Tumor Biol. (2016) 37:12033–12038
DOI 10.1007/s13277-016-5076-0

ORIGINAL ARTICLE

Retrospective multicenter evaluation of patients diagnosed with mucosal melanoma: a study of Anatolian Society of Medical Oncology

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Received: 28 February 2016 / Accepted: 5 May 2016 / Published online: 12 May 2016

Abstract Mucosal melanoma (MM) is a rare type of cancer that differs significantly from cutaneous melanoma. In this study, we aimed to evaluate clinical and demographical characteristics, prognoses and factors influencing survival, treatment alternatives, and features of different subtypes of the patients. The patients were followed up with and treated in different centers due to their diagnoses of MM. We retrospectively analyzed data of 107 patients who were diagnosed with MM in 14 different institutions in Turkey. The mean age of the patients was 64.5 years. Of the patients, 47 % were female and 53 % were male. The median overall survival (OS) was 17 months, and the mean follow-up duration was 27 months. The 2-year survival rate was 42 %, and the 5-year survival rate was 23 %. The best survival rate appeared in those patients with MM in the head-neck region (median survival rate was 27 months, $P = 0.034$). The most common anatomical site was the head-neck region. In a univariate analysis, variables including age ≥65 years, the anatomical site of the primary lesion other than head and neck region, the metastatic stage of the disease, high levels of lactate dehydrogenase (LDH), and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≥1 were found to be associated with poor survival ($P < 0.05$). However, in a multivariate analysis, only advanced stage disease (HR = 2.70; 95 % CI, 1.64–4.45; $P = 0.000$) and high LDH levels (HR = 2.31; 95 % CI, 1.40–3.80; $P = 0.001$) were determined to be adverse prognostic variables. Primary MM presents a more aggressive behavior and offers a poorer prognosis compared to cutaneous melanoma. Because the disease is rarely seen, is heterogeneous, and lacks randomized studies, issues concerning optimal treatment

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approaches and management and clinical characteristics of the disease have not been clarified yet.

Keywords Mucosal melanoma · Head and neck · Anorectal · Genitourinary

Background

Mucosal melanoma (MM) originates from melanocytes that derive from neural crest cells [1, 2]. MM is a rare variant of melanoma that accounts only for 1.4 % of all cases of melanoma [3]. The disease may arise from any mucosal surface, but it originates primarily from head-neck, anorectal, or vulvovaginal mucosa [4]. For a diagnosis of primary MM, metastatic melanoma must be excluded, and it is important to differentiate in situ melanoma or radial growth phase primary lesions from metastasis [5]. MM is seen frequently in seventh decade, about one decade after cutaneous melanoma [6]. Although cutaneous melanoma is more common in males, MM appears more frequently in females; the female-to-male ratio is 1.85–1 [3]. Vulvovaginal melanoma is the most common subtype of MM in females [7], whereas the most common MM subtype in males is the head-neck. Although the incidence of cutaneous melanoma is increasing, the incidence of MM is constant [6]. Risk factors for developing MM have not been determined yet. Factors that play significant roles in the development of cutaneous melanoma, such as tobacco, formaldehyde, and ultraviolet radiation, have no significant role in the development of MM [8–11]. Occult localization of the disease and rich vascularization cause it to be diagnosed at more advanced stages and to have higher mortality rates compared to cutaneous melanoma [12].

MM has different molecular characteristics, whereas a KIT mutation is found more frequently compared to cutaneous melanoma [13]. A BRAF mutation, which is commonly found in cutaneous melanoma, is rare [14–19].

The staging of the disease is somewhat difficult due to rare incidence rates and nonspecific signs and symptoms of the disease. Oncologists use different staging systems to determine the stage of MM. Prognostic factors regarding the disease are age, gender, anatomical site of the primary lesion, clinical stage, and presence of ulceration [20, 21]. There is no standard approach for treating MM, but a major part of treatment is surgery, whereas chemotherapy accounts for only a small part of it. Prognosis is poor despite aggressive surgical resections and adjuvant treatments; the 5-year survival rate is below 50 % in most cases [22].

Our aim in this study is to evaluate clinical and prognostic characteristics, treatment approaches, and subgroup differences using retrospective data of our patients in this rare disease for which a very limited number of studies have been conducted to date.

Materials and methods

In this study, which was conducted by the Anatolian Medical Oncology Society, we retrospectively evaluated data of 107 patients diagnosed with MM. These diagnoses were confirmed clinically and pathologically in 14 different centers in Turkey between 1998 and 2014. Clinical data regarding the patients' age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, anatomical site of tumor, LDH level, resection margin, presence of ulceration, mitotic rate, lymph node involvement, primary tumor size, stage, patterns of recurrence, treatment modalities, and survey were obtained from patient records. Staging of the patients was performed according to available pathological, clinical, and radiological findings.

For the descriptive statistics of data, mean, standard deviation, median lowest value, median highest value, frequency, and rates were used. To analyze survival rates, Kaplan–Meier and Cox regression analyses were used. For statistical analysis, SPSS program, version 17.0, was used.

Results

In this analysis, 107 patients were included. The mean age at diagnosis was 64 ± 13 years (range 30–88). Of these patients, 53 % ($n = 57$) were male, and the male-to-female ratio was 1.14.

Head and neck was the most common anatomical site (49 %, $n = 52$) for MM, which was followed by the anorectal (37 %, $n = 40$), genitourinary (9 %, $n = 10$), upper gastrointestinal tract (4 %, $n = 4$), and lung (0.9 %, $n = 1$) in order of frequency. Bleeding was the most common initial symptom (40 %, $n = 43$), followed by palpable mass (27 %, $n = 29$). Regarding stage, 62 % of the patients ($n = 67$) were at the locoregional stage, and 37 % of them ($n = 40$) were at the metastatic stage. Ulceration was present in 61 % of the patients ($n = 40$). ECOG performance status was 0 in 36 patients, and it was ≥1 in 71 patients. In terms of primary tumor size, the study group presented as follows: T1 ($n = 9$), T2 ($n = 8$), T3 ($n = 14$), and T4 ($n = 35$).

In this study, 61 patients had undergone curative surgical resections, 52 of which were R0 (complete resection) resections and 9 were R1 (microscopic residual tumor) resections (median OS was 37 and 27 months, respectively; $P = 0.023$). Of the patients undergoing operations, 34 % ($n = 21$) were node-positive, and 66 % ($n = 39$) were node-negative. Of the 61 operated patients, 33 had received adjuvant therapy (interferon $n = 20$, chemotherapy $n = 4$, radiotherapy + interferon $n = 2$, chemotherapy + radiotherapy $n = 5$, and radiotherapy $n = 2$). There were no significant differences between the

patients taking adjuvant treatment and those not taking adjuvant treatment with respect to progression-free survival (PFS) (16 and 18 months, respectively; $P > 0.05$). Relapse occurred in 36 of the patients who had undergone curative resections. Of those patients, 56 % ($n = 20$) of the occurrences were systemic relapses, and 44 % ($n = 16$) were local relapses. The most common metastatic sites were in the liver (26 %, $n = 18$) and the lungs (23 %, $n = 16$).

In all patients, the mean survival time was 40 months, the median survival time was 17 months, the mean follow-up period was 27 months, and the estimated 2- and 5-year OS rates in 107 patients were 42 and 22 %, respectively. At the time of analysis, 77.6 % of the patients ($n = 83$) were dead (Table 1).

The mean survival rates differed by anatomical sites ($P = 0.034$). The survival rates were as follows: the head-neck 53.6 months, upper gastrointestinal tract 34.2 months, anorectal 21.02 months, genitourinary 18.9 months, and lung 7 months. The best survival rate for both genders was in the head-neck region (Fig. 1, Table 2, and Table 3).

In a univariate analysis, variables including age ≥65 years, the anatomical site of the primary lesion other than head and neck region, the metastatic stage of the disease, having no surgery, high LDH levels, and an ECOG performance status of ≥1 had significant adverse impacts on survival ($P < 0.05$).

Table 1 Clinicopathologic data

		Min-max	Median	Avg. ± std./n-%	
Age		30–88	66	64.5	± 12.9
	<65			47	43.9
	≥65			60	56.1
Follow-up duration (months)		1–168	17	27.2	± 29.1
Status	Died			83	77.6
	Alive			24	24.4
PFS		1–71	14	18.6	± 15.5
Surgical status	No surgery			46	43.0
	R0 with adjuvant therapy			29	27.1
	R0 without adjuvant therapy			23	21.5
	R1 with adjuvant therapy			4	3.7
	R1 without adjuvant therapy			5	4.7
ECOG PS	0			36	33.6
	≥1			71	66.4
Anatomic site	Anorectal			40	37.4
	Upper GI tract			4	3.7
	Genitourinary			10	9.3
	Head and neck			52	48.6
	Lung			1	0.9
T stage	T1			9	13.6
	T2			8	12.1
	T3			14	21.2
	T4			35	53.0
Stage	Locoregional			67	62.6
	Metastatic			40	60.6
Ulceration	No			23	39.4
	Yes			40	60.6
Mitotic rate	≤5			7	38.9
	>5			11	61.1
Lymph node involvement	Negative			49	61.3
	Positive			31	38.8
LDH	Normal			47	53.4
	High			41	46.6

PFS progression-free survival, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *T stage* size of primary tumor stage, *LDH* lactate dehydrogenase

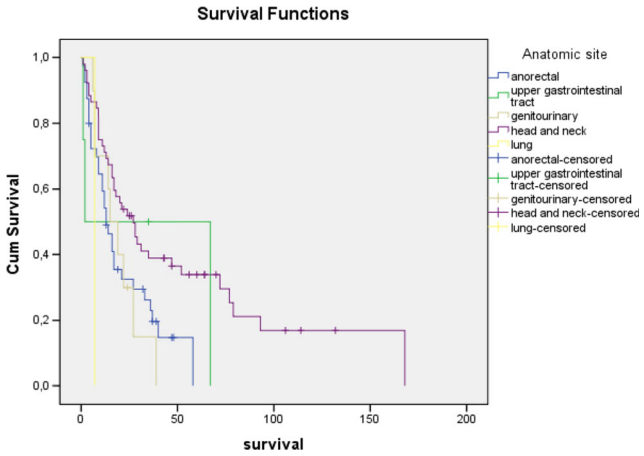

Fig. 1 Overall survival (OS) in patients with respect to anatomic site

Node positivity, the presence of ulceration, the mitotic rate, the gender of the patient, T-stage, and the status of receiving adjuvant treatment had no significant effect on survival. Advanced stage (HR = 2.70; 95 % CI, 1.64–4.45; $P = 0.000$) and high LDH levels (HR = 2.31; 95 % CI, 1.40–3.80; $P = 0.001$) were the two important variables associated with improved survival rates in the multivariate analysis (Table 4).

Discussion

MM is considered to be an aggressive subtype of melanoma. Even if patients with MM present with localized disease, a 5-year survival is rare. A possible reason for this is that a rich vascular and lymphatic submucosal network causes the development of early metastasis. A 5-year MM survival rate is only 25 % compared to the 5-year survival rates of cutaneous melanoma (80.8 %) and ocular melanoma (74.6 %) [7]. In our study, the 5-year survival rate of patients was 23 %, similar to that in the literature. In patients with cutaneous melanoma, 9 % of them have locoregional lymph node involvement; however, with MM, about one-third of the patients have lymph node involvement at the time of diagnosis [7]. In our study, the lymph node involvement rate in patients at the locoregional stage was 35 %.

Contrary to previous studies, our study showed that MM was more common among males (male-to-female ratio = 1.14). This may be due to the ratio of female patients with urogenital tract MM ($n = 10$, 9.3 %), which is more common among females, is lower in our study than the ratio found in literature.

In 2011, a study conducted by Tas F. et al. showed that clinical presentation and prognosis differed between subtypes of MM [23]. In another study conducted by Chang A.E. et al., the distribution of disease by regions was determined to be head-neck 55.4 %, female genital tract 18 %, anorectal 23.8 %, and urinary tract 2.8 % [7]. In our study, 49 % of the patients had the disease localized in the head-neck region. When we examined survival rates by anatomical sites, the best survival rates in both genders were in patients having MM in the head-neck region (53.6 months, $P = 0.034$). Anorectal and head-neck MM were more common in males, while genitourinary MM was more common in females.

A multicenter retrospective study was conducted in 2010. In 58 out of 70 patients who underwent R0 resections, systemic relapse occurred in 57 %, and local relapse occurred in 43 % of the patients [24]. In our study, however, resections were performed for 61 patients (R0 52, R1 9), and in 36 of the patients having curative resections, relapse occurred (56 % systemic, 44 % local).

DeMatos et al. presented a review composed of 119 patients. This review showed that >50 years and R1 resections were determined to be poor prognostic factors [20]. We categorized patients as <65 and ≥65 years of age. We found the survival rate to be significantly worse in the ≥65-year-old group (median survival times for ages <65 and ≥65 years were 31 and 12 months, respectively; $P = 0.015$). There was no statistical significance in patients undergoing R1 resections (median survival times for R1 resection and R0 resection were 27 and 37 months, respectively; $P = 0.23$).

In a study conducted by A.G. Shuman et al., it was found that regarding head-neck MM, the presence of ulceration and a high mitotic rate were determined to be associated with a poor prognosis [25]. However, in our study, we could not find that these factors contributed to a poor prognosis ($P > 0.05$).

Standard treatment of MM at the locoregional stage is a complete surgical resection, and it is the best choice for

Table 2 Overall survival (OS) in patients with respect to anatomic site

Kaplan–Meier (log-rank)		Median survival Time (months)	95 %		*P*
			Lower bound	Upper bound	
Anatomic site	Anorectal	21.00	14.80	27.30	0.034
	Upper gastrointestinal tract	34.20	0.00	73.50	
	Genitourinary	18.90	11.50	26.30	
	Head-neck	53.60	35.60	71.66	
	Lung	7.00	7.00	7.00	

Table 3 Gender and mean age with respect to anatomic site

		Anorectal	Upper gastrointestinal tract	Genitourinary	Head neck	Lung	Total	*P*
Gender	Female	15	2	10	22	1	50	0.006
	Male	25	2	0	30	0	57	
Total		40	4	10	52	1	107	
Mean age (years)		65.07	65.25	62.20	64.40	75.00	64.50	0.009

long-term survival; however, local or distant metastases are found in most patients. There are a limited number of studies concerning treatment modalities in MM, such as surgery, radiotherapy, and chemo-immunotherapy. In the only randomized phase 2 study concerning adjuvant treatment in MM, observation/high-dose interferon alpha-2b/chemotherapy arms in 111 operated patients with MM were compared. The median relapse-free survival and OS rates were found to be significantly better in the chemotherapy group [26]. In our study, adjuvant treatment was given to 33 of 61 operated patients (head-neck $n=16$, anorectal $n=14$, and genitourinary $n=3$) (interferon $n=20$, chemotherapy $n=4$, radiotherapy + interferon $n=2$, chemotherapy + radiotherapy $n=5$, and radiotherapy $n=2$). There were no significant differences between patients taking adjuvant treatment and those not taking adjuvant treatment with respect to PFS and OS ($P>0.05$). It has been shown in many retrospective studies [27–31] that postoperative radiotherapy promotes recovery in locoregional control. Thus, many authors recommend adjuvant radiotherapy for the primary tumor site and regional lymph nodes [2]. Ten patients received combined therapies or radiotherapy alone, all of whom were patients with head-neck MM. In the future, randomized controlled studies concerning the improvement of results by adjuvant radiotherapy are needed.

Because of the lack of sufficient data concerning systemic treatment methods in metastatic MM treatment, treatments similar to those used in cutaneous melanoma are used. A better understanding of genetic alterations in MM will be beneficial in the development of more effective and targeted treatment agents.

A retrospective design, the contributions of multiple centers (evaluation by different pathologists and different

Table 4 Cox regression model of overall survival (OS) in mucosal melanoma

	Univariate analysis				Mutivariate analysis			
		95 %				95 %		
	HR	Lower bound	Upper bound	*P*	HR	Lower bound	Upper bound	*P*
Age (<65, ≥65)	1.72	1.09	2.70	*0.018*				
Stage (locoregional, metastatic)	2.83	1.82	4.42	*0.000*	2.70	1.64	4.45	*0.000*
Gender (female, male)	1.07	0.69	1.66	0.742				
Anatomic site (head and neck, others)	1.91	1.21	3.03	*0.005*				
LDH value (normal, high)	2.48	1.51	4.07	*0.000*	2.31	1.40	3.80	*0.001*
Ulceration (no, yes)	1.30	0.71	2.39	0.384				
T stage (T1/T2, T3/T4)	1.64	0.79	3.42	0.183				
ECOG PS (0, ≥1)	1.94	1.19	3.18	*0.008*				
Mitotic rate (≤5, >5)	2.18	0.66	7.22	0.199				
Lymph node involvement (positive, negative)	1.19	0.87	2.55	0.137				
Type of therapy (not operated, operated)	0.30	0.19	0.48	*0.000*				
Type of therapy (no adjuvant therapy, adjuvant therapy)	0.69	0.42	1.15	0.160				
Type of therapy (R0 resection, R1 resection)	1.57	0.73	3.35	0.240				

HR hazard ratio, *LDH* lactate dehydrogenase, *T stage* size of primary tumor stage, *ECOG PS* Eastern Cooperative Oncology Group performance status

Italicized *p*-values represent statistical significance

clinicians and different treatment modalities), and a limited number of patients may be seen as negative aspects of our study. However, because there are limited studies available regarding MM, we believe it is worthwhile sharing our study of this rare disease.

Conclusion

MM differs both clinically and biologically from cutaneous melanoma. It takes a more aggressive course and offers a poorer prognosis compared to other subtypes of melanoma. As the disease is rare and heterogeneous, clinical characteristics and optimal treatment strategies have not been determined yet.

Compliance with ethical standards

Conflicts of interest None

Research involving human participants and/or animals Not applicable because the study was retrospective.

Informed consent No patient consent was required.

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