

Patients' Characteristics, Histopathological Findings, and Tumor Stage in Different Types of Malignant Melanoma: A Retrospective Multicenter Study

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Abstract- Cutaneous malignant melanoma (CMM) is currently the most fatal of skin cancers accounting for 50000 deaths annually. Five distinct melanomas are described histopathologically: superficial spreading, lentigo maligna, nodular, acral lentiginous and mucosal melanoma. The aim of this study was to investigate the characteristics of patients with various types of malignant melanoma and evaluate histopathological findings. In this retrospective study, we obtained our data from the records of 111 patients with melanoma. Biopsied specimens were collected and re-evaluated. Demographic information and histopathological findings were noted. SPSS 16 was used for analyzing data. Chi-square and one-way ANOVA was conducted for comparing categorical and numerical variables respectively. The mean age of patients was 59.33±14.68 years old. Most common melanoma type was acral lentiginous (40.5%), followed by nodular (35.1%) and mucosal (10.8%). The highest tumor thickness was viewed in nodular melanoma followed by mucosal melanoma. The highest rate of metastasis, microsatellitosis, perineural invasion and Clark level of the invasion were reported in nodular and acral lentiginous respectively. The most frequent rate of ulceration and vascular invasion was reported in mucosal melanoma. Distribution of melanoma types varies largely in different regions. Lack of classic presentations in some types necessitate specific public education about warning signs. Histopathological and pathological characteristics in melanoma can aid in better staging and management of the tumor.

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Keywords: Melanoma; Mitotic rate; Vascular invasion; Microsatellitosis; Tumor stage

Introduction

Malignant melanoma is the most fatal skin cancer causing around 50,000 deaths annually (1). The incidence of malignant melanoma has shown a steady increase in recent years. This has resulted in stable mortality despite better case management and improved prognosis (2). Current strategies for melanoma reduction may not show their effects in recent future (3). Melanoma accounts for a small percentage of skin cancers. However, it often causes death more than all other non-melanoma skin cancers (4). Considering high incidence and premature mortality, average of years of potential lost life due to melanoma is one of the highest in cancers in adults (5). Five distinct melanomas are described histopathologically: superficial spreading, nodular, lentigo maligna, acral lentiginous and mucosal

melanoma. It's not completely proven if this categorization conveys a significant prognostic value, but acral lentiginous melanoma seems to have the worst prognosis among cutaneous melanomas due to late diagnosis (6).

Superficial spreading melanoma is the most prevalent type seen in Caucasian populations. This type has a primary horizontal growth which may last from months to years. The superficial spreading tumor can be present on any site, but usually, it occurs on the back in males and on the legs in females. Acral lentiginous melanoma is mainly present on the palms, soles of the feet and under the nails. This type of melanoma is the most prevalent type found in Chinese and Japanese people. Nodular melanoma grows rapidly as a nodule which may or may not be pigmented. This lack of pigmentations in some cases mitigates the efficacy of

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classical criteria for the diagnosis of melanoma. Lentigo malignant melanoma is tumor of a sun-exposed area such as the scalp and face, usually seen in the elderly. A precursor of this type is sometimes referred to lentigo maligna symptomized initially by a freckle-like lesion which gradually grows and becomes darker (7-9). Mucosal melanoma originates from melanocytes in mucosal membranes of respiratory, gastrointestinal and urogenital tracts. UV does not play a role in mucosal melanoma unlike most cases of skin melanoma (10).

However, different items such as age, sex, and site have been implicated for determining prognosis in different types and stages of melanoma. The single most important prognostic factor is tumor thickness. Survival decreases with tumor thickness, and a linear relation between tumor thickness and the survival rate is assumed (11,12).

Accurate staging and determining tumor spread is essential for determining prognosis and choice of treatment. American staging method for melanoma is based on the regional lesion, lymphatic spread, and distant metastasis. This method was revised in 2001 (13). For accurate clinical and research purposes, it's also necessary to categorize tumors in a suitable histologic group and determine thickness, mitotic rate, lymphovascular invasions and presence of inflammatory cells.

Treatments usually include resection of the lesion with a safe margin in early melanoma. In advanced diseases, immunotherapy and chemotherapy may help for improving survival.

We investigated patients' demographic information and histopathological characteristics of various types of melanomas and evaluated the relationship of these findings to types of melanoma.

Materials and Methods

This was a retrospective multi-centered investigation. Data were obtained from retrospective

records of all patients with melanoma in Razi Dermatology Hospital and Cancer Institute (Imam Khomeini Hospital Complex) in two years. These two hospitals are tertiary reference centers in the country. Specimens were collected and re-evaluated by a dermatopathologist (AG). All specimens were investigated anonymously, and responsible dermatopathologist was not aware of the purpose of the study.

Demographic information of each patient including age and sex was enrolled. Pathologic features of Mitosis, Breslow's thickness; Clark's level of invasion, vascular invasion, perineural invasion, and metastasis and ulcer status was recorded. Based on American Joint Committee on cancer staging system for melanoma guidelines, tumor stage was configured. For determining number of mitosis in square millimeters, we considered the area with most mitotic count (hot spot area).

We used SPSS version 16 for data analysis. We conducted chi-square test to compare categorical values and one-way ANOVA to compare numerical values between different melanoma types. *P* of less than 0.05 was considered significant for all tests.

Results

The mean age of 111 patients was 59.33±14.68 years old, and the median age was 60. The oldest group was lentigo malignant melanoma patients. Man to woman ratio in our study was 1.09 (58 and 53 men and women respectively). Highest man to woman ratio was reported in nodular melanoma. Age and sex ratio difference between different melanoma types was not statistically significant. (*P*:0.68 and 0.26 respectively) (Table 1).

The most common type of melanoma seen in our study was acral lentiginous melanoma accounting for 40.5 % of cases, followed by nodular melanoma. The least prevalent melanoma in our study was superficial spreading melanoma (Figure 1).

Table 1. Age and sex of patients in different types of melanoma

Patients (N)	Acral (45)	Nodular (39)	Lentigo maligna (9)	Superficial spreading (6)	Mucosal (12)	Total (111)	<i>P</i>
Age	59.89±13.96	57.59±15.31	65.56±13.12	59.67±17.04	58.08±16.23	59.33±14.68	0.68
Male/female ratio	1.05	1.79	0.5	1	0.50	1.09	0.26

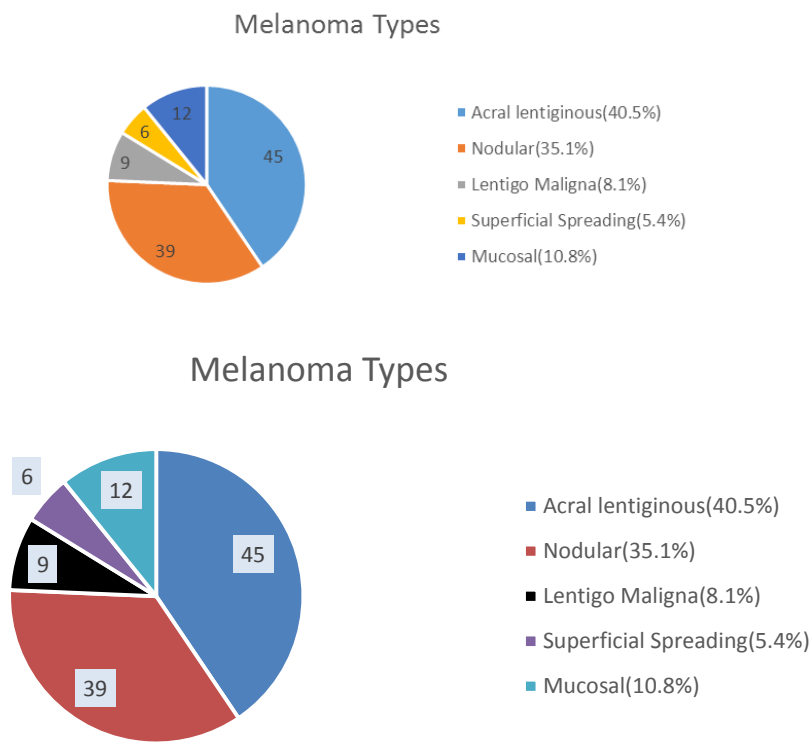


Figure 1. Prevalence of different melanoma types

In 55.86% of patients, ulceration was viewed. Ulceration was reported in 91.7%, 66.7%, 53.3% and 11.1% of mucosal, nodular, acral lentiginous and lentigo malignant melanoma, respectively. No ulceration was

seen in the superficial spreading group. There was a statistically significant relationship between ulceration and melanoma type (Table 2).

Table 2. Frequency of ulceration, microsatellitosis, vascular invasion, perineural invasion, metastasis, mitotic rate and tumor thickness in 111 melanoma patients categorized by type of melanoma

Histopathological findings	Acral	Nodular	Lentigo maligna	Superficial spreading	Mucosal	Total	p
Ulceration	24 (53.33%)	26 (66.67%)	1 (11.1%)	0 (0%)	11 (91.7%)	62 (55.86%)	0.00
Microsatellitosis	11 (24.4%)	14 (35.9%)	1 (11.1%)	0 (0%)	0 (0%)	26 (23.42%)	0.06
Vascular invasion	4 (8.9%)	17 (46.3%)	0 (0%)	0 (0%)	6 (50%)	27(24.32%)	0.00
Perineural invasion	4 (8.9%)	10 (25.6%)	1 (11.1%)	0 (0%)	1 (8.3%)	16 (14.41%)	0.16
Metastasis	8 (17.78%)	16 (69.57%)	1 (11.1%)	0 (0%)	2 (16.67%)	27 (24.32%)	0.038
Number of mitosis	2.84±1.75	4.33±2.88	1.75±1.39	1.83±0.75	5.00±3.62	3.47±2.58	0.001
Tumor thickness	4.03±3.74	15.09±17.51	2.65±7.26	1.85±1.73	9.46±6.68	8.27±12.20	0.00

Microsatellitosis was seen in 23.42% of patients. Almost all patients with microsatellitosis (96.1%) were in the acral or nodular groups. Relationship of microsatellitosis and melanoma type was marginally insignificant (Table 2) means Clark level in those with microsatellitosis was significantly higher than the other groups ($P:0.00$). Vascular invasion was seen in 46.6% of the cases with microsatellitosis compared to 18 % of patients without microsatellitosis. ($P:0.005$) Perineural invasion in those with or without microsatellitosis was 30.76% and 9.63% respectively ($P:0.13$).

Vascular invasion was reported in 24.32% of patients. Half the patients in the mucosal group had vascular invasion. No vascular invasion was seen in lentigo maligna or the superficial spreading group. There was a significant relationship between vascular invasion and melanoma type (Table 1). 14.41% of all patients had perineural invasion. Most cases of perineural invasions were seen in nodular and acral groups; however, the relation between perineural invasion and melanoma type was not determined statistically significant (Table 2).

24.32% of patients had metastasis. Most metastases was seen in nodular and acral melanomas while no metastasis was reported in the superficial spreading

group. There was a significant relationship between melanoma type and metastasis (Table 2).

The highest mitotic figure was seen in mucosal melanoma followed by the nodular type. Mean count of mitotic figures in all melanomas was 3.47. Relationship of melanoma type and mitosis were statistically significant (Table 2). The highest Clark level of invasion was determined in nodular melanomas. Clark level difference was statistically significant. ($P:0.00$) (Figure 2).

Mean tumor thickness in all patients was 8.27 mm. This variable was 15.09%, 9.46%, 4.03%, 2.65% and 1.85% in nodular, mucosal, acral lentiginous, lentigo maligna and superficial spreading types, respectively. Most and least thickness was observed in nodular and superficial spreading types, respectively. There was a significant relationship between melanoma type and tumor thickness ($P<0.005$).

In the staging of melanoma tumors specimens, stage I and II were the most prevalent ones. Most patients with acral, nodular and mucosal melanoma were in stage II. However, Stage I was more common in lentigo maligna and superficial spreading melanoma (Table 2). The relation between melanoma type and stages of cancer was statistically significant ($P:0.001$) (Figure 3).

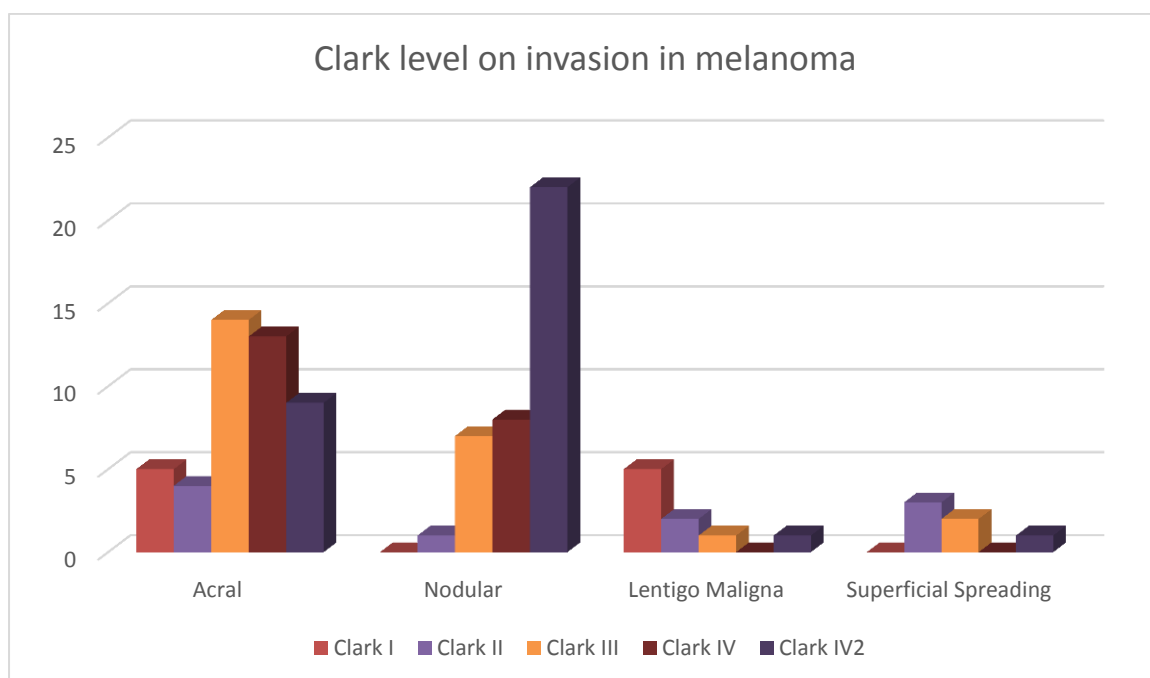


Figure 2. Clark level of invasion in different types of melanoma

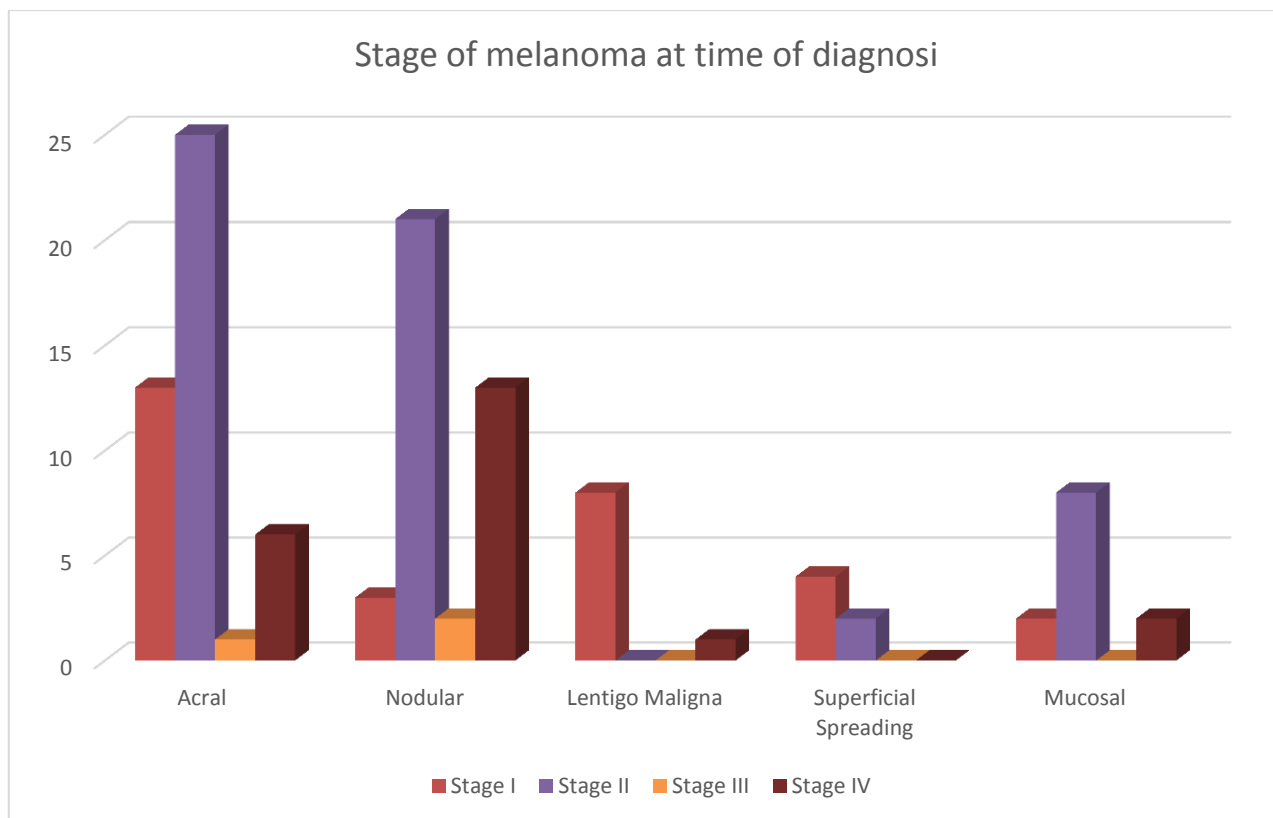


Figure 3. Stage of melanoma at time of diagnosis in different types of melanoma

Discussion

Mean and median age of melanoma patients in our study was 59.33 ± 14.68 and 60-year-old. This finding is similar to other studies. In a population based registry investigation by Porcia, mean age was 58.5 for cutaneous malignant melanoma and 62.8 for just acral lentiginous melanoma (14). In another study on different ethnic groups, mean age was 52 to 63 in different groups (15). The age difference between types of melanoma was not significant in our study.

Male to female ratio in our study was 1.09. Generally, melanoma affects men more than women and being male is a risk factor for melanoma (2). Some studies have shown a rapid increase in the incidence of melanoma in women in recent years (16). A higher incidence of malignant melanoma in women is reported in some ethnic groups (15). Also, sexual difference in the incidence of melanoma is believed to be age related. In the United States, the prevalence of melanoma in females is more than males in those younger than 49, but prevalence in males rapidly increases after the age of 50 (17). Male to female ratio difference was least in mucosal type between all the types scrutinized in our study. This is possibly due to high female genital

mucosal melanomas. In other studies, a similarly high rate in women was seen. However, the incidence of non-genital mucosal melanoma is similar between that of males and females (18).

In our study, the most and least common types of melanoma were acral lentiginous melanoma and superficial spreading melanoma, respectively. This finding is in contrast with white populations in other studies. In the Caucasian population, acral melanoma has a prevalence of 2 to 13%. The highest proportion of acral lentiginous melanoma is seen in the African-American population, followed by the Asian and Hispanic populations. However, this higher proportion does not necessarily mean a higher incidence. Overall malignant melanoma is far less common in darker skin pigmented populations (19). In the United States, superficial spreading is the most common type followed by lentigo maligna, nodular and acral lentiginous melanoma (20).

Timely diagnosis is a key factor for the successful management of melanoma (21). Diagnosis of melanoma in later stages also greatly increases the economic impact of melanoma management. In our study, most patients were diagnosed with stage II. Patients with acral, nodular and mucosal melanoma were in higher

stages compared to other melanoma types. Whereas patients with superficial spreading and lentigo maligna were mostly diagnosed in stage I. similar findings, have been reported in other studies but the mean stage at the time of diagnosis was determined to be higher in our study. In a similar study, most patients with nodular and acral melanoma presented in stage II, but most common stage presentation for superficial spreading and lentigo maligna was stage I. Stage III, and IV was reported more in nodular and acral lentiginous (20). Late diagnosis is also associated with higher tumor thickness in nodular melanoma (22). The difference in most common types of melanoma in a region can affect the overall stage of patients. In another study, overall stage at the time of diagnosis in populations with higher superficial spreading and lentigo maligna was lower compared to our study. This advanced stage at the time of diagnosis can result in decreased survival in our region.

Nodular melanoma is associated with most metastasis and higher stage at the time of diagnosis. This can be attributed to lack of classic ABCD diagnostic criteria resulting in later diagnosis of nodular melanoma. (23,24) However, localized melanoma can be treated by surgery; the presence of metastasis in melanoma would complicate management and decrease survival (25). In addition to the lack of classic features, many factors are implicated in delay for diagnosis such as the presence of lesion in a less noticeable area and rapid depth growing. Acral lentiginous melanoma is usually found on the soles of the feet and palms of the hands (26).

Microsatellitosis was observed in 23.9% of patients in our study. This rate is much higher compared to other studies. Microsatellitosis in two other studies was seen in 4.3% (27) and 6% (28) of the patients. This finding can be explained by a higher ratio of acral and nodular melanoma and a lower ratio of superficial spreading melanoma in our population. None of the patients with superficial spreading melanoma had microsatellitosis. Higher Clark level and tumor thickness are reported in patients with microsatellitosis. Microsatellitosis is also related to increased ulcer and lymphovascular invasion (28). This is consistent with our findings. We found greater Clark level, more vascular and perineural invasion and metastasis in those with microsatellitosis.

Mitotic rate is increasingly being identified as a prognostic factor, especially in thin melanoma (29). Mitotic rate was highest in mucosal, nodular and acral melanomas respectively in our study. The highest tumor thickness was seen in nodular melanoma. Nodular melanomas may be symmetric, elevated, and with

homogenous color. These atypical features for melanoma have resulted in less success in decreasing the thick melanomas in recent years despite general public knowledge. Earlier biopsy and increasing public awareness may be useful in decreasing this rate (23,30).

Ulceration has a prognostic value in malignant melanoma. It's also suggested to be a predictive marker for response to adjuvant interferon therapy. Also, some authors have suggested the need for further stratification of ulceration (31,32). In our study, most of the patients with mucosal, nodular and acral melanoma had ulceration at the time of diagnosis. This may be another factor for describing poor prognosis in these kinds of melanoma.

Distribution of melanoma types varies largely in different regions. Since these types are different in presentation and prognosis, preventive measures in each area also should be based upon common presentations. Acral lentiginous and nodular melanoma are the most common melanoma types in our study, which are not usually diagnosed timely. Histopathological and pathological characteristics in melanoma can aid in better staging and management of the tumor.

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