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Clinical and Morphological Characteristics of Cutaneous Melanoma

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SUMMARY The incidence of cutaneous melanoma has increased significantly worldwide over the last several decades. The aim of this study is to determine clinical and morphology characteristics of primary melanoma, since some of them are important prognostic factors. This retrospective study included 172 patients. The data were collected by the Consulting team for malignant skin tumors in the Banja Luka Clinical Centre from 2009 to 2011. We did not use dermoscopy as a diagnostic tool in our investigation. We determined that melanoma occurs equally commonly in both sexes, in women in the sixth decade and the seventh in men. The most common sub-type was nodular melanoma (59.5%, $P<0.05$), followed by superficial spreading (27.8%) and acral lentiginous melanoma (11.4%). The most common localization was on the back in men (34.3%) and on the legs in women ($P<0.05$). More than half of our patients (55.8%) had melanoma thickness from 1.0 to 4.0 mm, and 38% had a melanoma thicker than 4.0 mm. The average Breslow thickness is 4.6 mm. More women than men had melanoma thicker than 4 mm ($P<0.05$). Spread of the primary tumor localization was found in 31.4% of patients, more frequently in men than in women ($P<0.05$). In most cases it was abstraction of lymph nodes ($P<0.05$). The average thickness of the melanoma in our patients is much higher than the average in the world and the countries of Europe. The results of this study indicate a need for better unique regional registry in this part of Bosnia and Herzegovina and improvement of preventive measures in the early diagnosis of melanoma.

KEYWORDS: melanoma; incidence; Breslow thickness; lymph node involving

INTRODUCTION

The incidence of cutaneous melanoma has increased significantly worldwide over the last several decades (1). The incidence rates are highest in Australia/New Zealand and lowest in South-Central Asia with a lot of variations of incidence rates between the regions of the world for males and females. The incidence of melanoma varies widely within Europe from the highest rate in Switzerland, Sweden, and Denmark to the lowest of in Romania and Greece (2,3). Melanoma in South-East Europe shows varying incidence (cases per 100 000 residents) from 1.7 in Albania to 14.5 in Slovenia, but more detailed data from this region are scarce (4). Both genetic and environmental factors are related to melanoma pathogenesis. Risk factors are: history of sunburns and/or heavy sun exposure, blue or green eyes, blonde or red hair, fair complexion, numerous typical nevi and/or more than one atypical nevus, large congenital nevus, prior personal or family history of melanoma, germline mutations in the chromosome 9p21 tumor supresor gene, and somatic mutation in the BRAF gene (1).

Understanding prognostic factors in cutaneous melanoma has evolved over the last decade, allowing oncologists to provide appropriate treatment. Many

of the prognostic factors are interrelated. For localized primary melanoma, the dominant predictors of survival include lesion thickness, ulceration, and lymph node involvement. Factors such as age, sex, anatomic location, and satellite/in-transit lesions are important in localized melanoma (4). There is good prognostic correlation for the two micro-staging systems, Breslow depth and Clark level, commonly used to stage melanomas. Many investigators have reported that Breslow depth is the superior microstaging method (5,6). Thickness remains the single most useful variable. Prognosis declines more or less linearly with increasing thickness, modified by ulceration, mitotic rate, and other attributes (7). Tumors of greater Breslow depth are more likely to invade lymphatic or blood vessels allowing a route of passage for distant spread. Survival is accordingly shorter in such cases (8).

Due to the fact that there is no published data about melanoma in this region of Bosnia and Herzegovina, the aim of our study was to determine clinical and morphological characteristics of primary melanoma since some of them are important prognostic factors. Some similar results have been published in a study in the western part of Herzegovina (10).

PATIENTS AND METHODS

This retrospective study included 172 patients with primary melanoma, 93 (54%) women and 79 (46%) men. The data were collected by the Consulting team for malignant skin tumors in Banja Luka Clinical Centre from 2009 to 2011. This team consists of an oncologist, dermatologist, pathologist, plastic and maxillofacial surgeons, and a specialist of nuclear medicine; the team examins patients with malignant skin tumors from all parts Republic of Srpska (the eastern part of Bosnia and Herzegovina). Consulting team examination is the first step in the triage of patients with malignant skin tumors that are then referred for further diagnostic and therapeutic procedures. The analysis included: sex, age, type and localization of melanoma, Breslow thickness, lymph node involvement, and metastases. Type of melanoma was based on the classical division into nodular, superficial spreading, acral lentiginous, and lentigo maligna melanoma. Anatomical localization of the melanoma was divided into 5 groups: 1. head and neck, 2. front side of the trunk, 3. back, 4. hand and arm and 5. palm, sole, and finger. Mucosal melanomas were treated separately. Based on Breslow thickness patients with melanoma were divided into four groups. In the first group were patients with melanoma thickness less than 1.0 mm. Breslow thickness in second group was from 1.01 to 2.0 mm, and in third from 2.01 to 4.0 mm. Patients with melanoma thickness more than 4.01 mm were in the fourth group. Based on melanoma spreading from primary localization, patients were also classified into four groups. Patients with macro and micro lymph node involvement were in the first group. Micro lymph node involvement was confirmed by sentinel lymph node biopsy. Patients with melanoma spreading to the soft tissue and distant metastases were in the second group. Patients with lung metastases were in the third group, and patients with other visceral metastases in the fourth group.

STATISTICS

The SPSS software package (version 17.0) was used in this study. The data were analyzed by descriptive and inferential statistical methods. Descriptive methods were used to analyze mean (X) and standard deviation (SD). Pearson χ2-test, Student's t-test, and Kruskal Wallis test were used for inferential analysis. A *P* value of <0.05 was considered statistically significant. In cases when the study group had a small number of patients statistical significance was not calculated and was designated as not applicable.

RESULTS

The average age of our patients was 61 ± 14 years, 63 ± 13 in men and in 59 females in women. The

Table 1. Sub-types of melanoma.

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Sub-type	Total number of patients N (%)	Male N (%)	Female N (%)	*P*-value
Nodular	47 (59.5)	25 (67.6)	22 (52.4)	0.662
Superficial spreading	22 (27.8)	8 (21.6)	14 (33.3)	0.201
Acral lentiginous	9 (11.4)	3 (8.1)	6 (14.3)	NA*
Lentigo maligna	1 (1.3)	1 (2.7)	-	NA*
Total	79 (100)	37 (100)	42 (100)	0.574

*not applicable

Table 2. Anatomic localization of melanoma

Localization	Total number of patients N (%)	Sex		*P*-value
		Male N (%)	Female N (%)	
Head/neck	28 (16.3)	12 (7.0)	16 (9.3)	0.450
Trunk (the front side)	18 (10.4)	9 (5.2)	9 (5.2)	1.000
Back	59 (34.3)	35 (20.3)	24 (14.0)	0.152
Hand/arm	18 (10.5)	8 (4.7)	10 (5.8)	0.637
Leg	32 (18.6)	6 (3.5)	26 (15.1)	<0.05
Palm/sole/finger	9 (5.2)	3 (1.7)	6 (3.5)	NA*
Mucosa	8 (4.7)	6 (3.5)	2 (1.2)	NA*
Total	172 (100.0)	79 (45.9)	93 (54.1)	0.286

*not applicable

difference in average age between women and men was 4.4 years, which is statistically significant (*t* test; *P*=0.041). Melanoma was the most often diagnosed in patients in the sixth (27%) and seventh (25%) decade of life. In women, melanoma was most often diagnosed in the sixth decade, and in men in the seventh decade of life. The difference was not statistically significant. The peak of incidence in both sexes was the 64th year.

Out of 172 patients, in 93 (54.1%) there was no data about the type of melanoma, and in 79 (46.0%) patients, there were data. The most common subtype was nodular melanoma in 59.5%, following superficial spreading in 27.8%, and acral lentiginous melanoma in 11.4%. Only one patient had lentigo maligna melanoma. There was a statistically significant difference (χ2-test, *P*<0.05) between the number of patients with nodular melanoma compared to the other sub-types of melanoma, but there was no statistically significant difference with regard to gender and sub-type of melanoma (Table 1).

The most common localization of melanoma was on the back (34%), followed by the legs (19%), and arms and trunk (10%), while the rarest localization was on the palms, soles/fingers (5%). Bucal melanoma was diagnosed in 8 (5%) patients. The observed differences between the number of patients with melanoma on their back, legs, and head or neck were statistically significant (χ2-test, *P*< 0.05) compared to localized melanoma at other sites of the body. There was no statistically significant difference in the localization of melanoma with regard to gender, except in patients with melanoma of the legs which was more common in females (Pearson χ2 test *P*< 0.05) (Table 2).

Breslow thickness melanoma was known for 129 (75%) patients; we lacked the data for the remaining 25%. Median Breslow thickness was 4.6 mm. Breslow thickness over 4.0 mm was found in 38.0% patients, while only 6.2% patients had Breslow thickness less than 1.0 mm. In 55.8% patients Breslow thickness varied from 1.0 to 4.0 mm. There was a statistically significant difference between melanoma with Breslow thickness less than 1.0 mm and melanoma thicker than 1.0 mm both in the total sample and between men and women (χ2-test *P*<0.05). There was also a statistically significant difference (χ2-test; *P*<0.05) regarding gender for Breslow thickness a >4.0 mm, but there is no statistically significant difference regarding gender for other Breslow thickness values (Table 3).

The thickest melanomas were localized on palms, soles, and fingers, the thinnest on the trunk. Using the

Table 3. Breslow thickness of melanoma

Breslow thickness	Total number of patients N (%)	Sex		*P*-value
		Male N (%)	Female N (%)	
≤1.0 mm	8 (6.2)	2 (1.6)	6 (4.7)	NA*
1.0-2.0 mm	33 (25.6)	14 (10.9)	19 (14.7)	0.384
2.0-4.0 mm	39 (30.2)	23 (17.8)	16 (12.4)	0.262
> 4,0 mm	49 (38.0)	16 (12.4)	33 (25.6)	0.015
Total	129 (100.0)	55 (42.6)	74 (57.4)	0.286

*not applicable

Table 4. Lymph nodes involvement and metastasis of melanoma

	n (%)	Sex		
Spreading melanoma	Total number of patients n (%)	Male N (%)	Female N (%)	*P*-value
Total spreading	54 (31.4)	32 (40.5)	22 (23.6)	0.027
Lymph nodes involvement	36 (66.7)	21 (65.7)	15 (68.2)	0.499
Soft tissue/ Distant nodal metastasis	9 (16.7)	6 (18.8)	3 (13.7)	NA*
Lung metastasis	2 (3.7)	2 (6.2)	-	NA*
Other visceral metastasis	7 (12.9)	3 (9.3)	4 (18.1)	NA*
Patients without metastasis	118 (68.6)	47 (55.5)	71 (77.4)	0.027
Total patients	172 (100.0)	79 (45.9)	93 (54.1)	0.286

*not applicable

Kruskal Wallis test we found no statistically significant difference (P=0.546) in Breslow thickness regarding anatomical localization of melanoma.

Out of 172 patients, in almost one third (31.4%) we determined spreading of melanoma out of primary skin localization, more frequently in men than in women (χ2-test, P<0.05). Most commonly involved were the lymph nodes (66.6%, χ2-test, P<0.05). Less common was spreading involing soft tissue and distant nodal metastasis (16.7%), and other visceral metastases (12.9%). Only one patient had lung metastasis. Using χ2-test we found no statistically significant difference regarding gender and lymph node involvement (P=0.499). Due to the small number of patients with other metastasis sites, statistical significance is not applicable (Table 4).

DISCUSSION

The main findings of our research are that cutaneous melanoma usually occurs in elderly patients as a nodular sub-type, and that the tumor is diagnosed late because the average Breslow thickness is 4.6 mm.

In our study, melanoma was equally common in women and men. This is in contrast with the study by Brady *et al.* in which men are more likely than women to develop melanoma (67% higher incidence) (11). From the GLOBOCAN 2008 estimates all Western European countries, with the exception of Austria, have higher incidence rates for women than for men, and the same trend is apparent for most Northern European countries. In contrast, for most of Central, Eastern, and Southern Europe, incidence rates are higher in men. Melanoma mortality is higher in men compared with women throughout Europe (2). The average age of our patients with melanoma is 61 years. It is almost a decade more than in the data of Paek *et al.* in which the mean age of diagnosis was relatively young (at 52 years), and more than 25% of melanomas occured in persons younger than 45 years, but it is in accordance with the data from Croatia, where the greatest increase of melanoma incidence rates was in 60-year-old males (1,12). Melanoma statistics data reported the median age at diagnosis was between 45 and 55. Weih *et al.* concluded that invasive melanoma of the skin is the third most common cancer diagnosed among adolescents and young adults (aged 15-39 years) in the United States (13,14). However, our data are consistent with the results of the U.S. National Cancer Institute, which states that the median age at diagnosis for melanoma of the skin was 61 years of age (15). Our male patients were older than females. The average age in men was 63, and in woman 59, which is also in accordance with data from the United States where after age of 40 the men have a higher incidence rate and the difference becomes remarkably large with increasing age (1). We found that patients most often (60%) had nodular and superficial spreading (28%) sub-types of melanoma. This result is in contrast with data available from the literature. It is known that superficial spreading melanoma is the most common, and nodular is the second most common melanoma sub-type (9). The frequency of superficial spreading melanoma in the literature is about 64-70%, and about 14-30% for nodular melanoma. Many studies confirm this fact (1,3,10,16-18). Only 9% of our patients had acral lentiginous melanoma. This sub-type occurs less frequently in the literature as well. Although rare, it is potentially dangerous and has a poor prognosis compared with melanoma at other sites, which requiring specific management

from their prevention up to their treatment (19). The most common locations of melanoma in our study were the trunk (44.7%), legs (18.6%), and head/neck (16.3%). Several studies throughout the world have identified differences in the anatomic distribution of melanomas in men when compared with women (2,4). When it comes to anatomical localization, our results are similar to other countries in Europe and worldwide since the trunk and lower limbs appear to be the most frequent sites of melanoma (20). Similar to other countries, in our population melanomas were predominantly located on the trunk in men and on the lower limbs in women. Gender differences in body site distribution of melanoma lesions have been thought to be a result of inherent differences between men and women. Differences in clothing, hair style, occupation, sun-seeking behavior, preventive measures, and seeking medical care have all been considered as potential reasons for the higher incidence of lesions on the lower extremities in women and lesions of the head, neck, and trunk areas of the body in men. However, the reasons for the observed gender differences may go beyond societal differences among males and females, and depend on the relationship between steroid hormones (21). The anatomic location of the primary melanoma is an important independent predictor of sentinel lymph node status and prognosis. Patients with primary melanomas of the head/neck and trunk have a worse prognosis than those with primary melanomas on other anatomic locations (22). In our patients, melanomas were diagnosed in their later stages because the average Breslow thickness of melanomas was 4.6 mm. Thin melanomas (under 1.0 mm) were present only in 6.2% patients, whereas 55.8% had melanoma 1.0-4.0 mm thick, and 38% had melanoma thicker than 4.0 mm. A group of authors from the Mayo Clinic was exploring the association of socioeconomic status of patients with Breslow thickness and came to the conclusion that low socioeconomic status is associated with thicker melanoma and a poorer clinical outcome (23). It is known that Bosnia and Herzegovina is one of the countries with the lowest socioeconomic status in Europe. Poor socioeconomic status and the older age of our patients are probably the two most important reasons for having such thick melanomas. Similar results were found by Polish authors. In their study, in the ≥65 years group the median Breslow thickness was 5.0 mm (24). In Bulgaria and Romania, for instance, an estimated 25% of patients present with stage III and IV disease, while thin melanomas under 1.0 mm make for less than 10% of newly diagnosed cases. High rates of advanced-stage melanomas have been reported in the Russian Federation, and a median tumor thickness of 4.0 mm has been reported in Serbia. This is in sharp contrast to Western Europe, where up to 70% of newly diagnosed melanomas are <1 mm thick (2). However, some studies confirm that in rural parts of Western Europe mean Breslow thickness was much higher than previously observed in other regions in Western Europe (25). Our female patients tend to have melanoma of more than 4.0 mm more commonly than male patients ($P<0.05$), while for the other thickness there were no differences between men and women. These results are contrary to the finding of German authors, where male patients had significantly thicker melanoma (26). Anatomic locations included the head/neck and trunk, and age and Breslow thickness are an important independent predictors of sentinel lymph node status and prognosis (22). As in 61% of our patients, melanoma was localized on the head, neck and trunk, the average Breslow thickness was 4.6 mm, and those patients were elderly, which may be a reasons that almost one third (31.4%) of our patients had tumor spread beyond the primary location. In most cases (20.9%), there was regional macroscopic and microscopic lymph node involvement. Regarding age, our results confirms the conclusion of the American authors that higher incidence of local/in-transit metastases is seen among the elderly (27). In our study, lymph node involvement was greater in men than in women. In a study on a large number of patients in Germany, it was concluded that men had higher probability for developing metastases and distant metastases after diagnosis of a primary tumor. Additionally, if disease progression took place, women developed their first metastasis as well as distant metastasis significantly later compared with men. When the metastatic pathways are taken into consideration, women were more frequently first to progress to local sites in the form of satellite or in-transit metastases, and men more frequently exhibited direct regional lymph node metastasis. About two thirds of these patients, more men than women, showed further progression to distant sites (29).

CONCLUSION

We found that cutaneous melanoma occurs equally commonly in both sexes, in women in the sixth decade of life and the seventh in men. The most common sub-type was nodular melanoma. The most common localization was on the back in men and on the legs in woman. Melanoma among our patients was detected late since the average Breslow thickness was 4.6 mm, and nearly every third patient had spread beyond the primary tumor localization. We are aware that our study has some limitations. In our

investigation we did not use dermoscopy as a diagnostic tool. Our sample was small, and in a number of patients are missing all the relevant data, but we wanted to show that we found high incidence of dangerous thick melanomas, which indicates the need for a better unique regional registry in this part of Bosnia and Herzegovina and improved preventive measures in the early diagnosis of melanoma.

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