Original Article

J Nepal Health Res Counc 2021 Apr-Jun;19(51): 300-4

DOI: https://doi.org/10.33314/jnhrc.v19i2.3086

Primary Cutaneous Melanoma in a Tertiary Hospital: A Retrospective Study

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ABSTRACT

Background: Malignant melanoma, the most aggressive form of skin cancer worldwide is much often talked about in the western world and in Caucasian population as it is seen to be a rare disease in South Asians. This study aims to provide a better assessment on the spectrum of cutaneous melanomas in our context.

Methods: This was a retrospective, 11-year hospital-based study done in the Department of Pathology, Tribhuvan University Teaching Hospital. The data collected included age, sex, anatomical site, Breslow thickness in millimeter, Clark's level of invasion, presence of ulceration, Tumor infiltrating lymphocytes and melanoma subtypes. The anova test was used to compare the relationship between age and staging, whereas pearson's chi square test was used to determine the relationships of sex and histopathological subtype with staging.

Results: Out of total, 44 cases of primary cutaneous melanoma were seen, 23 (52.27%) were males and 21 (47.27%) were females. The mean age was 61.29 year with the majority in the age groups 61–70 and 71-80 comprising 11 cases each (25%). Lower extremity was the most frequent site (23 cases, 52.27 %). The largest group (18 cases) was composed of Nodular melanoma, followed by acral melanoma (17 cases). Nodular melanoma tended to occur at a higher stage than other types. Age and sex showed no correlation with staging. A significant association was found with histopathological type.

Conclusions: Primary melanoma is a commonly encountered malignancy. It is commomly appreciated equally among both gender among elderly populations. Nodular melanoma present late and is the commonest variety with lower extremity being the commonest site

Keywords: Breslow thickness; clark's level; cutaneous melanoma; nodular melanoma

INTRODUCTION

Melanoma, the most lethal skin cancer arises from activated and genetically altered melanocytes, the pigment-producing cells.[1] Fair-skinned populations, Caucasians, men, and people living in regions of lower latitude have the highest incidence. Such neoplasms though have a higher predilection among geriatric age group, are also not uncommon in adolescent and young adult populations.[2] Ultraviolet radiation (UVR) is the primary environmental cause of Melanoma.[3] In addition, people with increased number of moles, dysplastic nevi, genetic susceptibility and a positive family history are at increased risk.[4-6] Cyclin-dependent kinase inhibitor 2A(CDKN2A), Cyclin-dependent kinase CDK4, Tumor suppressor genes (PTEN, NF1) and protooncogenes (BRAF, NF1) and TERT mutations are implicated in the pathogenesis.[6] Cutaneous melanomas, though represent 5% of the skin cancers, make up for about 80% of deaths.[4] The four major subtypes include superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), and acral lentiginous melanoma (ALM).[7]

Malignant melanoma, the most aggressive form of skin cancer worldwide is much often talked about in the western world and supposedly to be a rare disease in Asians. Not many studies have been conducted till date stating the incidence of the same in Nepalese population. There are limited studies on melanoma conducted in Nepal so far. This study aims to determine the frequencies and analyze the pathological characteristics of primary cutaneous melanoma in in our center.

METHODS

A retrospective study was conducted to characterize cutaneous melanoma cases diagnosed from January 2009 to December 2019 (11 years) at Tribhuvan university teaching Hospital (TUTH), the largest referral center in Nepal. Ethical approval was obtained from Institutional

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Review Board of the Institute of Medicine. All confirmed, primary cutaneous malignant melanoma cases during the study period were retrieved. The data collected included age, sex, anatomical site, Breslow thickness in millimeter, Clark's level of invasion, presence of ulceration, Tumor infiltrating lymphocytes (TIL's) and melanoma subtypes. Anatomic sites were grouped as head and neck (including face), trunk, upper extremities, lower extremities and unspecified. Cases were further classified as nodular melanoma (NMM), superficial spreading melanoma (SSM), acral lentiginous melanoma (ALM) and lentigo maligna melanoma (LMM). Breslow thickness was categorized into four groups (≤1.00 mm, 1.01-2.0 mm, 2.01-4.0 mm, > 4.0 mm for pT1, pT2, pT3 and pT4 respectively) to determine the T stage as per the pTNM staging. The level of invasion was determined as defined by Dr. Wallace Clark (level I—confined to the epidermis, level II—invasion of the papillary dermis, level III—invasion to the papillary/reticular interface, level IV—invasion to the reticular dermis, level V—invasion to the subcutaneous tissue).[8] The anova test was used to compare the relationship between age and staging, whereas pearson's chi square test was used to determine the relationships of sex and histopathological subtype with staging. P-values <0.05 were considered to indicate statistical significance. Melanoma staging was performed according to CAP protocol. Data entry and analysis were made using Excel/SPSS software program and was depicted in tables as means and percentages.

RESULTS

Our study included 44 cases diagnosed in the study period. The age of the patients ranged from 12 to 93 years with mean age and median age being 61.29 years and 64.50 years, respectively. There were 23 (52.27%) males and 21 (47.27%) females with no obvious gender predilection and male to female ratio being 1.09:1. The cases peaked in the age groups 61-70 and 71-80 years comprising 11 (25%) cases each. (Figure 1)

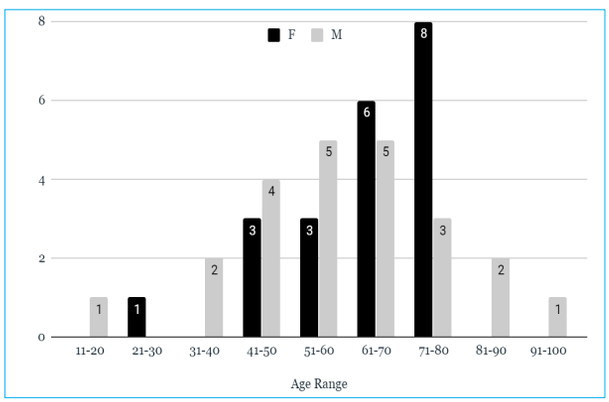

Figure 1. Age distribution of patients (n=44).

The most common site of primary tumors was the lower extremity (23 cases, 52.27 %), followed by head and neck (9 cases, 20.45%), upper extremity (5 cases, 11.36%), trunk (4 cases, 9.09%) and unspecified (3 cases, 6.81%). Out of 23 cases in lower extremities, 15 cases (34.10%) were noted on the soles. Correlating sites with gender, the commonest sites among both males and females in the current study were lower extremities with 12 and 11 cases respectively (Table 1)

Table 1. Melanoma distribution by anatomical sites and gender.

Anatomical site	Male	Female	Total
Lower extremity	12(52.17%)	11(52.38%)	23(52.27%)
Trunk	2 (8.69%)	2 (9.52%)	4(9.09%)
Head and neck	4 (17.39%)	5 (23.80%)	9(20.45%)
Unspecified	2 (8.69%)	1 (4.76%)	3(6.81%)
Upper extremity	3 (13.04%)	2 (9.52%)	5(11.36%)
	23 (100%)	21 (100%)	44 (100%)

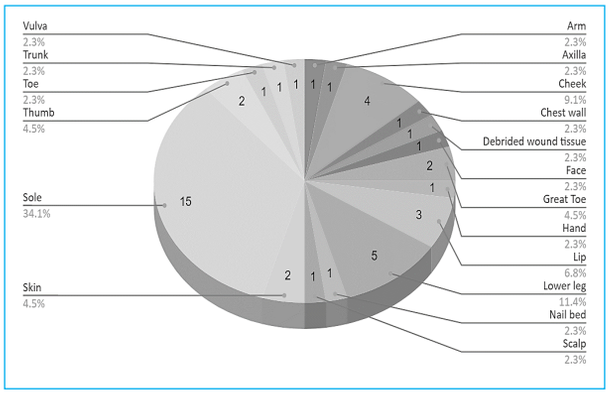

Figure 2. Site distribution of all cutaneous melanomas.

Regarding histopathological subtypes, the largest group (18 cases, 40.90%) was composed of Nodular melanoma, followed by acral melanoma (17 cases, 38.63%), superficial spreading melanoma (5 cases, 11.36%), and lentigo maligna melanoma (4 cases, 9.09%). (Table 2)

Table 2. Melanoma distribution by histopathological subtypes.

Histopathological types	Frequency (n=44)	Percentage (%)
Nodular melanoma	18	40.90
Acral melanoma	17	38.63
Superficial spreading melanoma	5	11.36
Lentigo maligna melanoma	4	9.09
Total	44	100

Breslow's thickness, Clark's level of invasion, TIL's,

status of epidermis (Presence/absence of ulceration) and pathological stage were assessed only in excisional biopsies.

14 cases of the 27 cases (51.85%) had Breslow thickness of ≥ 4.01 mm (corresponding to pT4 in the pathologic TNM staging). The Breslow thickness was not applicable in 2 cases (Being in situ), ≤ 1mm in 5, 1.01–2.00 mm in 4, and 2.01–4.00 mm in 2 corresponding to pTis, pT1, pT2 and pT3 respectively. Similarly, the Clarks level of invasion was also assessed in all cutaneous melanoma cases and 8 cases were each seen to have Clark level III and V respectively, 6 cases had Clark level IV, 3 cases had Clark level II and 2 cases had Clark level I. No significant relationships were observed between sex and staging (P = 0.379), age and staging (P = 0.598). However, a significant relationship was observed between histopathological subtype and staging (P =0.015).

Breslow's thickness, Clark's level of invasion, status of epidermis (Presence or absence of ulceration), Tumor infiltrating lymphocytes are depicted in Table 3.

Table 3. Distribution of Clark's level, Breslow's thickness, epidermal ulceration, pathological stage, and TILs in cutaneous melanoma (Excisional biopsies)

Particulars		Frequency (n)	%
Clark's Level	I	2	7.4
	II	3	11.11
	III	8	29.62
	IV	6	22.22
	V	8	29.62
Breslow Thickness	In situ	2	7.4
	≤1 mm	5	18.51
	1.01–2.00 mm	4	14.81
	2.01–4.00 mm	2	7.4
	≥4.01 mm	14	51.85
Ulceration	Present	13	48.14
	Absent	14	51.85
Pathological Stage	pTisNx	2	7.4
	pT1Nx	5	18.51
	pT2Nx	4	14.81
	pT3Nx	2	7.4
	pT4Nx	14	51.85
	NA	2	7.4
Tumor Infiltrating Lymphocytes	Absent	11	40.74
	Present, Brisk	2	7.4
	Present, Non-Brisk	12	44.44

DISCUSSION

There exists a limited body of literature on melanomas carried out in Nepal. We describe here the compilation of the data regarding primary cutaneous melanoma patients in the country. These data were obtained from TUTH, the largest tertiary care center in Nepal.

Our study included 44 cases diagnosed during the period of 11 years (2009 to 2019) and age ranged from 11 to 93 years. In a study done by Thapa S et al. in Nepal, 35 cases of melanoma were seen in a duration of 13 years. with age range from 15 to 84 years.[9] Likewise, in a study done by Kyung Wook Nam, 100 cases were identified over the course of 13 years and age ranged from 21-83 years.[10] In a study done by Curchin et al. in Victoria, a total of 58 497 tumors were seen in a duration of 15 years.[11] Such huge differences in the number of cases between different studies of different countries could be due to higher incidence rates in fair- skinned population.

Malignant melanoma affects predominantly adults and elderly patients and according to WHO, peaks around the 6th decade.[12] This statement was consonant with our results as the mean age at diagnosis was 57 years, with a peak in the 6th and 7th decades of life.

Our study that embodied 44 cases, 23 (52.27%) were males and 21 (47.27%) females with no obvious gender predilection with male to female ratio being 1.09:1. The observation was similar to the study done by Sharma K et al. in India and in Spain by Nagore E et al. with male to female ratio being 1.25: 1 and 1:1.2 respectively.[13,14]

Correlating sites with gender, the commonest sites among both males and females in the current study were lower extremities with 12 and 11 cases respectively. The findings were congruent with the study done in Malawi.[15] In a study done in Nepal, the most frequent sites in males and females were lower extremities and trunk respectively.[9] On the contrary, in western studies conducted in Joinville, Australia, Spain and England, trunk and lower extremities were the most common sites in males and females respectively.[11,14,16, 17]

In our study, 23 cases (52.27%) of all cutaneous melanomas were located in the lower extremity similar to the study done in South Korea and Malawi.[10,15] Sole accounted for 15 cases followed by lower leg and toe with 5 and 3 cases respectively. This was followed by head and neck (9 cases, 20.45%), upper extremity (5 cases, 11.36%), trunk (4 cases, 9.09%) and unspecified (3 cases, 6.81%).

Tumor thickness and ulceration are the dominant independent prognostic factors in cutaneous melanoma. Tumor depth is measured in millimeters from the base of the ulcer or granular layer of the epidermis to the deepest extent.[18] The maximum Breslow thickness of ≥ 4.01 mm (corresponding to pT4 stage) were seen in 14 cases and 9 of these cases were nodular melanomas. Many studies have described that nodular melanoma is associated with a poor prognosis which corresponds to our results where nodular melanoma was associated with a relatively high stage.[10,19] Two of the 27 cases with excisional biopsy involved in situ melanoma corresponding to pTis. The Breslow thickness was ≤ 1mm in 5 patients, 1.01-2.00 mm in 4 patients, 2.01-4.00 mm in 2 patients corresponding to pT1, pT2 and pT3 respectively.

In our study, 13 cases had epidermal ulceration corresponding to a higher stage. The presence of ulceration reflects an aggressive tumor associated with a poorer prognosis.[20] Histologically, ulceration denotes the absence of an intact epidermis overlying a portion of the primary tumor.

The Clark level has been used to describe the anatomic involvement of the tumor within the cutaneous and subcutaneous structures.[18] In the present study, majority of 8 cases (29.62%) were each seen to have Clark's level of invasion III and V respectively. This was similar to the study done by H J Wanebo et al with maximum cases to have Clark's level of invasion V.[21] Likewise, 6 cases were Clark's level IV, 3 cases were Clark's level II and 2 cases were Clark's level I in our study.

In the current study out of 23 cases of excisional biopsy, 2, 11 and 12 cases had brisk, absent and non-brisk TILs respectively. An article by Thomas et al. described TILs in 2,845 patients where they elucidated a definite survival benefit found with brisk and non-brisk TILs versus those with absent TILs.[22] Melanoma has been considered as an immunogenic malignancy containing number of immune cells and reflects a communication between host and tumor. The prognosis of patients with brisk inflammatory infiltrate is significantly better than that of patients with non-brisk or absent TIL.[23,24]

This being a single institutional study, the data may not reflect the incidence in population of Nepal. Hence, further research in a larger sample size should be conducted. This study did not look into the outcomes and survival of this malignancy. This could be an area of future research to better manage such malignancies.

CONCLUSIONS

Cutaneous melanoma may be an under-appreciated malignancy in Nepalese population as they constituted approximately 0.09% of the total biopsies received. Primary melanoma is a commonly encountered malignancy. It is commomly appreciated equally among both gender among elderly populations. Nodular melanoma present late and is the commonest variety with lower extremity being the commonest site.

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Competing interests: None declared

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