
Histological subtypes, no. (%)			0.005
ALM	22 (44)	0 (0)	
SSM	16 (32)	7 (58)	
NM	10 (20)	4 (33)	
Lentigo maligna melanoma	0 (0)	1 (8)	
Others	2 (4)	0 (0)	
Anatomical site, no. (%)			0.012
Head and neck	3 (6)	1 (8)	
Trunk, shoulder blade, groin	9 (18)	6 (50)	
Upper limb excluding hand	5 (10)	1 (8)	
Lower limb excluding foot	6 (12)	4 (33)	
Hand, dorsum	1 (2)	0 (0)	
Foot, dorsum	1 (2)	0 (0)	
Foot, plantar	23 (46)	0 (0)	
Foot, unspecified	2 (4)	0 (0)	
Median Breslow's thickness, mm	2.6	0.9	0.018
Ulceration, no. (%)			0.008
No	24 (48)	11 (92)	
Yes	26 (52)	1 (8)	
Mitotic rate[a], no. (%)			0.653
$<1/mm^2$	6 (21)	1 (10)	
$\geq 1/mm^2$	23 (79)	9 (90)	
Staging, no. (%)			0.046
I	12 (24)	7 (58)	
II	23 (46)	2 (17)	
III/IV	14 (28)	2 (17)	
Indeterminate	1 (2)	1 (8)	
Median time to diagnosis, months	24	12	0.233
Primary treatment,[a] no. (%)			0.373
Surgery			
Only wide excision	13 (32)	2 (33)	
Wide excision with SLNB or LND	22 (54)	4 (67)	

Table 3. Comparison of clinico-pathological characteristics between Asians and Caucasians (Cont'd)

Parameters	Asians (n=50)	Caucasians (n=12)	*P* value
Adjuvant therapy	1 (2)	1 (17)	
Patient did not undergo surgery	6 (15)	0 (0)	
Relapse,[a] no. (%)			0.046
No	14 (34)	5 (83)	
Yes	18 (44)	0 (0)	
Not applicable	6 (15)	1 (17)	
Unknown	3 (7)	0 (0)	
Time to relapse (months)	8	NA	NA
Dead,[b] no. (%)			0.022
No	17 (41)	6 (100)	
Yes	23 (56)	0 (0)	
Unknown	1 (2)	0 (0)	

ALM: acral lentiginous melanoma; LND: lymph node dissection; NA: not applicable; NM: nodular melanoma; SLNB: sentinel lymph node biopsy; SSM: superficial spreading melanoma

[a] Excluded patients with unknown mitotic rate

[b] Only 6 Caucasian patients and 41 Asian patients had treatment details

lesions compared to Caucasians (52% versus 8.3%, *P*=0.008).

Only 13 (21.0%) and 6 (9.7%) patients were tested for BRAF and c-KIT mutation, respectively. Four patients had BRAF and 1 had c-KIT mutation detected.

Staging data

Nineteen (30.6%), 25 (40.3%), 15 (24.2%) and 1 (1.6%) cases were diagnosed with stages I to IV disease, respectively. Two cases (3.2%) did not undergo staging procedure—1 patient opted to explore alternative medicine while the other patient declined in view of advanced age. Twenty eight percent of Asians were diagnosed with advanced melanoma (stage III or IV) at presentation, while 16.7% of Caucasians were diagnosed with advanced melanoma (*P*=0.046). Stratified by histological subtype of melanoma, only 27.3% and 13.0% of patients with ALM and SSM, respectively had advanced melanoma at presentation, while 50.0% of patients with nodular melanoma had advanced melanoma at presentation (*P*=0.04).

The median time interval to diagnosis (defined as the duration between the onset of a new pigmented lesion, change in an existing mole or previous normal surveillance and the diagnosis of melanoma) for the total study cohort was 24 months (range 1–240 months). When stratified against ethnicity, the delay was longer for Asians (24±50.3 months) than in Caucasians (12±6.9 months) although this did not reach statistical significance (*P*=0.23). Time interval to diagnosis in the last 5 years (2011–2015) compared to the preceding 5-year interval was not significantly shorter (*P*=0.65).

Treatment and outcomes data

Follow-up data were not available for 15 cases and they were excluded from treatment outcome analysis. Forty-one patients (87.2%) underwent wide excision (Table 1), while 2 (4.3%) had adjuvant chemotherapy or radiotherapy.

Twenty-one patients (44.7%), all with Breslow's thickness of 1mm or more, underwent sentinel lymph node biopsy (SLNB), of which 6 (28.6%) yielded positive SLNB necessitating subsequent CLND. Five patients (10.6%) had lymph node dissection (LND) without prior SNLB—1 patient had fluorodeoxyglucose avid nodes on positron emission tomography, 1 patient had enlarged nodes on computed tomography, 1 patient had fine needle aspiration cytology proven disease, and the reason for LND was not stated in 2 cases. Three of the patients who had LND had lymph node metastases. Of the 21 cases who had neither SLNB nor LND, 3 had pT1a or pT1b disease, 9

declined or were considered unfit for surgery, 2 defaulted follow-ups, and 7 had unclear reasons that were not documented.

Follow-up duration was defined as the time from the date of diagnosis to the date of the most recent review. Median follow-up duration was 22 months (range 1–199 months). Eighteen (38.3%) cases had relapse, higher than that in earlier studies of 18.5%[6] to 20.8%.[5] Of the patients who experienced a relapse, 10 had stage III disease, 9 had stage II disease, and 1 had stage I disease. The median duration between the most recent treatment and date of relapse was 8 months (range 1–31 months). Of the 18 patients who relapsed, 50.0% had locoregional relapse, 27.8% had concurrent locoregional and distant relapse, and 22.2% had distant relapse. Seven patients (38.9%) declined further treatment, 7 patients (38.9%) underwent repeat surgery, 2 (11.1%) had palliative radiotherapy to distant metastases, and 1 (5.6%) had palliative chemotherapy. One patient with c-KIT mutation was treated with imatinib and is still alive at the time of writing.

The median overall survival (OS) was 68 months, the relapse-free survival (RFS) was 31 months and the 5-year OS rate was 55.3% (95% CI 41.2–74.1) (Fig. 1). The median OS time for ALM and non-ALM were 55 and 102 months, respectively (P=0.58). The median RFS time for ALM and non-ALM were 26 and 102 months respectively (P=0.75). The median OS and RFS for Asians are 55 and 23 months, respectively.

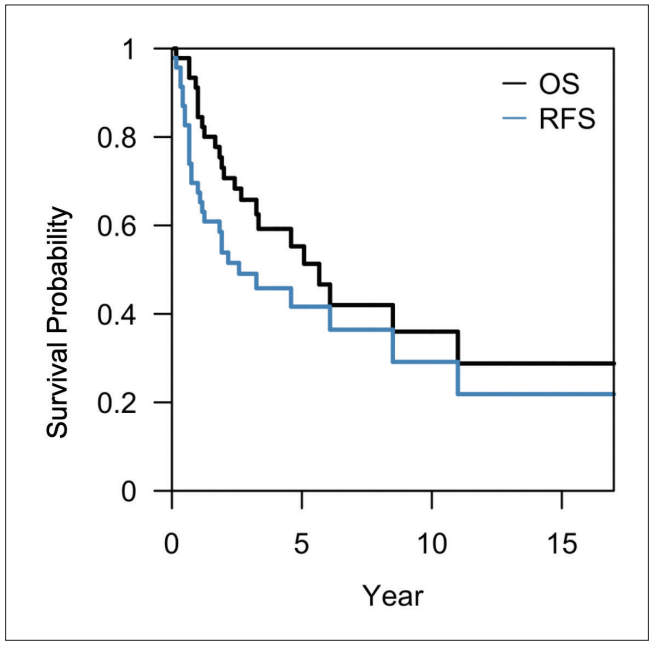

Fig. 1. Kaplan-Meier curves for overall survival (OS: black line) and relapse free survival (RFS: blue line) of patients with melanoma in our study.

The 5-year survival rate stratified by American Joint Committee on Cancer (AJCC) stage is 100% (95% CI 100–100), 45.7% (95% CI 27.1–77.1), 43.1% (95% CI 22.1–84.0) for stages I, II and III, respectively. There was no significant improvement in overall survival in the last 5 years (2011–2015) compared to the preceding 15 years of our study (HR 0.73, 95% CI 0.29–1.83, P=0.498).

Multivariable analysis demonstrated that the subtype of melanoma was not an independent prognostic factor for OS and RFS, but an older age at diagnosis (HR=1.07 and 1.06, P=0.006 and 0.02, respectively) and thicker Breslow's measurements (HR=1.21 and 1.63, P=0.045 and 0.01, respectively) were independent adverse prognostic factors for OS and RFS, respectively (Table 4).

Patients who relapsed were more likely to be Asian (P=0.027), 60 years old or older (P=0.045), have deeper Breslow's thickness (median 5.5mm versus 1.8mm, P=0.0013), presence of tumour-infiltrating lymphocytes (P=0.006) and positive sentinel lymph node involvement for melanomas thicker than 1mm (P=0.04).

Twenty-three patients in our cohort died, of which the cause of death in 14 patients (60.9%) was unknown. Significantly, all 8 patients (34.8%) who died from melanoma were Asians. Of these, 46.2% had ALM, 30.8% had SSM and 23.1% had NM. In the study group, 88.4% had stage II or III disease at diagnosis, and 34.6% either declined salvage treatment or defaulted follow-up. The mortality rate for Asians versus Caucasians was 52% and 0%, respectively.

DISCUSSION

In our study, the incidence rate of melanoma was 0.12 per 100,000 and 4.33 per 100,000 person-years for Asians and Caucasians, respectively, between 2011 and 2015. This is in contrast to 0.2 to 0.65 per 100,000 person-years in other Asian studies,[5-14] 21.9 per 100,000 person-years in the US, and 1.3 to 35.8 per 100,000 person-years in Europe.[15]

Worrisome features observed in our study included thicker Breslow's thickness, later stage at diagnosis and poorer overall prognosis for Asians. Despite a call for greater education efforts on early melanoma detection in Singapore since 2001,[6] the Breslow's thickness has not decreased significantly in the last

Table 4. Multivariable analysis of prognostic factors for overall survival (OS) and relapse-free survival (RFS) for 47 patients diagnosed with primary stage I–IV cutaneous melanoma 1996–2015

	OS		RFS	
	Hazard ratio (95% CI)	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Age	1.07 (1.02, 1.13)	**0.006**	1.06 (1.01, 1.12)	**0.02**
Breslow's thickness	1.21 (1, 1.46)	**0.045**	1.63 (1.12, 2.38)	**0.01**
AJCC Staging				
I	1		1	
II	8.56 (0.72, 101.91)	0.089	7.37 (0.68, 79.59)	0.10
III	9.10 (0.58, 142.76)	0.116	9.45 (0.53, 169.85)	0.13
IV/ Indeterminate	4.73 (0.11, 205.73)	0.420	3.94 (0.15, 100.08)	0.41
Sentinel lymph node biopsy performed				
Negative	1		1	
Positive	1.00 (0.16, 6.43)	0.997	0.16 (0.00, 17.80)	0.44
Not done/ Unknown	0.85 (0.12, 5.86)	0.869	0.40 (0.02, 9.61)	0.57
BRAF mutation done				
No	1		1	
Yes	1.79 (0.44, 7.25)	0.412	5.73 (0.61, 53.72)	0.13
Ulceration				
No	1		1	
Yes	0.31 (0.09, 1.05)	0.061	0.24 (0.02, 3.10)	0.28
Perineural invasion				
No	1		1	
Yes	3.09 (0.37, 25.62)	0.295	0.35 (0.01, 8.70)	0.53
Adjuvant treatment				
No	1		–	
Yes	0.27 (0.02, 3.47)	0.315	–	–
Treatment modality				
Surgery/ adjuvant chemotherapy/ adjuvant radiotherapy	1		–	
None	1.92 (0.37, 9.87)	0.433	–	–
Unknown	4.02 (0.38, 42.69)	0.249	–	
None	1.92 (0.37, 9.87)	0.433	–	–
Clark level				
IV	–		1	
V	–	–	0.24 (0.02, 3.10)	0.28
Unknown	–	–	5.31 (0.73, 38.74)	0.10

AJCC: American Joint Committee on Cancer; CI: confidence interval

5 years. In fact, compared with previous melanoma studies in Singapore, our study cohort has a higher proportion of advanced disease at presentation, and a longer time interval to diagnosis (Table 5). Moreover, the incidence rate of melanoma between 2011 and 2015 had risen. We postulate that this could be due to the lack of skin cancer awareness among the Singapore population. In our study, 75% of Caucasians who had no previous skin cancer self-referred for a mole check and had the melanoma detected during the routine skin check. In contrast, only 10% of Asians consulted a dermatologist for a total body skin examination or mole check. Education directed at both general practitioners (GPs) and the public should be tailored to our mainly Asian population[17] with a predominance of the ALM subtype of melanoma.[18] The public should be taught how to self-monitor moles on the palms and soles, and pigmented bands on nails. Opportunistic melanoma screening may be performed strategically during annual health screening to include screening for pigmented lesions on the body, soles and palms.

GPs may use the acronym CUBED[19] which stands for Coloured lesion, Uncertain diagnosis, Bleeding lesion on the foot or under the nail, Enlargement of a lesion, and Delay in healing to identify ALM. With regards to nail unit melanoma, melanoma is suspected when the first finger or toe is involved, two-thirds of the nail plate is pigmented, black-grey pigmentation is present, irregularly-sized, coloured-band, and Hutchinson signs are present.[20]

Cost-effectiveness analysis for melanoma screening had been conducted predominantly in Caucasian populations, in which the incidence rate of melanoma is significantly higher than in Singapore with a predominantly Asian population.[20-22] We did not find any cost-effectiveness analysis studies for melanoma screening in Asian countries. However, there are several reasons to support melanoma screening in Singapore. Firstly, the incidence of melanoma in recent years is rising. Secondly, visual examination is a relatively simple and inexpensive screening modality. Thirdly, melanoma is a potentially curable disease if identified early, and non-operable melanoma has a high mortality and systemic treatment is expensive.

The prognosis of patients in our series is poor with almost 40% of our patients treated with curative intent experiencing subsequent relapse. As we seek to raise awareness about ALM in the Singapore population, it is also critical to identify risk factors that may predispose patients to ALM. In the recent decade, immune checkpoint inhibitors such as cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) inhibitors and programmed death (PD-1) inhibitors have shown promising results mainly for patients with non-acral cutaneous melanoma in Caucasian populations.[27-29] However, 2 recent studies suggest that Asian patients with advanced ALM are relatively unlikely to respond to PD-1 blockade monotherapy[30] or toripalimab[31] compared to Caucasians. In our study, no patients received immune checkpoint, precluding us from drawing meaningful conclusions about whether the introduction of these drugs has improved the survival of melanoma in our population. This was because PD-1 inhibitors were only approved to be used in Singapore in 2016, which was after our study period. Another postulated reason may be due to the high costs of checkpoint inhibitors. Among the various genetic markers, patients were only tested for BRAF and c-KIT perhaps due to the low incidence of NRAS mutation in melanomas occurring in the Asian population.[33]

One of the limitations of this study was its retrospective nature and high dropout rates in the Caucasian and non-resident population, precluding a detailed assessment of treatment outcomes in these patients. This is not unusual as these patients may have left the country and continued follow-up back in their home countries. For Singapore patients who were lost to follow-up, we propose a closer working relationship between oncologists and dermatologists to ensure that these patients have dermatologic follow-up for assessment for melanoma recurrence and regular skin surveillance.

There is a partial overlap of our current study population and an earlier melanoma study in Singapore.[5] However our duration of data collection and cohort size is significantly larger than this previous study. We have tabulated a comparison of epidemiology, clinical features, staging and outcomes of patients in our study and 2 previous Singapore melanoma studies (Table 5).

Our centre sees a significantly lower proportion of Malay patients and a significantly higher proportion of other ethnic groups, especially Caucasian patients ($P<0.0001$) when compared to our country's population consensus. However, we believe that the lower incidence of melanoma in ethnic groups of higher skin phototypes may reflect more than only sampling bias as a similar melanoma study conducted by the National Cancer Centre Singapore[32] also had a significantly lower proportion of Malay and Indian patients compared proportionately to population consensus. People with higher skin phototypes rarely or never sunburn and

Table 5. Comparison of patients in previous Singapore melanoma studies and current study

Study		Tan et al.[6]	Lee et al.[5]	Current study
Study period		1989–1998 (10 years)	1998–2008 (11 years)	1996–2015 (20 years)
Study size		24 patients	48 patients	62 cases in 61 patients[a]
Demographics	Mean age, years	54 (range 15–83)	60 (range 29–95)	61 (range 27–99)
	Male to female ratio	0.8:1	1.3:1	1.7:1
	Resident versus expatriate population	Data on number of non-resident expatriate patients unavailable	Consists of 38 (79.2%) resident ethnic patients, and 10 (20.8%) non-resident expatriate patients	Consists of 47 (75.8%) resident ethnic patients, and 15 (24.2%) non-resident expatriate patients
Clinical features	Most common site of presentation	The extremities (lower limbs more than upper limbs)	On the palms and soles	On the palms and soles Asians: sole of foot (46.0%) Caucasians: back (33.3%) and lower limb (33.3%)
	Time interval to diagnosis	1 month to 240 months (mean 20 months) (median 9 months)	1 to 120 months (mean 20 months) (data on median unavailable) Mean duration: Asians: 22.8 months Caucasians: 7.4 months	1 month to 240 months (mean 38 months) (median 24 months) Mean duration: Asians: 24 months Caucasians: 12 months
Histology	Top 3 most common subtypes of melanoma in decreasing order of frequency	NM (41%), ALM (41%) and SSM (7%)	ALM (50%), SSM (37.5%) and NM (12.5%)	SSM (37.1%), ALM (35.5%) and NM (22.6%)
	Breslow's thickness	Median Breslow's thickness was 3.1mm (range 0.2–16mm)	Mean Breslow's thickness was 2.3mm (data on range unavailable)	Median Breslow's thickness was 2.5mm (range 0.2–15mm) Asians: 2.6mm Caucasians: 0.9mm
Staging		All patients presented with either stage I or II disease	16 (36%), 23 (52%), 4 (9%), and 1 (2%) patients were diagnosed with stages I to IV disease, respectively	19 (30.6%), 25 (40.3%), 15 (24.2%), and 1 (1.6%) cases were diagnosed with stages I to IV disease, respectively
Outcomes	Number of patients who had relapse	5 patients (20.8%)	10 patients (21%)	18 cases (38.3%)
	Time to relapse	Duration between initial diagnosis and date of relapse was between 12 and 84 months	Duration between initial diagnosis and date of relapse was between 4 and 60 months	Duration between the most recent treatment and date of relapse was between 1 month and 31 months
	Number of patients who died from melanoma	3 patients (12.5%)	Data on the number of patients who died from melanoma is unavailable	8 patients (12.9%)

ALM: acral lentiginous melanoma; NM: nodular melanoma; SSM: superficial spreading melanoma
[a]One patient had 2 melanomas on different anatomical regions diagnosed at different time points
Superscript numbers: Refer to REFERENCES

tan easily, reducing the risk of many skin cancers including melanoma. In addition, ethnic groups with more conservative clothing styles may have less sun exposed areas, resulting in less ultraviolet-induced types of melanoma.

CONCLUSION

Given our study findings, we propose more thorough and targeted education for primary healthcare providers and integration of efforts to teach patients self-examination of pigmented lesions on the soles, palms and nails alongside opportunistic screening efforts. Prognosis is stage-dependent with good OS seen in patients with early disease and worse outcomes in patients with advanced melanoma. With our population, we should strive to improve survival of melanoma with earlier detection. Further research is needed to identify modifiable risk factors for ALM to address this increasing trend in the incidence of melanoma. Affordability of and healthcare financing models for genetic testing and targeted therapy or immune checkpoint inhibitors should also be re-evaluated as they offer better disease control for patients with metastatic or inoperable melanoma,[34,35] yet their current high costs at present may deter uptake of their use.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019;144:1941-53.
2. Chang JW, Guo J, Hung CY, et al. Sunrise in melanoma management: Time to focus on melanoma burden in Asia. Asia Pac J Clin Oncol 2017;13:423-7.
3. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471-74.
4. StataCorp. 2017. Stata Statistical Software: Release 15. College Station, US: StataCorp LLC.
5. Lee HY, Chay WY, Tang MB, et al. Melanoma: differences between Asian and Caucasian patients. Ann Acad Med Singap 2012;41:17-20.
6. Tan E, Chua SH, Lim JT, et al. Malignant melanoma seen in a tertiary dermatological centre, Singapore. Ann Acad Med Singap 2001;30:414-8.
7. Pailoor J, Mun KS, Leow M. Cutaneous malignant melanoma: clinical and histopathological review of cases in a Malaysian tertiary referral center. Malays J Pathol 2012;34:97-101.
8. Ingkaninanda P, Visessiri Y, Rutnin S. Clinicopathological Features and Prognostic Factors of Malignant Melanoma: A Retrospective Analysis of Thai Patients in Ramathibodi Hospital. J Med Assoc Thai 2015;98:820-7.
9. Chi Z, Li S, Sheng X, et al. Clinical presentation, histology, and prognoses of malignant melanoma in ethnic Chinese: A study of 522 consecutive cases. BMC Cancer 2011;11:85.
10. Chan KK, Chan RC, Ho RS, et al. Clinical Patterns of Melanoma in Asians: 11-Year Experience in a Tertiary Referral Center. Ann Plast Surg 2016;77:S6-S11.
11. Chang JW. Cutaneous Melanoma: Taiwan experience and literature review. Chang Gung Med J 2010;33:602-12.
12. Kim JE, Chung BY, Sim CY, et al. Clinicopathologic Features and Prognostic Factors of Primary Cutaneous Melanoma: a Multicenter Study in Korea. J Korean Med Sci 2019;34:e126.
13. Ishihara K, Saida T, Otsuka F, et al. Statistical profiles of malignant melanoma and other skin cancers in Japan: 2007 update. Int J Clin Oncol 2008;13:33-41.
14. Panda S, Dash S, Besra K, et al. Clinicopathological study of malignant melanoma in a regional cancer center. Indian J Cancer 2018;55:292-6.
15. Melanoma Patient Network Europe. Melanoma – The Facts, December 2019. Available at: http://www.melanomapatientnetworkeu.org/melanoma.html. Last accessed on 15 April 2020.
16. Levit EK, Kagen MH, Scher RK, et al. The ABC rule for clinical detection of subungual melanoma. J Am Acad Dermatol 2000; 42:269-74.
17. Kundu RV, Kamaria M, Ortiz S, et al. Effectiveness of a knowledge-based intervention for melanoma among those with ethnic skin. J Am Acad Dermatol 2010;62:777-84.
18. Merkel EA, Gerami P. Malignant melanoma of sun-protected sites: a review of clinical, histological and molecular features. Lab Invest 2017;97:630-5.
19. Albreski D, Sloan SB. Melanoma of the feet: misdiagnosed and misunderstood. Clin Dermatol 2009;27:556-63.
20. Benati E, Ribero S, Longo C, et al. Clinical and dermoscopic clues to differentiate pigmented nail bands: an International Dermoscopy Society study. J Eur Acad Dermatol Venereol 2017;31:732-6.
21. Losina E, Walensky RP, Geller A, et al. Visual Screening for Malignant Melanoma: A Cost-effectiveness Analysis. Arch Dermatol 2007;143:21-8.
22. Gordon LG, Rowell D. Health system costs of skin cancer and cost-effectiveness of skin cancer prevention and screening: a systematic review. Eur J Cancer Prev 2015;24:141-9.
23. Adamson AS, Jarmul JA, Pignone MP. Screening for Melanoma in Men: a Cost-Effectiveness Analysis. J Gen Intern Med 2020; 35:1175-81.
24. Curtin JA, Busam K, Pinkel D, et al. Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol 2006;24:4340-6.
25. Hayward NK, Wilmott JS, Waddell N, et al. Whole-genome landscapes of major melaoma subtypes. Nature 2017;545:175-80.
26. Liang WS, Hendricks W, Kiefer J, et al. Integrated genomic analyses reveal frequent TERT aberrations in acral melanoma. Genome Res2017;27:524-32.
27. Yeh I, Jorgenson E, Shen L, et al. Targeted Genomic Profiling of Acral Melanoma. J Natl Cancer Inst 2019;111:1068-77.
28. Ascierto PA, Long GV, Robert C, et al. Survival Outcomes in Patients With Previously Untreated BRAF Wild-Type Advanced Melanoma Treated With Nivolumab Therapy: Three-Year Follow-up of a Randomized Phase 3 Trial. JAMA Oncol 2019;5:187-94.
29. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med 2019;381:1535-46.
30. Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. The Lancet Oncology 2019; 20:1239-51.

31. Nakamura Y, Namikawa K, Yoshino K, et al. Anti-PD1 checkpoint inhibitor therapy in acral melanoma: a multicenter study of 193 Japanese patients. Ann Oncol 2020;3:1198-1206.
32. Tang B, Chi Z, Chen Y, et al. Safety, Efficacy and Biomarker Analysis of Toripalimab in previously treated advanced melanoma: results of the POLARIS-01 multicenter phase II trial. Clin Cancer Res 2020;26:4250-9.
33. Teh YL, Goh WL, Tan SH, et al. Treatment and outcomes of melanoma in Asia: Results from the National Cancer Centre Singapore. Asia Pac J Clin Oncol 2018;14:e95-e102.
34. Sheen YS, Liao YH, Liau JY, et al. Prevalence of BRAF and NRAS mutations in cutaneous melanoma patients in Taiwan. J Formos Med Assoc 2016;115:121-7.
35. Guo J, Carvajal RD, Dummer R, et al. Efficacy and safety of nilotinib in patients with KIT-mutated metastatic or inoperable melanoma: final results from the global, single-arm, phase II TEAM trial. Ann Oncol 2017;28:1380-7.
36. Guo J, Si L, Kong Y, et al. Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification. J Clin Oncol 2011;29:2904-9.