

Clinical and Histopathological Factors in the Prognosis of Cutaneous Malignant Melanoma- An Ambispective Study

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ABSTRACT

Introduction: Melanomas are the most dangerous among the different skin cancers, they can arise from a pre-existing lesion or may arise de novo. Among the common skin cancers, melanoma is the most dangerous. It accounts for approximately 75% of all skin cancer-related deaths, although it comprises only 3% of all skin cancers diagnosed each year. The incidence of Cutaneous Malignant Melanoma (CMM) is increasing worldwide faster than any other cancer.

Aim: To study the clinical and histological factors in relation to the outcomes among patients diagnosed with the CMM in a tertiary care centre in Southern India.

Materials and Methods: This ambispective study was conducted in Kasturba Medical College, Manipal (MAHE), Karnataka, India (tertiary care centre), from June 2001 to June 2016. A total of 87 patients, aged more than 18 years with histopathological evidence of cutaneous malignant melanoma and patients with more than one year of follow-up were enrolled in present study. Data obtained included sex, age at diagnosis, site over the body, histological subtype, Clark's level, Breslow's thickness, lymph nodal status (clinical and pathological), treatment received and status at the time of review. Descriptive statistics were presented as mean, median and standard deviation, Chi-square test was used for the analysis of qualitative variables and 't' test was used for continuous variables.

Results: The mean age in the present study (N=87) was 57±10 years with maximum cases 32 (36.78%) aged between 61-70 years, followed by the 22 (25.29%) case aged between 51-60 years and 18 (20.69%) aged between 41-50 years. Maximum patients, 27 (42.19%) in disease free group and 37 (57.81%) in non disease free group were aged >50 years. A total of 48 (55.17%) males patient and 39 (44.83%) females were included in present study. Out of total, 71 (81.6%) patients had primary lesion on the extremities and 16 (18.40%) patients had primary lesions on the trunk, head and neck. Ulceration was present in total 56 patients. Out of these 56 patients ulceration was present in 34 (60.71%) in non disease free group and in 22 (39.29%) in disease free group. Clark's level was unknown for 23 patients. Out of 64 patients, in disease free group, maximum patients 11 (78.57%) were in Clark's level II, while in non disease free group maximum patients 13 (76.47%) were in Clark's level IV followed by the 12 (63.16%) in Clark's level III. Maximum cases 7 (63.63%) in disease free group were seen in <1 mm and 7 (41.18%) in 1.01-2 mm group.

Conclusion: Significant relation between Clark's levels and prognosis of the CMM was seen. The study also showed statistically significant association of Breslow's thickness on prognosis. The common histological type of malignant melanoma in the study was nodular type.

Keywords: Breslow's thickness, Clark's levels, Disease status, Lentigo malignant melanoma, Skin, Superficial spreading melanomas

INTRODUCTION

Cutaneous Malignant Melanoma (CMM) is a malignancy arising from the melanocytes that can arise from de novo or from a pre-existing lesion such as acquired, congenital or dysplastic (atypical) nevus. Cutaneous malignant melanoma are malignancy arising from the melanocytes. It accounts for approximately 75% of all skin cancer related deaths although, it comprises only 3% of all skin cancers diagnosed each year [1]. According to World Health Organisation (WHO), the incidence of melanoma cases worldwide is increasing faster than any other cancer [2]. Incidence varies geographically with "high incidence regions" such as Australia, "moderate incidence regions" like USA and Canada, and "low incidence regions" such as India and Scotland [3].

Whereas the overall prognosis of an earlier diagnosed tumour is excellent, melanomas diagnosed later have much poorer survival rates and there are no satisfactory cures for advanced melanoma [4]. Prognosis for those patients with locoregional or metastatic systemic disease is poor, with a median survival of 24 months and six months, respectively [5]. The overall prognosis is dependent on various parameters like age, sex, size, anatomic location, type of

the primary, ulceration, level of invasion, thickness, as well as status and number of regional nodes involved among others [6].

Although it is a vastly studied tumour, documentation of its clinical presentation and incidence in the dark skinned individuals of India or Asia is far from complete [7,8]. The aim of the present study was to evaluate the clinical and histological factors in relation to the outcomes and prognosis among diagnosed CMM patients at a tertiary care centre in Southern India.

MATERIALS AND METHODS

This ambispective study was conducted in Kasturba Medical College, Manipal (MAHE), Karnataka, India (tertiary care centre), from June 2001 to June 2016. The ethical clearance was obtained from Institutional Ethical Committee (No-IEC 172/2010). Written informed consent was taken from all the study participants.

Inclusion criteria: All patients with age more than 18 years with histopathological evidence of CMM and who were followed-up for atleast one year were included in the study.

Exclusion criteria: Patient aged less than 18 years, follow-up less than one year, no proper histopathological diagnosis and patients

with ocular and visceral malignant melanoma were excluded from the study.

A total of 87 patients with cutaneous malignant melanoma, who presented in the department within the study period, were enrolled in the study. Total 58 patients diagnosed with CMM at a tertiary care Hospital in Southern India, from June 2001 to June 2011 were studied retrospectively and 29 patients from July 2011 to June 2016 were studied prospectively.

The study patients were divided into two groups:

Group A (Disease free): Disease free refers to the status at last follow-up.

Group B (Non disease free): Non disease free status includes death, loco regional recurrence and distant metastasis.

Study Procedure

Survival was analysed by the prognostic factors that were known from the patient's individual records with the Medical records available at the hospital. Data such as gender, age at diagnosis, site over the body, histological subtype, Clark's level [5], Breslow's thickness [6], lymph nodal status (clinical and pathological), treatment received and status at the time of review. The patient population was divided gender wise and their survival rates were compared. The patients were categorised into eight groups based on their age at intervals of 10 years except the first group which comprised of patients between the ages of 18-20 years in order to facilitate comparison with other studies. Within the study group, the patients were divided to two groups based on age (less than 50 years and more than 50 years) for statistical analysis.

- Body site was subdivided into neck, head and trunk and extremities.
- Histopathological subtype was divided into conventional histological subtypes as into [2,3]:
Lentigo malignant melanoma (Lentigo Maligna),
Superficial Spreading Melanomas (SSM),
Nodular Melanoma (NM)
Acral lentiginous and
Amelotonic melanoma
- Wherever available, subdivision were made into melanomas with a thickness less than 1.0 mm, between 1.01-2.0 mm, 2.01-3.00, 3.01-4 mm and >4.00 according to Breslow's thickness [6].
- The patients disease status was compared against Clark's levels I-V [5]. If data for Clark's levels and Breslow's thickness were not available, patients were also included in the study as long as other inclusion criteria were met.

STATISTICAL ANALYSIS

Microsoft excel Statistical Package for Social Sciences (SPSS) version 26.0 was used to gather data. Descriptive statistics were presented as mean, median and standard deviation, Chi-square test was used for the analysis of qualitative variables and Student's t-test was used for continuous variables.

RESULTS

The mean age in the present study (N=87) was 57±10 years with maximum cases 32 (36.78%) aged between 61-70 years, followed by the 22 (25.29%) case aged between 51-60 years and 18 (20.69%) aged between 41-50 years [Table/Fig-1].

Maximum patients, 27 (42.19%) in disease free group and 37 (57.81%) in non disease free group were aged >50 years. A total of 48 (55.17%) males patient and 39 (44.83%) females were included in present study. Out of total, 71 (81.6%) patients had primary lesion on the extremities and 16 (18.40%) patients

Age groups (years)	n, %
18-20	1 (1.15%)
21-30	2 (2.3%)
31-40	2 (2.3%)
41-50	18 (20.69)
51-60	22 (25.29%)
61-70	32 (36.78%)
71-80	8 (9.2%)
>80	2 (2.3%)

[Table/Fig-1]: Age-distribution of the participants.

had primary lesions on the trunk, head and neck. Ulceration was present in total 56 patients. Out of these 56 patients, ulceration was present in 34 (60.71%) in non disease free group and in 22 (39.29%) in disease free group [Table/Fig-2].

Variables	Disease free (n, %)	Non disease free (n, %)	Total (n, %)	p-value (Chi-square test)
Age (years)				
≤50	14 (60.87%)	9 (39.13%)	23 (26.44%)	0.124
>50	27 (42.19%)	37 (57.81%)	64 (73.56%)	
Gender				
Female	19 (48.71%)	20 (51.29%)	39 (44.83%)	0.789
Male	22 (45.84%)	26 (54.16%)	48 (55.17%)	
Site				
Extremities	32 (45.07%)	39 (54.93%)	71 (81.6%)	0.418
Head, neck and trunk	9 (56.25%)	7 (43.75%)	16 (18.4%)	
Ulceration				
Absent	19 (61.29%)	12 (38.71%)	31	0.49
Present	22 (39.29%)	34 (60.71%)	56	

[Table/Fig-2]: Distribution according to age, gender, anatomical location of the primary lesion and ulceration.
p-value <0.05 was statistically significant

Distribution according to the histological type of malignant melanoma revealed that Superficial Spreading Melanoma (SSM) was seen in 7 (77.78%) patients in disease free group and 2 (22.22%) patients in non disease free group. maximum case were seen with lentigo maligna 16 (59.26%) in disease free and nodular 23 (69.70%) in non disease free group [Table/Fig-3].

Histological type	Disease free (n, %)	Non disease free (n, %)	Total	p-value (Chi-square test)
SSM	7 (77.78%)	2 (22.22%)	9	0.010
Nodular	10 (30.30%)	23 (69.70%)	33	
Lentigo Maligna	16 (59.26%)	11 (40.74%)	27	
Acral Lentiginous	5 (33.33%)	10 (66.67%)	15	
Amelotonic	3 (100%)	0	3	
Total	41	46	87	

[Table/Fig-3]: Distribution according to the histological type of malignant melanoma.
p-value <0.05 was statistically significant

Clark's level was unknown for 23 patients. out of 64 patients, in disease free group, maximum patients 11 (78.57%) were in Clark's level II, while in non disease free group maximum patients 13 (76.47%) were in Clark's level IV followed by the 12 (63.16%) in Clark's level III [Table/Fig-4]. Distribution according to Modified Breslow's thickness of tumour is shown in [Table/Fig-5]. Maximum cases 7 (63.63%) in disease free group were seen in <1 mm and 7 (41.18%) in 1.01-2 mm group. In non disease free group maximum cases 12 (92.30%) were seen in 3.01-4 mm group [Table/Fig-5].

Clark's levels	Disease free (n, %)	Non disease free (n, %)	Total	p-value (Fischer's-Exact test)
Unknown	12 (52.17%)	11 (47.83%)	23	0.003
I	7 (77.78%)	2 (22.22%)	9	
II	11 (78.57%)	3 (21.43%)	14	
III	7 (36.84%)	12 (63.16%)	19	
IV	4 (23.53%)	13 (76.47%)	17	
V	0	5 (100%)	5	
Total	41	46	87	

[Table/Fig-4]: Comparison of the disease free and non disease free groups based on Clark's levels.
p-value <0.05 was statistically significant

Thickness	Disease free (n, %)	Non disease free (n, %)	Total	p-value (Fischer's-Exact test)
Not available	19 (65.51%)	10 (34.49%)	29	0.014
<1 mm	7 (63.64%)	4 (36.36%)	11	
1.01-2 mm	7 (41.18%)	10 (58.82%)	17	
2.01-3 mm	3 (33.33%)	6 (66.67%)	9	
3.01-4 mm	1 (7.70%)	12 (92.30%)	13	
>4 mm	4 (50%)	4 (50%)	8	
Total	41	46	87	

[Table/Fig-5]: Distribution according to Modified Breslow's thickness of tumour.
p-value <0.05 was statistically significant

In the present study, out of total 87 patients, 53 patients had no palpable nodal disease or distant disease metastasis, while 24 patients had palpable nodal metastasis and 10 had distant disease metastasis. Out of 53 patients with no palpable nodal disease or distant disease metastasis, 35 patients underwent wide local excision only, while 18 patients underwent wide local excision coupled with elective regional node dissection. Among the 18 patients who underwent elective node dissection, two nodes were reported as positive and 16 were negative. Out of these 53 patients with no palpable nodal disease, 34 (64.15%) were disease free at the time of last follow-up. Similar analysis of the 24 patients with palpable nodal disease, only 7 (29.17%) were disease free at the time of last follow-up.

DISCUSSION

In the present study 87 patients were included with histopathological diagnoses of CMM during the study period. Of the 87 patients in present study group, 48 (55.17%) were males. The disease recurrence rate for both males and females were nearly similar 26 (54.16%) among males vs 20 (51.29%) among females. The disease free status when analysed was not statistically significant (p-value of 0.789). This is in variance with the findings of previous studies [7,8].

The mean age of the patients in the present study was 57±10 years which is marginally lower than the mean age reported in several studies [9-12]. Various studies have concluded that disease free survival declines with advancing age. Austin PF et al., demonstrated a 55% relapse-free survival rate at 5 years in patients greater than 65 years of age compared to 65% in patients 65 years or younger [11]. A study that included 488 patients with no sign of metastatic disease by Schuchter L et al., an 84% 10-year survival rate for patients less than 60 years of age compared with 57% for patients 65 years of age or greater [9]. The study by Uehara S et al., concluded that the 5 year survival rate by age group was 85.7% for 30 or younger, 75.8% for 31 to 50, 81.5% for 51 to 70, and 74.0% for 71 or older [12]. However, the study concluded that there was no substantial difference in five year survival rate among the different age groups. This study too reached a similar conclusion with higher incidence rates among the older age groups but no statistically significant disease free survival advantage among the

younger age group. One of the reasons for this observation may be due to more aggressive form of the disease in the younger group. Other reasons could be the overall lower life expectancy among our population, when compared to the western world besides other confounding factors.

Schuchter L et al., in a study of 488 patients with no indication of metastatic disease showed an 86% 10-year survival rate for women compared with 68% for men [9]. On the contrary, a study by Uehara S et al., based on 103 patients in Osaka, Japan came to the conclusion that the survival benefit based on gender is not significant [12]. The lack of survival advantage among females in the present study group may be due to other confounding factors and also may be attributed to poorer general health status of females when compared to males in this part of the world.

Among the 87 patients, 71 patients had a primary lesion over the extremities with only 16 patients with a lesion over the trunk. However, a primary of the extremity did not confer any survival advantage as nearly 40% this group had a loco regional recurrence as against only ~25% recurrence among those with a trunk primary. This is contrary to the findings of most studies including the study by Schuchter L et al., which concluded that in the lack of metastatic disease and for all tumour thickness ranges, a 10 year survival rate of 90% was observed when the primary melanoma was in the extremities compared to 70% when in the neck, head and trunk [9]. In a series of 5,093 patients with invasive primary cutaneous melanoma, Garbe C et al., showed that locations that were associated with a significantly higher risk of death caused by primary cutaneous melanoma included the neck, scalp, back, thorax and upper arm [13]. The present study did not show any statistical significance with respect to disease free survival based on the anatomical position of the primary (p-value=0.418). One of the reasons for this discrepancy could be, the stage of disease at the time of presentation among others.

Among those included in the study, the largest group of 33 patients (37.9%) were histopathologically diagnosed with nodular type of melanoma of whom only 30.3% were disease free at last follow-up. This is in variance with normal incidence of histological types where superficial spreading melanoma is the utmost common (upto 70%) of all melanomas. In a study by Forman BS et al., lentigo maligna was the most common subtype of melanoma. Of the 771 cases of melanoma reviewed in their study, lentigo maligna and lentigo maligna melanoma accounted for 429 (56%) [14]. The present study group showed statistically significant association between the histological type and disease free survival (p-value=0.010). This finding could be one of the reasons for the absence of survival benefit among the younger age group of the study group as nodular type of malignant melanoma is known to afflict younger individuals more commonly and is also more aggressive.

Of the 87 patients, Breslow's thickness was available only for 58 patients. In our study, increased Breslow's tumour thickness corresponded to increased mortality/locoregional recurrence with almost 82% of patients with thin melanomas less than 1 mm having disease free survival at the end of follow-up period while 62.5 % of those with tumour thickness greater than 4 mm having loco regional recurrence/distant disease or death. Though on the lower side, this finding is in line with the findings of other study by Balch CM et al., which attribute a 95%, 5 year overall survival rate in patients with thin tumours lacking other adverse prognostic factors [15]. A similar conclusion was reached to by Schuchter L et al., in their study [9]. The five year overall survival rate in patients with thin tumours without other adverse prognostic factors is 95% or larger [5,9]. This study supports these findings with a statistically significant survival advantage among patients with thinner melanomas (p-value=0.014). Out of the 87 patients included in the study, 56 patients had an ulcer at the time of first presentation of whom only 34% were disease free. On the other hand, of the 31 patients without ulcer, 71% were

disease free. These findings fit in with the observations of other studies which postulate that the presence of ulceration diminishes survival in all tumour thickness categories.

According to Balch CM et al., thin (<1.0 mm) ulcerated tumours have approximately a 4% decreased 5-year survival rate as compared to non-ulcerated tumours. This survival decrement is as high as 22% in thick (>4.0 mm) tumours [6]. The present study, though did not confer survival benefit to patients without ulceration. This may in part be due to other confounding factors like stage of disease at the time of presentation. Among the 64 patients for whom Clark's levels were available, nine fell into level I of whom nearly 89% were disease free. Similarly, Level II had a 78% disease free patients while only 20% of those in Level V were disease free. These numbers are comparable to those of Dessureault S et al., who in 1997 predicted the 5 year survival rate as 95% for Clark level II melanomas, between 80% and 85% for Clark level III and IV melanomas, and 55% for Clark level V melanomas [16]. Similarly, Uehara S et al., concluded that the five year survival rate was 93.8% for level I, 100% for level II, 100% for level III, 79.7% for level IV, and 44.4% for level V [12]. The present study too conferred statistically significant advantage in disease free survival to those with a lower Clark's level (p-value=0.003).

In the present study, 53 patients had no palpable nodal disease or distant disease of whom 35 patients underwent wide local excision only while 18 patients underwent wide local excision coupled with elective regional node dissection. Among the 18, who underwent elective node dissection, two nodes were reported as positive and 16 were negative. Twenty four out of the 87 had palpable nodal metastasis while 10 had distant disease. Studies by Balch CM et al., predict ten-year survival rates in the presence of a single macroscopic vs microscopic node are 47% vs 63%, respectively [6]. In the present study out of the 53 patients with no palpable nodal disease, 34 (64.15%) were disease free at the time of last follow-up. Similar analysis of the 24 patients with palpable nodal disease, only 7 (29.17%) were disease free at the time of last follow-up. In the 2001 AJCC analysis, 37% of all patients with nodal metastases survived 10 years and 48% survived five years [8,9].

To summarise, the current study came with some findings which are in variance with other published literature from the west [8-10]. The exact reasons for this discrepancy are not known. This may be partly attributed to the bias in the analytical results, due to the lesser number of subjects of the present study, geographical location, associated risk factors when compared to subjects in the US and rest of the western world, where most of the studies are based. It is anticipated that similar studies, but at larger scales, will be performed in India to overcome some of these glitches.

Limitation(s)

The study sample is small sample for any conclusive interferences.

CONCLUSION(S)

The most common histological type of CMM in present study group was nodular type. The association between histological type and prognosis was statistically significant in this study. Significant relation between Clark's levels and prognosis of the CMM was seen. The study also showed statistically significant association of Breslow's thickness on prognosis. Further studies, on a larger scale, should be undertaken in India to have a better understanding of this disease in our part of the world.

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