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Research Article

Retrospective evaluation of malignant melanoma patients: A single-center experience

Malign melanom hastalarının retrospektif değerlendirilmesi: Tek merkezli bir deneyim

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Abstract

Introduction: Melanoma is a cancer arising from the malignant transformation of melanocytes. It is mostly seen in the skin, eyes, mucosal membranes, and meninges. Melanoma is one of the fastest rising of all cancers in the world.

Methods: We retrospectively examined the medical records of adult patients who were diagnosed with melanoma between January 2005 and December 2013 according to the Hospital-Based Cancer Registry (HBCR) of Hacettepe University Oncology Hospital.

Results: A total of 338 patients [193 (57.1%) men and 145 (42.9%) women] were included in the study. The male to female ratio was 1.3/1. The mean age of patients was 55.2±15.2 years (minimum-maximum: 16-87 years). The rate of male patients was higher in patients with cutaneous and uveal melanoma (respectively, 56.8% and 58.6%), whereas the rate of female patients was higher in patients with mucosal melanoma (female: 55.6% and male: 44.4%; respectively, p=0.746 and p=0.518). The median follow-up time was estimated to be 27.7 months (1-103 months). During follow-up period, 127 (37.6%) patients died, and 16 (4.7%) patients were lost to follow-up. The median overall survival time was 76.3 months. The 5-year survival rate was 53%. When all patients were evaluated according to melanoma subtypes, patients with melanoma of unknown primary origin had the lowest median survival time (6.4 months).

Conclusions: It is necessary to increase the awareness of people about melanoma and to make physicians more sensitive about skin examination in order to detect cutaneous melanomas in the early stages.

Keywords: Melanoma, demographic factors, pathology, survival

Öz

Giriş: Melanom, normal melanositlerin malign transformasyonu ile oluşan bir kanserdir. En fazla ciltte olmak üzere gözde, mukozalarda ve meninkslerde görülmektedir. Melanom tüm kanserler arasında sıklığı en fazla artan kanser türüdür.

Yöntem: Hacettepe Üniversitesi Onkoloji Hastanesi'nin, Hastaneye Dayalı Kanser Kayıt Merkezine göre Ocak 2005- Aralık 2013 tarihleri arasında melanom tanısı alan yetişkin hastaların tıbbi kayıtlarını retrospektif olarak inceledik.

Bulgular: Çalışmaya 193'ü (%57,1) erkek ve 145'i (%42,9) kadın olmak üzere toplam 338 hasta alındı. Çalışmaya alınan hastaların, erkek/ kadın oranı 1.3/1 olarak bulundu. Hastaların yaş ortalaması 55.2±15.2 idi (minimum ve maksimum: 16-87 yaş). Cilt ve uveal melanomlu hastalarda erkek cinsiyet daha fazla sıklıkta iken (%56,8 ve %58,6), mukozal melanomlu hastalar arasında kadın cinsiyetin daha baskın olduğu bulundu (kadın: %55,6, erkek %44,4; sırasıyla p=0.746ve p=0.518). Çalışmaya alınan hastalarda ortanca izlem süresi 27,7 ay (1-103 ay) olarak saptandı. Bu süre içinde hastaların 127'si (%37,6) kaybedildi, 16 hasta (%4,7) ise izlem-dışı kaldı. Ortanca genel sağkalım süresi tüm melanomlu hastalar için 76,3 ay iken, 5 yıllık sağkalım süresi %53 olarak bulundu. Melanom tipine göre ayrı ayrı hastalar değerlendirildiğinde, kökeni bilinmeyen melanomlu olgularda ortanca sağkalım en kötü idi (6,4 ay).

Sonuç: Kişilerin melanom konusunda farkındalıklarının artırılması ve hekimlerin cilt muayenesi konusunda daha duyarlı hale getirilmesi, kütanöz melanomların erken evrelerde tespit edilebilmesi için gereklidir.

Anahtar kelimeler: Melanom, demografik faktörler, patoloji, sağkalım

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Introduction

Melanoma is a cancer arising from the malignant transformation of melanocytes. It is mostly seen in the skin, eyes, mucosal membranes, and meninges [1]. Melanoma is one of the fastest rising of all cancers in the world. The lifetime risk of developing melanoma in the American population was 1/600 in 1965 and 1/150 in 1985. According to the data collected between 2004 and 2006, this risk was significantly increased to 1/37 in men and 1/56 in women [2]. Diagnosis, staging, treatment, and survival rate differ according to melanoma subtypes [3]. In the United States (US), melanoma is the fifth most common cancer among men and the seventh most common cancer among women [4]. The median age of melanoma diagnosis is 59, whereas 21% of melanoma patients are under 45 years of age at diagnosis [5]. While melanoma is the most common cancer in American women aged 25-29 years, it ranks second after breast cancer in American women aged 30-34 years [2]. The true incidence of melanoma has increased more rapidly when compared to incidence rates of other cancers.

Despite the fact that there has been an increase in the incidence of melanoma, melanoma treatments have improved significantly in recent years. Both adjuvant treatments and BRAF/MEK inhibitors and anti-cytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA-4)/ anti programmed cell death 1 (anti-PD-1) antibodies used in the treatment of metastatic melanoma patients have reduced the risk of recurrence and improved survival.

In Turkey, the incidence of melanoma is lower. In parallel with this, there is not enough data for melanoma in our country [6]. In this study, we aimed to retrospectively examine demographic, clinical and pathological data, treatment modalities, survival and factors affecting survival in melanoma patients followed in our hospitals between 2005 and 2013.

Methods

We retrospectively examined the medical records of 338 adult patients who were diagnosed with melanoma between January 2005 and December 2013 according to the Hospital-Based Cancer Registry (HBCR) of Hacettepe University Oncology Hospital. Information on gender, age and date of diagnosis, tumor localization, size and histological subtype, types of melanoma (cutaneous, mucosal, choroidal), Breslow depth, Clark level, presence of spontaneous regression and ulceration, mitotic index, presence of satellite nodules and capsular invasion, BRAF mutation status, nodal involvement, surgical margin, and Tumor, Nodes, Metastasis (TNM) stage were obtained from pathology reports and operation notes. Metastatic sites detected at the time of diagnosis or at follow-up were recorded. We also recorded immunotherapy, targeted therapy and chemotherapy regimens and their start and stop times, number of cycles, curative or palliative surgical procedures and their dates, and curative or palliative radiotherapy and their dates.

Ethical Approval

Our study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Board (Decision Date: 24/1/2014 and Decision No: GO 14/62).

Patient Evaluation

Treatment response assessment was made after 2-3 cycles of chemotherapy and at the end of chemotherapy by comparing imaging examinations performed at baseline staging in patients treated with chemotherapy. The RECIST criteria version 1.1 [Complete Response (CR): disappearance of all non-target lesions, Partial Response (PR): at least a 30% decrease in the sum of the diameters of target lesions, Progressive Disease (PD): at least a 20% increase in the sum of the diameters of target lesions/appearance of new lesions, and Stable Disease (SD): it does not meet either PR or PD criteria] were used for treatment response assessment. Clinical and laboratory parameters of patients were also monitored. Metastatic patients treated with targeted therapy were followed up monthly until progression.

Statistical analysis

While continuous variables were expressed as mean±standard deviation or median (minimum-maximum), categorical variables were expressed as number (n) and percentage (%). While the Student's t-test and analysis of variance (ANOVA) were used for comparing continuous variables between two groups, the Pearson's chi-square test was used for comparing categorical variables between two groups. Overall survival was estimated by the Kaplan-Meier method and compared by the Log-rank test. However, the Kaplan-Meier method was used to estimate the life expectancy and 95% confidence interval for each risk factor. All statistical analyzes were performed as two-sided hypotheses with a 5% significance level and a 95% confidence interval. A p-value less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS 18.0 Statistical Package Program (SPSS Inc. Chicago, IL, USA).

Results

A total of 338 patients [193 (57.1%) men and 145 (42.9%) women] were included in the study. The male to female ratio was 1.3/1. The mean age of patients was 55.2±15.2 years (minimum-maximum: 16-87 years). The mean age was similar for both men and women (p=0.652) but was statistically significantly different according to melanoma subtypes (p=0.001). Patients with mucosal melanoma had a higher mean age than patients with cutaneous and ocular melanoma (respectively, 68, 54 and 56 years).

The rate of male patients was higher in patients with cutaneous and uveal melanoma (respectively, 56.8% and 58.6%), whereas the rate of female patients was higher in patients with mucosal melanoma (female: 55.6% and male: 44.4%; respectively, p=0.746 and p=0.518). The sociodemographic and tumor characteristics of all patients included in the study are shown in Table 1.

All treatments administered to patients and their frequencies are shown in Table 2. In metastatic patients, the median number of cycles was 6 for

primary-level palliative care, 4 for secondary-level palliative care, 3.5 for tertiary-level palliative care, and 5.5 for quaternary-level palliative care. While 17 patients received ipilimumab therapy, 16 patients received vemurafenib therapy.

Table 1. Sociodemographic and tumor characteristics

	n	%
Gender		
Female	145	42.9
Male	193	57.1
Age (years)		
< 40	56	16.6
40-64	192	56.8
≥65	90	26.6
Localization		
Ocular	145	42.9
Skin	169	50.0
Head-neck	46	27.2
Trunk	31	18.3
Upper extremity	33	19.5
Lower extremity	45	26.7
Localization undetermined	14	8.3
Mucosal	18	5.3
Rectum	6	33.3
Oral mucosa	12	66.7
Undetermined	6	1.8
Histology		
Histology of skin	169	50.0
Acral lentiginous melanoma	6	3.5
Nodular melanoma	38	22.5
Lentigo maligna melanoma	10	5.9
Superficial spreading melanoma	58	34.4
Histology undetermined	57	33.7
Ocular melanoma	145	43.0
Mucosal	18	5.3
Undetermined	6	1.7
Metastatic site		
Brain	20	5.9
Lung	34	10.1
Liver	36	10.7
Skin	28	8.3
Abdomen	16	4.7

Table 2. All treatments administered to patients and their frequencies

	n	%
Surgical	251	74.3
Tumor excision	134	54.0
Enucleation	106	41.9
Local treatment		
TTT	10	4.0
Radiotherapy	68	78.2
Adjuvant	19	27.9
Palliative	13	19.1
CyberKnife	21	30.9
Brachytherapy	15	22.1
Adjuvant Interferon Therapy	61	74.4
Primary-level palliative care		
Temozolomide	78	75.7
Temozolomide+cisplatin	8	7.8
Vemurafenib	6	5.8
Cisplatin+DTIC	5	4.9
Dartmouth Protocol	5	4.9
Others	1	1.0
Secondary-level palliative care		
Temozolomide	1	2.4
Temozolomide+cisplatin	1	2.4
Ipilimumab	14	34.1
Vemurafenib	6	14.6
Cisplatin+DTIC	1	2.4
Dartmouth Protocol	5	12.2
Paclitaxel	5	12.2
Others	8	19.4
Tertiary-level palliative care		
Ipilimumab	3	23.1
Vemurafenib	3	23.1
Dartmouth Protocol	1	7.7
Paclitaxel	5	38.5
Others	1	7.7
Quaternary-level palliative care		
Vemurafenib	1	50.0
Paclitaxel	1	50.0

Vemurafenib-related side effects and their frequencies are shown in Table 3.

Table 3. Vemurafenib-related side effects and their frequencies

	Grade	Number (n=16)
Arthralgia	2	6
Skin dryness	1	2
	2	8
Fatigue	1	1
	2	8
Keratoacanthoma	3	1
Nausea	1	1
	2	2
Alopecia	2	1
Actinic keratosis	1	1
	2	2
Skin tumor	-	0

Survival Analysis

The median follow-up time was estimated to be 27.7 months (1-103 months). During follow-up period, 127 (37.6%) patients died, and 16 (4.7%) patients were lost to follow-up. The median overall survival time was 76.3 months. The 5-year survival rate was 53%. When all patients were evaluated according to melanoma subtypes, patients with melanoma of unknown primary origin had the lowest median survival time (6.4 months). While the median survival time could not be determined in patients with choroidal melanoma, it was 61 months in patients with cutaneous melanoma and 9.9 months in patients with mucosal melanoma. There was a statistically significant difference in the median survival time between melanoma subtypes ($p<0.001$).

The median survival time was also examined according to histological subtypes in patients with cutaneous melanoma. While the median survival time could not be determined in patients with acral lentiginous melanoma (66.9 months), lentigo maligna melanoma (86.1 months) and superficial spreading melanoma (0.1 months), it was 59.4 months in patients with nodular melanoma. It was 30.4 months in patients with cutaneous melanoma of unknown primary origin. Tumor stage was determined to be a prognostic factor for survival in patients with cutaneous melanoma ($p<0.001$) (Figure 1).

Similarly, the survival analysis was performed after patients with cutaneous melanoma were classified into 3 groups as lymph node negative, lymph node positive, and distant metastasis. Accordingly, there was a statistically significant difference in the median survival time between these groups ($p<0.001$). While the median survival time could not be determined in LN-negative patients, it was 43.3 months in LN-positive patients and 16.2 months in patients with distant metastasis. Survival curves are shown in Figure 2.

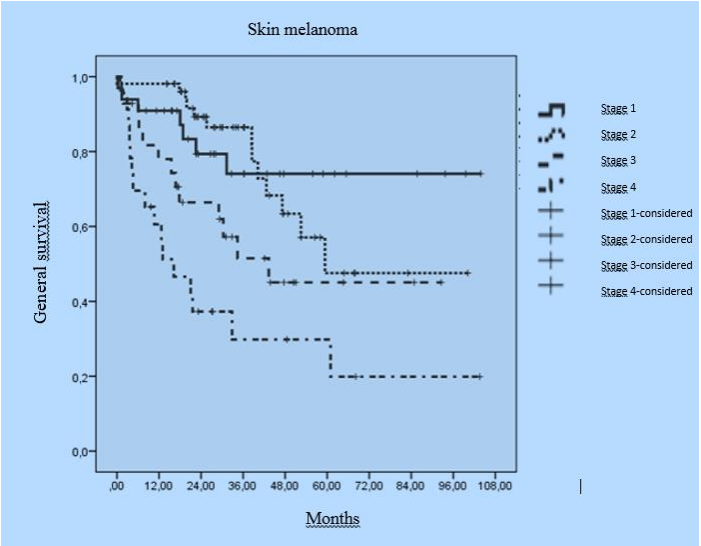

Figure 1. Overall survival curves according to stage in patients with cutaneous melanoma
Kaplan-Meier survival plot of overall survival according to stage, ($p<0.001$; log-rank test)

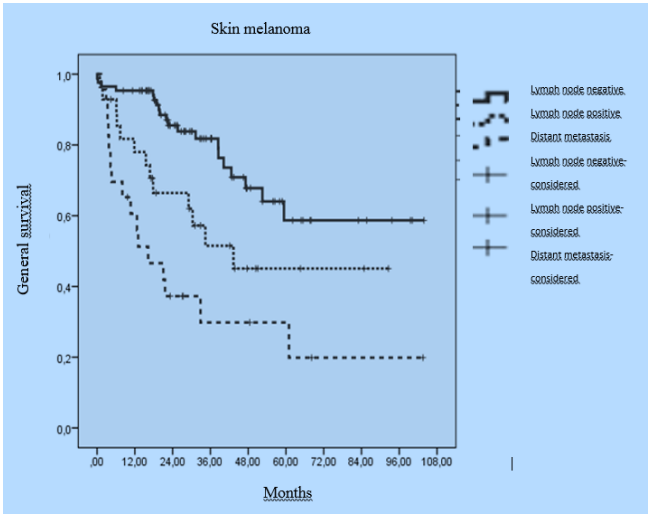

Figure 2. Overall survival curves according to metastasis in patients with cutaneous melanoma
Kaplan-Meier survival plot of overall survival according to metastasis, ($p<0.001$; log-rank test)

Discussion

In this study, we aimed to evaluate the clinical and pathological features of adult patients diagnosed with melanoma at Hacettepe University Hospitals between 2005 and 2013. Our study revealed that the male to female ratio was 1.3/1 and that the mean age of patients was 55.2±15.2 years. The mean age for patients with cutaneous, mucosal, and choroidal melanoma was respectively 56, 68, and 54 years. Tas et al. determined that the male to female ratio was 1.1/1 and that the median age of diagnosis was 50 years [7]. Chang et al. retrospectively analyzed the medical records of 84,836 patients diagnosed with melanoma in the US between 1985 and 1994 in the National Cancer Database and reported that the mean age of patients with cutaneous melanoma was 55.3 years and the male to female ratio was 1.19/1 [8]. The same study showed that patients with mucosal melanoma were diagnosed at older age than patients with cutaneous melanoma (respectively, 67 and 55 years) [8]. The mean ages of patients with all melanoma subtypes in our study were consistent with both the studies conducted in our country [7] and the US SEER data [8].

Our study revealed that the rate of male patients was higher in patients with cutaneous and uveal melanoma, whereas the rate of female patients was higher in patients with mucosal melanoma. In consistent with our findings, the SEER database demonstrated that the incidence of cutaneous and ocular melanomas was higher in male patients [8]. Male patients constituted 52% of ocular melanoma cases and 54.3% of cutaneous melanoma cases. Female patients constituted 63.5% of mucosal melanoma cases. The main reason for this difference may be particularly related to the fact that these types of melanoma are directly exposed to sunlight and that men are more exposed to sunlight in their business life than women.

Melanoma is a malignant tumor of melanocytes that arise from the neural crest and migrate to the epidermis, meninges, uveal tract, and ectodermal mucosa. As a result, melanoma can occur in the skin, eyes, meninges, and all mucosal membranes. They were examined in different titles as cutaneous, ocular and mucosal melanoma in our study since their treatment, staging and prognosis are different.

Our study revealed that 50% had cutaneous melanoma, 5.3% had mucosal melanoma, 42.9% had ocular melanoma, and 1.8% had melanoma of unknown primary origin. In an epidemiological study conducted by Chang et al., they found that 91.2% had cutaneous melanoma, 5.3% had ocular melanoma, 1.3% had mucosal melanoma, and 2.2% had melanoma of unknown primary origin [8]. In a single-center study retrospectively examining cases diagnosed with melanoma between 1991 and 2010 in our country, it was determined that 68% had cutaneous melanoma, 12% had mucosal melanoma, 14% had ocular melanoma, and 4% had melanoma of unknown primary origin [9]. Since the melanoma data from the only two major centers in Turkey have been presented, the incidence rate of ocular melanoma cases seems to be higher than the incidence rates reported in the literature. One of the main reasons for the higher incidence rate of ocular melanoma cases may be that surgeons experienced in choroidal melanoma work in our hospital. Another reason may be that CyberKnife treatment, which has been increasingly used in the treatment

of choroidal melanoma in recent years, exists in our hospital. However, the epidemiological data on the incidence of melanoma subtypes could not be reached because the incidence of melanoma in our country is lower. Although several histological subtypes have been identified in the classification of cutaneous melanomas, there are four major histological subtypes as indicated by studies [10]. The most common histological subtype is superficial spreading melanoma (75%), followed by nodular melanoma (15-30%). Lentigo maligna melanoma (4-15%) and acral lentiginous melanoma (2-8%) are more rarely observed [10-14]. In our study, the most common histological type was superficial spreading melanoma (34.3%), followed by nodular melanoma (22.5%), acral lentiginous melanoma, and lentigo maligna melanoma (5.9%).

It is known that the anatomical origin of cutaneous melanomas is different in men and women. It is frequently derived from the trunk in men and often occurs in the extremities in women. Axial melanomas have a poor prognosis [15]. Our study showed that the most common localizations were the extremities (mostly the lower extremities), head-neck, and trunk, regardless of their gender distribution. Similarly to our results, Tas et al. also reported that cutaneous melanomas were most commonly seen in the extremities with a rate of 43.4% [7].

In our study, when patients with cutaneous melanoma were evaluated at diagnosis, 23.6% had stage 1 melanoma, 39.3% had stage 2 melanoma, 20.0% had stage 3 melanoma, and 17.1% had stage 4 melanoma. The SEER database demonstrated that when 17,329 patients were evaluated at diagnosis, 11.4% had stage 0 melanoma, 50.4% had stage 1 melanoma, 23.2% had stage 2 melanoma, 9.4% had stage 3 melanoma, and 5.5% had stage 4 melanoma. Tas et al. reported that 63.4% had stage 1-2 melanoma, 24.6% had stage 3 melanoma, and 12% had stage 4 melanoma. Our study showed that the number of patients admitted at localized stage was higher in accordance with the literature [7]. The number of patients diagnosed at metastatic stage in Turkey was found to be approximately 2 times more when compared to the American data. The difference between the countries can be attributed to the low awareness of skin cancer and the perception of nevus as a benign disease.

In our study, it was found that lesions were derived from the anal-rectal mucosa in 6 patients with mucosal melanoma and from the head-neck mucosa in 12 patients with mucosal melanoma. Chang et al. found that mucosal melanoma was most commonly located in the head-neck mucosa (53.9%), followed by the anal-rectal mucosa (23.7%) and the female genital mucosa (19.1%) [8]. Although there was no mucosal melanoma of the female genital tract in our screening, other localizations were consistent with data reported in the literature. In another study from Turkey examining 83 patients with mucosal melanoma, it was reported that that mucosal melanoma was most commonly located in the head-neck mucosa (53%), followed by the gastrointestinal tract mucosa (37%) [9].

In our study, when all melanoma patients were examined together, it was found that the median overall survival time was 76.3 months and that the 5-year survival rate was 53%. In a large study of Chang et al. using the US national records, the 5-year survival rate was estimated to be 78.8% [8]. In our study, when the survival of melanoma patients was examined separately according to tumor localization, it was found that patients with cutaneous melanoma had the second longest median survival time, whereas the median survival time could not be determined in patients with choroidal melanoma. It was also shown that patients with mucosal melanoma and melanoma of unknown primary origin had the lowest median survival times (less than one year). Our study revealed that there was a statistically significant difference in the median survival time between melanoma subtypes. Similarly to our results, Tas et al. reported that the 5-year survival rate was highest for patients with ocular melanoma (93.5%), followed by patients with cutaneous melanoma (50.5%), patients with mucosal melanoma, and patients with melanoma of unknown primary origin [9]. The SEER database demonstrated that the 5-year survival rate was highest for patients with cutaneous melanoma (80.8%), followed by patients with ocular melanoma (74.6%), patients with melanoma of unknown primary origin (29%), and patients with mucosal melanoma (25%) [8].

When the data from the US and Turkey are evaluated together, it is seen that melanoma subtypes display different rankings in terms of survival rate and that the survival rate of patients with cutaneous melanoma is lower in Turkey than in the US. This difference can be linked to the fact that the rate of patients with cutaneous melanoma diagnosed at stage 3 and 4 in Turkey is almost twice higher than that of the US.
When cutaneous melanomas were examined in terms of survival rate, the survival rate was highest for patients with lentigo maligna melanoma, followed by patients with superficial spreading melanoma, patients with acral lentiginous melanoma, and patients with nodular melanoma in accordance with the literature. The survival rate was found to be the lowest in patients with cutaneous melanoma of unknown primary origin [8]. Histological subtype was determined to be a prognostic factor for survival in patients with cutaneous melanoma ($p<0.001$).

Charles M et al. examined data from approximately 40,000 patients in the AJCC melanoma database in order to revise the American Joint Cancer Committee (AJCC) staging system for cutaneous melanoma in 2009 and found that tumor stage at the time of diagnosis was the most important prognostic factor [16]. In our study, the survival analysis was performed after patients with cutaneous melanoma were classified into 3 groups as lymph node negative, lymph node positive, and distant metastasis. Accordingly, there was a statistically significant difference in the median survival time between these groups in accordance with the literature.

In our study, while the median survival time could not be determined in LN-negative patients, it was 43.3 months in LN-positive patients and 16.2 months in patients with distant metastasis. Tas et al. found that the median survival time was significantly lower in patients with stage IV metastatic melanoma (9.9 months) [7]. The survival difference in metastatic melanoma patients between these two studies was thought to be due to new drugs recently introduced for melanoma.

While enucleation is the only treatment option for choroidal melanomas until recent years, alternative treatment options are now preferred for protecting the eyes and existing vision. Plaque or charged particle radiotherapy and Gamma Knife or Cyberknife radiosurgery can be performed in selected cases. Cryotherapy, laser photocoagulation, transpupillary thermotherapy (TTT), local resection and less frequently photodynamic therapy, monoclonal therapy are available as local treatment options for small tumors [17, 18]. Our study showed that the most common treatment

option for choroidal melanoma was enucleation, followed by radiotherapy and TTT in accordance with the literature.

Choroidal melanomas differ from cutaneous melanomas both clinically and pathologically. Our study revealed that 24 patients with choroidal melanoma had metastatic sites at the time of diagnosis or at follow-up. In the literature, it has been reported that the liver is the most common site of metastasis in melanoma patients and that liver and other organ metastases are available together in approximately one third of patients [19]. Similarly, our study showed that the liver was the most common site of metastatic spread. It was found that one third of patients had liver and other organ metastases in accordance with the literature.

Many treatments have been tried as adjuvant in high-risk cutaneous melanoma patients undergoing surgery, but only IFN treatment has been shown to make contributions [20]. There were no BRAF inhibitors or immune checkpoint inhibitors in the adjuvant treatment of malignant melanoma during the treatment period of the cases included in the study. A review of studies on adjuvant IFN therapy in different doses and schemes demonstrated that IFN did not make a contribution to overall survival, whereas disease-free survival was increasingly extended especially at higher doses [21]. In our study, adjuvant IFN therapy was used in 60 (35.5%) patients with cutaneous melanoma. High-dose IFN (20 MU/m^2) was administered in only 17.3% of 46 patients having dosage information from among these patients.

Many chemotherapeutics have been tried alone or combined with other agents in patients with metastatic cutaneous melanoma. Studies found that the response rate and duration of response for dacarbazine, the only FDA approved chemotherapeutic agent for metastatic melanoma, were respectively 8-20% and 4-6 months [22]. It has been reported that the results obtained with other chemotherapeutics are similar to those for single-agent therapies [23-26]. Although the response rates to combination therapies are slightly higher, no significant difference has been shown in overall survival between single-agent therapies and combination therapies [22]. The most commonly used chemotherapeutic agents in the world are dacarbazine and its analogue temozolomide. In our study, the most commonly used chemotherapeutic agent was temozolomide with a rate of 73.1%.

While the BRAF mutation is positive in approximately 50% of cutaneous melanomas, the V600E mutation is the most common mutation [27]. A phase III trial involving 675 patients with previously untreated, metastatic melanoma with the BRAF V600E mutation revealed that overall and progression-free survival rates were significantly higher in patients treated with vemurafenib than in patients treated with dacarbazine [28]. In our center, we detected the BRAF mutation in 16 of 51 patients with cutaneous melanoma within the scope of the early access program and administered vemurafenib to them [28]. Our patients received vemurafenib at different treatment steps. In the study conducted on indication, the dose of vemurafenib had to be adjusted due to its side effects in 38% of patients. In our study, the dose of vemurafenib had to be reduced due to fatigue in two patients and could not again be increased up to the recommended treatment dose (2x960 mg) [28]. In addition, the dose of vemurafenib had to be reduced due to arthralgia in one patient and could again be increased up to the recommended treatment dose after appropriate treatment. This patient did not complain again. In the study conducted on indication, the most common side effects were respectively grade 2 or higher arthralgia (21%), rash (18%), and fatigue (13%) [28]. In our study, the most common side effects were respectively rash (8 patients, 50%), fatigue (8 patients, 50%), and arthralgia (6 patients, 37.5%). In the study conducted on indication, 8% of patients had keratoacanthoma and 12% of patients had cutaneous squamous cell carcinoma [28]. In our study, only 1 (6.25%) patient had keratoacanthoma, whereas none of our patients developed cutaneous squamous cell carcinoma.

Although the incidence rate of melanoma in Turkey is low and does not change over time, it is among the 10 most common types of cancers diagnosed for both genders in developed countries [4, 29]. Interestingly, the US data have demonstrated that melanoma is the most rapidly increasing cancer [2]. Although many theories have been developed to explain this increase, one of the most important factors is thought to be an increasing tendency to bronze skin in the modern world. Both natural and non-natural (solarium etc.) methods are used for tanning. Both methods are known to be important risk factors for melanoma [30-32]. Similar trends are also increasing in Turkey. It is thought that it is not wrong to expect an increase in the incidence of melanoma in Turkey. For this reason, it will be appropriate to perform awareness-raising activities on tanning.

Two studies on cutaneous melanoma in Turkey have shown that the rate of patients with stage IV cutaneous melanoma in Turkey is twice higher than that of the US. If melanomas can be diagnosed and treated in the early stages, more than 90% of them can be cured. However, the survival rate is very low in the late stages despite promising improvements in the treatment.

In the light of these information, it is understood that it is necessary to increase the awareness of people about melanoma and to make physicians more sensitive about skin examination in order to detect cutaneous melanomas in the early stages.

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Author Contributions		Author Initials
SCD	Study Conception and Design	MS, SK, IC
AD	Acquisition of Data	MS
AID	Analysis and Interpretation of Data	MS
DM	Drafting of Manuscript	MS, SK, IC
CR	Critical Revision	MS, SK, IC

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