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Evaluation of Demographic and Clinical Characteristics of Turkish Patients With Primary Cutaneous Melanoma: A 5-Year Experience of a Tertiary Referral Center

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ABSTRACT

Introduction: Data about the demographic and clinical characteristics of melanoma patients in Turkey is limited.

Objectives: Data about the demographic and clinical characteristics of melanoma patients in Turkey is limited. We aimed to review the features of patients with primary cutaneous melanoma (PCM) diagnosed and treated in a tertiary referral center.

Methods: The medical records of melanoma patients followed up by the Departments of Dermatology and Medical Oncology were retrospectively reviewed.

Results: Within a 5-year period, 180 patients had been diagnosed with melanoma. Of all, 158 (87.8%) had PCM, 9 (5%) had mucosal melanoma, 9 (5%) had unknown primary melanoma, and 4 (2.2%) had ocular melanoma. Of 146 patients with PCM, 32.9% had stage I, 28.8% had stage II, 17.8% had stage III, and 20.5% had stage IV disease. The most common subtype was superficial spreading melanoma (38.8%). A statistically significant correlation was found between the patients Breslow thickness and lymph node involvement, histopathological subtype, and tumor ulceration (P < 0.001). Among all PCM patients, those in stage IV had the lowest 5-year survival rate when compared to the other disease stages (P < 0.001).

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Conclusions: Relatively younger age at melanoma diagnosis, frequent presence of thick (> 4 mm) tumor, and frequent acral lentiginous subtype are the most remarkable features that suggest the low awareness and knowledge of melanoma in our population.

Introduction

Various genetic and environmental factors, such as UV radiation, induce uncontrolled malignant proliferation of melanocytes, resulting in melanoma. Although the frequency of melanoma is as low as 1.3% among all skin cancers, it is responsible for about 75% of skin cancer-related deaths [1]. The incidence of melanoma is variable due to geographical and ethnic factors; however, current data points out a remarkable increase every year around the world. There are few studies on melanoma patients' demographic and clinical characteristics in Turkey [2-5]. Therefore, in this study, we aimed to analyze the demographic and clinicopathological characteristics of Turkish patients with primary cutaneous melanoma [PCM] who were diagnosed and followed up in a tertiary referral hospital over 5 years.

Objectives

We aimed to review the features of patients with primary cutaneous melanoma (PCM) diagnosed and treated in a tertiary referral center.

Methods

The medical records of melanoma patients who sought care at our center from October 2016 to October 2021 underwent a comprehensive review. Demographic, clinical (age at the time of diagnosis, survival time, localization of the tumor, stage of the disease according to the AJCC 8th melanoma staging system; the number of lymph nodes and metastatic organ involvement.), and histopathological features (Breslow thickness, tumor ulceration status, melanoma subtype, BRAF mutation status if available) of the patients were all noted. Statistical analyses were performed with the IBM SPSS 25.0 (SPSS Inc) program. Mean ± standard deviation (SD) or median and minimum-maximum values were used for continuous variables, and frequencies (N) and percentages (%) were used for categorical variables. Categorical variables were compared by Pearson chi-square or Fisher exact test. The normality of the continuous variables was evaluated by Kolmogorov-Smirnov test. Differences between the groups for continuous variables were determined by independent samples t-test. Overall survival was estimated by the Kaplan-Meier method and survival curves were compared by the Log-rank test. P values of 0.05 and below were considered statistically significant. The study was approved by the local ethics committee (Date: 25/11/2021; #379).

Results

Of 180 patients, 158 (87.8%) had PCM, 9 (5%) had mucosal melanoma, 9 (5%) had melanoma of unknown primary, and 4 (2.2%) had ocular melanoma. The age of diagnosis ranged from 4 years to 92 years (N=177; mean ± SD: 54.7 ± 18.7 years). The mean age at diagnosis was statistically similar in both genders (55.5±18.1 years for males versus 53.7±19.5 years for females; P = 0.540). When the characteristics of patients with PCM were detailed (Table 1), 81 were males and 77 were females (1.05/1). The age of PCM diagnosis ranged from 4 to 92 years (mean ± SD: 53.8 ± 19 years); the mean age at diagnosis was statistically similar in both genders (mean ±S D: 54.8 ± 18.8 years for males versus mean ± SD: 52.3 ± 19.5 years for females P = 0.440). The most common histopathological subtype was superficial spreading melanoma (SSM) (38.8%). When evaluated according to the AJCC 8th guideline, most patients (61.7%) were in the early local stage (I and II), 17.8% of the patients were in the nodal stage (III) and 20.5% of the patients were diagnosed with metastatic melanoma (IV), respectively (Table 1). Anatomical localization of PCM was similar in both genders (P = 0.341). The lower extremities were the most frequently involved, followed by trunk involvement (Table 2). The range of tumor Breslow thickness was 0.15-20.00 mm (mean ± SD: 3.72 ± 3.98 mm) in 137 patients. The most common T stages in men were T3 (64.1%) and T4 (55.3%), while T1 (58.8%) and T2 (56.0%) stages were most common in women (Table 3). However, the T stage did not differ between genders (P = 0.196). While Breslow thickness correlated considerably with histopathological subtype (P < 0.001) (Table 3), lymph node involvement (P < 0.001), ulceration (P < 0.001), and 5-year overall survival (P = 0.014), no correlation was found with anatomical location and Breslow thickness. Due to technical and insurance issues, the BRAF mutation analyses could be performed in only 53 patients. The data revealed wild type in 54.7% and mutant type in 45.3%. Lymph nodes were involved in 50 of 147 patients with PCM (34%). The lymph node involvement

Table 1. Patient and Tumor Characteristics of Primary Cutaneous Melanoma Patients.

Features	N	(%)
Histopathological Subtype (N = 152)		
SSM	59	38.8
NM	51	33.6
ALM	26	17.1
LMM	8	5.3
Others	8	5.3
Age (N = 155), years		
<18	1	0.6
18-30	23	14.8
31-45	32	20.6
46-65	49	31.6
>65	50	32.3
Gender (N = 158)		
Male	81	51.3
Female	77	48.7
Breslow thickness (N = 137)		
T1 (≤ 1 mm)	37	27.0
T2 (1.1-2 mm)	23	16.8
T3 (2.1-4 mm)	35	25.5
T4 (>4 mm)	42	30.7
Ulceration (N = 92)		
Present	51	55.4
Absent	41	44.6
Lymph node involvement (N = 147)		
N0	97	66.0
N1	23	15.6
N2	4	2.7
N3	23	15.6
Metastasis (N = 151)		
M0	121	80.1
M1	30	19.9
BRAF mutation (N = 53)		
Wild type	29	54.7
Mutant type	24	45.3
Overall survival (N = 158)		
Alive	131	82.9
Dead	27	17.1
Stage (N = 146)		
I	48	32.9
II	42	28.8
III	26	17.8
IV	30	20.5
Sentinel lymph node involvement (N = 55)		
Negative	34	61.8
Positive	21	38.2

ALM = acral lentiginous melanoma; LMM = lentigo malignant melanoma; NM = nodular melanoma; SSM = superficial spreading melanoma.

significantly correlated with tumor ulceration status, presence of metastasis, histopathological subtype, and age at diagnosis (all P < 0.05) (Table 4). Compared with patients with SMM, patients with ALM and patients with NM had more lymph node involvement (60%, P = 0.002 and 42.6%, P < 0.001, respectively). The patients over 45 years had more lymph node involvement than younger ones (P = 0.015), whereas it did not differ for both genders and localizations of tumors (P > 0.05). Of all PCM patients for whom staging information was available, 30 (20.5%) had distant metastases. Within the 30 (20.5%) patients diagnosed with stage IV metastatic PCM, metastatic organ data were available for 22 individuals, revealing that eight patients presented with multiple organ metastases, while 14 patients exhibited single organ involvement (Table 5). The overall survival data of 178 patients with melanoma was evaluated at the time of the study. According to the statistical analysis, the median follow-up period was 32.5 months (range 1-162 months). During the follow-up, 41 patients have died. The estimate of the mean overall survival time was 50 months (95% confidence interval: 46.6 – 52.5). For PCM patients, 27 patients have died during the follow-up time. The estimate of the mean overall survival time was 53 months (95% confidence interval: 50 – 55). For all PCM patients, the 5-year survival rate of T1 was significantly higher than T2, T3, and T4 (P = 0.016) (Figure 1A). The 5-year survival rate was highest in T1 patients (100%), 87% in T2, 77.1% in T3, and 76.0% in T4 patients, respectively. The results of the log-rank test regarding death for each Breslow thickness stage showed that the survival rate of T1 was the highest compared to patients in other stages (P = 0.016). When the 5-year survival is analyzed based on the stage determined by AJCC 8th for all PCM patients, the survival rate of stage IV patients was the lowest compared to patients in other melanoma stages (P < 0.001). The estimate of the mean overall survival time for stage IV was 32.8 months (95% confidence interval: 32.8 – 48.1). In the context of the 5-year survival analysis concerning factors influencing overall survival in melanoma, a significant relationship was observed with ulceration (P < 0.001), Breslow thickness (P = 0.016), AJCC 8th stage (P < 0.001), and age (P = 0.008). However, there was no significant relationship detected concerning gender (P = 0.374) and localization (P = 0.540) (Figure 1, A-F).

Conclusions

Our findings, indicating a mean age of melanoma diagnosis at 54.7 years, align closely with prior research conducted in Turkey [2-5], which is younger than the most recent data of the American Cancer Society reporting the average age of diagnosis for melanoma as 65 years [6]. Notably, the mean age of melanoma diagnosis in Turkey is younger than in the

Table 2. Tumor Localization Distribution Across Gender Groups.

Parameters		Involved site N (%)					P
		Head-neck	Trunk	Upper extremity	Lower extremity	Total	
Gender	Male	16 (20.3)	26 (32.9)	9 (11.4)	28 (35.4)	79 (100)	0.341
	Female	12 (17.1)	17 (24.3)	14 (20.0)	27 (38.6)	70 (100)	
Total		28 (18.8)	43 (28.9)	23 (15.4)	55 (36.9)	149 (100)	

Table 3. Breslow Thickness Distribution Across Gender, Histopathological Subtype of Primary Cutaneous Melanoma, Lymph Node Involvement, Ulceration, 5-Year Overall Survival, and Tumor Localization.

Parameters		≤1 mm N (%)	1.1-2 mm N (%)	2.1-4 mm N (%)	>4 mm N (%)	P
Gender	Male	14 (41.2)	11 (44.0)	25 (64.1)	21 (55.3)	0.196
	Female	20 (58.8)	14 (56.0)	14 (35.9)	17 (44.7)	
Histopathological subtype	SSM	25 (46.3)	14 (25.9)	11 (20.4)	4 (7.4)	<0.001
	NM	1 (2.1)	2 (4.3)	22 (46.8)	22 (46.8)	
	ALM	5 (26.3)	6 (31.6)	2 (10.5)	6 (31.6)	
	LMM	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	
	Others[a]	2 (28.6)	1 (14.3)	2 (28.6)	2 (28.6)	
Lymph node involvement	(-)	32 (97.0)	21 (84.0)	21 (56.8)	18 (48.6)	<0.001
	(+)	1 (3.0)	4 (16.0)	16 (43.2)	19 (51.4)	
Ulceration	(+)	0 (0)	7 (46.7)	14 (53.8)	18 (64.3)	<0.001
	(-)	21 (100)	8 (53.3)	12 (46.2)	10 (35.7)	
Overall survival	Died	0 (0)	3 (13.0)	10 (27)	10 (23.8)	0.014
	Alive	37 (100)	20 (87.0)	27 (73)	32 (76.2)	
Localization	Head-Neck	4 (13.3)	2 (8.0)	7 (18.9)	11 (29.7)	0.194
	Trunk	12 (40.0)	9 (36.0)	13 (35.1)	5 (13.5)	
	Upper extremity	4 (13.3)	5 (20.0)	7 (18.9)	5 (13.5)	
	Lower extremity	10 (33.3)	9 (36.0)	10 (27.0)	16 (43.2)	

[a]Rare subtypes (amelanotic, animal type, desmoplastic)

ALM = acral lentiginous melanoma; LMM = lentigo malignant melanoma; NM = nodular melanoma; SSM = superficial spreading melanoma.

USA and England [7,8]. Intense sun exposure starting from an early age and low awareness of UV protection may be the main reasons for younger melanoma diagnoses in our country. The incidence studies conducted in different countries revealed different male/female ratios. While most western and northern European countries report higher incidence rates in women than in men [9], most eastern, southern, and central European countries have reported higher incidences of melanoma in men [10]. However, our data is similar to the gender ratios of melanoma patients diagnosed in the USA, eastern Europe, and Australia [11].

In the existing literature, the distribution of melanoma is documented with approximately 90-95% cutaneous, 5% in ocular, 3% metastases from an unknown primary site, and 1% in mucosal tissues [12,13]. When compared, percentages of cutaneous and non-cutaneous melanoma patients and distribution of histopathological subtypes of PCM our findings are compatible with the results of related literature [14], the ALM subtype remarkably emerged as the third most prevalent subtype within our study population (17.1%). According to population-based data, ALM accounts for approximately 5% of melanoma cases among the four major histologic subtypes of PCM in the USA [14]. In contrast, it appears to be relatively more common among African Americans, constituting approximately 36% of melanoma cases [15]. The striking frequency of ALM in our cohort patients may be related to the data of a referral hospital serving with an experienced multidisciplinary approach to a considerable number of patients applying from various regions of our country. Nevertheless, further investigations are needed

Table 4. Lymph Node Involvement According to Subtype, Ulceration, Age, Metastasis Status, Localization and Gender.

|	Lymph Node Involvement			
	LN (-)	LN (+)	Total	
Subtype	N (%)	N (%)	N (%)	P
SMM	49 (86.0)	8 (14.0)	57 (100)	<0.001
NM	27 (57.4)	20 (42.6)	47 (100.0)	
ALM	10 (40.0)	15 (60.0)	25 (100.0)	
LMM	3 (42.9)	4 (57.1)	7 (100.0)	
Rare subtype[a]	5 (55.6)	4 (44.4)	9 (100.0)	
Ulceration				
Present	41 (80.4)	1 (19.6)	51 (100.0)	<0.001
Absent	23 (52.3)	21 (47.7)	44 (100.0)	
Age group				
18-30	19 (86.4)	3 (13.6)	22 (10)	0.015
31-45	24 (70.6)	10 (29.4)	34 (100)	
46-65	28 (52.8)	25 (47.2)	53 (100)	
>65	27 (51.9)	25 (48.1)	52 (100)	
Metastasis status				
Present	97 (78.2)	27 (21.8)	124 (100)	<0.001
Absent	2 (5.4)	35 (94.6)	37 (100)	
Localization				
Head-Neck	18 (64.3)	10 (35.7)	28 (100)	0.491
Trunk	31 (73.8)	11 (26.2)	42 (100)	
Upper extremities	1 3(59.1)	9 (40.9)	22 (100)	
Lower extremities	31 (59.6)	21 (40.4)	52 (100)	
Gender				
Male	4 (57.0)	37 (43.0)	86 (100)	0.251
Female	50 (65.8)	26 (34.2)	76 (100)	

[a]Rare subtypes (amelanotic, animal type, desmoplastic)

ALM = acral lentiginous melanoma; LMM = lentigo malignant melanoma; LN = lymph node; NM = nodular melanoma; SSM = superficial spreading melanoma.

Table 5. Metastatic Sites of Stage IV Patients With Primary Cutaneous Melanoma.

Metastatic site	N	%
Lung	10	45
Brain	9	40
Liver	5	23
Bone	7	32
Single organ/tissue involved	14	64
Lung	7	32
Brain	4	18
Liver	2	9
Bone	1	4
Multiple organ/tissue involvement	8	36

to explain the reasons for the high frequency of ALM patients, including detailed clinical characteristics and risk factors. In our analysis, lower extremities predominated as the most common site, followed by the trunk in both genders, diverging from reports indicating a primary involvement of the trunk in males and lower extremities in females [16]. We observed that our patients' tumors were mainly thicker than 4 mm in contrast to studies conducted in western countries; most of their patients were diagnosed at an early stage [17]. Male gender is a poor prognostic criterion for Breslow thickness [18]. As the tumor thickness increases in PCM, malignant cells are more likely to spread to regional lymph nodes by lymphatic invasion. The analysis of our study data also pointed out the correlation between tumor thickness
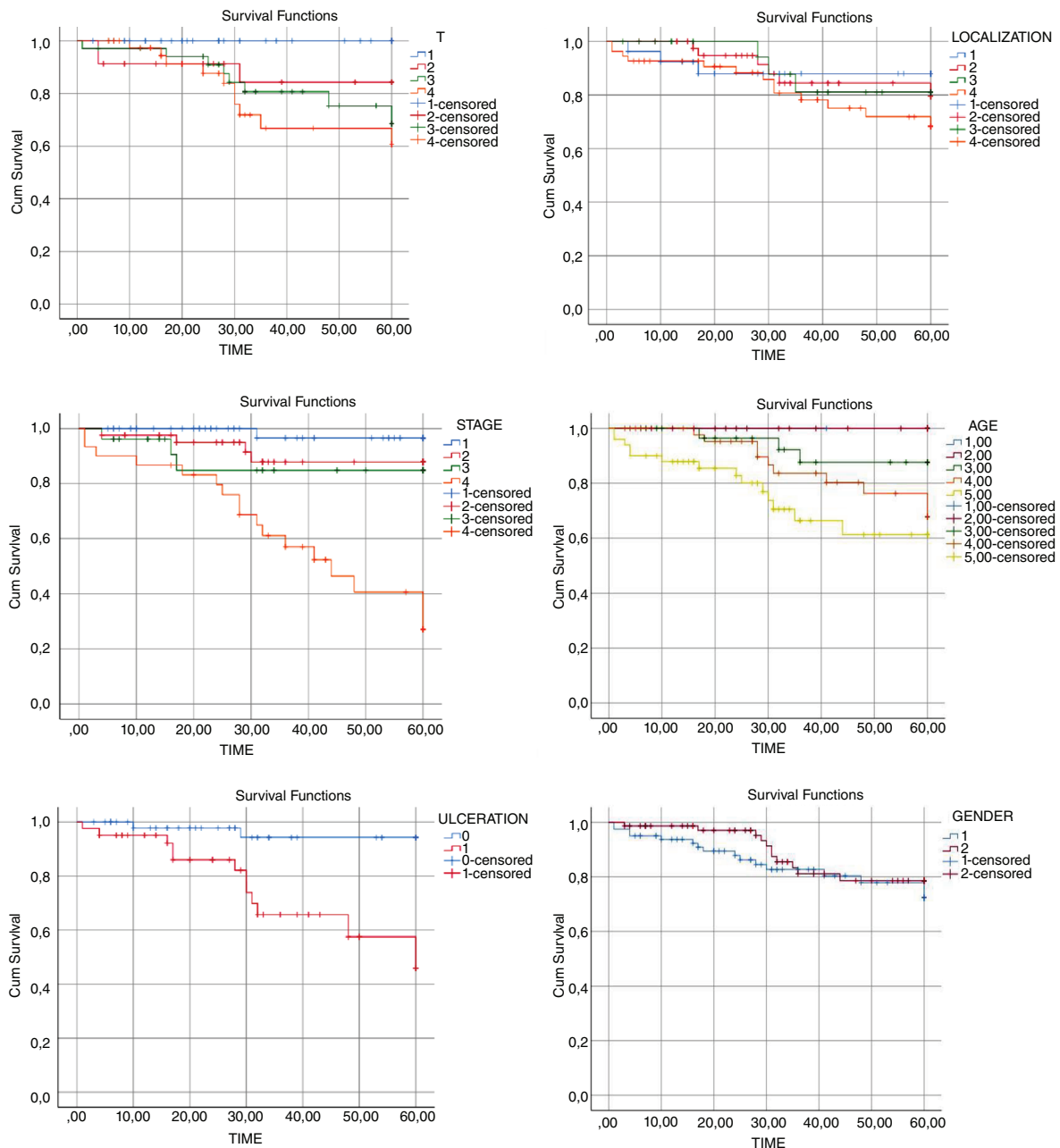
Figure 1. Kaplan-Meier survival plots of overall survival according to: (A) Breslow thickness (P = 0.016; log rank test); (B) Localization—1 head and neck, 2 trunk, 3 upper extremities, and 4 lower extremities (P = 0.540, log rank test); (C) AJCC 8th stage (P = 0.001, log rank test); (D) Age group: (group 1: <18, group 2: 18-20, group 3: 30-45, group 4: 45-65, and group 5: >65) (P = 0.008, log rank test); (E) Tumor ulceration status (1 ulcerated, 0 not ulcerated) (P = 0.001, log rank test); (F) Gender—1 male, 2 female (P = 0.374, log rank test).

and regional lymph node involvement and ulceration. As expected, in our study, locoregional spread was higher in ulcerated than non-ulcered tumors. The most common histopathological subtype to be associated with lymph node involvement is ALM [19]. Similarly, in our study group, patients with ALM and LMM had more common lymph node involvement than patients with SSM and NM. Detection of BRAF mutation in melanoma patients gives them a chance for targeted immunotherapy [20]. Helen Davies et al [21] reported a 50% and 60% mutation rate in all human cancers and 66% in melanoma. One of the limitations of our study

is the small number of patients having BRAF mutation analysis. Although limited data was available, mutant BRAF was positive in 45.3% of 53 patients in our study population. Of our study patients, 32.9% had stage I, 28.8% had stage II, 17.8% stage III, and 20.5% had stage IV PCM. In contrast, patients in stage IV were reported to be higher at 25% to 48.7% in different patient study groups [9]. The distribution of melanoma patients data in Turkish studies is complex, reflecting diverse data sources encompassing multiple medical departments such as oncology, dermatology, and plastic surgery. Our data align with findings from specialized

referral hospitals, particularly within oncology and dermatology departments [2-5]. Based on melanoma patients diagnosed in the USA between 2012 and 2018, according to the SEER [Surveillance, Epidemiology, and End Results] data of the American Cancer Society, the 5-year relative survival rate in the localized stage is 99%, 71% in the regional, and 32% in the distant stage, respectively [22]. In the context of global melanoma survival studies, several factors consistently emerge as adverse prognostic indicators for survival, including age, male gender, Breslow thickness, advanced disease stage, the presence of ulceration, and the localization of tumors on the trunk and head-neck regions [12]. However, the results of our study deviate from this established pattern, as we found no statistically significant difference in 5-year survival rates concerning gender and localization characteristics of PCM. Instead, the results align with existing literature, underscoring the significance of Breslow thickness, the presence of ulceration, advanced disease stage, and patient age as critical criteria for predicting poor prognosis. On the other hand, relatively higher overall survival (35%) for stage IV patients may depend on the launch of new therapeutic agents (immunotherapies and targeted therapies) in 2015, which positively affected the survival of our patients whose data between 2016 and 2021 were studied. Among the recent studies reported from the UK, the 5-year overall survival increases up to 52% in patients using current promising treatments such as ipilimumab and nivolumab [23]. It is predicted that in the future, more updated SEER data will report an increase in the 5-year survival rate of IV stage melanoma patients [22].

The results of this study show that patients with PCM followed up in one of the referral health centers of Turkey have a relatively young age at melanoma diagnosis, frequent presence of thick tumor (>4 mm), and frequent ALM subtype. All these data suggest that patients might have experienced critical environmental triggers such as intense ultraviolet exposure from a very young age, living in a country with relatively long and sunny days, climate changes, and ignorance of effective protective behaviors from sunlight. Future studies comprehensively analyzing the risk factors of the patients are needed especially for ALM, that is an histopathological subtype with an etiology less related to acute and chronic sun exposure.

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