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Factors Associated with Distant Metastasis from Cutaneous Melanoma: A Study at Maharaj Nakorn Chiang Mai Hospital

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ABSTRACT

OBJECTIVE Cutaneous melanoma is an aggressive tumor associated with high mortality, particularly in the advanced stages. The objective of this study is to identify risk factors for distant metastasis in melanoma patients.

METHODS This retrospective analytical study included all patients diagnosed with cutaneous melanoma and treated at Maharaj Nakorn Chiang Mai Hospital between January 2002 and July 2019.

RESULTS One hundred and forty patients were enrolled in the study. Distant metastasis was found in 45% of the patients (n = 63) and the most common site was the lung (27.9%, n = 39). Multivariable analysis detected two significant prognostic factors for distant metastasis: Breslow thickness 2-4 mm and > 4 mm (p = 0.048 and 0.045, respectively) and nodal metastasis (p < 0.0001).

CONCLUSIONS Breslow thickness > 2 mm and nodal metastasis are associated with distant metastasis and the lung is the most common site of distant metastasis. The patients found to be at risk should be aggressively investigated for distant metastasis.

KEYWORDS melanoma, skin cancer, distant metastasis, risk factor, nodal metastasis, Breslow thickness

INTRODUCTION

Cutaneous melanoma is a cancer originating from melanocytes. Estimates of the global incidence and mortality of cutaneous melanoma in 2018 indicated that the age-standardized incidence in South-Eastern Asia was 0.46 per 100,000 patient-years in males and 0.40 per 100,000 patient-years in females, while in the United States, the incidence of melanoma was 19.7 per 100,000 population (1). The disease is an aggressive tumor with high mortality in the advanced stages and the highest mortality rate of cutaneous malignancy (2).

A study by Carolina et al. in a Brazilian population reported that of patients who had no metastasis when diagnosed, during follow-up metastasis had occurred in 26% of cases. Factors associated with metastasis are male gender, nodular melanoma, Breslow thickness > 4 mm and ulceration (3). Patients with metastasis had a 5 year survival rate of less than 15% (4). The primary organ of distant metastasis is an important factor in the survival rate (5). In melanoma with metastasis, the average survival periods in patients with metastasis in 1, 2, or 3 or more organs are 7 months, 4 months and 2 months, respectively, and the 1-year survival rates are 36%, 13% and less than 1%, respectively. The site of organ metastasis also affects survival. Metastasis in the brain and liver shows a median survival of 4 months; where there is metastasis into the skin and lymph nodes there is a median survival rate of 15 months (6).

Staging of melanoma is based on the system described in the AJCC 8th edition. The criteria include the depth of melanoma proliferation invasion, metastasis to lymph nodes and distant metastasis to other organs. If diagnosis is made at an early stage, wide excision of the tumor is usually sufficient, resulting in a high survival rate. However, cutaneous melanoma is an aggressive tumor with a trend of metastasis to distant organs. In the advanced stages, surgery is often unsuccessful, and the disease becomes very difficult to treat (7).

The long-term prognosis in cutaneous melanoma with metastasis is poor with a mean survival rate after treatment with immunotherapy such as Ipilimumab of between 8 and 12 months. Combined treatment of surgery, chemotherapy, immunotherapy and radiotherapy may increase the mean survival rate many years (8).

There have been few studies of cutaneous melanoma in Thailand to date and no studies have been conducted at Maharaj Nakorn Chiang Mai Hospital.

OBJECTIVES

The main purpose of this study is to research the factors related to distant metastasis of cutaneous melanoma. The secondary objectives of this study are to consider factors related to lymph node, lung and brain metastasis and disease-free survival of cutaneous melanoma metastasis.

METHODS

This retrospective study was conducted by collecting data on factors affecting distant metastasis of cutaneous melanoma including primary sites of cutaneous melanoma, histopathological characteristics, and the time between no metastasis and distant metastasis.

Inclusion criteria

1. Patients who had been diagnosed with or treated for cutaneous melanoma and had been followed up at Maharaj Nakorn Chiang Mai Hospital from 1 January 2005 to 31 July 2019.

2. Availability of histopathology studies confirming diagnosis of cutaneous melanoma.

Exclusion criteria

1. Patients who had no histopathology studies.

2. Patients who had been diagnosed with other malignancies which were being treated or which were not in remission.

Population

The number of subjects required for the study was calculated following the study "Prognostic factors for metastasis in cutaneous melanoma". If the distant metastasis of cutaneous melanoma is 0.263 (26.3%), risk of distant metastasis of cutaneous melanoma from the expected factor of 2.5-3 times with a 95% confidence interval, an 80% power of the test required a sample size in the range of 110-158 patients (3).

Data collection

Data collected included: 1) basic data on cutaneous melanoma patients (gender, age, date of diagnosis); 2) primary site of the cutaneous melanoma; 3) histopathology study results including subtype of cutaneous melanoma, Breslow thickness, Clarke level, ulceration, and tumor infiltrated lymphocytes; 4) lymph node metastasis, distant metastasis and organ(s) of the disease metastasis; 5) date the first distant metastasis was detected and the first organ(s) of distant metastasis; 6) date of onset of signs and symptoms of cutaneous melanoma, and 7) date lost to follow-up or death.

Statistical analysis

Descriptive data (gender, primary site of cutaneous melanoma, clinicopathological subtypes, Clark level, Breslow thickness, ulceration, mitotic index, lymphocyte infiltrate, *BRAF* 600, other organ metastasis) are presented as percentages; continuous variables (age) are presented as mean and standard deviation. The Kaplan-Meier method is used for survival analysis of the interval from occurrence of metastasis in patients with cutaneous melanoma according to lymph node metastasis and Breslow thickness. Univariate analysis and multivariable analysis of the risk factors of melanoma metastasis to distant organs and the risk factors for melanoma metastasis to lymph nodes, lung, and brain using Cox regression with penalized likelihood for factors related with metastasis was conducted. A p-value < 0.05 was considered statistically significant.

All statistical analyses were carried out using SPSS version 23.0.

This study was approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University (MED-2561-05770).

Definitions

Cutaneous melanoma is a skin cancer that originates from melanocytes. Breslow thickness is the thickness of the melanoma measured from the top of the granular cell layer of the epidermis to the deepest point of melanoma invasion. Clark level is a 5-stage system describing the depth of invasion by the melanoma into the skin. Nodal metastasis is where there is metastasis of the melanoma into the lymph nodes. Distant metastasis is the metastasis of the melanoma to distant organs. Disease-free survival is the period during which the cancer is in remission.

RESULTS

One hundred and forty patients were diagnosed with melanoma at Maharaj Nakorn Chiang Mai Hospital between 1 January 2005 and 31 July 2019. Seventy-two were male (51.4%) and 68 female (48.6%). The average age of the patients was 60.88 ± 14.42 years. The primary sites were hands and feet in 101 cases (2.1%), lower extremities in 12 cases (8.5%), trunk in 12 cases (8.5%), head and neck in 10 cases (7.1%) and upper extremities in 5 cases (3.5%) (Table 1). The mean time interval from diagnosis of first-ever melanoma to distant metastasis was shown in Appendix.

The histopathologic subtypes were nodular melanoma in 57 cases (40.7%), superficial spreading melanoma in 44 cases (31.4%), acrolentiginous melanoma in 35 cases (25.0%), desmoplastic melanoma in 2 cases (1.4%), and lentigo maligna in 2 cases (1.4%). The most common depth of tumor invasion by Clark level was Clark level IV in 64 cases (45.7%) and by Breslow thickness was Breslow thickness > 4 mm in 92 cases (65.7%). Other findings include ulceration in 85 (60.7%) and no ulceration in 12 cases (8.6%), tumor infiltrated lymphocytes in 17 cases (12.1%), and no tumor infiltrated lymphocytes in 8 cases (5.7%) (Table 1).

After follow-up treatment, regional lymph node metastasis was present in 110 cases (78.6%), distant metastasis in 63 cases (45%), lung metastasis in 39 cases (27.9%), brain metastasis in 16 cases (11.4%), liver metastasis in 13 cases (9.3%), bone metastasis in 8 cases (5.7%) and gastrointestinal metastasis in 5 cases (3.6%).

Primary outcomes

Multivariable analysis indicated that the risk factors Breslow thickness > 2 mm (p = 0.045) and regional lymph node metastasis (p < 0.0001) were statistically significantly related to distant metastasis (Table 2).

Breslow thickness greater than 4 mm was associated with an increased risk of distant metastasis of 3.45 times (p = 0.018, HR = 3.45) compared to a Breslow thickness less than 2 mm Multivariable analysis found that a Breslow thickness greater than 2 mm was significantly associated with distant metastasis of melanoma with a statistical significance of p = 0.048, HR = 2.98.

Metastatic invasion of the melanoma into the regional lymph nodes increased the risk of distant metastasis by 48.52 times compared to no nodal metastasis ($p \leq 0.0001$, HR = 48.52). Regional lymph node metastasis was statistically significantly associated with distant metastasis of melanoma ($p \leq 0.0001$, HR = 59.99).

Desmoplastic melanoma increased the risk of distant metastasis by 4.6 times compared to superficial spreading (p = 0.044, HR = 4.6) but the association was not statistically significant. Microscopic ulceration increased the risk of distant metastasis by 3.56 times (p = 0.034, HR = 3.56) compared to no ulceration, but the association was not statistically significant.

Gender, primary site of cutaneous melanoma, mitotic rate and *BRAF* mutation did not show any statistically significant association with distant metastasis of cutaneous melanoma.

Secondary outcomes

The risk factor associated with lymph node metastasis was a Breslow thickness greater than 4 mm (p = 0.027, HR = 2.12), while the risk factor associated with lung metastasis was regional lymph node metastasis ($p \leq 0.0001$, HR

Table 1. Patient characteristics

Characteristic Variable	N = 140 Number (%)
Age	
Age mean±SD (year)	60.88 ± 14.42
Gender	
Male	72 (51.4)
Female	68 (48.6)
Site	
Head and neck	10 (7.1)
Trunk	12 (8.5)
Upper limbs	5 (3.5)
Lower limbs	12 (8.5)
Acral	101 (72.1)
Clinicopathological subtype	
Superficial spreading	44 (31.4)
Nodular	57 (40.7)
Acrolentigenous	35 (25.0)
Lentigo maligna	2 (1.4)
Desmoplastic	2 (1.4)
Clark level	
I	2 (1.4)
II	7 (5.0)
III	18 (12.9)
IV	64 (45.7)
V	49 (35.0)
Breslow thickness	
< 1 mm	7 (5.0)
1 - 2 mm	12 (8.6)
2 - 4 mm	29 (20.7)
> 4 mm	92 (65.7)
Ulceration	
Present	85 (60.7)
Not present	12 (8.7)
Mitotic index	
0	7 (5.0)
1 - 4	27 (19.3)
5 - 10	25 (17.9)
≥ 11	14 (10.0)
No information	67 (47.9)
Lymphocyte infiltrate	
Present	17 (12.1)
Not present	8 (5.7)
No information	115 (82.1)
BRAF 600	
Positive	8 (5.7)
Negative	2 (1.4)
Not investigate	130 (92.9)
Nodal metastasis	
Present	110 (78.6)
Not present	27 (19.3)
No information	3 (2.1)
Distant metastasis	
Present	63 (45.0)
Not present	77 (55.0)
Lung metastasis	
Present	39 (27.9)
Not present	101 (72.1)
Liver metastasis	
Present	13 (9.3)
Not present	127 (90.7)
Bone metastasis	
Present	8 (5.7)
Not present	132 (94.3)
Brain metastasis	
Present	16 (11.4)
Not present	124 (88.6)
GI metastasis	
Present	5 (3.6)
Not present	135 (96.4)

= 32.07). Multivariable analysis indicated that the presence of regional lymph node metastasis was a risk factor statistically significantly associated with lung metastasis ($p \leq 0.0001$, HR = 59.99) (Table 3).

A risk factor that showed a statistically significant association with brain metastasis according to the multivariable analysis was the presence of an acral lesion which reduced the risk of brain metastasis by 0.14 times ($p = 0.037$, HR = 0.014) compared to lesions on the head and neck. Lentigo maligna increased the risk of brain metastasis by 38.14 times ($p = 0.009$, HR = 38.14) compared to superficial spreading. Multivariable analysis showed that lentigo maligna increased the risk of brain metastasis by 4.48 times (Table 3).

Analysis of disease-free survival

Statistical analyses of disease-free survival were conducted using the Kaplan-Meier method and the log-rank test based on factors affecting distant metastasis of cutaneous melanoma found statistically significant association with Breslow thickness greater than 2 mm ($p = 0.048$) and regional lymph node metastasis ($p < 0.0001$) (Figures 1, 2).

DISCUSSION

Cutaneous melanoma is an aggressive tumor with a high mortality rate. In Thailand, the incidence of cutaneous melanoma is 0.1-0.4 per 100,000-person years, which is less than in Western countries (Switzerland (20.3:100,000

Table 2. Analysis of risk factors for metastasis of melanoma to distant organs including Cox regression with penalized likelihood multivariable analysis

Variables	Univariate analysis			Cox regression with penalized likelihood		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Clinicopathological type						
Superficial spreading	Ref.			Ref.		
Nodular	1.46	0.79 - 2.69	0.222	0.73	0.38 - 1.44	0.360
Acrolentigenous	1.52	0.75 - 3.08	0.245	1.07	0.51 - 2.21	0.860
Lentigo maligna	0.89	0.12 - 6.73	0.912	5.78	0.52 - 39.95	0.132
Desmoplastic	4.60	1.04 - 20.30	0.044	2.26	0.43 - 7.81	0.290
Breslow thickness						
< 1 - 2 mm	Ref.			Ref.		
2 - 4 mm	2.80	0.93 - 8.44	0.067	2.98	1.01 - 11.58	0.048
> 4 mm	3.45	1.24 - 9.64	0.018	2.77	1.02 - 10.33	0.045
Ulceration						
Present	3.56	1.10 - 11.48	0.034	0.97	0.35 - 3.64	0.954
Not present	Ref.			Ref.		
Nodal metastasis						
Present	48.52	6.98-6127.28	0.000	59.99	6.96- 8176.44	0.000
Not present	Ref.			Ref.		

CI, confidence interval; HR, hazard ratio; ref., reference group

Table 3. Analysis of risk factors for metastasis of melanoma to lymph nodes, lung, brain with Cox regression with penalized likelihood multivariable analysis

	Univariate analysis			Cox regression with penalized likelihood		
	HR	95% CI	*p*-value	HR	95% CI	*p-value*
Nodal metastasis						
Breslow thickness						
< 1 - 2 mm	Ref.					
2 - 4 mm	1.59	0.77 - 3.26	0.207	1.40	0.66 - 2.97	0.379
> 4 mm	2.23	1.18 - 4.21	0.014	2.12	1.09 - 4.13	0.027
Lung metastasis						
Nodal metastasis						
Present	32.07	4.54 - 4062.14	0.000	27.96	3.77 - 3577.56	0.000
Not present	Ref.					
Brain metastasis						
Site						
Head and neck	Ref.			Ref.		
Trunk	0.46	0.110 - 2.116	0.302	0.365	0.049 - 3.398	0.347
Upper limbs	0.12	0.001 - 1.307	0.088	0.068	0.000 - 1.293	0.075
Lower limbs	0.19	0.018 - 1.175	0.074	0.267	0.018 - 3.120	0.275
Acral	0.14	0.041 - 0.563	0.009	0.104	0.015 - 0.859	0.037
Clinicopathological type						
Superficial spreading	Ref.					
Nodular	1.39	0.442 - 4.920	0.576	1.020	0.319 - 3.694	0.973
Acrolentigenous	1.38	0.309 - 5.699	0.652	1.647	0.329 - 8.154	0.530
Lentigo maligna	7.23	1.255 - 32.823	0.030	4.279	0.417 - 37.761	0.210
Desmoplastic	5.03	0.037 - 50.677	0.380	2.481	0.016 - 57.604	0.620
Nodal metastasis						
Present	4.84	1.16 - 44.73	0.027	6.510	1.445 - 64.912	0.012
Not present	Ref.			Ref.		

CI, confidence interval; HR, hazard ratio; ref., reference group

cases per year), the Netherlands (19.4:100,000 cases per year), Denmark (19.2:100,000 cases per year), Norway (18.8:100,000 cases per year), and Sweden (18.0:100,000 cases per year)) (9).

One hundred and forty cases of malignant melanoma confirmed by histopathology between 1 January 2005 and 31 July 2019 were included in the study. We found that a Breslow thickness greater than 2 mm and regional lymph node metastasis were important risk factors related to distant metastasis. Deeper melanoma invasion showed a greater risk of distant metastasis (p = 0.048 for Breslow thickness 2-4 mm and p = 0.045 for Breslow thickness > 4 mm) (10), a finding that adds weight to reports in previous studies. Increased depth of melanoma invasion has been demonstrated to cause invasion into blood vessels and then metastasis to distant organs (11). Brauer et al. reported that increased depth of invasion heightened the risk of rapid metastasis and spread to lymph nodes (12).

Our study found that gender was not a risk factor for melanoma metastasis. Interestingly Pollack et al. determined that male was a significant risk factor for melanoma metastasis which reduced survival rates by 1 to 5 years (13). de Vries et al. found that males faced a greater risk of death from melanoma than females by a factor of 1.87 (14). Mervic et al. followed up 7,338 melanoma patients and found that females had a lower risk of distant metastasis than males (15). The cause of the greater incidence of metastasis in males is not obvious. It may be that females are more likely to react more rapidly to body changes rather than being related to male or female chromosomes or sex hormones. Some studies reported that oxygen free radicals are related to abnormal development of melanocytes that cause melanoma (16).

Patients with desmoplastic melanoma have a 4.6 times higher risk of metastases compared to patients with the superficial spreading subtype. The characteristics of desmoplastic melanoma are different from other types. The appearance of desmoplastic melanoma, a pale nodule, often does not immediately appear serious and thus results in delays in seeking treatment and diagnosis, while the pathological characteristics are similar to soft tissue sarcoma (17).

We found that ulceration increased the risk of cancer spreading by 3.56 times when compared to no ulceration (p = 0.034, HR = 3.56), but the multivariable analysis indicated no statistical significance. A previous study determined that ulceration was related to a negative prognosis including reduced disease-free survival (18). Balch et al. found that ulceration decreased the 5-year survival rate from 80% to 5%. Ulcerated lesions show greater thickness and are more likely to be related to a nodular growth pattern (19).

Our study also found that the primary site of the melanoma, mitotic rate, and *BRAF* mutation were not statistically significant when assessing the risk of melanoma metastasis. A previous study by de Vries et al. collected data from 10,538 patients diagnosed with melanoma from 1993 to 2004 in the Netherlands. The results of that study showed the primary site of melanoma and the mitotic rate are not statistically significant factors in melanoma distant metastasis (14). Ny et al. found that *BRAF* mutation is statistically significantly associated with reduced overall survival (HR [95% confidence interval (CI)]: 1.23 [1.09–1.38]) (20) and *BRAF* mutation in melanoma is most likely to occur prior to the development of metastatic disease (21). That some of these in this study were not found to be statistically significant may be due to the fact that this was a retrospective study and that only a few of the patients had been checked for *BRAF*.

LIMITATIONS

Our retrospective study collected data from medical records, resulting in instances of incomplete information regarding follow-up to ensure there had been sufficient time to accurately determine the incidence of melanoma metastasis. Additionally, the study was carried out at a single center, a tertiary care hospital in the north of Thailand, so the results may not be representative of the population of the entire country.

CONCLUSIONS

Factors associated with distant metastasis of cutaneous melanoma include Breslow thickness greater than 2 mm and metastasis into regional lymph nodes. Patients with these factors

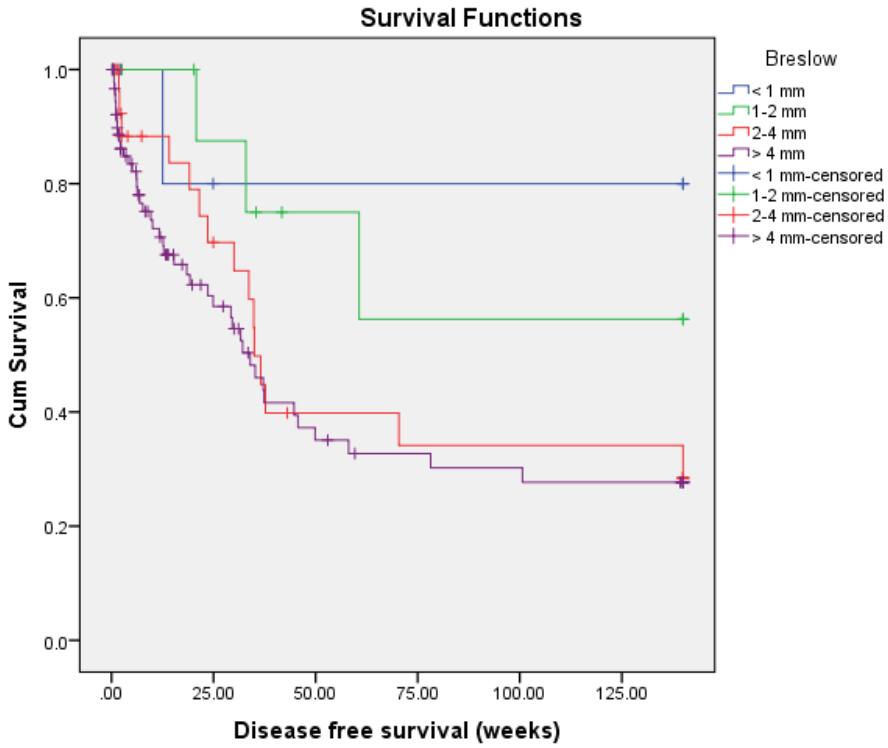

Figure 1. Kaplan-Meier curve showing the time interval for occurrence of metastasis in patients with cutaneous melanoma as a function of Breslow thickness

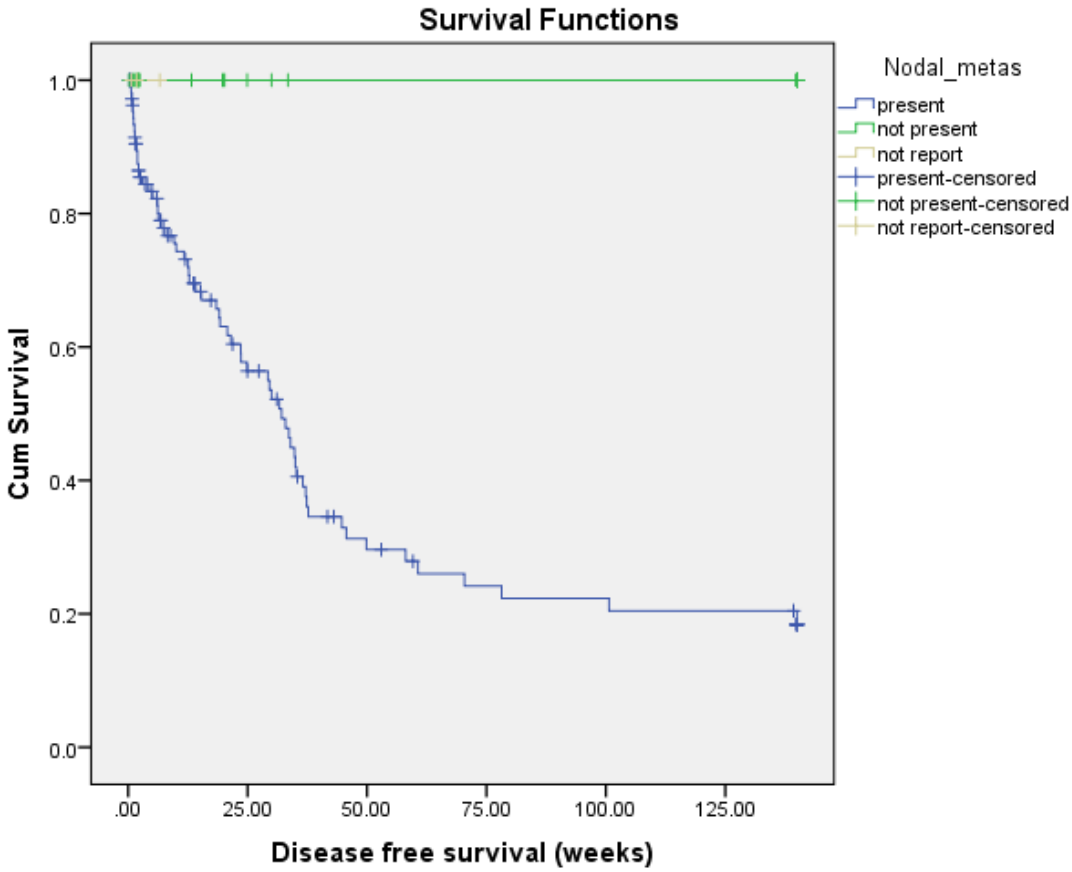

Figure 2. Kaplan-Meier curve showing the interval for occurrence of metastasis in patients with cutaneous melanoma according to lymph nodes metastasis

should be aggressively investigated for distant metastasis.

Disclosable non-financial conflicts of interest will also include membership or affiliation to nongovernmental organizations that have an interest in the submission and no significant financial support for this work that could have influences its outcome.

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Appendix. The mean time interval from diagnosis of first-ever melanoma to distant metastasis

Variable	Time (weeks)
Gender	
Male	58.66
Female	70.10
Site	
Head and neck	41.41
Trunk	65.75
Upper limbs	73.52
Lower limbs	68.56
Acral	65.10
Superficial spreading	79.34
Nodular	60.83
Clinicopathological subtype	
Acrolentigenous	54.39
Lentigo maligna	80.36
Desmoplastic	15.88
Clark level	
I	12.56
II	103.46
III	82.47
IV	67.56
V	49.78
Breslow thickness	
< 1 mm	114.51
1 - 2 mm	96.83
2 - 4 mm	66.03
> 4 mm	56.83
Ulceration	
Present	45.54
Not present	99.12
Mitotic index	
0	50.83
1 - 4	46.76
5 - 10	37.19
≥ 11	43.50
Lymphocyte infiltrate	
Present	100.50
Not present	62.76
BRAF 600	
Positive	45.53
Negative	51.23
Nodal metastasis	
Present	30.79
Not present	68.02