RESEARCH ARTICLE

A Retrospective Multicenter Evaluation of Cutaneous Melanomas in Turkey

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Abstract

Background: We defined melanoma distribution in a large series of Turkish patients and evaluated the prognostic parameters of melanomas. Materials and Methods: A total of 1574 patients' data was retrospectively collected at 18 centers in Turkey. Demographic characteristics were questioned and noted. Prognostic parametres were evaluated based on sentinel lymph node involvement. Results: Mean age was 56.7 (4-99) years. While 844 (53.6%) cases were male, 730 (46.4%) cases were female. One thousand four hundred forty-seven (92%) cases were invasive melanoma and 127 (8%) cases were in-situ melanoma. The most common histopathological form was the superficial spreading melanoma (SSM) which was found in 549 patients (37.9%). It was followed by nodular melanoma in 379 (26.2%), acral lentiginous melanoma (ALM) in 191 (13.2%) and lentigo maligna melanoma in 132 (9.1%), respectively. On univariate analysis, lymphovascular invasion (p<0.001), tumor thickness (p<0.001), histopathological subtype (p<0.001), Clark level (p=0.001), ulceration (p<0.001), ≥6/mm^2 mitosis (p=0.005), satellite formation (p=0.001) and gender (p=0.03) were found to be associated with sentinel lymph node positivity. Regression was associated with sentinel lymph node negativity (p=0.017). According to multivariate analysis, lymphovascular invasion and tumor thickness were significant independent predictive factors of SLN positivity. Patient age, tumor localization, precursor lesions, lymphocytic infiltration and neurotropism were not related with sentinel lymph node involvement. Conclusions: In this retrospective analysis, it was found that the prevalence of SSM is at a lower rate while the prevalence of ALM is at a higher rate when compared to western countries. According to Breslow index; most of the melanoma lesions' thickness were greater than 2 mm, corresponding Clark IV. Vascular invasion and tumor thickness are the most important factors for sentinel lymph node involvement.

Keywords: Melanoma - skin - prognostic factors

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Introduction

Malignant melanoma (MM) is one of the most aggressive tumors with high metastatic potential. Also the incidence of MM has increased in recent years (Simard et al., 2012; Gajda and Kaminska, 2014). According to the GLOBOCAN-2012, the incidence of melanoma is highest in Australia/ New Zealand: 10.5 new cases in men and 10 in women, annually, per 100,000. The incidence in Northern America is 4.7/100,000 for men and 3.6/100,000 for women, in Euorope it is 2.9/100,000, in Latin America and Carribean 1.3/100,000 in Africa 0.8/100,000 and in

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Asia it is 0.3/100,000 in descending order (Ferlay et al., 2013). It is estimated that there are 752 new MM cases in men and 800 new MM cases in women in Turkey. 630 cases were died because of MM (Ferlay et al., 2013). Its incidence ranges from 0,7 to 2,3 in Turkey, per 100,000 (Eser et al., 2010; Ferlay et al., 2013).

Growth phase (vertical or radial) that is the first important morphological prognostic factor is used to distinguish between melanoma in-situ (Mis) and MM. Staging system published in 2009 by American Joint Committee on Cancer (AJCC) has also been frequently used nowadays for MM (Balch et al., 2009).

Histopathologically, Breslow tumor thickness, mitotic rate, and presence or absence of ulceration are the most important prognostic and staging factors in MM (Balch et al., 2009). In addition these parameters, level of invasion (Clark method), lymphovascular invasion, perineural infiltration, regression, microsatellitosis and tumor infiltrating lymphocytes are generally accepted criteria in a routine pathology report (Frishberg et al., 2009).

As Turkish dermatopathology study group, we believe that our study is the largest series from Turkey with its detailed histopathological results. The main goal of this study was to display the descriptive statistics of clinical and histopathological profile of primary cutaneous melanoma in Turkish patients in a period of five years (2008-2012), and to compare them with data of literature. In addition, we evaluated the prognostic factors based on the SLN involvement.

Materials and Methods

Appropriate permission for the study was obtained from Ethic Committee of Hacettepe Medical Faculty (approval no: GO 14/03-47). The study was designed as a retrospective clinical and histopathological features on cutaneous MM patients. Firstly prognostic parameters were determined and sent to the participants of Turkish dermatopathology study group. Then a common database was created by email from participants. One thousand five hundred seventy-four patients to whom performed excisional biopsy between 2008 and 2012 selected in the study. Non-cutaneous MM is excluded from the study.

Variables consisted of clinical features of the patients (age, gender and localization), current published prognostic and predictive factors including histological subtype, presence or absence of ulceration, Breslow tumor thickness, Clark level of invasion, pT, neurotropism, satellitosis (absent, microsatellitosis or macrosatellitosis), growth phase (radial, vertical or both of them), regression (absent, mild: ≤50%, moderate: >50% or complete), lymphocytic infiltration (absent, nonbrisk or brisk), precursor lesions and treatment (surgical excision, presence of sentinel or other lymph node dissection).

The age of patients were classified into three different groups: ≤20, 21-40 and ≥41 years old. Primary tumors were categorized into seven distinct groups based on the anatomical sites: head and neck, front side of the trunk, back side of the trunk, upper extremities, lower extremities, scalp, axillary-pubic region. According to the AJCC staging system, tumor thickness was classified into four groups: 0-1mm, >1-2 mm, >2-4 mm and >4mm. The level of tumor invasion was also categorized by using Clark level system. The histological subtype of primary tumor was grouped based on WHO classification: superficial spreading melanoma, nodular melanoma, lentigo malign melanoma, acral lentiginous melanoma, desmoplastic melanoma and neurotropic melanoma, melanoma arising from blue nevus, melanoma arising in giant congenital nevus, childhood melanoma, nevoid melanoma, persistent melanoma and local metastasis of melanoma and unclassified type

Statistical analysis: After the all data were enterred into computer, they were assessed by SPSS for Windows version 15.0 (SPSS Inc. Chicago, IL, US). Frequency, percentage, average and standard deviation were given as a descriptive statistical value. Differences between groups were tested for significance by chi-square test. Logistic regression analysis was also used to investigate the multivariate relationship of clinical and pathologic factors predicting SLN positivity. Differences were considered as significant at $P<0.05$.

Results

Between 2008 and 2012, a total of 1574 patients' data was sended from 18 centers in Turkey. Mean age was 56.7 (4-99) years. Twenty-six cases (1.7%) were 20≤ years old. Two hundred and sixty-six cases (17%) were between 21-40 years old. One thousand two hundred eighty-two cases (81.4%) were 41≥ years old. While 844 (53.6%) cases were male, 730 (46.4%) cases were female. One thousand four hundred forty-seven (92%) of 1574 cases were invasive melanoma, 127 (8%) cases were melanoma in-situ. The most common Mis form was lentigo maligna (70; 55%), followed by superficial spreading type Mis (39; 31%), unclassified type Mis (14; 11%) and acral lentiginous type Mis (4; 3%).

In following years, according to our database there were 383 MM cases in 2008, 261 cases in 2009, 308 cases in 2010, 293 cases in 2011 and 329 cases in 2012, respectively. The most common site of MM was lower extremity (27.3%), followed by head and neck (25.7%), and trunk (23.1%). The lower extremity was the most common localization in both sexes (Table 1). The most common histopathological form was the superficial spreading melanoma (SSM), which was found in 549 patients (37.9%), followed by nodular melanoma (NM) in 379 (26.2%), acral lentiginous melanoma (ALM) in 191 (13.2%), lentigo maligna melanoma (LMM) in 132 (9.1%) , nevoid melanoma in 16 (1.1%), persistent melanoma in 14 (1%), desmoplastic melanoma in 10 (0.7%), melanoma developing from congenital nevus in 9 (0.6%), melanoma developing from blue nevus in 5 (0.3%), childhood melanoma in 6 (0.4%) and unclassified type in 136 (9.4%) (table 2).

While the median Breslow thickness was 2,7 mm, majority of tumors were in Clark level IV (650; 44.9%). pT4b (363; 25.1%) was the most common stage. Ulceration was present in 651 (45%) cases. While majority of MMs (51.3 %) showed non-brisk lymphocytic infiltration, 31.3% of MMs possessed brisk lymphocytic

infiltration. Lymphovascular invasion were seen in 10.6% of all cases. Microsatellite formation was observed in 5.4%, whereas macrosatellit formation was seen in 1.4% of cases. Partial, marked and complete regression was present in 18.2%, 3.1% and 0.4% of cases, respectively. Neurotropism was found in 18.3% of all cases. The most common precursor lesion was ordinary nevus (9.1%), followed by dysplastic nevus (5.3%), congenital nevus (0.6%) and blue nevus (0.3%).

SLN biopsy was performed in 417 patients. Metastases of SLN was noticed in 37.2% (155/417) of these patients. Lymphadenectomy was performed in 302 cases. Metastases of other lymph nodes were detected in 48.3% (146/302). All parameters compared to SLN positive and negative patients. On univariate analysis, lymphovascular invasion ($p<0.001$), tumor thickness ($p<0.001$), histopathological subtype ($p<0.001$), Clark level ($p=0.001$), ulceration ($p<0.001$), ≥6/mm^2 mitosis ($p=0,005$), satellite formation ($p=0.001$) and gender ($p=0.03$) were found to be associated with SLN involvement. Regression was associated with SLN negativity ($p=0.017$). On multivariate analysis, independent characteristics of the melanoma among the prognostic variables were lymphovascular invasion and tumor thickness (table 3). SLN involvement was not statistically significant relation with age, tumor localization, lymphocytic infiltration, precursor lesions and neurotropism.

Table 1. Anatomic Distribution of MM by Gender

	Male	Female
Head and Neck	175 (12.1%)	197 (13.6%)
Frontal Side of the Trunk	75 (5.2%)	29 (2%)
Back Side of the Trunk	154 (10.6%)	68 (4.7%)
Upper Extremity	105 (7.3%)	113 (7.8%)
Lower Extremity	189 (13.1%)	206 (14.7%)
Scalp	41 (2.8%)	13 (0.9%)
Axillar and Pubic	12 (0.8%)	18 (1.2%)
Trunk	5 (0.3%)	3 (0.2%)
Unknown	23 (1.6%)	21 (1.5%)

Table 2. Histopathological Subtype Distribution of Mis and MM

Histopathological subtype	n (%)
Melanoma in-situ	
Lentigo maligna	70 (55)
Superficial spreading type	39 (31)
Unclassified type Mis	14 (11)
Acral lentiginous type	4 (3)
Total	127 (100)
Malignant Melanoma	
Superficial spreading melanoma	549 (37.9)
Nodular melanoma	379 (26.2)
Acral lentiginous melanoma	191 (13.2)
Lentigo maligna melanoma	132 (9.1)
Nevoid melanoma	16 (1.1)
Persistent melanoma	14 (1)
Desmoplastic melanoma	10 (0.7)
Melanoma developing from congenital nevus	9 (0.6)
Childhood melanoma	6 (0.4)
Melanoma developing from blue nevus	5 (0.3)
Unclassified type	136 (9.4)
Total	1447 (100)

Table 3. Statistical Evaluation of Histopathological Parameters

	SLN positive	SLN negative	P*	P**
Histological subtype				
SSM	49	132	<0.001	
NM	55	46		
ALM	31	43		
LMM	2	17		
Others	18	24		
Clark level				
II	4	19	0.001	
III	32	82		
IV	80	128		
V	39	33		
Tumor thickness (mm)				
≤1	6	46	<0.001	0.002
1.1-2	24	76		
2.1-4	47	76		
>4	78	64		
Ulcer				
Present	99	112	<0.001	
Absent	56	150		
Mitosis (mm^2)				
<6	91	200	0.005	
≥6	64	62		
Lymphovascular invasion				
Absent	103	251	<0.001	<0.001
Present	52	11		
Satellite formation				
Absent	143	258	0.001	
Micro	12	2		
Macro	0	2		
Regression				
Absent	127	187	0.017	
<%50	25	64		
≥%50	3	11		

*Chi-square test, **Binary logistic regression analysis; SLN: Sentinel lymph node, SSM: superficial spreading melanoma, NM: nodular malignant melanoma, ALM: acral lentiginous melanoma, LMM: lentigo maligna melanoma

Discussion

Melanoma localization varies according to gender in literature. While MM is most often seen on the back of the trunk in men, it is predominantly seen on the lower extremities in women (Weedon, 2010). However, a previous study revealed that the tumors of trunk and extremities did not show gender differences (Gyrylova et al., 2014). In our study, the most common sites were lower extremity followed by the head and neck for both sex. MM effects mostly elderly patients, with a peak of incidence around the sixth decade of life (LeBoit et al., 2006). In our study, the mean age found was 56.7 years. Acording to a recent study, the lesions of the head and neck, older age, and male sex were associated with an increased risk of recurrence after a negative SLNB result (Jones et al., 2013). In addition, the overall survival (OS) of men with melanoma was also worse compared to those of women in a study from Turkey (Uysal-Sonmez et al.,

2013). Although being older than 65 years was found to be an independent prognostic factor of OS, gender and tumor localization were not associated with OS and disease-free survival (DFS) (Wu et al., 2013). However, another study reported that tumor location, gender and age were not correlated with DFS and OS (Namikawa et al., 2012). In another study from Japan, age and gender were not associated with DFS for patients with thick melanoma (Fujisawa et al., 2012). In our study, male gender was associated with SLN positivity but it was not an independent predictive factor on multivariate analysis. In addition, SLN involvement was not statistically significant relation with age and tumor localization.

SSM is the most common subtype and accounts for 60-70% of all MM in Caucasians. NM is the second most frequent subtype and constitutes 10-15% of all melanomas in light-skinned people (LeBoit et al., 2006). Acral melanoma forms 2% and 80% of cutaneous melanomas in Caucasian and heavily pigmented people, respectively (LeBoit et al., 2006). Some studies from Asia have reported that ALM is the most common form in MM and its frequency is about 50%. (Chang et al., 2004; Lee et al., 2012). The most common histopathological form in our study was SSM (37.9%), followed by NM (26.2%) and ALM (13.2%). Our study revealed that SSM was lower and ALM was higher compared to western countries. However, our ALM frequency was similar to another study from Turkey but it was not as high as in reported studies from Asian countries (Chang et al., 2004; Tas et al., 2006; Lee et al., 2012). When the histological subtypes which were categorized as ALM and nonALM, it was not associated with DFS and OS for patients with thick melanoma (Fujisawa et al., 2012). In our study, histological subtypes were associated with SLN positivity but it was not independent predictive factor.

The role of elective lymph node dissection (ELDN) in treatment process and SLN mapping studies to determine the lymphatic invasion are among the most prominent changes. To reduce morbidity of ELND, intraoperative lymphatic mapping and sentinel lymph node biopsy (SLNB) are increasingly common used methods (Testori et al., 2013). SLNB, when used in appropriate indications by ELDN is less time consuming, easy to implement, cost advantages, and most importantly for patients comprise less morbidity. In our study, SLN data was known in 417(28.8%) of 1447 patients.

A previous study revealed that vascular invasion was an independent predictive factor of metastasis and survival in melanoma (Kashani-Sabet et al., 2001). On a multivariate analysis, vascular invasion was the second most important factor after the tumor thickness (Kashani-Sabet et al., 2001). The prognosis of malignant melanoma depends on mostly clinical stage at the time of diagnosis. Therefore, Breslow thickness is another important predictor of survival (Mervic, 2012). In a recent study, it is found to be an independent prognostic factor for DFS and OS (Wu et al., 2013). In our study, both of them are significant independent predictors on multivariate analysis.

Mitotic rate and ulceration are currently the staging factors in MM based on AJCC. Another study also reported that high mitotic rate (per mm^2) was associated with poor prognosis and an important independent predictive factor of survival (Azzola et al., 2003). However, some authors stated that the mitotic rate was not an independent prognostic factor because it was significantly associated with tumor thickness and ulceration (Weedon, 2010). Ulceration is the loss of continuity of the epithelium on the surface. The presence of ulceration changes in the stage of TNM classification. Ulceration is regarded as an independent prognostic factor for melanoma (Ivan and Prieto, 2011); yet, some authors have not identified ulceration as an independently significant prognostic attribute (Azzola et al., 2003, Uysal-Sonmez et al., 2013, Wu et al., 2013). In addition, another study found that ulceration of the primary lesion was significantly associated with nodal disease on univariate, but not on multivariate analysis (Fontaine et al., 2003). In our study, high mitotic rate and presence of ulceration were related with SLN involvement on univariate but not on multivariate analysis.

Clarks group classified the lymphocytic infiltrate into absent, nonbrisk, and brisk based on distribution and intensity (Clark et al., 1989). They also found that tumor-infiltrating lymphocytes (TIL) were a favorable feature. Although some studies have failed to demonstrate such an association (Gimotty et al., 2005; Taylor et al., 2007), other studies revealed that the presence of TIL in melanoma was associated with a favorable prognosis (Bogunovic et al., 2009; Mandala et al., 2009; Burton et al., 2011). A previous study (Taylor et al., 2007) showed that TILs predicted SLN positivity but, in contrast to other study (Azimi et al., 2012), were not associated with survival. In addition, another study revealed no correlation between TILs and SLN positivity (Minutilli et al., 2007). Therefore TIL is controversial whether their presence is an independent prognostic factor. Evaluation of TIL were also subject to considerable interobserver variability (Monshizadeh et al., 2012). In our study there was no statistical significant relation between TIL and SLN positivity. Regression can be recognized by the presence of fibrosis, vascular proliferation, melanophages and lymphocytic infiltration. Partial regression was associated with poorer prognosis (Guitart et al., 2002), due to dermal component could have metastasized before it regressed. A previous study revealed there were no association between partial regression of the primary melanoma and SLN involvement by the disease (Fontaine et al., 2003). Another study showed that regression in primary cutaneous melanoma is not predictive for lymph node metastasis (Alquier-Bouffard et al., 2007). In our series, most of case showed partial regression and in contrast to literature, we found that the regression was related with SLN negativity on univariate analysis. But, it was not independent predictor on multivariate analysis. When we examine the literature, we think that regression is a controversial issue like TIL; besides, there was a discrepancy between regression and the percence of brisk TIL which is as a potentially different form of immunological regression is accepted as good prognostic indicator.

Satellites are defined as discontinuous foci of a primary melanoma and it is classified as stage IIIB/C disease. Some

authors acclaimed that microsatellites predict locoregional relapse but not overall survival (Shaikh et al., 2005). Acording to a recent study, SLN positivity rate was 43 % in microsatellite patients (Bartlett et al., 2014). However, in our study, SLN positivity rate was 85,7 % (12/14) in these patients. In addition, being of satellites was found to be associated with SLN positivity, but it was not independent predictor on multivariate analysis.

As a result, vascular invasion and tumor thickness are significant independent predictors for SLN involvement. In our study, we had a large series of cases that were collected for 5 years. Although these study have been performed in major consultation centers, further population based multicentric studies presented each region of Turkey are necessary to determine epidemiologic values in Turkish patients.

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