A MULTICENTRE STUDY OF CLINICOPATHOLOGICAL FEATURES AND PROGNOSTIC FACTORS OF CUTANEOUS MELANOMA IN MALAYSIA

by

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LEE JIA YUAN

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ABSTRAK

PENGENALAN:

Melanoma merupakan sejenis kanser kulit yang agresif dengan kadar kematian yang tinggi. Tujuan kajian ini adalah untuk mengenal pasti ciri-ciri tersebut dan jangka hayat pesakit selepas didapati menghidap kanser kulit melanoma dalam kalangan rakyat Malaysia.

KAEDAH:

Kajian ini menggunakan kaedah retrospektif dan melibatkan pesakit-pesakit kanser kulit melanoma di empat hospital rujukan di Malaysia, iaitu Hospital Universiti Sains Malaysia, Hospital Kuala Lumpur, Hospital Sultanah Bahiyah dan Hospital Queen Elizabeth I. Semua laporan perubatan serta data pesakit kanser kulit melanoma dari Januari 2012 sehingga December 2018 telah diperolehi untuk siasatan lanjut mengenai demografik, ciri-ciri klinikal, patologi serta rawatan yang telah diberikan kepada pesakit-pesakit tersebut. Masa kemandirian median pesakit dianalisis dengan menggunakan kaedah Kaplan-Meier. Segala faktor prognostik yang penting untuk riwayat pesakit kanser kulit melanoma dikaji melalui analisis univariat dan multivariat.

KEPUTUSAN:

Kajian ini melibatkan sebanyak 99 pesakit. Purata umur semasa diagnosis adalah 60.4 tahun, dengan nisbah antara wanita dan lelaki adalah 1:1.1. Kebanyakkan pesakit yang menghidapi kanser kulit melanoma terdiri daripada bangsa Melayu (52%) dan 51.5% pesakit berada dalam tahap III dan IV. *Nodular melanoma* adalah yang paling kerap

didapati, iaitu 50.5%. Purata ketebalan Breslow adalah 7.9 mm. Masa kemandiran median untuk pesakit kanser kulit melanoma adalah 673 days. Kadar kelangsungan hidup selama satu, tiga dan lima tahun adalah 47.5%, 11.1% dan 15.2%. Kadar mitotik dan ketebalan Breslow adalah antara faktor-faktor prognostik yang ketara dalam mempengaruhi kematian riwayat pesakit kanser kulit melanoma.

KESIMPULAN

Kebanyakan pesakit kanser kulit melanoma di Malaysia mempunyai kanser yang telah merebak setempat, iaitu tahap kedua. Masa kemandirian median di kalangan pesakit kanser kulit melanoma di malaysia adalah sangat rendah berbanding dengan negara-negara Asia yang lain. Justeru, program kesedaran tentang kanser kulit melanoma perlu digalakkan supaya saringan dan pengesanan awal dapat dilakukan untuk melanjutkan jangka hayat pesakit-pesakit kanser kulit melanoma di malaysia.

KATA KUNCI

Kanser kulit melanoma, faktor-faktor prognostik, riwayat hidup

ABSTRACT

INTRODUCTION:

Cutaneous melanoma is an aggressive skin cancer with high mortality rate. This study aimed to describe the clinicopathological characteristics and to identify the independent prognostic factors and median survival time of patients diagnosed with primary cutaneous melanoma in Malaysia.

MATERIAL AND METHOD:

This was a retrospective study conducted in Hospital Universiti Sains Malaysia, Hospital Kuala Lumpur, Hospital Sultanah Bahiyah and Hospital Queen Elizabeth I, Malaysia. All traceable medical records on patients with primary cutaneous melanoma between January 2012 till December 2018 were investigated based on the demographic data, histopathological and management. Median survival time was analysed using Kaplan-Meier method. Univariate and multivariate analysis of prognostic factors associated with survival were performed.

RESULTS:

Nighty-nine patients were included and analysed. The mean age during diagnosis was 60.4 years old, with female: male ratio of 1:1.1. Majority of the patients were Malays (52%) and 44.4% had clinical stage II on presentation. Nodular melanoma was the commonest subtype (50.5%) in Malaysia. Histologically, the mean Breslow thickness was 7.9 mm. The median survival time was 673 days. The 1-, 3-, 5- year survival rates

were 47.5%, 11.1% and 15.2%. Mitotic rate and Breslow thickness were independent risk factors for poor prognosis ($p<0.05$).

CONCLUSION:

Most patients with cutaneous melanoma in Malaysia diagnosed with locally advanced disease and had poorer prognosis as compared to other Asia countries. Much work is needed to create an awareness of cutaneous melanoma based on the local data for early detection and treatment.

KEYWORDS:

Cutaneous melanoma, Prognostic factors, Survival

CHAPTER 1:

INTRODUCTION

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INTRODUCTION

Malignant melanoma is an aggressive, therapy-resistant malignant neoplasm of melanocytes. Although more than 95% of the tumours are found in the skin, primary melanoma can also occur at extracutaneous sites such as ocular, mucosal, gastrointestinal, genitourinary, meninges and lymph nodes. Cutaneous melanoma is one of the fast risen and deadliest skin cancers, with the global incidence in 2015 reported to be 351880 cases with an age-standardize rate of 5 cases per 100 000 persons(1).

The five world regions with the greatest incidence rates were Australia, North America, Western Europe, Central Europe and Eastern Europe(1). In contrary, the incidence is lower in East and Southeast Asia with the age standardised rate of melanoma is about 0.4-0.5 per 100 000 persons as opposed to the reported incidence of 5.3-21.9 per 100 000 for Europe and north America(2). Nevertheless, population in the East and Southeast Asia is almost one third of the global population, therefore the significance of the burden disease exists in terms of absolute patient(2).

Malaysia is a part of Southeast Asia countries located near the equator which is unique in its diversity of racial and ethnicity. In year 2011, the population was estimated to be 29.1 million including the non-citizens, which consists of 54.7% Malays, 24.3% Chinese, 7.3% Indians, 12.8% Bumiputra and 0.9% minority

ethnicity. In addition, there were almost 2.5 million non-citizens (8.4%) in Malaysia(3).

Based on the Malaysia national cancer registry report, a total number of 103,507 new cancer cases were diagnosed in Malaysia during the period of 2007 to 2011. Of these, there were 322 reported cases (0.3%) of cutaneous melanoma, represented by 167 cases (52%) and 155 cases (48%) in males and females respectively(3).

While cutaneous melanoma represents less than 5% of all cutaneous melanoma, it accounts for majority of skin cancer deaths. In the last 50 years, the incidence of cutaneous melanoma is rising rapidly worldwide, such that it is now the sixth and seventh most common new cancer among men and women respectively in United States(4). From year 1975 to 2005, data from National Cancer Institute Surveillance, Epidemiology and End Results (SEER) showed that the incidence of melanoma nearly tripled. These increasing rates had adverse impact on the public health and resulted an economic burden of disease.

In United States, the trend of mortality rate from melanoma had increased by about 20% from 1970s to 1990 but had been stabilised since then with downward mortality trend and decreased by 0.3% per year. Currently, In United States, one person dies each hour from metastatic melanoma(5). The slow increase mortality trend is also seen in high risk regions such as New Zealand, Australia, North America and Australia. Inversely, Asian population with melanoma typically presented with advanced disease with poorer prognosis(6,7). The lack of

general awareness had resulted cutaneous melanoma to be overlooked, underreported and undertreated especially in Asian population.

In Malaysia, comprehensive data on cutaneous melanoma from different ethnicity and its mortality is limited, with the published articles are mainly case series from single institution(8,9) and the latest reviews dated till year 2008(8,9). Therefore, causing dilemma for the managing healthcare professionals to evaluate the incidence, mortality and the treatment outcome in the local population with cutaneous melanoma.

An established diagnosis of cutaneous melanoma could only be made after histopathologic analysis based on the biopsy result from the suspicious pigmented skin lesion. The clinical clues for melanoma included pigment variation, an irregular or ill-defined border, asymmetry in colour or shape, ulceration and development of a nodule within a pre-existing lesion. Conventional melanomas were histopathologically classified as superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM) and acral lentiginous melanoma (ALM). Clinical evidence increasingly suggested that melanoma presents differently in Asian patients as compared to Caucasian patients, with clear distinctions in prevalent subtype, site of presentation, thickness and risk factors seen(7). At the same time, different histological subtype presentation in different ethnic was not well described in Southeast Asia population.

By studying the clinicopathological features of cutaneous melanoma in the local population, it is hope that the current standard of care can be improved with the management tailored towards educational awareness campaign, prevention and early surgical and oncologic treatment.

CHAPTER 2:

LITERATURE REVIEW

2.0 LITERATURE REVIEW

2.1 CLINICOPATHOLOGICAL PRESENTATION

Based on the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) 2001 to 2005, the median age at diagnosis for melanoma was 59 years old and the median age at death was 68 years old. The incidence of melanoma increased linearly after 15 years old until the age of 50 years old. Approximately half the incidence is in between ages of 35 and 65 years and 80% occurring in population age range of 20 to 74 years old. Males were approximately 1.5 times more likely to develop melanoma than females and more than twice as many men died from melanoma(5,10).

The site of distribution for cutaneous melanoma varies, where in Caucasian patients from Australia, Canada, Europe and United States, the most common areas were the back for men and arms and legs for women. In contrast, in Asian populations, 50.8% - 82.9% of melanoma cases developed over the extremities, particularly the feet and hands. There were four major histological subtypes of cutaneous melanoma. In descending order of frequency based on analysis from National Cancer Institute Institute Surveillance, Epidemiology and End Results (SEER), they were superficial spreading melanoma (70%), nodular melanoma (15%), lentigo maligna melanoma (13%) and acral lentiginous melanoma (2-3%). In contrast, studies from Taiwan, Singapore, China, Japan and South Korea indicated that acral lentiginous melanoma constitutes 41.8% - 65%

of the cases(6,7,11–15). Melanomas in Asian patients also appeared thicker and prone to ulcerate.

The risk factors could be divided into environmental factors and host factors. Cutaneous melanoma was often associated with environmental risk from high amount exposure of ultraviolet radiation (UVR) from sunlight and depletion of ozone layer. Outdoor occupation such as farmer, previous history of sunburns and tanning bed exposure (non-solar sources of UVR) conferred higher risk of cutaneous melanoma. Patients with xeroderma pigmentosum, a genetic disorder with deficient DNA repair mechanism and hypersensitivity to UVR damage, had substantially higher risk of developing melanoma(5). Other intrinsic risk factors were Fitzpatrick skin type 1-III, lighter hair and eye colour, presence of atypical mole or numerous moles, melanocytic neaevi and family history of melanoma. Interestingly, in Asian populations, genetics were postulated a key role in tumorigenesis, rather than sun-seeking behavior of lifestyle factors as seen in Western countries. The melanomas in Asian populations were mainly hidden away from sun exposure, located at the sole or heel of the feet, thereby refuted the causative risk of UVR exposure. Instead, cutaneous melanomas were attributed to long-term physical stress and trauma at these weight bearing areas(7).

It had been reported *BRAF*, *NRAS* and *KIT* proto-oncogenes mutation were commonly found in cutaneous melanoma cases. The frequency of reported NRAS and BRAF mutations among primary cutaneous melanoma varies from 4-50% and 20-80% respectively, with significantly less in Asian populations. *KIT* mutation

was mainly seen in acral and mucosal melanomas, which are observed in Asian patients(7,16).

2.2 PROGNOSTIC FACTORS AND STAGING IN CUTANEOUS MELANOMA

Prognostic indicators in primary cutaneous melanoma may be clinical or pathological. By far, the most significant and consistent prognostic factor in all series over the past 20 years was the Breslow or tumour thickness of the primary melanoma. Clinicopathological features such as age at presentation, sex, diameter of the lesions, presence of ulceration and mitotic rate of the tumour cells were regarded as independent prognostic significance(17). Subtype of the melanoma was however not an independent prognostic factor when tumour thickness is taken into consideration(17).

Studies revealed that older patients had poorer prognosis as compared to younger patients with tumours of equal thickness. The significance seen in disease-free 5-year survival was evident in patients aged 60 or over at the time of diagnosis. Female had slightly advantage in survival regardless the thickness of the tumour. However, the reason for it was not well established. The size of the primary cutaneous melanoma was deemed an independent prognostic factor, reflecting the duration of growth of the lesion and the total number of malignant cells present.

In recent year 2018, American Joint Committee on Cancer (AJCC) had updated the 7th tumour-nodes-metastasis (TNM) staging classification (2002) to 8th edition(18). **[Figure 1]**. The revision was based on the database of patient records from 10 institutions in United States, Europe and Australia with well annotated clinicopathological and follow up data for patients who had stage I through III melanomas at initial diagnosis and had treatment since year 1998. The important evidence-based prognostic variables were well documented in the TNM staging classification to facilitate the clinicians in managing cutaneous melanoma.

In comparison, most Asian cutaneous melanoma typically present with more advanced disease and the prognosis is generally worse than Caucasian. In a study of 181 cutaneous melanoma in Taiwan, 59% of the patients would present with stage III or IV with the 5 years survival rate of 34.7% and 0% respectively(15). Simultaneously, in Japan, a 10 years statistical study of 2978 cases of cutaneous melanoma reported 33% of the patients presented with advanced melanoma and the 5 years survival rate were 74% for stage IIIA, 58% for stage IIIB, 39% for stage IIIC and 21% for stage IV respectively(11). The numbers were almost equivalent in China and Hong Kong, with 37.9% and 27% presented with advanced disease respectively with poor prognosis(19,20). By contrast, data from the US Surveillance, Epidemiology and End Results Cancer Statistics demonstrated only 8% for stage III and 4% for stage IV disease. The achievable 5-year survival rates are 46.6% - 69% for stage III and 10% for stage IV disease(7).

Surgical excision is still the main definitive therapeutic intervention in the management of cutaneous melanoma. The thicker the tumour, the higher rate of local recurrences and hence requiring wider surgical margins during excision. A randominsed trial study by World Health Organisation (WHO) Melanoma Programme had demonstrated comparable clinical outcomes (regional and distant metastatic rates) in patients of more than 2mm thickness cutaneous melanoma with the excision margins of 1 cm or 3 cm. However, three patients in the 1 cm margin group with tumour >1mm had local recurrence, thereby concluded that a margin of 1 cm is adequate for patients with melanoma thickness <1mm. The Intergroup Melanoma Surgical Trial on long term surgical results for intermediate thickness melanoma (1.0 to 4.0 mm) had concluded that surgical margin of 2cm and 4cm were equally effective in achieving comparable rates of local control and survival. The recurrence rate was influenced by melanoma thickness and presence or absence of ulceration. On follow up of 10 years, there was no difference noted in survival or local recurrence rates between patients with either stipulated excision margin.

Novel immune-oncology therapies such as antiCTLA4 antibodies (example ipilimumab) and anti-PD1 antibodies (example pembrolizumab and nivolumab), have recently achieved good outcomes against advanced melanoma in clinical trials with significant survival benefit. BRAF/MEK inhibitor are listed as the first line therapy for melanoma treatment in the latest 2015 European Society for Medical Oncology (ESMO) cutaneous melanoma clinical guidelines. Nevertheless, the affordability, accessibility and the efficacy of these novel

treatment in Asian populations remains controversial and challenges to overcome for optimal treatment in melanoma.

2.3 LOCAL STUDIES AND DATA

In Malaysia, a single institution review of 32 patients diagnosed with cutaneous melanoma from year 1998 till 2008 by Pailoor et al have shown that majority were Chinese (59%), followed by Malay and Indian ethnicity which was 31% and 9% respectively. Clinically, 46% of the patients presented late, with 15% died within one year of diagnosis and 40% were dead within the first 3 years. The lesions were primarily presented at the sole and pathological subtype was mainly nodular melanoma(8).

The results were as concurred by a review of 23 cases of malignant melanoma done in Hospital Kuala Lumpur, suggested that it was mainly presented in Chinese population (70%) and 86% of the histopathological subtype results were nodular melanomas, followed by subtype lentigo maligna and superficial spreading melanoma, each represented 6.7% in frequency. Mean survival rate was not analysed(9).

Figure 1: AJCC 8th edition TNM staging of cutaneous melanoma

Definitions

Primary Tumor (T)

- **TX** Primary tumor cannot be assessed (for example, curettaged or severely regressed melanoma)
- **T0** No evidence of primary tumor
- **Tis** Melanoma in situ
- **T1** Melanomas 1.0 mm or less in thickness
- **T2** Melanomas 1.1 - 2.0 mm
- **T3** Melanomas 2.1 - 4.0 mm
- **T4** Melanomas more than 4.0 mm

NOTE: a and b subcategories of T are assigned based on ulceration and thickness as shown belowt:

T CLASSIFICATION	THICKNESS (mm)	ULCERATION STATUS
T1	≤1.0	a: Breslow < 0.8 mm w/o ulceration b: Breslow 0.8-1.0 mm w/o ulceration or ≤ 1.0 mm w/ ulceration.
T2	1.1-2.0	a: w/o ulceration b: w/ ulceration
T3	2.1-4.0	a: w/o ulceration b: w/ ulceration
T4	>4.0	a: w/o ulceration b: w/ ulceration

Regional Lymph Nodes (N)

- **NX** Patients in whom the regional nodes cannot be assessed (for example previously removed for another reason)
- **N0** No regional metastases detected
- **N1-3** Regional metastases based on the number of metastatic nodes, number of palpable metastatic nodes on clinical exam, and presence or absence of MSI[2]

NOTE: N1-3 and a-c subcategories assigned as shown below:

N CLASSIFICATION	# NODES	CLINICAL DETECTABILITY/MSI STATUS
N1	0-1 node	a: clinically occult[1], no MSI[2] b: clinically detected[1], no MSI[2] c: 0 nodes, MSI present[2]
N2	1-3 nodes	a: 2-3 nodes clinically occult[1], no MSI[2] b: 2-3 nodes clinically detected[1], no MSI[2] c: 1 node clinical or occult[1], MSI present[2]
N3	>1 nodes	a: >3 nodes, all clinically occult[1], no MSI[2] b: >3 nodes, ≥1 clinically detected[1] or matted, no MSI[2] c: >1 nodes clinical or occult[1], MSI present[2]

Distant Metastasis (M)

- **M0** No detectable evidence of distant metastases
- **M1a** Metastases to skin, sub cutaneous, or distant lymph nodes
- **M1b** Metastases to lung
- **M1c** Metastases to all other visceral sites
- **M1d** Metastases to brain

NOTE: Serum LDH is incorporated into the M category as shown below:

M CLASSIFICATION	SITE	Serum LDH
M1a-d	Skin/subcutaneous/nodule (a), lung (b) other visceral (c), brain (d)	Not assessed
M1a-d(0)	Skin/subcutaneous/nodule (a), lung (b) other visceral (c), brain (d)	Normal
M1a-d(1)	Skin/subcutaneous/nodule (a), lung (b) other visceral (c), brain (d)	Elevated

ANATOMIC STAGE/PROGNOSTIC GROUPS

	Clinical Staging[3]				Pathologic Staging[4]		
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	..	..		T1b	..	..
	T2a	..	..	IB	T2a	..	..
Stage IIA	T2b	N0	M0	IIA	T2b	M0	M0
	T3a	..	..		T2a	..	..
Stage IIB	T3b	..	..	IIB	T3b	..	..
	T4a	..	..		T4a	..	..
Stage IIC	T4b	..	..	IIC	T4b	..	..
Stage III	Any T	≥N1	M0	IIIA	T1-2a	N1a	M0
	..	..	..		T1-2a	N2a	..
	..	..	..	IIIB	T0	N1b-c	M0
	..	..	..		T1-2a	N1b-c	..
	..	..	..		T1-2a	N2b	..
	..	..	..		T2b-3a	N1a-2b	..
	..	..	..	IIIC	T0	N2b-c	M0
	..	..	..		T0	N3b-c	..
	..	..	..		T1a-3a	N2c-3c	..
	..	..	..		T3b-4a	Any N	..
	..	..	..		T4b	N1a-2c	..
	..	..	..	IIID	T4b	N3a-c	M0
Stage IV	Any N	Any N	M1	IV	Any T	Any N	M1

CHAPTER 3:

OBJECTIVES

CHAPTER 3

OBJECTIVES

3.1 GENERAL:

a. To describe the clinicopathological presentation, determine the median survival time and association of selected prognostic factors of cutaneous melanoma in four hospital centres in Malaysia

3.2 SPECIFIC:

a. To describe the demographic, clinical and pathological characteristic of patients with cutaneous melanoma in four hospital centres in Malaysia
b. To determine the median survival time of the patients from the point of confirmed pathological diagnosis with cutaneous melanoma in four hospital centres in Malaysia
c. To determine the association of selected prognostic factors (example: age, histopathological type, tumour thickness, staging, surgical margin) that affect the outcome (death) in cutaneous melanoma.

CHAPTER 4:

MANUSCRIPT

4.1 TITLE PAGE

A MULTICENTRE STUDY OF CLINICOPATHOLOGICAL FEATURES AND PROGNOSTIC FACTORS OF CUTANEOUS MELANOMA IN MALAYSIA

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Visualization: JY Lee.

Writing – original draft: JY Lee. Writing – review & editing: Wan Azman WS, Sharifah Emilia TS.

Approval of final manuscript: all authors.

DISCLOSURE:

There are no financial conflicts of interest to disclose

RUNNING TITLE:

Clinicopathological Features and Prognostic Factors of Cutaneous Melanoma

4.2 ABSTRACT

INTRODUCTION:

Cutaneous melanoma is an aggressive skin cancer with high mortality rate. This study aimed to describe the clinicopathological characteristics and to identify the independent prognostic factors and median survival time of patients diagnosed with primary cutaneous melanoma in Malaysia.

MATERIAL AND METHOD:

This was a retrospective study conducted in Hospital Universiti Sains Malaysia, Hospital Kuala Lumpur, Hospital Sultanah Bahiyah and Hospital Queen Elizabeth I, Malaysia. All traceable medical records on patients with primary cutaneous melanoma between January 2012 till December 2018 were investigated based on the demographic data, histopathological and management. Median survival time was analysed using Kaplan-Meier method. Univariate and multivariate analysis of prognostic factors associated with survival were performed.

RESULTS:

Nighty-nine patients were included and analysed. The mean age during diagnosis was 60.4 years old, with female: male ratio of 1:1.1. Majority of the patients were Malays (52%) and 44.4% had clinical stage II on presentation. Nodular melanoma was the commonest subtype (50.5%) in Malaysia. Histologically, the mean Breslow thickness was 7.9 mm. The median survival

time was 673 days. The 1-, 3-, 5- year survival rates were 47.5%, 11.1% and 15.2%. Mitotic rate and Breslow thickness were independent risk factors for poor prognosis ($p<0.05$).

CONCLUSION:

Most patients with cutaneous melanoma in Malaysia diagnosed with locally advanced disease and had poorer prognosis as compared to other Asia countries. Much work is needed to create an awareness of cutaneous melanoma based on the local data for early detection and treatment.

KEYWORDS:

Cutaneous melanoma, Prognostic factors, Survival

4.3 INTRODUCTION

Malignant melanoma is an aggressive, therapy-resistant malignant neoplasm of melanocytes. Although more than 95% of the tumours are found in the skin, primary melanoma can also occur at extracutaneous sites such as ocular, mucosal, gastrointestinal, genitourinary, meninges and lymph nodes. Cutaneous melanoma is one of the fast risen and deadliest skin cancers, with the global incidence in 2015 reported to be 351880 cases with an age-standardize rate of 5 cases per 100 000 persons(1).

The five world regions with the greatest incidence rates were Australia, North America, Western Europe, Central Europe and Eastern Europe(1). In contrary, the incidence is lower in East and Southeast Asia with the age standardised rate of melanoma is about 0.4-0.5 per 100 000 persons as opposed to the reported incidence of 5.3-21.9 per 100 000 for Europe and north America(2). Nevertheless, population in the East and Southeast Asia is almost one third of the global population, therefore the significance of the burden disease exists in terms of absolute patient(2).

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Based on the Malaysia national cancer registry report, a total number of 103,507 new cancer cases were diagnosed in Malaysia during the period of 2007 to 2011. Of these, there were 322 reported cases (0.3%) of cutaneous melanoma, represented by 167 cases (52%) and 155 cases (48%) in males and females respectively(3).

In Malaysia, comprehensive data on cutaneous melanoma from different ethnicity and its mortality is limited, with the published articles are mainly case series from single institution(8,9) and the latest reviews dated till year 2008(8,9). Therefore, causing dilemma for the managing healthcare professionals to evaluate the incidence, mortality and the treatment outcome in the local population with cutaneous melanoma.

This study aimed to describe the epidemiological and clinicopathological characteristics of primary cutaneous melanoma in Malaysia, as well as to determine the association of selected prognostic factors and median survival time of patients diagnosed with primary cutaneous melanoma in Malaysia.

4.4 MATERIALS AND METHODS

Data Collection

This is a retrospective study involving secondary data collection in four tertiary hospital centres in Malaysia, including Hospital Kuala Lumpur, Hospital Universiti Sains Malaysia, Hospital Sultanah Bahiyah and Hospital Queen Elizabeth I. These hospitals are one of the referrals tertiary centers in Malaysia, consisting of multidisciplinary team of dermatologist, orthopaedic tumour surgeon, plastic and reconstructive surgeon and oncologist, who are responsible in treating the disease. Computerised databases from the pathology departments were used to identify the patients by keying the words 'malignant melanoma'.

All patients regardless of their age who had confirmed the diagnosis of cutaneous melanoma as primary tumour based on histopathological finding from wedge biopsy for investigation or wide local excision surgical treatment from 1st January 2012 till 31st December 2018 were included and had their clinical data retrieved from the medical records for further data collection. Any irretrievable or incomplete data were excluded from the study. The demographic, clinical presentation and histologic data were reviewed. The staging and histologic features were recorded as according to the eighth edition of American Joint Committee on Cancer (AJCC) staging system for melanoma. The information on follow up and clinical status at the date of last contact of the patients (alive or dead) were documented. Collaboration with the National Registration Department in the state of Kelantan was done to confirm the final status and cause of death of the patient who was lost to follow up. Death due to evolution of melanoma was mortality resulted from recurrence and distant metastasis of melanoma to lung,

visceral and brain. On the other hand, death unrelated to melanoma was defined as mortality resulted from patient's coexisting medical conditions, infectious disease or traumatic event.

Statistical analysis

The collected data were analysed using Statistical Package for Social Sciences (SPSS) software. Descriptive statistics were charted to summarize the social demographic (age, gender, race), clinical features (family history, site, staging, survival) and pathological presentation (histological subtype, Breslow thickness, Clark's level, ulceration) of the patients diagnosed with cutaneous melanoma. Numerical variable such as age was presented in mean and standard deviation (SD) for normally distributed data. All categorical variables were presented in frequency (n) and percentage (%).

The survival time was calculated from the date of pathological diagnosis of cutaneous melanoma to the date of the patient died or until the date of study closure for patients who are still alive. Survival curves were plotted. Kaplan-Meier was used to estimate event for individual data while Log Rank Test was used to compare survival curves between the categorical factors. Univariable analysis of the association between the prognostic factors and survival was perform using Simple Cox Regression. Variables with a *p*-value below 0.25 by univariate analysis were further analysed using multivariable cox proportional hazard models to evaluate the effect of multiple covariates on survival.

Preliminary main effect model was obtained after comparing model using backward and forward logistic regression methods. Backward stepwise Cox proportional regression model was applied. Log-minus-log plot, hazard function plot and partial residuals were applied to check the model assumption and were found fulfilled. All possible two-way interactions and proportional hazard assumptions were checked before the final model was made.

Ethical Consideration

The privacy and confidentiality of the patients were respected. This study was performed in accordance with the ethical standards of the National Research Committee, Medical Research and Ethics Committee (MREC): NMRR-18-3988-44055(IIR) and our Institutional Review Board (IRB): JEPeM/19110746.

4.5 RESULTS

CLINICOPATHOLOGICAL PRESENTATION

Age, Sex and Racial distribution

A total of 99 patients were evaluated. A total of 54 patients were excluded due to inadequate clinical information. The mean age at the first diagnosis was 60.4 years, ranging from the age of 11 to 94 years old. Majority of the patients (80.8%) were diagnosed after their fifth decade of life. Only two patients, 0.02% were diagnosed at the paediatric age group of below 12 years old. 47.5% were females and 52.5% were males, with a female:male ratio of 1:1.1. Cutaneous melanoma was found predominantly in the Malay population (52%), followed by the Chinese (24.2%) and others racial group (21.2%) who were residing in Malaysia. These included the minor ethnic groups from the aborigins, Murut, Kadazan, Dusun, Bajau, Eurasian and Caucasian population. Indians were the least (2%) to be diagnosed with cutaneous melanoma. **[Table 1]**

Anatomic Sites of Primary Melanoma

Of the 99 cases of cutaneous melanoma, most of the cases located at the lower extremity, as evidence by 53.5% at the feet and 14.1% at the thigh and leg. 12.1% were detected at the trunk. 14.2% of the lesions were found at the upper extremity. 8.1% of them were found at the arm and forearm, whilst 6.1% located at the hand. **[Table 1]**

MEDIAN SURVIVAL AND PROGNOSIS

A comparison of the prognostic factors was made between patients who had died and survived from cutaneous melanoma. As tabulated in Table 3, the result showed a significant association between the histology subtype, widest width, Breslow thickness, ulceration, staging, oncology treatment, and recurrence between the group of patients (died versus survived) ($p<0.05$).

Based on histological subtype, death befallen on 38 (55.1%) NM patients and 24 (34.8%) ALM patients, as compared to a total of 10.1% of SSM, LMN and other histological subtypes patients who died. A total of 57 (82.6%) patients with widest width more than 20 mm died and only 16 (53.3%) patients survived in this group. A total of 54 (81%) of patients with more than 4 mm Breslow thickness and 28 (40.6%) of stage IV cutaneous melanoma patients had died. **[Table 3]**

Median Survival Time

The median survival time of patient diagnosis with cutaneous melanoma in Malaysia was 673 days (95% CI: 469.55, 876.45) [**Figure 4].** However, there was no significant difference in the median survival time between the causes of death ($p>0.05$). **[Table 4 and Figure 5]**