Clinicopathological Features and Prognostic Factors of Malignant Melanoma: A Retrospective Analysis of Thai Patients in Ramathibodi Hospital

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Objective: *To present the clinicopathological characteristics of cutaneous melanoma in Thai patients and to define the possible clinicopathological prognostic factors.*
Material and Method: *A retrospective study of primary cutaneous melanoma in Thai patients in Ramathibodi Hospital between January 2007 and December 2012 was conducted. All medical records and skin biopsies were reviewed for demographic data and histopathological features. Univariate and multivariate analysis for overall survival, and prognostic factors, according to clinical and histopathological features were performed.*
Results: *Fourty-three patients with pathologically confirmed primary cutaneous melanoma were identified and reviewed. The median age of onset was 58 years, with male:female ratio was 1:1.05. Acral lentiginous melanoma (ALM) was the most common type (76.7%). The majority of patients had clinical stage II (56.1%). Histologically, the median tumor thickness was 2.9 mm, 88.2% had Clark's level IV and V, 47.1% were ulcerated, and 76.5% had dermal mitotic rate of ≥1 mitoses/mm^2. The 5-year overall survival rates was 38.3%. Univariate analysis demonstrated that clinical stage IV, Breslow's thickness of >3 mm, and dermal mitotic rate of ≥3 mitoses/mm^2 were bad prognostic factors. Multivariate analysis demonstrated that advanced clinical staging (stage III and IV), Breslow's thickness of >3 mm, ulceration, palmoplantar or subungual site, and histologic subtype of ALM were the independent risk factors for poor prognosis.*
Conclusion: *Most patients with cutaneous melanoma in Thai patients had the histologic subtype of ALM, and were diagnosed with locally advanced disease (stage II). The prognosis depends on clinical staging, Breslow's thickness, ulceration, primary location of tumor, and histologic subtype.*

Keywords: *Malignant melanoma, Prognostic factors, Overall survival, Thai patients*

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Cutaneous malignant melanoma (MM) is the most common cause of mortality among skin cancers in Caucasian populations with incidence rates of 21.3 per 100,000 patient years in 2011 in the United States[1]. The incidence rates of melanoma in most European countries are also rapidly increasing and are expected to continue rising[1,2]. Superficial spreading melanoma (SSM) is the most common subtype, accounting for approximately 70%, and occurs most often on the trunk. Acral lentiginous melanoma (ALM) was the least common subtype, accounting for approximately 2% to 3%, and carried worse prognosis when compared with other MM histologic subtypes[3,4]. Clinical staging, tumor thickness, ulceration, and mitotic rate were significant prognostic factors[5]. In contrast to Asia, the incidence is significantly lower with incidence rates of 0.2 to 0.5 per 100,000 patient years and histologic subtypes are quite different[6-8]. The most common histological subtype in Asians is ALM, which accounts for approximately 41.8% of all cases[9,10]. Lentigo maligna melanoma (LMM) was the least common subtype, accounting for approximately 0.6%. Clinical staging and ulceration were significant prognostic factors[9,11].

Although MM is a rare disease in Asia, it is the most common cause of mortality among skin cancers. There have been a few reports on the features of melanoma in Asia, particularly in Southeast Asia[6,9,11-14]. Furthermore, there has never been report on MM in Thai patients. The main objective of our study is to describe the clinicopathological

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characteristics of cutaneous MM in Thai patients and to define the possible clinical and histopathological prognostic factors of MM based on Thai patients in Ramathibodi Hospital.

Material and Method

The computerized database diagnosed with malignant melanoma at Ramathibodi Hospital between January 1, 2007 and December 31, 2012 was studied. Inclusion criteria included only ethnic Thai patients (those belonging by birth and identity card) with histopathologically proven primary cutaneous malignant melanoma in Ramathibodi Hospital. We excluded other ethnics, cutaneous melanoma whose medical records or histopathologic specimens were not available for evaluation, recurrent MM, mucosal MM, and metastatic MM with unknown primary location. All medical records and skin biopsies were reviewed for clinicopathological features, including age, sex, primary location, time to diagnosis, size of lesion, histologic subtype, metastatic site, and clinical staging. The histologic characteristics were also reassessed independent by another dermatopathologist from the available pathologic specimens in Ramathibodi Hospital. If there was disagreement in histopathological reviews, the slides were reexamined by the third independent dermatopathologist. The histologic features of each specimen were reviewed according to the seventh edition of American Joint Committee on Cancer (AJCC) staging system for melanoma[15], including Clark's level, Breslow's thickness, ulceration, dermal mitotic rate, margin status, microsatellitosis, angiolymphatic invasion, histologic subtype, neurotropism, regression, T-stage classification, tumor infiltrating lymphocytes, and vertical growth phase[15,16]. The present study protocol was approved by the Ramathibodi Institutional Review Board.

Statistical analysis

Univariate analysis and multivariate analysis of prognostic factors, according to clinical and histopathological features were performed by means of Cox proportional hazard model. The 5-year overall survival rate was calculated by Kaplan-Meier model. The duration of overall survival was calculated from the pathologic diagnosis of MM until death or until the date of the last follow-up. Phone interview was done if the patient loss follow-up. Variables with a *p*-value less than 0.20 in univariate analysis were included in multivariate analysis. The *p*-value less than 0.05 were considered significant.

Results

Demographic data

Ninety-one patients with pathologically confirmed diagnosis of MM were identified. Forty-eight patients were excluded due to mucosal MM (n = 30), metastatic MM with unknown primary site (n = 14), no available medical records (n = 2), Caucasian (n = 1), and recurrent MM (n = 1). There were 43 patients of primary cutaneous MM with 34 available histopathology patients. Clinicopathological characteristics of patients with primary cutaneous MM are summarized in Table 1. Of these, 21 patients (48.8%) were males and 22 patients (51.2%) were females with male:female ratio of 1:1.05. The median age of onset was 58 years. The most common primary location was palmoplantar/subungual site (76.8%). Median time to diagnosis was 18 months (range, 1-240 months). Median size of lesion was 2 cm (range, 0.3-5 cm). ALM was the most common histologic subtype (76.7%), followed by SSM (18.6%), and nodular melanoma (NM) (4.7%). No patient had LMM.

The majority of patients had clinical stage II (23/41, 56.1%), which were local invasive melanoma. There were eight stage I patients (8/41, 19.5%), eight stage III patients (8/41, 19.5%) and two stage IV patients (2/41, 4.9%). Two patients could not be staged due to incomplete data. Sentinel lymph node biopsy was done in 20 patients with four positive results. Twenty-one patients had metastasis (21/43, 48.8%) and the median duration of metastasis was 2.5 months. Lymph node was the most common site of metastasis (19/43, 44.2%), followed by lungs (10/43, 23.3%), and skin (9/43, 20.9%).

Histopathological features

Thirty-four patients with available histopathology were analyzed in the present study (Table 1). Thirty patients had Clark's level IV and V (30/34, 88.2%). The median Breslow's thickness was 2.9 mm, whereas 44.1% (15/34) of the patients had tumor thickness more than 4 mm. Forty-seven percent (16/34) of the patients had ulceration and 76.5% (26/34) of the patients had dermal mitotic rate of $\geq$1 mitoses/mm^2.

Overall survival and prognosis

The 1-, 3-, and 5-year overall survival rates were 79.1%, 54.7%, and 38.3% respectively (Fig. 1). Median time to follow up was 31.7 months (range, 0.9-77.5 months).

Table 1. Clinicopathological characteristics of Thai patients with cutaneous melanoma

Clinicopathological characteristics	Number of patients (%)
Clinical characteristics (n = 43)	
Age (years)	
<40	7 (16.3)
40-49	4 (9.3)
50-59	14 (32.6)
60-69	9 (20.9)
≥70	9 (20.9)
Sex	
Male	21 (48.8)
Female	22 (51.2)
Primary location	
Head and neck	1 (2.3)
Trunk	4 (9.3)
Palmoplantar/subungual	33 (76.8)
Upper extremities	4 (9.3)
Lower extremities	1 (2.3)
Size of lesion (cm)*	
≤1	12 (28.6)
1.1-3	22 (52.4)
>3	8 (19.0)
Histologic subtype	
Superficial spreading melanoma	8 (18.6)
Acral lentiginous melanoma	33 (76.7)
Nodular melanoma	2 (4.7)
Lentigo maligna melanoma	0 (0.0)
Stage**	
I	8 (19.5)
II	23 (56.1)
III	8 (19.5)
IV	2 (4.9)
Histopathological characteristics (n = 34)	
Clark's level	
I	0 (0.0)
II	2 (5.9)
III	2 (5.9)
IV	23 (67.6)
V	7 (20.6)
Breslow's thickness (mm)	
≤1	6 (17.7)
1.01-2	6 (17.7)
2.01-4	7 (20.6)
>4	15 (44.1)
Ulceration	16 (47.1)
Dermal mitotic rate (mitoses/mm^2)	
<1	8 (23.5)
≥1	26 (76.5)
Margin status	
Positive peripheral margin	2 (5.9)
Positive deep margin	3 (8.8)

* Incomplete data in one patient
** Incomplete data in two patients

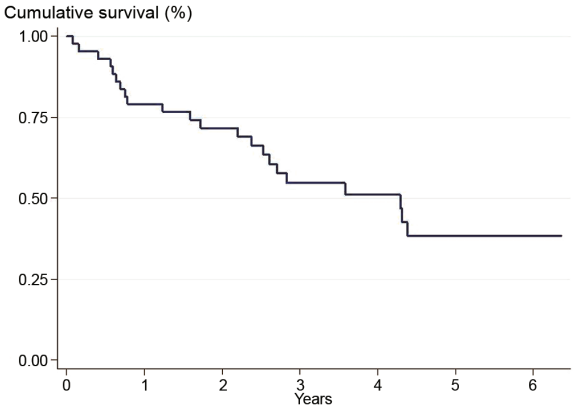

Fig. 1 Kaplan-Meier analysis of overall survival.

With univariate analysis, clinical stage IV, Breslow's thickness of >3 mm and dermal mitotic rate of ≥3 mitoses/mm^2 were statistically significant poor prognostic factors; hazard rate ratios (HRR) were 17.438, 3.469, and 3.489, respectively (Table 2). The size of lesion, primary location of tumor, histologic subtypes of ALM, ulceration and margin status had the tendency toward poorer prognosis, but without statistically significant differences. Other prognostic factors including demographic and histopathologic data were not statistically significant.

In multivariate analysis, there were five statistically significant poor prognostic factors. They included advanced clinical staging (stage III and IV) (HRR = 4.834, $p = 0.008$), primary location of tumor on palmoplantar site (HRR = 10.548, $p = 0.005$), histologic subtype of ALM (HRR = 10.548, $p = 0.005$), Breslow's thickness of >3 mm (HRR = 4.425, $p = 0.011$), and ulceration (HRR = 3.666, $p = 0.025$) (Table 3). Primary location of tumor on palmoplantar site and histologic subtype of ALM were shown to be the most significant factor in predicting survival.

Discussion

The incidence of cutaneous MM in Asians is significantly lower than Caucasians[2,3,5]. It may be because of the ability of melanin in protecting the skin from UV radiation by the lower UV-induced DNA damage and the more removal of UV-damage cells in darker skin than in fair skin[17]. In the last two decades, there have been only a few studies on Asian melanoma and none of these has focused thoroughly on histopathological features according to the 2010 AJCC staging system, such as dermal mitotic rate, margin status, microsatellitosis, angiolymphatic invasion, histologic subtype, neurotropism, regression, T-stage

Table 2. Univariate analysis of prognosis factors in Thai patients with cutaneous melanoma

Factors	n	HRR	95% CI	*p*-value
Age (years)				
<40	7	1		
40-49	4	2.050	0.286-14.716	0.475
50-59	14	2.219	0.477-10.316	0.316
60-69	9	1.916	0.349-10.523	0.455
≥70	9	1.521	0.293-7.893	0.618
Sex				
Male	21	1		
Female	22	0.569	0.241-1.341	0.197
Primary location of tumor				
Non-palmoplantar/subungual	10	1		
Palmoplantar/subungual	33	2.862	0.837-9.779	0.094
Size of lesion (cm)				
≤1	12	1		
1.01-3	22	2.128	0.673-6.727	0.198
>3	8	3.235	0.906-11.555	0.071
Histologic subtype				
Non ALM	10	1		
ALM	33	2.862	0.837-9.779	0.094
Stage				
I	8	1		
II	23	2.454	0.542-11.101	0.244
III	8	3.133	0.718-19.357	0.118
IV	2	17.438	2.197-138.420	0.007
Clark's level				
I, II, III	4	1		
IV, V	30	0.921	0.210-4.039	0.913
Breslow's thickness (mm)				
≤3	17	1		
>3	17	3.469	1.226-9.815	0.019
Ulceration	16	1.867	0.722-4.832	0.198
Dermal mitotic rate (mitoses/mm^2)				
<3	15	1		
≥3	19	3.489	1.135-10.729	0.029
Margin status				
Positive peripheral margin	2	2.937	0.648-13.302	0.162
Positive deep margin	3	3.261	0.889-11.959	0.075

HRR = hazard rate ratios; ALM = acral lentiginous melanoma
Significant level $p<0.05$

classification, tumor infiltrating lymphocytes, and vertical growth phase[6,9,11-16]. To the best of our knowledge, there has never been report of clinicopathological features and prognostic factors of MM in Thai patients. From our current study, ALM histologic subtype and primary location of tumor on palmoplantar/subungual site were the most common in Thai patients (76.7%) and were higher percentages than any other Asian studies[6,9,11-14]. It was confirmed that histologic subtypes in Asian differ from Western populations where ALM represents 2% to 3% of all melanoma[3,4]. There was no significant sex predominance, and the median age of onset was 58 years, which similar to the results in other Asians studies[6,9,11-14]. In previous studies, the mean age was 54 to 65.5 years, and no significant sex difference in acral melanoma except more male predominance in Taiwan patients. The majority of our patients had

Table 3. Multivariate analysis of prognosis factors in Thai patients with cutaneous melanoma

Factors	n	HRR	95% CI	*p*-value
Stage				
I, II	31	1		
III, IV	10	4.834	1.510-15.472	0.008
Primary location				
Non palmoplantar/subungual	10	1		
Palmoplantar/subungual	33	10.548	2.004-55.527	0.005
Histologic subtype				
Non ALM	10	1		
ALM	33	10.548	2.004-55.527	0.005
Breslow's thickness				
≤3	17	1		
>3	17	4.425	1.406-13.928	0.011
Ulceration				
No	18	1		
Yes	16	3.666	1.174-11.446	0.025
Dermal mitotic rate (mitoses/mm^2)				
<3	15	1		
≥3	19			0.673
Margin status				
Negative margin	31	1		
Positive margin	3			0.707
Size of lesion (cm)				
≤3	34	1		
>3	8			0.864

Significant level $p<0.05$

clinical stage II (56.1%) which were local invasive melanoma. Thirty-nine percent of these patients turned to stage III or IV with the median time of 2.5 months, and the 5-year overall survival rate was 38.3%. Clinicopathological characteristics of our study also indicated a high ulcerative rate (47.1%) and high proportion of Breslow's thickness of 4 mm or more (44.1%; T stage 4), which might explain the lower 5-year survival rate. The five-year survival rates of acral melanoma reported from Asian countries, where ALM is the main type, were less than 65%[9,11-14]. Because of a lack of awareness of melanoma, lesions are often misdiagnosed as benign, contributing to the delay in diagnosis. According to our study, 14 patients (32.6%) were initially misdiagnosed as chronic ulcer, nevi, liposarcoma, glomus tumor and adnexal tumor. Similarity to Caucasian populations, one third of all ALMs were initially diagnosed as benign lesions such as warts, calluses, tinea pedis, foreign body reactions, non-healing foot ulcers, nevi, keratoacanthoma, onychomycosis, subungal hematoma, and ingrown toenails[18,19].

On the issue of prognosis, advanced clinical stages (stage III and IV) and presence of ulceration demonstrated poor prognostic factors in multivariate analysis as shown in previous Asian studies. Interestingly, the present study found that Breslow's thickness of >3 mm, palmoplantar/subungual site and ALM were also independent poor prognostic factors, while non ALM was bad prognosis in Taiwan and Japan[13,14].

According to AJCC guideline[15], there is strong evidence to support that three histologic features including Breslow thickness, ulceration, and mitotic rate are the most important characteristics of the primary tumor to predict the outcome. Tumor thickness ≤1 mm determined by Breslow method is defined to thin melanoma and classified to stage I malignant melanoma, which has a favorable prognosis. In general, the 5 to 10 year survival for patients with localized thin primary melanoma is more than 90%[20]. From our study, we found that Breslow's thickness of >3 mm was an independent poor prognostic factor and we were unable to demonstrate dermal mitotic rate as a

significant poor prognosis. The discrepancies were possible from most of our patients presented with locally advanced disease, thick melanoma with median Breslow's thickness of 2.9 mm, and delay in diagnosis from palmoplantar site in Thai patients. Furthermore, we were unable to provide any significant poor prognostic factor with age onset of patient as seen in Japanese study[14].

Conclusion

To our knowledge, this is the first study that demonstrated the clinicopathological characteristics and define the possible prognostic factors of primary cutaneous melanoma in Thai patients. Most of our cases in the present study had the histologic subtype of ALM, and were diagnosed with locally advanced disease. The prognosis depends on clinical staging, Breslow's thickness, ulceration, primary location of tumor, and histologic subtype. Early recognition, detection, and diagnosis of thin melanomas will provide a more favorable prognosis.

Limitations

Our study was the retrospective design and had some incomplete data. There was the small numbers of patients and the results of a single center study may not be generalizable. The larger patient populations may be needed.

What is already known on this topic?

Malignant melanoma is a rare disease in Asia but it is the most common cause of mortality among skin cancers. There have never been report on melanoma in Thai patients and no study has focused thoroughly on the histopathology according to the American Joint Committee on Cancer staging system guideline.

What this study adds?

This is the first study that provided clinicopathological features and prognostic factors of malignant melanoma in Thai patients. From our study, the prognosis depends on clinical staging, Breslow's thickness, ulceration, primary location of tumor, and histologic subtype.

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Potential conflicts of interest

None.

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ลักษณะอาการ ผลตรวจชิ้นเนื้อทางพยาธิวิทยา และปัจจัยที่มีผลต่อการพยากรณ์โรคของมะเร็งผิวหนังชนิดมาลิกแนนท์ เมลาโนมา: การศึกษาแบบย้อนหลังของผู้ป่วยชาวไทยในโรงพยาบาลรามาธิบดี

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วัตถุประสงค์: *เพื่อศึกษาลักษณะอาการ ผลตรวจชิ้นเนื้อทางพยาธิวิทยาของโรคมะเร็งผิวหนังชนิดมาลิกแนนท์ เมลาโนมา ในผู้ป่วยชาวไทย และปัจจัยที่มีผลต่อการพยากรณ์โรค*

วัสดุและวิธีการ: *การศึกษาแบบศึกษาข้อมูลย้อนหลังในโรคมะเร็งผิวหนังชนิดมาลิกแนนท์ เมลาโนมา ในผู้ป่วยชาวไทยที่มารับการรักษาที่โรงพยาบาลรามาธิบดี ระหว่างเดือนมกราคม พ.ศ. 2550 ถึง ธันวาคม พ.ศ. 2555 โดยทบทวนเวชระเบียนและชิ้นเนื้อทางพยาธิวิทยา ในด้านข้อมูลพื้นฐานของผู้ป่วย และลักษณะทางพยาธิวิทยา แล้วนำมาวิเคราะห์แบบตัวแปรเดี่ยวและตัวแปรพหุ เพื่อหาอัตราการรอดชีวิต และปัจจัยที่มีผลต่อการพยากรณ์โรค*

ผลการศึกษา: *พบผู้ป่วยโรคมะเร็งผิวหนังชนิดมาลิกแนนท์ เมลาโนมา ที่มีการตรวจชิ้นเนื้อทางพยาธิวิทยา 43 ราย อายุมัธยฐานที่เริ่มเป็นโรคเท่ากับ 58 ปี อัตราการเป็นโรคชายต่อหญิงเท่ากับ 1:1.05 โดยพบชนิด acral lentiginous melanoma (ALM) มากที่สุด (76.7%) ส่วนใหญ่ผู้ป่วยจะมาพบแพทย์เมื่อเป็นโรคระยะที่ 2 (56.1%) ลักษณะทางพยาธิวิทยาพบความหนามัธยฐานของมะเร็ง 2.9 มม. Clark's level 4 และ 5 มีมากถึง 88.2% มีลักษณะของแผล 47.1% dermal mitotic rate ≥1 mitoses/mm^2 พบ 76.5% อัตราการรอดชีวิตที่ 5 ปีเท่ากับ 38.3% จากการวิเคราะห์แบบตัวแปรเดี่ยว พบว่าปัจจัยที่ทำให้การพยากรณ์โรคไม่ดี ได้แก่ โรคมะเร็งระยะที่ 4 ความหนาของมะเร็งมากกว่า 3 มม. และ dermal mitotic rate ≥3 mitoses/mm^2 และจากการวิเคราะห์แบบตัวแปรพหุ พบว่าปัจจัยที่ทำให้การพยากรณ์โรคไม่ดี ได้แก่ โรคมะเร็งระยะลุกลาม (ระยะที่ 3 และ 4) ความหนาของมะเร็งมากกว่า 3 มม. แผล รอยโรคที่ฝ่ามือฝ่าเท้าหรือใต้เล็บ และลักษณะทางพยาธิวิทยาชนิด ALM*

สรุป: *โรคมะเร็งผิวหนังชนิดมาลิกแนนท์ เมลาโนมา ในผู้ป่วยชาวไทยส่วนใหญ่เป็นชนิด ALM และมาพบแพทย์เมื่อเป็นโรคระยะที่ 2 การพยากรณ์โรคขึ้นอยู่กับระยะของโรค ความหนาของมะเร็ง แผล ตำแหน่งรอยโรคเริ่มแรก และลักษณะทางพยาธิวิทยา*