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ORIGINAL ARTICLE

Cutaneous melanoma in Turkey: analysis of 1157 patients in the Melanoma Turkish Study

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Summary

Purpose: *To develop a large Turkish National Melanoma registry in order to define demographic and clinicopathologic characteristics of patients with melanoma.*

Methods: *The data was collected from 1635 patients with melanoma through a web-based registry system in 22 centers. Herein we present the results of 1157 patients with cutaneous melanoma.*

Results: *The patient median age was 56.4 years and 646 (55.8%) were males. The commonest subtype was superficial spreading type (357, 30.9%). The commonest primary site was the lower extremities (N=353, 30.5%). The most common Breslow thickness was 1-2 mm (361 patients, 43.5%). Only 104 (12.5%) patients had a thickness <1mm. Among 694 patients with available data, 136 (19.6%) presented with stage 4 disease while the most frequent stage was stage 3, encountered in 393 (56.6% patients).*

Conclusion: *Our melanoma registry is the largest in our country providing a snapshot view of cutaneous melanoma and its care. Our patients presented with more advanced stages and they had worse prognosis compared to SEER database.*

Key words: *clinical features, cutaneous melanoma, pathology, registry, staging, Turkey*

Introduction

Malignant melanoma constitutes 4% of all skin cancers [1]. Of note, melanoma is responsible for approximately 75% of mortality due to skin cancers [1]. High mortality in advanced stages and high incidence in young individuals rendered this disease the focus of several preclinical and

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clinical research in recent years. However, it has become a major public health issue because of its high mortality rate in advanced stages and its preventable nature by limiting sun exposure [2].

Prevention must be the most important strategy by limiting the exposure to sun and use of sun-screens, as they have been shown to reduce the development of melanoma [3,4]. When diagnosed at early stages, the disease is highly curable with wide local excision plus sentinel lymph node dissection and completion lymph node dissection in appropriate cases [2,5,6]. Interferon has been the subject of many adjuvant phase III trials, and proved to be marginally effective [2,7–12]. Newer agents that have been effective in advanced stages are being tested in the adjuvant setting (Ongoing BRIM8 study NCT NCT01667419), and ipilimumab has already shown promising activity in this setting [13]. Recent developments in molecular oncology and immuno-oncology greatly improved the prognosis of metastatic cutaneous melanoma [14–18].

In Turkey, age-standardized incidence of malignant melanoma (per 100,000 population) is 2.1 in males and 1.6 in females [19]. Besides this incidence data provided by the Ministry of Health of Turkey, some small retrospective single-institution studies investigating the epidemiology of malignant melanoma in Turkey are available [20–22]. Most of these studies include small numbers of patients and published in local journals. Important epidemiological information representing the whole country is absent. Our aim was to develop a large Turkish National Melanoma registry to define demographic and clinicopathologic characteristics of patients with melanoma.

Methods

The study was planned as a registry analysis by the Turkish Oncology Group, Melanoma Study Group. The data was collected through a web-based registry system in 22 centers, which entered directly to the database.

A total of 1635 melanoma patients was registered, diagnosed between 14/12/1989 and 25/07/2013. All patients had histologically confirmed diagnosis of malignant melanoma. Of these patients, 128 (8.3%) had mucosal melanoma and 269 (17.5%) ocular melanoma. Because clinical and molecular characteristics of disease in these patients differ significantly from those with cutaneous disease [8,9], they are planned to be reported separately elsewhere. Patients with in situ melanoma were excluded. Analyses of the remaining 1157 patients with cutaneous melanoma are presented in this report.

Statistics

Data were extracted as excel spreadsheet from the website. Categorical variables were expressed as percentages. Age was expressed as median. Overall survival was calculated from the date of diagnosis to death or last contact and expressed in months. Survival was analyzed with Kaplan-Meier Method and log-rank test was used to compare the effect of prognostic factors on survival. A p value of <0.05 was considered statistically significant. Statistics were performed using SPSS 17.0 (Statistical Package for Social Sciences v 17.0).

Results

Of the analyzed 1157 patients, 646 (55.8%) were male and 505 (43.6%) female. Sex was not recorded in 6 patients. Their median age was 56.4 years (range: 13.5-94.8). The most common histologic subtype was superficial spreading melanoma, found in 357 (30.9%) patients, whereas in 318 (27.5%) patients histological subtype was not available (Table 1). In 3 patients, the site of origin could not be identified. In the remaining patients, the disease was most commonly localized in the lower extremities (N=353, 30.5%) (Table 1).

Breslow thickness was not available in 327 (28.3%) patients. Among the remaining 830 patients, the most common Breslow thickness encountered was 1-2 mm (361 patients, 41.5%), followed by melanoma thicker than 4 mm (221 patients, 26.6%). Only 104 (12.5%) patients presented with a melanoma with thickness <1 mm (Table 1).

Information on lymph node involvement, in-transit metastasis and satellite nodules was not available in a significant number of patients from the registry. Furthermore, since the relevant data were missing, we could not identify the rates of sentinel lymph node or formal dissection in a solid way. Nevertheless, nodal information was available in 615 patients (53.2%), out of which only 167 (27.1%) did not have nodal involvement. Information of ulceration was available in 745 patients (64.4%). Among them, ulceration was present in 385 patients (51.7%).

The final stage could be identified in 694 (60.0%) patients (Table 1). Of them, 136 (19.6%) presented with stage 4 disease and the most frequent stage was stage 3, encountered in 393 (56.6%) patients.

Of 582 patients with tumors >2 mm thick, adjuvant therapy was given to 340 patients (58.4%). All of these patients received intermediate dose

Table 1. Patient characteristics

Characteristics	*Patients (N=1157) (%)*
Median age, years (range)	56.4 (78)
Sex (M/F)[1]	646/505 (55.8/43.6)
Histological subtype	
Superficial spreading	357 (30.9)
Nodular	331 (28.6)
Acral lentiginous	103 (8.90)
Lentigo maligna	48 (4.10)
Others & unclassified	318 (27.5)
Localization	
Lower extremity	353 (30.5)
Trunk	281 (24.3)
Head & neck	241 (20.8)
Upper extremity	184 (15.9)
Others & unknown	98 (8.50)
Breslow (N=830) (mm)	
<1	104 (12.5)
1.01-2	361 (43.5)
2.01-4	144 (17.3)
>4	221 (26.6)
Number of nodes involved (N=615)	
0	167 (27.2)
1	196 (31.9)
2-3	246 (40.0)
≥4	6 (0.90)
Stage (N=694)	
I	64 (9.20)
II	101 (14.6)
III	393 (56.6)
IV	136 (19.6)

[1]Sex was not recorded in 6 patients

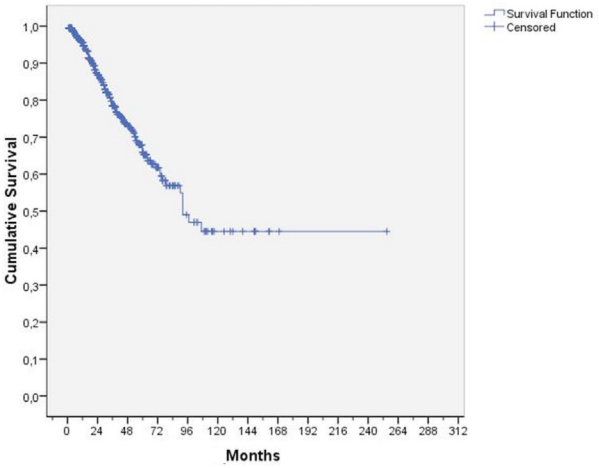

Figure 1. Overall survival of 842 patients with available survival data. Median survival is 92 months (95% CI:72.3 -113.7).

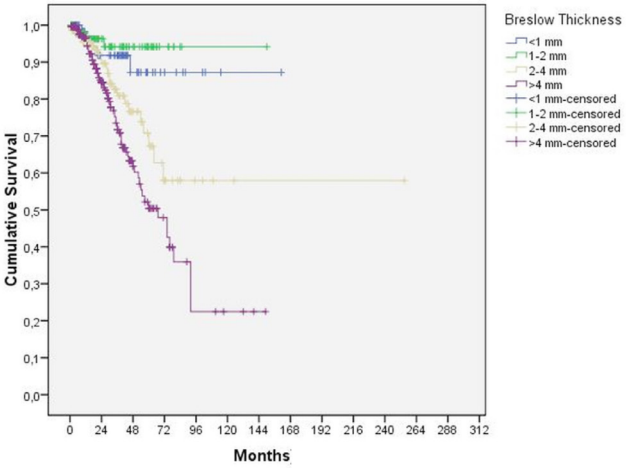

Figure 2. Overall survival according to Breslow thickness, based on 642 patients with available data. Log rank test, p<0.001.

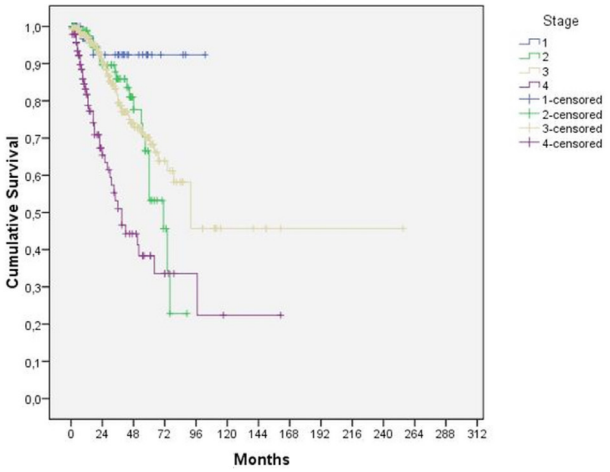

Figure 3. Overall survival according to stage, based on 550 patients with available data. Log rank test, p<0.001.

interferon as adjuvant therapy. Among the patients with metastatic disease (N=434), temozolomide was the most frequently used modality as a single agent or part of a combination with other chemotherapeutic agents (N=279, 64.2%). Targeted therapies and immunotherapies were seldom used (ipilimumab in 11 patients and vemurafenib in 5 patients).

Overall survival data were missing in many cases. Median follow up time was 25.0 months (95% CI 21.9-28.1). Nevertheless, median overall survival of 842 patients with available data was 92.0 months (95% CI 72.3 -113.7) and 5-year overall survival was 66.0%, as shown in Figure 1. Survival curves were constructed according to Breslow thickness (p<0.001) and stage (p<0.001), as depicted in Figures 2 and 3). Overall surviv-

al was negatively affected by male sex (median 79.0 months; 95% CI: 57.5-110.5), as compared to female sex with median overall survival not reached (p<0.001).

Discussion

This study is the first nationwide melanoma registry performed in Turkey. Median age at presentation was 56.4 years and there was a slight male preponderance. Lower extremities were the most commonly involved body site and superficially spreading melanoma was the most common subtype. Most of the patients presented in stage 3 or 4.

Compared to a large single-institution study from Turkey, published in 2006 [20], the median age was higher in our registry (50 vs 56.4 years). The question of whether this inconsistency represents a real shift towards more advanced ages in time, or simply a difference in the patient populations remains to be answered. Since our patients were collected from many centers around the country, 56.4 years of age at presentation may be more representative of the country. Our patients were younger than those in USA where the median age was 62 years according to SEER database [23].

Histological subtype distribution was basically the same with the largest Turkish single-institution data [20], as was the male predilection, which was in line with SEER database and a Norwegian study [23,24].

The most common location of the primary site in our registry was the extremities, in contrast to the Norwegian study, where the trunk was the most common primary location [24]. This may be due to some ethnic or behavioral (tanning behavior) reasons. Skin type, sun exposure (Norway is located near the North Pole where UV light is much higher), cultural factors, like for example dressing, are different between the two countries.

Compared to the single-institution experience [20] where 63% of the patients had stage 1 or 2 disease, fewer patients (23.8%) presented in stages 1 and 2 in the present study. Of the patients, only 12.5% presented with melanoma <1 mm in our registry, compared to 20.7% in the previously reported study [20]. However, the percent of patients with melanoma up to 2 mm was around 50% in both studies. The previous experience [20] was from a major center in the most developed part of the country, which may indicate socio-economic differences. Our registry was based on 23 medical oncology clinics, to where patients with rather advanced stages are usually referred to. Stage distribution was worse compared to SEER database as well [23], where 84% of the patients presented with localized stages without lymph node metastases.

Overall survival at 5 years was 66.0% (Figure 1), which is much lower than the SEER database (91.3%). The reason for worse survival is probably related to stage distribution in our registry, since in our registry about 75% of the patients presented with stage 3 or 4. As it can be seen in Figures 2 and 3, patients did well in the long-term at early stages of disease. Survival of stage 2 and 3 was similar (Figure 3), which was probably due to low rates of sentinel lymph nodes dissection in our country. It is highly probable that many patients from stage 2 would have been staged as 3 if they had undergone sentinel lymph node dissection. Survival of stage 4 disease was unexpectedly high and survival of patients with melanoma <1 mm was worse compared to those with melanoma 1-2 mm, two facts that are not easy to explain. We did our best to rule out the coding errors in database. The reason of long survival in stage 4 disease may be that those stage 4 patients with short survival are underrepresented in our registry. We think that survival data from our registry should be interpreted with caution.

Adjuvant treatment was administered in about 60% of patients with melanoma >2 mm. Many medical oncologists probably are advocates of adjuvant interferon in our country, although it is still not a uniformly accepted adjuvant therapy around the world. The most commonly used 1st line therapy for metastatic melanoma was temozolomide, which is not standard of care in the rest of the world. It probably reflects reimbursement policy in our country and its ease of administration, which may change later in time. Ipilimumab and vemurafenib are available in our country, but reimbursed only after a line of systemic treatment.

We noticed that many major prognostic factors were missing in a substantial proportion from the patient records from our registry. It is highly probable that those prognostic factors are missing from pathology reports and patient files. This low quality of our database may reflect a need for improvement in the care of melanoma from diagnosis to death in our country.

Despite its incompleteness, our registry is the largest in our country, reflecting a snapshot view of cutaneous melanoma and its care. Our patients presented with later stages and they had

worse prognosis compared to SEER database. The incidence of melanoma is increasing. Education of population to prevent or diagnose it at early stages is a crucial need. The quality of care for melanoma needs to be improved in our country.

Conflict of interest

The authors declare that they received financial support from Bristol Myers Squib for data collection and statistical analyses.

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