Dermatology Practical & Conceptual

Age-related Survival Declines in Turkish Patients with Cutaneous Melanoma: A Retrospective Analysis

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ABSTRACT

Introduction: In cancer patients, the age of a patient at the time of diagnosis is considered among the important clinical indicators.

Objectives: We aimed to investigate this significance in melanoma patients by creating patient age groups.

Methods: A total of 1,496 adult skin melanoma patients were evaluated retrospectively. Patients were divided into six age groups: under 30 (<30), 31–39 (30s), 40–49 (40s), 50–59 (50s), 60–69 (60s), and 70 and older (70+).

Results: The median age was 52 years (range 16-104), and the most common age group was the 50s (n=340, 22.7%). As age increased, so did the Clark level (*P*=0.0001), the rate of ulceration (*P*=0.0001), and the rate of BRAF wild-type (*P*=0.002). The recurrence rates of early-stage patients were similar for all age groups. A significant overall survival (OS) advantage was found only between the following age groups: <30 and 60s (*P*=0.04) and <30 and 70+ (*P*=0.01). Five-year OS were, from young to old: 70.5%, 66%, 63.1%, 66.3%, 57.2%, and 46.8%. A significant OS advantage was found only between the following age groups: <30 and 60s (*P*=0.04) and <30 and 70+ (*P*=0.01). The 70+ group had significantly worse OS rates in all age groups (<30: *P*=0.0001; 30s *P*=0.0001; 40s: *P*= 0.001; 50s: *P*=0.0001; and 60s: *P*=0.04).

Conclusion: While some unfavorable histopathological prognostic factors are associated more frequently with increasing age, clinical stage and recurrence do not differ significantly between age groups. A possible explanation for this might be that the elderly have more comorbidities and die of different causes.

Introduction

Skin melanoma is the most fatal cutaneous malignancy in the world and is the fifth most common type of cancer in men (6%) and women (4%) in the US [1]. In 2023, 97,610 patients in the US were expected to be diagnosed with melanoma, and 7,990 patients were expected to die of melanoma [1]. Its incidence continues to dramatically increase: the lifetime risk of developing melanoma is 1 in 28 males and 1 in 41 females. The survival of melanoma depends mainly on the stage at presentation of the disease [2]. In locoregional disease, outcome also depends on nodal involvement, tumor depth, and various histopathological features, such as ulceration and mitosis [2]. Apart from these important prognostic factors, the patient's age at the time of the diagnosis is also considered among the significant clinical indicators, albeit not as substantial. Studies comparing young and old melanoma patients, with patients in various age groups, showed that older patients generally have worse survival rates mainly because they have worse prognostic factors; not surprisingly, younger patients live longer owing to better prognostic factors [3-9].

Objectives

However, there are also criticisms of the results found in studies on age; the most important of these are that age limits vary among the studies, and the number of age groups compared do not exceed two or three. Considering these controversies, we examined the clinical significance of age in Turkish melanoma patients by creating more age groups in this study.

Methods

Patients

The data of 1,496 adult skin melanoma patients who were admitted to the Oncology Institute between 1993 and 2022 were included in the analysis and evaluated retrospectively. The patient-related records were retrieved from the cancer registry for review of the demographic, clinical, and pathological characteristics and survival. In our study, the AJCC 8th edition was used for staging the disease [2]. Lymph node status was determined by either sentinel lymph node SLN biopsy or lymph node dissection. The treatment and follow-up of the patients were carried out as recommended by internationally accepted standard guidelines, including the European Society of Medical Oncology and the National Comprehensive Cancer Network Guidelines. The study was reviewed and approved by our Regional Ethics Committee. Patients were divided into six age groups by decades, from young to old: I: under 30 years old (<30), II: 31–39 years old (30s), III: 40–49 years old (40s), IV: 50–59 years old (50s), V: 60–69 years old (60s), and VI: 70 years old and older (70+). The impacts of clinicopathological variables on age groups were determined using the chi-squared test. Recurrence-free survival (RFS) was calculated from the date of pathologic diagnosis to the date of the clinical recurrence, which was defined as detected by imaging studies or by clinical examination. Overall survival (OS) was defined as the time from the date of diagnosis to the date of death from any cause or the date of the last follow-up. Survival values and graphs were determined using the Kaplan-Meier method. General statistical analysis was performed using SPSS 21.0 software (SPSS Inc., Chicago, Illinois, USA).

Results

Patient Characteristics

A total of 1,496 patients with skin melanoma were included in the study. The median age of patients was 52 years (range 16-104 years). The most frequent age group was the 50s (N=340, 22.7%), with the other groups are as follows in descending order: 40s (N=300, 20.1%), 60s (N=292, 19.5%), 30s (N= 232, 15.5%), 70+ (N=198, 13.2), and <30 (N=134, 9%) (Figure 1). Other demographic and clinicopathological characteristics of the patients are shown in Table 1.

Association Between Clinicopathological Parameters and Age Group

The differences between age groups were found statistically significant in the following parameters: sex (P=0.0001), Clark level (P=0.0001), ulceration (P=0.0001), BRAF mutation (P=0.002), neurotropism (P=0.008), and lymphovascular invasion (P=0.05) (Table 1). Furthermore, various clinicopathological variables, such as Clark level (P=0.0001), ulceration (P=0.003), regression (P=0.008), BRAF mutation (P=0.002), and association with preexisting nevus (P=0.04), between younger (under 30 years) and elderly (over 70 years) patients were found statistically significant (Table 1). However, TNM clinical stage, which is considered to be the most important clinical prognostic factor, was not found significantly different among all age groups, only in young–old (under 30 vs over 70) patients (P>0.05) (Table 1).

Recurrence and RFS

The recurrence rates of early-stage patients were not significantly different among all age groups, only in old-young patients (P>0.05) (Table 1). The 5-year RFS values were as follows: from young to old: 69.7, 62.5, 56.2, 60, 56.5, and 55.9% (Figure 2). The RFS curves according to age group are shown in Figure 3. A significant survival advantage was found only between the following age groups: the <30 and the 60s (P=0.04) and the <30 and the 70+ (P=0.01).

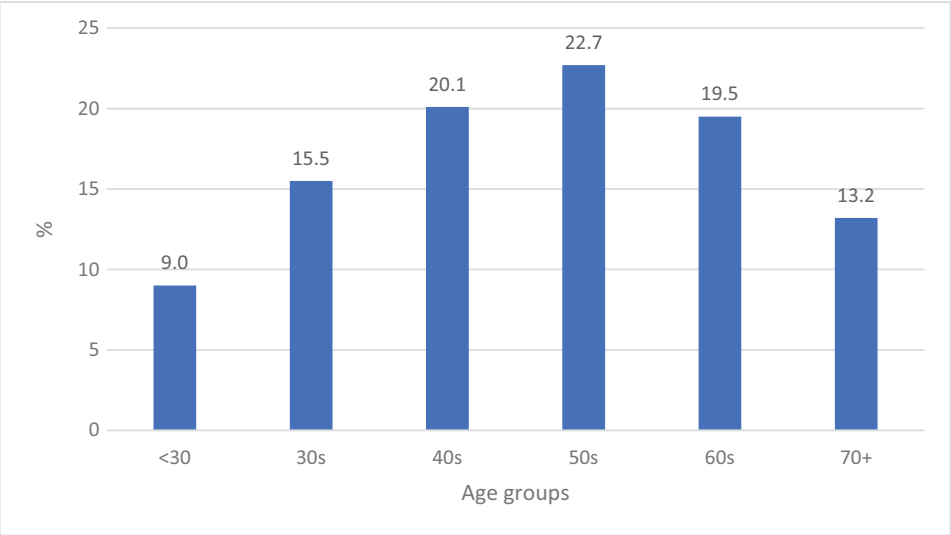

Figure 1. Distribution of patients by age group.

OS

The 5-year OS values from young to old were as follows: 70.5, 66, 63.1, 66.3, 57.2, and 46.8% (Figure 4). The OS curves according to age group are shown in Figure 5. A significant survival advantage was found only between following age groups: <30 and 60s (P=0.04) and <30 and 70+ (P=0.01). The 70+ patient group had significantly worse survival rates compared to all age groups (with <30: P=0.0001; with 30s: P=0.0001; with 40s: P= 0.001; with 50s: P=0.0001; and with 60s: P=0.04). Apart from these, a significant difference in survival was shown only between <30 and 60s in other age groups.

Conclusions

In our retrospective study, 1,496 melanoma patients were generally clustered in or around the 50s age group; the median age of patients was 52 years (range 16-104 years). There was a significant increase in the Clark level and the presence of ulceration with aging. Moreover, we found that the BRAF mutation rate was the highest in young people and that it decreased with age, dropping to the lowest rate in elderly patients. On the other hand, clinical stage distribution and recurrence rates were not significantly different between all age groups. Regarding relapse-free survival, patients younger than 30 years had better survival than those >60 years, especially those >70 years. Also, younger patients had significantly better survival than those over age 60 years, and patients over age 70 years showed significantly worse overall survival than younger patients from all age groups. Both the incidence of melanoma and the median age of the patients have continued to increase significantly in the USA over the years [3]. In the SEER data, the median age of melanoma at diagnosis was 51 years for 1974–1978 and 65 for 2014–2018. However, no difference was found in the median age of Turkish skin melanoma patients between 1988 and 2017. In a novel study, we found that the median age of the patients between 2011 and 2020 was 53 years, which was 12 years younger than the US patients according to SEER data from 2014 to 2018 [3]. In many melanoma studies, patient age at diagnosis has been shown to be a significant prognostic factor for the outcome. Older age was correlated with lower melanoma survival because primary melanomas in older patients have more unfavorable clinicopathological characteristics; they are thicker, more ulcerated, and have greater mitotic rates [3-6]. In an earlier study, we grouped 1,169 melanoma patients as young (<40 years), middle-aged (40-59 years), and old (≥60 years) [7]. We found that although patient age did not have a significant predictive role in terms of nodal involvement, recurrence, or metastasis, an age of ≥60 years may be associated with more aggressive histological features (non-superficial spreading histology, higher Clark level, and ulceration) and poorer outcomes. The older patients had poorer survival compared with the other ages (P=0.009 for young patients and P=0.012 for middle-aged patients). While a significant correlation was found for overall survival, patient age was not significantly associated with relapse-free survival (P=0.327). Similarly, a large analysis (N=17,600) demonstrated that older melanoma patients had more advanced primary tumors and lower melanoma survival [4]. In another large multinational study, although melanoma patients had a lower rate of node positivity, patients over age 70 years had melanomas with the most aggressive prognostic features, such as head and neck localizations, thicker and more ulcerated melanomas, and greater mitotic rates [5]. Likewise, a single institutional study on 225 stage 3 melanomas showed that older patients had higher tumor stages, higher Breslow depths, higher rates

Table 1. Distribution of the Clinicopathological Variables in Age Groups.

Variable	<30 N (%)	30s N (%)	40s N (%)	50s N (%)	60s N (%)	70+ N (%)	*P* for All	*P* <30 vs 70+
Sex								
Female	72 (53.7)	120 (51.7)	132 (44.0)	119 (35.0)	139 (47.6)	94 (47.5)	0.0001	0.2
Male	62 (46.3)	112 (48.3)	168 (56.0)	221 (65.0)	153 (52.4)	104 (52.5)		
Site of lesion								
Axial	73 (56.6)	133 (60.2)	163 (56.4)	202 (62.0)	148 (53.0)	99 (52.1)	0.1	0.4
Limbs	56 (43.4)	88 (39.8)	126 (43.6)	124 (38.0)	131 (47.0)	91 (47.9)		
Histopathology								
Others	66 (68.8)	121 (72.0)	157 (73.4)	181 (71.8)	155 (71.1)	97 (69.8)	0.9	0.8
Nodular	30 (31.2)	47 (28.0)	57 (26.6)	71 (28.2)	63 (28.9)	42 (30.2)		
Clark level								
1-3	41 (39.0)	75 (41.2)	73 (30.6)	94 (34.9)	74 (32.6)	23 (15.3)	0.0001	0.0001
4-5	64 (61.0)	107 (58.8)	165 (69.4)	175 (65.1)	153 (67.4)	127 (84.7)		
Breslow depth								
<2 mm	38 (36.9)	80 (44.2)	80 (34.5)	103 (40.1)	75 (33.6)	44 (29.3)	0.06	0.2
≥2 mm	65 (63.1)	101 (55.8)	152 (65.5)	154 (59.9)	148 (66.4)	106 (70.7)		
TIL								
No	37 (43.0)	72 (46.5)	88 (45.1)	105 (45.3)	95 (47.3)	69 (55.2)	0.5	0.08
Yes	49 (57.0)	83 (53.5)	107 (54.9)	127 (54.7)	106 (52.7)	56 (44.8)		
Mitotic rate								
<3/mm^2	45 (50.0)	93 (57.4)	90 (46.9)	112 (49.8)	89 (45.6)	55 (43.7)	0.2	0.3
≥3/mm^2	45 (50.0)	69 (42.6)	102 (53.1)	113 (50.2)	106 (54.4)	71 (56.3)		
Ulceration								
No	45 (50.0)	94 (57.3)	99 (46.5)	125 (52.1)	90 (43.5)	41 (30.1)	0.0001	0.003
Yes	45 (50.0)	70 (42.7)	114 (53.5)	115 (47.9)	117 (56.5)	95 (69.9)		
VGP								
No	5 (8.5)	14 (13.1)	11 (8.3)	16 (9.9)	10 (7.3)	7 (7.2)	0.6	0.7
Yes	54 (91.5)	93 (86.9)	122 (91.7)	146 (90.1)	127 (92.7)	90 (92.8)		
Regression								
No	69 (84.1)	104 (77.0)	135 (74.6)	160 (74.1)	127 (76.0)	74 (67.3)	0.1	0.008
Yes	13 (15.9)	31 (23.0)	46 (25.4)	56 (25.9)	40 (24.0)	36 (32.7)		
Neurotropism								
No	63 (95.5)	99 (95.2)	135 (97.8)	169 (97.1)	141 (94.6)	84 (87.5)	0.008	0.08
Yes	3 (4.5)	5 (4.8)	3 (2.2)	5 (2.9)	8 (5.4)	12 (12.5)		

LVI								
No	73 (88.0)	137 (93.2)	164 (88.6)	203 (89.4)	169 (88.5)	99 (80.5)	0.05	0.1
Yes	10 (12.0)	10 (6.8)	21 (11.4)	24 (10.6)	22 (11.5)	24 (19.5)		
Association with nevus								
No	38 (56.7)	70 (60.3)	96 (62.7)	128 (72.3)	96 (67.1)	70 (72.2)	0.08	0.04
Yes	29 (43.3)	46 (39.7)	57 (37.3)	49 (27.7)	47 (32.9)	27 (27.8)		
BRAF mutation*								
No	8 (33.3)	10 (31.2)	25 (41.7)	25 (45.5)	32 (57.1)	28 (73.7)	0.002	0.002
Yes	16 (66.7)	22 (68.8)	35 (58.3)	30 (54.5)	24 (42.9)	10 (26.3)		
Node positivity**								
No	83 (67.5)	141 (68.1)	161 (60.8)	200 (66.2)	177 (68.3)	115 (68.0)	0.4	0.9
Yes	40 (32.5)	66 (31.9)	104 (39.2)	102 (33.8)	82 (31.7)	54 (32.0)		
Metastasis***								
No	123 (91.8)	206 (88.8)	266 (88.7)	302 (88.8)	257 (88.0)	169 (85.4)	0.6	0.07
Yes	11 (8.2)	26 (11.2)	34 (11.3)	38 (11.2)	35 (12.0)	29 (14.6)		
Relapse**								
No	92 (74.8)	144 (69.9)	164 (61.7)	200 (65.8)	172 (66.9)	112 (66.3)	0.1	0.1
Yes	31 (25.2)	62 (30.1)	102 (38.3)	104 (34.2)	85 (33.1)	57 (33.7)		

*BRAFV600E and BRAFV600K; ** in stages I-III patients; ***at the time of diagnosis.

Abbreviations: LVI=lymphovascular invasion; TIL = tumor infiltrating lymphocytes; VGP=vertical growth pattern.

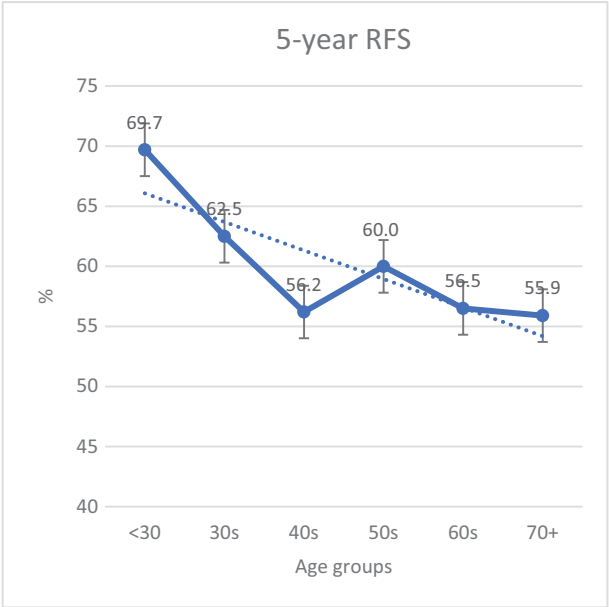

Figure 2. Five-year recurrence-free survival (RFS) values per age group.

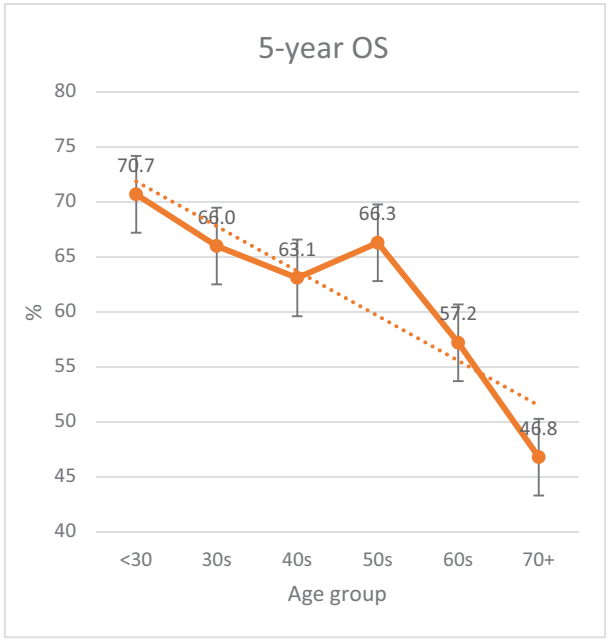

Figure 4. Five-year overall survival (OS) values per age group.

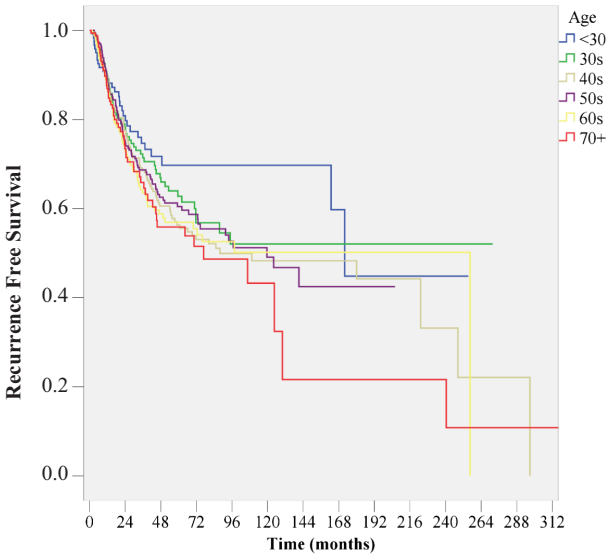

Figure 3. Recurrence-free survival curves in melanoma Patients according to age group (<30 vs 30s, *P*=0.2; <30 vs 40s, *P*=0.08; <30 vs 50s, *P*=0.1; <30 vs 60s, *P*=0.04; <30 vs 70+, *P*=0.01, 30s vs 40s, *P*=0.4; 30s vs 50s, *P*=0.6; 30s vs 60s, *P*=0.2; 30s vs 70+, *P*=0.1; 40s vs 50s, *P*=0.8; 40s vs 60s, *P*=0.7; 40s vs 70+, *P*=0.4; 50s vs 60s, *P*=0.5; 50s vs 70+, *P*=0.2, and 60s vs 70+, *P*=0.7).

of tumor ulceration, and poorer outcomes than did younger patients [6]. Melanoma accounts for 10–11% of all malignancies in adolescent and young adult patients between ages 15 and 39 [8]. This type of melanoma differs from adult melanoma in histopathological characteristics and clinical courses. In our previous study, we observed that melanomas under age 40 (N=297) were found mostly in females and that they were associated with low Clark level, thin Breslow depth, low mitotic rate, and absence of ulceration [7]. The majority of young patients harbored BRAF V600E mutation (59.1%). Even though age is not considered a significant indicator of nodal involvement, recurrence, and/or metastasis, being under age 40 may be associated with favorable histopathological features and better survival compared to more advanced ages, especially beyond age 60. A national cohort study from the Netherlands showed that advanced melanoma patients between ages 15 and 39 (N=210) were more frequently female (51 vs 40%, *P*=0.001) harboring BRAF mutation (68 vs 46%, *P*<0.001), non-nodular histopathology (88 vs 78%, *P*=0.003), and thin Breslow thickness (≤2 mm) (43 vs 32%, *P*<0.0001) compared with older melanomas [9]. There was an overall survival advantage for young melanomas over older patients, with a 1-year survival of 64.7 vs 55% (*P*<0.001). This longer overall survival observed in these young patients was explained by the increased cumulative incidence of non-melanoma-related deaths in older adults. In another study, we investigated 146 melanomas in their 20s and compared them with 1,139 older melanomas [8]. The majority of the lesions were associated with favorable prognostic indicators such as non-nodular histotype (68%), lower mitotic rate (58.1%), low lymphovascular invasion (87.5%), BRAF mutation (70.6%), node negativity (70.1%), and nonmetastatic disease (91.8%). The 5-year disease-free and overall survival rates for vicenarians versus adult melanomas were similar compared with older melanomas.

Some unfavorable prognostic factors, such as high Clark levels, presence of ulceration, and fewer BRAF mutations, are encountered more frequently with increasing age; however,

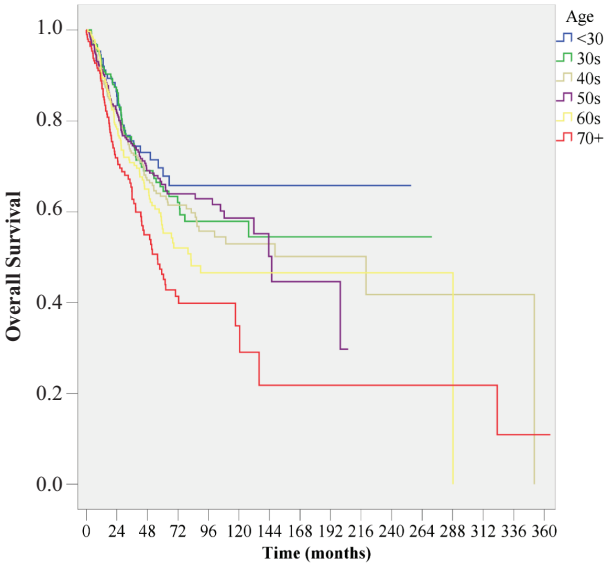

Figure 5. Overall survival curves in melanoma patients according to age group (<30 vs 30s, *P*=0.4; <30 vs 40s, *P*=0.1; <30 vs 50s, *P*=0.2; <30 vs 60s, *P*=0.04; <30 vs 70+, *P*=0.0001, 30s vs 40s, *P*=0.4; 30s vs 50s, *P*=0.7; 30s vs 60s, *P*=0.09; 30s vs 70+, *P*=0.0001; 40s vs 50s, *P*=0.7; 40s vs 60s, *P*=0.2; 40s vs 70+, *P*=0.001; 50s vs 60s, *P*=0.09; 50s vs 70+, *P*=0.0001, and 60s vs 70+, *P*=0.04).

other significant clinical prognostic factors, such as clinical stage and recurrence, do not differ between age groups. The possible explanation for shorter overall survival and partly shortened disease-free survival of older melanoma patients may be that since the elderly have more comorbidities, they may die of different causes. The heterogeneity of primary melanomas and the differences in outcomes between young and elderly melanoma patients have yet to be defined in more prospective studies with greater patient numbers and more detailed age groups.

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