RESEARCH ARTICLE

Multicenter Evaluation of Patients with Cutaneous Malignant Melanoma in Turkey: MELAS Study

Ozlem Uysal-Sonmez[1], Ozgur Tanriverdi[2]*, Onur Esbah[3], Ummugul Uyeturk[4], Kaan Helvaci[3], Oznur Bal[3], Ulku Yalcintas-Arslan[3], Burcin Budakoglu[3], Berna Oksuzoglu[3]

Abstract

Background: Malignant melanoma is a cancer that demonstrates rapid progression and atypical clinically features with a poor prognosis. Aim: This study was performed to determine the clinical characteristics and treatment outcomes of patients with malignant melanoma in Turkey. Methods: The medical records of 98 patients between 2007- 2012 at our centers were retrieved from the patient registry. Overall survival (OS) was calculated using the Kaplan-Meier method. Results: In our study, with the median follow-up of all patients with cutaneous MM of 46.3 months, the median OS rate of all cases was 43.6 months and 5-year OS was 48.6%. However, five-year OS rates of patients with localized disease (stage I-II) and node involvement (stage III) were 60.3% and 39.6%, respectively. The median OS of stage IV patients was 8.7 months and 1-year OS rate was 26.2%. We showed that advanced stage, male gender, and advanced age in all patients with MM were significant prognostic factors of OS. Conclusions: Compared with the results of current studies from Western countries, we found similar findings concerning demographical features, histological variables and survival analyses for our patients with cutaneous MM in Turkey.

Keywords: Cutaneous malignant melanoma - survival - prognostic factors - Turkey

Asian Pacific J Cancer Prev, **14 (1)**, 533-537

Introduction

Melanoma is a aggressive tumor of the cells, called melanocytes, which give color of the skin and producing melanin pigment. Malignant melanoma (MM) mostly seen especially in light colored skin people and it is the second cancer increasing in frequency after the lung cancer in women (Verma et al., 2006). It is 2-3% of all the cancers but it is the most death cause among the skin cancers and is still a potentially fatal malignancy in worldwide (MacKie et al., 2007; Markovic et al., 2007; Jemal et al., 2009, Reed et al., 2012). Melanoma can metastasize either by the lymphatic or by the hematogenous spread and metastasis may arise from very small tumors. However, about 90% of MM are diagnosed as primary tumors without any metastatic evidence (Mervic, 2012). Therefore, early diagnosis and urgently surgical excision in early stage are the most important in patients with MM. However, patients with advanced or metastatic MM has a poor prognosis with a median survival time of approximately 8 months. Additionally, the 5-year survival rates are 68-93% in stages I-II, 45-49% in stage III, and 11-18% in stage IV disease (Tas et al., 2006; Chi et al., 2011)

The significant prognostic factors in cutaneous MM are the tumor thickness, ulceration, mitotic rate, Clark level of invasion, anatomic location, age, and sex. Similarly, the strongest predictive factors of survival are the Breslow tumor thickness, the presence or absence of ulceration in stages I-II, total number of lymph node metastases, tumor burden, and primary tumor ulceration in stage III and anatomic location of metastases in stage IV (Mervic, 2012). However, important and independent predictive factors of primary cutaneous MM survival that are not recently in the American Joint Committee on Cancer (AJCC) staging system include the age, gender and the anatomic location of primary disease (Balch et al., 2001).

The aim of this study to contribute to the current but limited English literature about recent treatment approaches, clinical features, and survival analyses of Turkish patients with cutaneous MM.

*[1]Department of Medical Oncology, Sakarya University Education and Research Hospital, Sakarya, [2]Department of Medical Oncology, Mugla Sitki Kocman University Education and Research Hospital, Mugla, [3]Clinic of Medical Oncology, Dr. Abdurrahman Yurtarslan Oncology Education and Research Hospital, Ankara, [4]Division of Medical Oncology, Department of Internal Medicine, Abant Izzet Baysal University Faculty of Medicine, Duzce, Turkey *For correspondence: ozgurtanriverdi@hotmail.com*

Materials and Methods

Patients and study variables

The study was planned as a retrospective study for survival analyses on cutaneous MM patients. The subjects of the present study were selected from 154 patients with cutaneous MM who were treated at the outpatient department of our institutions between April 2007 and June 2012.

We studied a total of 98 selected patients with cutaneous MM whose pathologically diagnosis was confirmed and medical file information was complete. In situ melanoma patients and non-cutaneous MM not included in the study.

Study variables were based on current published prognostic and predictive factors in addition to basic demographic characterization, and included features of the patients (age at diagnosis, gender, and performance status), disease (anatomic location of primary tumor, histological subtype, presence of ulceration, Breslow tumor thickness, Clark level of invasion, stage, and site of recurrence), treatment (type of surgical treatment, presence of lymph node dissection, adjuvant or palliative systemic molecules used), and follow-up (survival analysis).

The AJCC staging system with 6th edition was used for either clinical or histopathological staging. Study group was classified into two different age groups: 65 years or younger and more than 60 years old. The anatomical regions of the primary tumors were divided into four groups: head and neck, trunk, upper extremities, and lower extremities. Breslow tumor thickness was divided into four groups according to the AJCC staging system: less than and equal to 1 mm, 1.01-2 mm, 2.01-4 mm, and >4 mm. The level of tumor invasion was classified according to the stratification system described by Clark. Similarly, the histological subtype of primary tumor was divided into four groups: superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), and acral lentiginous melanoma (ALM).

Ethics

The protocol for this retrospective study was compatible with the local ethical guidelines. The study was approved by the Academic Committees in our center and written informed consent was obtained from all patients.

Statistical analyses

The data are expressed as the mean±standard deviation or the median and interquartile range (25-75%). The distribution of variables was analyzed with the Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with a two-tailed, independent Student's t test. Nonparametric variables were analyzed with the Mann-Whitney U test. However, qualitative parameters were analyzed with the Chi-square test and Fisher's test. The Kruskal-Wallis test was used for comparisons between clinical and demographic variables.

Overall survival (OS) were calculated by the use Kaplan-Meier method. The duration of OS was analyzed from the histopathological diagnosis of MM until death or until the date of the last control for patients still alive. Multivariate analysis of prognostic factors for OS were calculated by the use of the Cox proportional-hazards model.

A significance value of $P<0.05$ was accepted as statistically significant. All of the analyses were performed using the Statistical Program for Social Sciences (SPSS) version 15

Results

General distribution

The distribution of clinical and histopathological characteristics are shown in Table 1. All of the patients were Caucasians. Of all patients, 51 (52%) were male and 47 (48%) were female.

The age of the all patients ranged from 41-89 years (median: 68.2 years). However, women were significantly younger at diagnosis than men (P=0.042).

As primary sites of disease, 39 (40%) patients had it in head and neck, 25 (26%) in lower extremities, 23(23%) in upper extremities, and 11 (11%) in trunk. The NM was the most common histological sub-type (n=41, 42%).

Of the 98 patients with complete staging evaluation, the incidence of stage I-II (localized disease) was 59 (60%), followed by stage III (nodal disease) and stage IV (metastatic disease) with the incidence of 22 (22%) and 17 (18), respectively.

Analyses of surgical treatment

All patients with localized disease (n=59) had undergone complete resection: 24 and 35 patients received local or extended surgery, respectively. However, among the 22 patients with nodal involvement, followed by local excision, extended surgery, and extended excision with regional lymph node dissection were performed in 1,3,18 cases, respectively. Tumor invasion clustered mainly at Clark level III and IV (Table 1). Additionally, about of 28% lesions were ulcerated (Table 1).

In 22 patients with stage III, for the 36% cases (n=8) had only one metastatic lymph node. Sentinel lymph node biopsy was performed in 11% patients with clinically node negative status.

Analyses of adjuvant therapy

Among patients had stage I-III diseases, 41 (42%) cases had intermediate-dose interferon (IFN)α-2b treatment and 11 (11%) patients received adjuvant radiation. However, 7 (7%) cases received no adjuvant therapy include biological, chemotherapeutical, and radiation.

Analyses of palliative systemic treatment for stage IV disease

Local recurrence was seen as the most common (n=38, 47%) in patients with stage I-III (n=81). Distant metastases was 12 (15%) patients in stage I-III (n=81). In 17 (18%) patients with metastatic stage at presentation, the most common solid metastasis sites were lung (n=7, 41%) and brain (n=4, 24). The 5-year disease-free survival rate of 81 patients with stage I-III was 14.8 (95%CI, 8.15%-21.3%). In metastatic setting first line treatment 21 (76%) patients had temozolamide, 2 (12%) patients had IFNα-2b, 2 (12%)

patients had cisplatin-dacarbazine regimen. Additionally, temozolamide treatment were given to 4 (24%) patients, carboplatin-paclitaxel combination treatment were given to 11 (65%) patients, and cisplatin-dacarbazine regimen were given to 2 (31%) patients in first progression of disease. Five patients (29%) had received carboplatin-paclitaxel chemotherapy, five patients (29%) received ipilimumab with humanitarian-early access program in Turkey, at the second and third progression of disease.

Analyses for overall survival

The median follow-up of 98 patients with cutaneous MM was 46.3 months (range:3-57 months). The median OS of all cases was 43.6 months (range:3-49 months). A median 5-year OS was 48.6%. In correlation analysis, OS was significantly negatively correlated with male, advanced stages, and elderly patients (r=-0.495, P=0.038; r=-0.506, P=0.038; and r=-0.564, P=0.044), but the location of primary tumor did not correlated with survival (r=0.298, P=0.345). Univariate and multivariate analyses for OS has been shown in Tables 2 and 3.

Table 1. Characterizations at the Diagnosis of all Patients in Study

Characteristics		n	%
	Patients (n)	98	100
Age (years)	≤65	43	44
	≥65	55	56
Gender	Male	51	52
	Female	47	48
Anatomic location of primary tumor			
	Head and neck	39	40
	Trunk	11	11
	Upper extremities	23	23
	Lower extremities	25	26
Histological sub-type	SSM	20	20
	NM	41	42
	LMM	6	6
	ALM	13	13
	Unknown	18	19
Ulceration status	With	27	28
	Without	63	64
	Unknown	8	16
Breslow thickness	≤1 mm	14	14
	1.01-2.0 mm	23	23
	2.01-4 mm	22	23
	>4 mm	8	8
	Unknown	31	32
Clark level	1	4	5
	2	8	8
	3	19	19
	4	14	14
	5	13	13
	Unknown	40	41
Surgical treatment	Excision	25	26
	Wide excision	38	39
	WE and LND	18	18
	Not-surgical approaches	6	6
	Incision	11	11
Stage	I	23	23
	II	36	37
	III	22	22
	IV	17	18

*SSM, superficial spreading melanoma; NM, nodular melanoma; LNM, lentigo maligna melanoma; ALM, acral lentiginous melanoma

Table 2. Univariate Analyses of Prognostic Factors for Overall Survival in Patients with Cutaneous Malignant Melanoma

Factors		Median OS (m)	P value*
Age (years)	≤65	53.4	0.046*
	≥65	43.5	
Gender	Male	38.6	0.048*
	Female	43.7	
Anatomic location of primary tumor			
	Head and neck	41.7	0.145
	Trunk	47.1	
	Upper extremities	51.7	
	Lower extremities	55.4	
Histological sub-type	SSM	46.4	0.265
	NM	43.3	
	LMM	46.9	
	ALM	51.3	
Ulceration status	With	42.1	0.094
	Without	53.4	
	Unknown	46.4	
Breslow thickness (mm)	≤1	52.1	0.105
	1.01-2.0	49.3	
	1/2/04	47.2	
	>4	42.4	
Stage	I	55.9	0.027*
	II	52.2	
	III	29.4	
	IV	6.2	

*P; A two tailed p value of <0.05 was considered statistically significant. m, months; SSM, superficial spreading melanoma; NM, nodular melanoma; LNM, lentigo maligna melanoma; ALM, acral lentiginous melanoma

Table 3. Multivariate Analyses of Prognostic Factors for Overall Survival in Patients with Cutaneous Malignant Melanoma

Factors	Hazard ratio (95%CI)	P value*
Age (≤65 years vs. ≥65 years)	1.8 (1.1-4.6)	0.034*
Sex (male vs. female)	1.45 (1.21-6.1)	0.042*
Anatomic location of primary tumor (head and neck vs. extremities)	1.32 (0.45-6.8)	0.145
Histological sub-type (NM vs. SSM and ALM)	1.1 (0.76-4.35)	0.182
Ulceration status (with vs. without)	1.47 (0.98-2.2)	0.174
Breslow thickness (mm)	1.24 (0.75-2.67)	0.193
Stage (stage I-II vs. III-IV)	1.24 (1.18-7.69)	0.045*

*P; A two tailed p value of <0.05 was considered statistically significant. m, months; SSM, superficial spreading melanoma; NM, nodular melanoma; LNM, lentigo maligna melanoma; ALM, acral lentiginous melanoma

The median OS of 59 patients with early stages (localized disease; stage I-II) was 55.4 months (range:12-56 months). The 5-year OS was 60.3%. The NM, deeper tumor depth, extensive tumor invasion, presence of tumor ulceration, presence of recurrence with visceral metastasis, male gender, and advanced age were found to be strongest poor prognostic factors for OS in patients with stage I-II disease.

Similarly, the median OS of 22 node positive patients (stage III) was 29.4 months (range:8-34 months) and the 5-year OS was 39.6%. OS of patients in this stage was significantly negative correlated with recurrence after IFN treatment (r=-0.521, P=0.041.) and male gender (r=0.498, P=0.046). However, other variables include age, number

of metastatic lymph nodes and location of primary tumor were not found to be significant predictive factors of prognosis on survival.

In patients with metastatic stage (stage IV), the median OS of 17 patients was 6.2 months (range:3-9). The 1-year OS rate was 26.2%. The responses to systemic therapy, distant visceral metastases, platin-based regimen, and multiple metastatic sizes were found to be poor prognostic factors for OS. However, age and gender and location of primary tumor did not effect on survival.

Discussion

In this study, we found that prognostic factors of cutaneous MM diagnosed in Turkish population not differ from those current reported in Western patients with cutaneous MM. We showed that advanced stage, male gender, and advanced age in all patients with MM were the significant prognostic factors of OS. Additionally, histological sub-type, deeper tumor depth, extensive tumor invasion, presence of tumor ulceration, presence of recurrence with visceral metastasis, male gender, and advanced age in patients with localized disease (stage I-II) whereas recurrence after IFN treatment and male gender in patients with node positive MM (stage III). However, in stage IV patients these strongest prognostic factors were found to be distant visceral metastases, and multiple metastatic sizes.

In the previously current studies, the most important prognostic factors are the tumor thickness and ulceration in stages I and II, number of lymph node in stage III and anatomic region of metastases in stage IV. In additionally, negative prognostic factors include melanoma lesions located on the head and neck, and trunk, patient age more than 60 years, male gender and racial status (Tas et al., 2006; Uehara et al., 2009; Chi et al., 2012; Mervic, 2012).

In our study, with the median follow-up of all patients with cutaneous MM of 46.3 months, the median OS rate of all cases was 43.6 months and 5-year OS was 48.6%. However, Five-year OS rates of patients with localized disease (stage I-II) and node involvement (stage III) were 60.3% and 39.6%, respectively. The median OS of stage IV patients was 6.2 months and 1-year OS rate was 26.2%. These results of our analysis were reasonably worse than those observed in the Western recent reports and the current data from United States (5-year survival rate of 91.4% in data of United States) (Lindholm et al., 2004; Gimotty et al., 2005; Lasithiotakis et al., 2008; Chi et al., 2011). However, the most important limitation of our study was the small sample size and this situation was limited our results for analysis of survival.

In previously study, stage of cutaneous MM and Breslow tumor thickness have been repeatedly demonstrated to be the most strongest prognostic factor for MM. Many studies reported a high significant correlation between increasing tumor thicknesses and 10-year survival rate for melanoma (Mervic, 2012). In the study of AJCC melanoma staging system, 10-year survival rate in all of 11,841 patients with tumors thinner than 1.0 mm was 92%. However, ten-year survival in 8,046 patients with melanoma tumors thicker than 1.01 mm but thinner than 2.0 mm was 80%, and it was 63% in the 5,291 patients with melanomas measuring from 2.01-4.0 mm. Ten-year survival rate in the 2,461 patients with tumors thicker than 4.0 mm was 50%. Finally, Breslow tumor thickness is the most important and significant prognostic factor of survival at the primary tumor stage in patients with localized melanoma (Gimotty et al., 2005; Tas et al., 2006; Chi et al., 2011; Mervic, 2012). The results of our study are consistent with the basic information in the current literature.

Previously studies have showed the negative association of primary tumor ulceration with disease survival (Mervic, 2012). In the population based study, 5-year survival in patients with tumor ulceration was 66.2%, compared to 91.6% in patients with non-ulceration melanoma (Spatz et al., 2003; Eggermont et al., 2012; Mervic, 2012).

In the 2010 AJCC staging system, Clark level of tumor invasion is no longer suggested as a current staging criterion. However, if there are not data about the mitotic index of tumor (i.e, our study due to technical problem) or the mitotic index cannot be accurately assessed in the thin tumors, Clark level of tumor invasion can still provide additional prognostic assessment (Thompson et al., 2010; Mervic, 2012). However, in previous studies demonstrated that patients with level II, level III, level IV, and level V had the 5-year survival of 98.8%, 92.5%, 76.7%, and 75%, respectively (Barnhill et al., 1996; Tas et al, 2006; Mervic, 2012). The results of our study are consistent with the basic information in the current literature. However, tumor invasion level was not demonstrated to be an independent prognostic factor on survival in our study.

Cutaneous MM on the trunk, head and neck have a worse prognosis than melanomas located on upper and lower extremities. The anatomic location of a MM is an independent predictive factor of survival in patients with cutaneous MM (Chao et al., 2004; Mervic, 2012). The results of our study are consistent with the basic information in the current literature.

For patients with metastatic disease, the survival were measured in months because of only a minority of patients with MM live beyond one year (Chi et al., 2011). These patients are usually treated with systemic biological and/or chemotherapy. In previously studies, aggressive treatment including combination therapy with chemotherapeutical and immunotherapy or targeted therapy failed to show additive efficacy (Hauschild et al., 2009; Hainsworth et al., 2010; O'day et al., 2010). The results of treatment response is inadequate because of limited number of treated patients with stage IV.

In conclusion, compared with the results of current studies from Western countries, we found similar findings concerning demographical features, histological variables and survival analyses for our patients with cutaneous MM in Turkey. However, some findings such as histological sub-type are not similar compared with Asian population-based studies (Chi et al., 2011).

References

Balch CM, Buzaid AC, Soong SJ, et al (2001). Final version of

the American joint committee on cancer staging system for cutaneous melanoma. *J Clin Oncol*, **19**, 3635-48.
Barnhill RL, Fine JA, Roush GC, Berwick M (1996). Predicting five-year outcome for patients with cutaneous melanoma in a population-based study. *Cancer*, **78**, 427-32.
Chao C, Martin RC, Ross MI, et al (2004). Correlation between prognostic factors and increasing age in melanoma. *Ann Surg Oncol*, **11**, 259-64.
Chi Z, Li S, Sheng X, et al (2011). Clinical presentation, histology, and prognoses of malignant melanoma in ethnic Chinese: a study of 522 consecutive cases. *BMC Cancer*, **11**, 85-95.
Gimotty PA, Botbyl J, Soong SH, Guerry D (2005). A population-based validation of the American Joint Committee on Cancer melanoma staging systemç. *J Clin Oncol*, **23**, 8065-75.
Hainsworth JD, Infante JR, Spigel DR, et al (2010). Bevacizumab and everolimus in the treatment of patients with metastatic melanoma: a phase 2 trial of the Sarah cannon oncology research consortium. *Cancer*, **116**, 4122-9.
Hauschild A, Agarwala SS, Trefzer U, et al (2009). Results of a phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma. *J Clin Oncol*, **27**, 2823-30.
Jemal A, Siegel R, Ward E, et al (2009). Cancer statistics, 2009. *CA Cancer J Clin*, **59**, 225-49.
Lasithiotakis K, Leiter U, Meier F, et al (2008). Age and gender are significant independent predictors of survival in primary cutaneous melanoma. *Cancer*, **112**, 1795-804.
Lindholm C, Andersson R, Dufmats M, et al (2004). Invasive cutaneous malignant melanoma in Sweden, 1990-1999. A prospective, population-based study of survival and prognostic factors. *Cancer*, **101**, 2067-78.
MacKie RM, Bray C, Vestey J, et al (2007). Melanoma incidence and mortality in Scotland 1979-2003. *Br J Cancer*, **96**, 1772-7.
Markovic SN, Erickson LA, Rao RD, et al (2007). Malignant melanoma in the 21st century, part 2: staging, prognosis, and treatment. *Mayo Clin Proc*, **82**, 490-513.
Mervic L (2012). Prognostic factors in patients with localized primary cutaneous melanoma. *Acta Dermatovenerologica*, **21**, 27-31.
O'Day S, Hodi FS, McDermott DF, et al (2010). A phase III, randomized, double-blind, multicenter study comparing monotherapy with ipilimumab or gp100 peptide vaccine and the combination in patients with previously treated, unresectable stage III or IV melanoma. *J Clin Oncol*, **28**, 4.
Reed KB, Brewer JD, Lohse CM, et al (2012). Increasing incidence of melanoma among young adults: an epidemiological study in Olmsted County, Minnesota. *Mayo Clin Proc*, **87**, 328-34.
Spatz A, Cook MG, Elder DE, et al (2003). Interobserver reproducibility of ulceration assessment in primary cutaneous melanomas. *Eur J Cancer*, **39**, 1861-5.
Tas F, Kurul S, Camlica H, Topuz E (2006). Malignant melanoma in Turkey: a single institution's experience on 475 cases. *Jpn J Clin Oncol*, **36**, 784-9.
Thompson JF, Soong SJ, Balch CM, et al (2011). Prognostic significance of mitotic rate in localized primary cutaneous melanoma: an analysis of patients in the multi-institutional American joint committee on cancer melanoma staging database. *J Clin Oncol*, **29**, 2199-205.
Uehara S, Kamo R, Harada T, Ishii M (2009). Survival analysis of malignant melanoma in Japan-multivariate analysis of prognostic factors. *Osaka City Med J*, **55**, 35-52.
Verma S, Quirt I, McCready D, et al (2006). Systematic review of systemic adjuvant therapy for patients at high risk for recurrent melanoma. *Cancer*, **106**, 1431-42.