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A 10-year retrospective study of melanoma stage at diagnosis in the academic emergency hospital of Sibiu county

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Abstract. Melanoma is considered to be the most aggressive skin cancer, with an increasing incidence worldwide. An accurate staging of melanoma is crucial in describing the cancer status, estimating prognosis and deciding the optimal treatment solution. In the present study, melanoma staging highlights the importance of early detection, most of the patients having been diagnosed with advanced stages of this skin cancer. A retrospective study was conducted among 117 patients of the Academic Emergency County Hospital of Sibiu, diagnosed with melanoma between 2007 and 2016. The staging of the patients with melanoma was made using the American Joint Committee on Cancer (AJCC) 7th edition, and reconsidered in the light of the AJCC 8th edition. The results showed that the majority of the cases had distant metastases, 40.17% were diagnosed with stage IV melanoma. 25.65% of the patients were diagnosed with stage III melanoma, having a regional disease. The rest of the cases had localized melanoma (stages I and II, 30.76%), while only 3.42% of them were diagnosed with melanoma *in situ*, the melanoma type with the greatest chances of survival. Analyzing the Breslow index, it was observed that the most common tumor thickness was 2.1 to 4 mm (34.19%). In conclusion, as the incidence of melanoma increases in Romania, further efforts are needed to improve the early detection of melanoma. There are hopes that with the correct and early diagnosis of melanoma, the mortality rate of this neoplasm will decrease in the future.

Introduction

Melanoma is the most aggressive cutaneous tumor that has shown a constantly increasing incidence in the last decades and a mortality rate that has reached a plateau lately (1,2).

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There is an overall sharp discrepancy in melanoma incidence rates reported between Eastern Europe and Western Europe, whereas the mortality rates are similar (3). This is related in part due to the underreporting of this data in Eastern Europe (4).

In Romania, according to the International Agency for Research on Cancer, the melanoma incidence from 5 years ago was of 4.7 cases/100.000 inhabitants, a lower rate in comparison to other European countries (the average rate of 14 cases/100.000 inhabitants), but with a mortality rate (1.7/100.000 inhabitants) comparable with the European countries (5,6). At the same time, melanoma prognosis in Romania and in the neighboring Eastern countries is among the lowest in Europe, with a five-year survival rate of 50-60%, likely reflecting problems of late diagnosis (7,8).

On the one hand, the actinic aggression of the skin, developed after the frequent exposure to the natural or artificial UV radiation, the absence or insufficiency of photoprotection and other factors (9-11) increases the incidence of melanoma. On the other hand, the diagnosis rate of melanoma is higher due to the developments in melanoma diagnosis (dermoscopy (12), immunohistochemistry and cytogenetics), especially in its early stages. In all White Caucasian populations, melanoma represents an important public health issue, involving significant financial and human resources (13). As such, the establishment of an early diagnosis and adoption of the right attitude are tools that can enable to decrease the mortality, morbidity and costs of melanoma and to increase survival in certain tumor stages (14).

The melanoma staging is crucial in appreciating the neoplastic status, assessing the degree of invasion of tumor cells and establishing a certain profile of patients (15).

Using the tumor-node-metastasis (TNM) melanoma staging, the diagnosed patients can be included in different stages, from melanoma *in situ* (stage 0) until stage IV (metastatic melanoma). This staging method is useful in finding the best treatment options, establishing the prognosis and the survival rate.

The American Joint Committee on Cancer (AJCC) staging of melanoma has highlighted the importance of the Breslow index (BI) in melanoma's medical management (16). Other important parameters in the TNM staging are the presence or absence of ulceration, the tumor's mitotic rate and the tumor microsatellites in lymph nodes (17).

Materials and methods

Subjects. We conducted an analytical, observational, retrospective study of melanoma cases diagnosed and dermato-oncologic monitored in Sibiu County, located in the center of Romania. They are diagnosed with melanoma between January 1, 2007 and December 31, 2016 from the Dermatology and Oncology Departments of Sibiu County were included in this study. A total of 117 cases included adult patients (25-87 years), with a sex ratio of 1.17 (female/male). Diagnose of melanoma respected the clinical, dermoscopical, histopathological criteria and in some selected cases the immunohistochemistry melanoma criteria. Excisional biopsy of the tumors were analyzed by the pathologists of our hospital. Processed data included patient characteristics (sex, age and tumor location) and tumor characteristics (clinical forms, Breslow index, the size of the tumor, the presence/absence of the lymph nodes metastases, the degree of distant invasion and the TNM stage). To evaluate the melanoma stages we used the 7th edition of the American Joint Committee on Cancer (AJCC) (16) and it was reconsidered in the light of the AJCC 8th edition (17).

All the patients provide an informed consent to participate in this study which was approved by the Ethics Committee of Clinical Hospital (Sibiu, Romania).

Statistical analysis. The statistical analysis was performed using a free trial of the Statistica software (version 13.3.0; Tibco Software Inc., Palo Alto, CA, USA) with an α=0.05 and SPSS Statistics software (version 25.0; IBM Corp., Armonk, NY, USA). The nominal variables were expressed in numbers and percentages. The results are presented as median ± standard deviation (mean±SD). To estimate the significant correlations, we calculated the p-values using Shapiro-Wilk and Kolmogorov-Smirnov test. Comparison was evaluated with Chi-square test. P≤0.05 was considered to indicate a statistically significant difference.

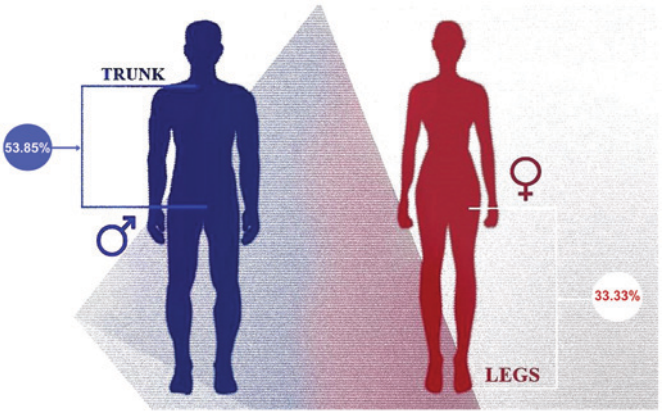

Figure 1. Melanoma distribution according to anatomical areas and sex. Our results are concordant with the literature and revealed that melanoma in women vs. men was most frequent on legs vs. trunk.

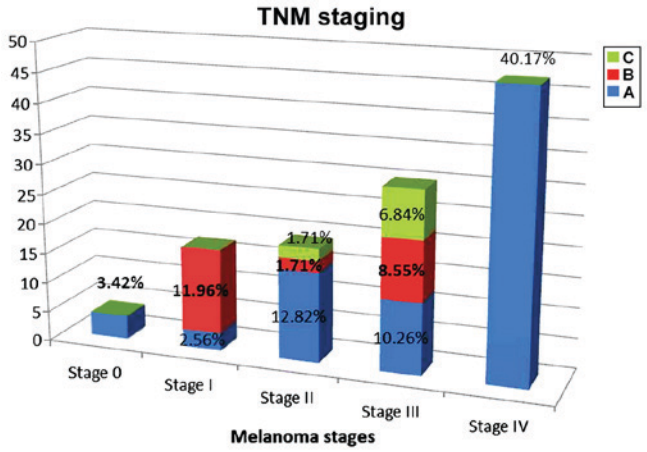

Figure 2. TNM staging in our study. In our study melanoma were diagnosed most common in stage IV and most rare in stage 0 (*in situ*). In stage I, more cases in stage IB vs. IA were identified. In stages II and III, more patients in stages IIA/IIIA vs. IIB/IIIB/IIIC were identified. TNM, tumor-node-metastasis.

Results

A demographic analysis of the studied group revealed a more frequent distribution of melanoma in females (53.85%). The patients ages ranged between 25 and 87 years (a median age of 59±13.17). The most affected age category was the one between 51-70 years of age (58.12%) (P=0.0420) (Table I).

Among women, melanoma was more frequent on the lower extremities (33.33%). Among men, the most affected anatomical site was the trunk (53.85%) (P=0.111) (Fig. 1).

The distribution of the studied group according to clinical forms of melanoma and BI revealed a high frequency of nodular melanoma (31.62%) and thick melanomas (48.73% melanoma diagnosed with a BI of over 2 mm) (P<0.001) (Table I). The median values of BI were 2.435±2.38 mm.

TNM staging of all the cases diagnosed with melanoma initially included an analysis based on the T (tumor), N (lymph nodes) and M (metastasis) criteria.

Analyzing the T criterion, the majority of the patients with melanoma were diagnosed with a BI of 2.01-4 mm (T3, 34.19%). The T3 stage was followed by the T1 and T2 stages (18.81 and 17.95%), T4 (14.54%) and Tis (3.42%). For the melanoma staging where we did not have a BI (11.09%), the tumor we categorized as Tx and the tumor stage was calculated as any T.

Regarding the assessment of the degree of lymph nodes invasion (using the N criterion) it was observed that the majority of the patients were diagnosed with regional unique or multiple metastases: N2 with 2-3 lymph nodes (48.72%), N3 with over 4 lymph nodes (15.38%), N1 with 1 lymph node (3.42%). Approximately 1/3 of the patients were in the N0 stage (32.48%).

A percent of 37.61% of the patients had distant metastases, most frequently at a visceral level (brain, liver, kidney, bone, bone marrow, ovary, uterus, gastric and mesenteric, thyroid). Only 3.42% of them had pulmonary metastases. Epidermotropic metastases were found in 13.68% of the patients.

According to the AJCC 8th edition of melanoma TNM staging, the majority of the patients were diagnosed in the stage IVof the disease (40.17%). Melanoma cases (25.65%) were in stage III, 16.24% in stage II and 14.52% in stage I. The low percentage of patients with melanoma *in situ* (3.42%) is worth mentioning (Fig. 2).

Table I. The distribution of the group according to the age, clinical forms of melanoma and Breslow index.

Variables	Cases (n, %)	P-value
Age (years)	59±13.17	0.0420
<30	3 (2.57)	
31-50	24 (20.51)	
51-70	68 (58.12)	
>71	22 (18.80)	
Clinical forms of melanoma		<0.001
Superficial spreading melanoma	32 (27.35)	
Nodular melanoma	37 (31.62)	
Lentigo malign melanoma	2 (1.71)	
Acral melanoma	1 (0.86)	
Acromic melanoma	4 (3.42)	
In situ	4 (3.42)	
Unknown	37 (31.63)	
Breslow index		<0.001
Under 1 mm	22 (18.81)	
1-2 mm	21 (17.95)	
Over 2 mm	57 (48.73)	
In situ	4 (3.42)	
Unknown	13 (11.09)	

Discussion

Taking into account that the inhabitants of Sibiu County represent <5% of the Romanian population, in the future, the extension of this report at a national level can provide more valuable information on melanoma staging, incidence and mortality rate in Romania.

The increasing incidence of melanoma in the last decades is more evident in male patients, except for the patients under the age of 40 (18). This can be explained by the fact that males do not pay much attention when examining their skin, and find it difficult to apply sunscreen daily. Men also have more hobbies and outdoors activities compered to women.

In this study, the incidence of melanoma was slightly higher in females (53.85%), data concordant with the demographic profile of Romanian population (51.19% women) (19) and similar with to the Rockberg *et al* study (50.60%) (6).

Although the average age for the melanoma diagnosis within the studied lot was 59 years, and the most affected age category was 51 to 70 years, it was a notice that 10.25% of the patients were young persons aged between 25 and 40 years. The study published by Rockberg *et al* in 3,554 melanoma patients obtained an average diagnosis age of 61.3 vs. 59 years in this study. The average lower age and the important number of cases in younger patients, under 40, are warning signs for both the Romanian dermatologists and general population.

The more frequent occurrence of melanoma in women on the lower extremities (33.33%), and in men on the trunk area (53.85%) is a well-known data in the dermatological literature and it is also confirmed by the present study. The distribution according to clinical forms of melanoma reveals the fact that nodular melanoma was more encountered (31.62%), as opposed to the data from the literature that show a frequency of 50.60% of the superficial spreading melanoma (20).

The melanoma staging showed that a significant percentage of the patients (40.17%) were diagnosed with stage IV of the disease, including distant, multiple organ metastases. Approximately 1/4 of the patients were diagnosed in stage III, being followed by stage II (16.24%), stage I (14.52%) and stage 0 (3.42%). The large number of patients diagnosed in late stages of the disease (stages III and IV, 65.82%) were correlated with a higher BI (48.73% had a BI over 2 mm). Enninga *et al* reported 13.3% late stages of melanoma which were correlated with BI >2 mm (12.3%) (18). In this study, the data about late melanoma detection in patients with advanced stages corresponds to other publications from Eastern Europe but it is in a sharp contrast with the reported data from Western and Northern Europe (21-25).

Rockberg *et al* reported results opposed to our data, the majority of the melanoma cases being diagnosed in stages I and II (92%), while in stage IV being only 1.30% (6). In stage I there were 14.52% of the patients in this study vs. 7.80% of the Andersson *et al* (26) and 62.50% of the Eriksson *et al* (27). Most of the melanoma from the Enninga *et al* study were diagnosed in incipient stages I and II (83.40%) and in late stage IV (3.40%). The correlations between our results and other studies showed that in Eastern Europe as in Romania a much greater effort is needed to improve early detection. The limitation of the study is that the inhabitants of Sibiu County represent a small percentage of Romania's population (<5%).

In conclusion, corroborating the results of this study, it may be concluded that melanoma were diagnosed more frequently in nodular forms, with higher BI's, of more than 2 mm, in late stages of disease, with regional and distant metastases.

Considering the clinical impact of these data, better and more efficient measures of tumor prophylaxis are required, with the enhancement of the educational efforts. Furthermore, it is important to raise awareness of the general population of the vital risk induced by the late diagnosis of melanoma. It is imperative to increase skin self-examination by educating individuals how to perform it; also the awareness in general population about the importance of complete dermatological examination for detecting new pigmented lesions or changes in the preexisting lesions should be raised.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

MR contributed to the conception and design, analysis and interpretation of the data, manuscript drafting and critical

revision of the manuscript for important intellectual content. CRJ was responsible for the acquisition, analysis and interpretation of the data, manuscript drafting and design. GMI contributed to the analysis and interpretation of the data, manuscript drafting and critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Clinical Hospital (Sibiu, Romania), and a written informed consent was provided by all the patients included in this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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