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Original Research Article

A study of prognostic factors in cutaneous malignant melanoma

M. N. Sasikumar*, Annie Sandhya Kurian

Department of Surgery, General Surgery, Government Medical College, Kottayam, Kerala, India

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***Correspondence:**
Dr. M. N. Sasikumar,
E-mail: drmnsasikumarktm@gmail.com

ABSTRACT

Background: Melanocytes are cells of neural crest origin that migrate principally to basement membrane of skin at dermo-epidermal junction. These cells when exposed to carcinogens result in malignant melanoma. Melanoma accounts for only 4% to 5% of all skin cancers but causes majority of deaths from skin cancers. Several factors affect its prognosis. Most reports agree that tumour thickness is the most important factor, but several others also interact.
Methods: From the department of Medical College, Kottayam the cancer of patient who had histopathologically proven malignant melanoma during 2008-2012 were obtained from this HPR, details of the lesion such as Breslows thickness, level of invasion, presence of ulceration, mitoses, lymphocytic infiltration, tumor vascularity etc. were recorded. The case records of the some patients were then obtained from the record library, from which the clinical details of the lesions and follow up were recorded. These patients were followed till 2013. The significance and each of these factors were these analysed.
Results: There were a total of 64 cases with equal gender distribution. The incidence reflected the global trend of increasing number of cases. The factors which affect prognosis included nodal status, thickness, level of invasion, ulceration, mitoses, lymphocyte infiltration, vascularity and lymphovascular emboli. A striking finding was most of the patients presented at an advanced stage, unlike the West.
Conclusions: Malignant melanoma is a deadly disease especially when diagnosed late. Many factors in addition to thickness were found to have prognostic significance.

Keywords: Malignant melanoma, Prognostic factors, Thickness, Nodal status, Lymphocyte infiltration, Lymphovascular emboli

INTRODUCTION

Cutaneous melanoma is one of the most serious skin cancers. It arises from neural crest-derived melanocytes – (pigmented cells present normally in the epidermis and sometimes in the dermis). Incidence of melanoma is dramatically increasing.[1] The lifetime risk of melanoma in 1935 was 1 in 1,500 persons in 1960, 1 in 600 persons and in 2000, 1 in 75 persons.

Although the prognosis of thin melanoma is excellent, prognosis becomes poor with increasing thickness of the lesion.[2] The poor prognosis is mainly due to the well-established tendency of melanoma to metastasise, which accounts for 75 percent of all deaths associated with skin cancer. In addition, melanomas are highly resistant to most forms of chemotherapy and radiation; therefore, cure of the disseminated disease is uncommon.

Most reports agree that tumour thickness is the most important prognostic factor, but several other factors seem to interact, including gender, presence or absence of ulceration, level of invasion, age at diagnosis, site of tumour and type of tumour.

Objectives

- Study of the incidence of prognostic factors, other than tumour thickness, in cases of cutaneous malignant melanoma.
- Follow-up of these patients to assess the significance of these factors with regard to disease outcome.

METHODS

This study was conducted in General Surgery Department, Govt. Medical College, Kottaym during the year 2008 to 2012 (5 years). This was a Retrospective analytical study. The patients who had under gone wide local excision for cutaneous malignant melanoma during this period were included in this study. A total of 64 patents were analysed.

The patients with proved malignant melanoma, who under gone wide local excision were included in this study. There were no exclusion criteria. Histopathology reports of these patents were collected from pathology department to evaluate the extent and characteristics of these lesions. Then these patients were followed up for maximum of 5 years and minimum of 1 year. The details of the outcome were obtained and these were compared with the clinical and histopathology reports.

Procedure in detail

The details of patients with histologically proven malignant melanoma were obtained from pathology department histopathology registers. The case sheets of these patients were then accessed from medical record library and the radiotherapy department, and the details recorded. The patients were followed up until October 2013 using Radiotherapy Department case records. The data was properly coded and entered in excel. Further analysis was done in SPSS 16.0 version. For testing association of prognostic factors chi-square test was used. A p value of less than 0.05 was taken as significant.

RESULTS

There are a total of 64 patients; 33 male and 31 female (Table 1).

Table 1: Total number of cases.

Patients	Number of cases
Male	33
Female	31
Total	64

Breslow thickness is taken in 4 categories: l- <l mm, 2- l-2 mm, 3- 2-4 mm, 4- >4 mm. For analysis, 1 and 2, and 3 and 4 were combined. Breslow thickness was, as is expected, a significant poor prognostic factor. 11 cases were in cat 1 and 53 in cat 2 (Table 2).

The age-gender cross-tabulation showed a difference in incidence between males and females in the two age groups; but this was found to be not significant (p>0.05) (Table 3).

Table 2: Breslow thickness: prognosis cross tabulation.

			Prognosis		Total
			Good	Bad	
Breslow thickness	1	Count	8	3	11
		% within Breslow thickness	72.7	27.3	100.0
		% within PR GP	28.6	27.3	100.0
	2	Count	20	33	53
		% within Breslow thickness	37.7	62.3	100.0
		% within PR GP	71.4	91.7	82.8
Total		Count	28	36	64
		% within Breslow thickness	43.8	56.2	100.0
		% within PR GP	100.0	100.0	100.0

Table 3: Age group sex cross tabulation.

		Sex		Total
Age group (in years)		**Male**	**Female**	
<60	Count	15	10	25
	% within age group	60.0	40.0	100.0
>60	count	18	21	39
	% within age group	46.2	53.8	100.0
Total	count	33	31	64
	% within age group	51.6	48.4	100.0

Table 4: Gender and age group cross tabulation.

			Prognosis		Total
			Good	Bad	
Age group (in years)	<60	Count	15	10	25
		% within age group	60.0	40.0	100.0
		% within PR GP	53.6	27.8	39.1
	>60	Count	13	26	39
		% within age group	33.3	66.7	100.0
		% within PR GP	46.4	72.2	60.9
Sex	Male	Count	12	21	33
		% within sex	36.4	63.6	100.0
		% within PR GP	42.9	58.3	51.6
	Female	Count	16	15	31
		% within sex	51.6	48.4	100.0
		% within PR GP	57.1	41.7	48.4

Table 5: Body sites.

		Prognosis		Total
Site		Good	Bad	
Extremities	Count	27	33	60
	% within site	45.0	55.0	100.0
	% within PR GP	96.4	91.7	93.8
Trunk	Count	1	3	4
	% within site	25.0	75.0	100.0
	% within PR GP	3.6	8.3	6.2
Total	Count	28	36	64
	% within site	43.8	56.2	100.0
	% within PR GP	100.0	100.0	100.0

Table 6: Type of prognosis cross-tabulation.

			Prognosis		Total
			Good	Bad	
Clarke's level	1	Count	2	0	2
		% within Clarke's level	100.0	0.0	100.0
		% within PR GP	7.1	0.0	3.1
	2	Count	5	1	6
		% within Clarke's level	83.3	16.7	100.0
		% within PR GP	17.9	2.8	9.4
	3	Count	6	1	7
		% within Clarke's level	85.7	14.3	100.0
		% within PR GP	21.4	2.8	10.9
	4	Count	11	17	28
		% within Clarke's level	39.3	60.7	100.0
		% within PR GP	39.3	47.2	43.8
	5	Count	4	17	21
		% within Clarke's level	19.0	81.0	100.0
		% within PR GP	14.3	47.2	32.8
Ulceration	0	Count	11	3	14
		% within ulceration	78.6	21.4	100.0
		% within PR GP	39.3	8.3	21.9
	1	Count	17	33	50
		% within ulceration	34.0	66.0	100.0
		% within PR GP	60.7	91.7	78.1

Continued.

			Prognosis		Total
			Good	Bad	
Mitoses	0	Count	19	5	24
		% within mitoses	79.2	20.8	100.0
		% within PR GP	67.9	13.9	37.5
	1	Count	9	31	40
		% within mitoses	22.5	77.5	100.0
		% within PR GP	32.1	86.1	62.5
Lymphinfil	0	Count	10	30	40
		% within lymphinfil	25.0	75.0	100.0
		% within PR GP	35.7	83.3	62.5
	1	Count	18	6	24
		% within lymphinfil	75.0	25.0	100.0
		% within PR GP	64.3	16.7	37.5
Tumourvas	0	Count	26	15	41
		%within tumourvas	63.4	36.6	100.0
		% within PR GP	92.9	41.7	64.1
	1	Count	2	21	23
		%within tumourvas	8.7	91.3	100.0
		% within PR GP	7.1	58.3	35.9

The cases were divided into 2 age groups- less than 60 and, 60 and above. A significant difference was seen between the outcome in both these groups- p value 0.036 (<0.05) (Table 3).

Cross-tabulation of gender with prognosis showed a worse prognosis for male gender and this was found to be significant (Table 4).

The body sites were divided into 3: 1- extremities, 2- trunk and 3- head and neck. Majority of the cases were found to be in the extremities (93.8%) and the rest in the trunk. There were no cases in the head and neck area. Because of the gross difference in incidence statistical significance in prognosis was not obtained (Table 5).

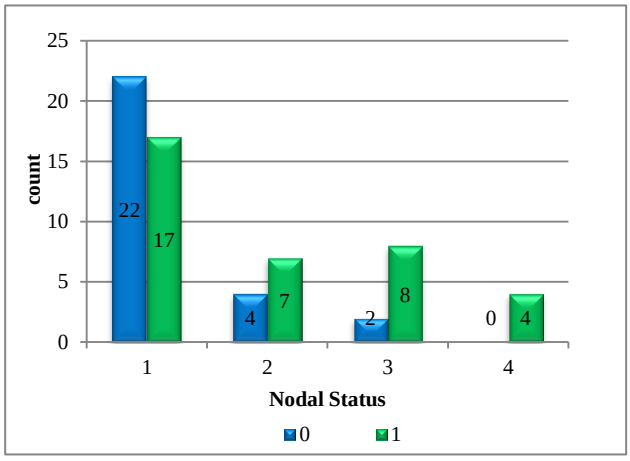

Figure 1: Comparison of nodal status with prognosis.

Of the 64 patients, 39 were found to have no nodal status and 25 had positive nodal status. When comparing the outcome of these two groups, a significant difference was found in prognosis (p=0.042 i.e. <0.05) (Figure 1).

The cases were divided into 5 according to the Clarke's level. Maximum number of cases was found in level 4 followed by level 5. As would be expected, a significant difference was seen in prognosis according to level (Table 6).

The pathological assessment of post-excision margin, whether free- 0 or involved- 1 was cross-tabulated with prognosis. Majority of cases were found to be with margins free (87.5%). Because of the skewed nature of the data, the statistical difference could not be assessed (Table 6).

The presence of microscopic ulceration was recorded and compared to prognosis. Presence of ulceration was found to be a significant poor prognostic factor (Table 6).

In pathological assessment, presence of mitoses >0-1/mm^2 was taken to be high- (1) and less than that as low- (0). Increased mitoses is, as expected, a poor prognostic factor (Table 6).

Tumor-invading lymphocytes or lymphocytic stromal invasion was found to be a significant good prognostic factor (Table 6).

Increased tumor vascularity was seen in 36% of the cases and was found to be a significant poor prognostic factor (Table 6).

31% of cases were found to have lymphovascular emboli and this was found to be a significant poor prognostic factor (Figure 2).

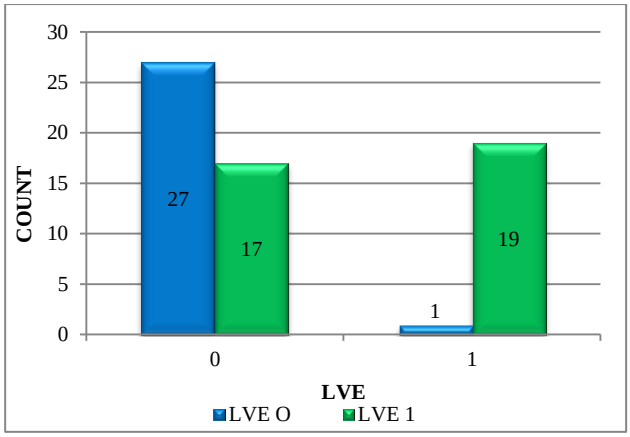

Figure 2: Comparison of LVE with prognosis.

DISCUSSION

Incidence

There were a total of 64 patients, 33 male and 31 female, over 5 years. All cases between January 2008 and December 2012 were taken and followed up until October 2013.

There is marked rise in the number of cases over the 5 years, with 6, 5 and 6 cases in 2008, 2009 and 2010 respectively; 15 and 32 cases in 2011 and 2012 respectively. There was not much difference between the incidence in males and females.

The cases were divided into 2 age groups- less than 60 and, 60 and above. Age group-gender cross-tabulation showed more males in less than 60 age group and more females in the 60 and above age group. This difference was found to be statistically not significant.

Different prognostic factors were compared with the recorded disease outcome of the patients. Local recurrence and distant metastases, occurring during follow-up, were both taken as poor disease outcome-(poor prognosis).

Breslow thickness

Breslow thickness is accepted as the most important prognostic factor. The cases were divided into 4 groups according to Breslow thickness. Most of the cases presented with BT 3 and 4. For the purpose of analysis, groups 1 and2 and groups 3 and 4 were combined. As expected, increased thickness is poor prognostic factor. 53 of 64 patients were in group 2; 62% of them had poor prognosis. Only 27% of those in group 1 had poor disease outcome. This was found to be statistically significant ($p<0.05$).

Studies have shown that Breslow thickness have an effect on local, regional and systemic recurrence.[3]

Age group

Comparison between age group and prognosis showed worse prognosis for those in 60 and above age group. 60% of those in <60 age group had good prognosis while 56% of those in 60 and above age group were found to have poor prognosis. This difference was found to be statistically significant.[3-5]

Gender

Gender -prognosis cross-tabulation showed that, as much as 64% of male patients had poor prognosis while, only 48% of female patients had a poor disease outcome. This difference was found to be statistically significant ($p=0.038$ i.e. <0.05).

The incidence of melanoma is similar for women and men; however, there is a slightly greater risk for men.[3,6] Furthermore, for essentially all patient subgroups, the prognosis is better for women than men.[7-9]

Site of lesion

The site of the lesion was put into 3 categories: 1-extremities, 2- trunk, 3- head and neck. 94% of the cases had the lesion in the extremities-specifically the lower limbs. 4 patients had the lesion on the trunk. None of the patients had the lesion in the head and neck region. As there was such a big difference in distribution it was not possible to compare prognosis in the 2 groups.

Location of tumors has prognostic relevance in that head-and neck melanomas have poorer outcome than trunk or extremity melanomas.[9-11]

Nodal status

61% of cases presented with no nodal status; 79% of whom had good prognosis. As nodal status increased, more patients were seen to have poor disease outcome; with 100% of N3 patients having poor outcome. As expected this difference is statistically significant-$p=0.042$.

In the both previous version of the AJCC staging system and the new, (revised version), regional nodal tumor burden is the most important predictor of survival in patients without distant disease.[12]

Clarke's level

77% of the patients presented with Clarke's level 4 and 5 lesions-(44% and 33% respectively). These patients had much poorer prognosis, with distant metastases and/or local recurrence in 61% and 81% of these patients. This difference was found to be significant-$p=0.002$.

Marghoob et al, in an analysis based in 919 patients, with AJCC stage I and II disease found that level of invasion

was a significant predictor of death from melanoma in each of the four thickness categories. Their analysis of these patients, who were followed for an average of 10.9 years, revealed that both level and thickness were significant independent variables.[13]

Post-excision margins

Post-excision margins were taken as positive for patients with excision margins grossly positive or with clearance less than 1 mm. Most of the cases (87.5%) were f0Un (i to have resected margins free. The significance in the difference in prognosis could not be assessed due to the skewed nature of the data.

Ulceration

Microscopic ulceration was seen in 50 of the 64 cases, with 66% of these patients showing poorer prognosis. Of the 14 patients without ulceration, 79% had good prognosis. This was found to significant.

Ulceration of the primary lesson has been identified as an important negative prognostic features and is incorporated in the current staging system. In an analysis of prognostic features in more than 17,000 patients from many centers, the prognosis of an ulcerated lesion was comparable to that of a nonulcerate lesion, one T level, higher.[3]

Mitoses

Presence of mitoses more than 0-1/mm^2 was taken as 'high' mitoses. 63% of patients were found to have high mitoses; 78% of whom had distant metastases and/or local recurrence during follow-up. Only 21% of those with low mitoses had poor prognosis. This was found to be statistically significant.

Studies have shown that mitotic rate in the dermal component has poorer prognosis especially where 6 or more mitoses per mm.[4,5,14]

Lymphocytic invasion

Lymphocytic infiltrating tumor was found to be a good prognostic factor. Stromal infiltration of lymphocytes is quantified as 'brisk' or 'scanty'. 24 of 64 patients had brisk infiltration. Of these cases 75% had good outcome. Of the cases without infiltration, 75% had poor prognosis. This was found to be significant.

Studies show that 5-and 10-years survival rates for melanoma with a vertical growth phase and a brisk infiltrate were 77% and 55%, respectively. For tumors with a non–brisk infiltrate, the 5- and 10 years survival rates were 55% and 45%, respectively, and for tumors with absent tumor- infiltrating-lymphocytes, the 5 and 10 years survival rates were 37% and 27% respectively.[15]

Tumour vascularity

Increased tumour vascularity is a poor prognostic factor. Increased tumour vascularity was recorded in 23 cases, 91% of whom had poor prognosis. Of the cases with decreased tumour vascularity, 37% had poor prognosis. Chi-square test showed $p<0.001$- significant.

Lymphovascular emboli

Lymphovascularemboli is, as expected, a poor prognostic factor. 20 of 64 patients had LVE; of whom 95% had poor disease outcome. Only 39% of those without LVE had poor outcome.

There is evidence, and biologic rationale, that angiolymphatic invasion has negative prognostic significance and that microscopic satellites are associated with poorer prognosis.[3,5,16]

CONCLUSION

This study was conducted at Medical College, Kottayam, over duration of 3 months. It is a retrospective study. The case records and histopathological report of all patients with histologically proven malignant melanoma, treated in this hospital between January 2008 and December 2012 were studied and the cases followed up until October 2013.

There were 64 cases, 33 male and 31 female. There was a marked rise in incidence over the 5 years. A rapidly increasing incidence of the disease, as seen in western studies may be partly responsible for this difference; along with, this in our setting, better awareness and increased diagnosis of cases. May be contributing factor Males and females were seen to be almost equally affected.

Breslow thickness was, as expected, found to be an important prognostic factor. Patients with increased BT had a poorer disease outcome.

Several factors other than Breslow thickness were seen to have prognostic value. Disease outcome was seen to be worse in those above 60 years of age, male gender, Clarke's level 4 and above, high mitoses, ulceration, higher nodal status, absence of lymphocyte infiltration, lymphovascular emboli and increased tumour vascularity.

Certain differences were seen in this study when compared to western data. In studies done on predominantly white populations, site of lesions was more evenly distributed between the different areas i.e. extremities, trunk, and head and neck. Conversely, in this study, 60 of the 64 patients had lesions in the extremities, specifically in the lower limbs. Only 4 patients had lesions on the trunk, and none of the patients had head and neck lesions. Due to this disparity, the significance of site as a prognostic factor could not be assessed.

Like-wise, post-excision margins, as a prognostic factor, could not be assessed as most patients had free, margins.

Another glaring difference between western statistics and our figures was the high percentage of patients who presented with advanced lesions in our study. This shows the appalling lack of awareness in our population or delay in diagnosis.

Studies have shown that most melanomas have a period of radial growth before they become invasive. Such 'thin' melanomas have excellent prognosis; hence the need for urgent public education.

This study has lent further credence to the claim that factors other than Breslow thickness should also be used to asses prognosis in cases of malignant melanoma, and that this should influence the management plan.

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