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Research Article

Histopathological and Survival Analysis of 157 Malignant Melanoma Cases Over a 10-Year Period

Göksu Yavuz Abdioğlu[1*], Sevdegül Aydın Mungan[2]

[1] Kanuni Training and Research Hospital, Department of Pathology, Trabzon, Türkiye, goksu61@hotmail.com

[2] Karadeniz Technical University, Faculty of Medicine, Trabzon, Türkiye, drsevdegul@gmail.com, ror.org/03z8fyr40

* Corresponding Author

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Abstract

Objective: Malignant melanoma (MM) is an aggressive cancer responsible for 80% of deaths caused by skin cancers. Despite the increase in the incidence of MM in our country, existing studies are limited in number and mostly focus on cutaneous melanomas. The aim of this study is to evaluate the epidemiological and clinicopathological characteristics and survival data of MM patients diagnosed at our clinic and to contribute to the literature.

Methods: A total of 157 malignant melanoma cases were retrospectively examined in terms of gender, age, tumor location, histological subtype, lymph node involvement, Clark and Breslow stages, mitotic count, presence of satellite lesions, ulceration, regression, tumour lymphocytic response, metastasis sites, treatment methods applied, and survival.

Results: The majority of cases were found to be at an advanced stage and had high tumour thickness. Most histological and clinical parameters showed predominantly high-risk features. Metastasis distribution and overall survival analyses supported the poor prognosis associated with late presentation.

Conclusions: In Türkiye, data suggest the incidence of MM is increasing but available studies are limited in number. In this study, we indicate that MM cases in our region are frequently diagnosed at an advanced stage This situation reveals that the society needs to be more aware of malignant melanoma, risk factors and prevention methods. We aimed to describe the epidemiologic, clinicopathologic, and survival characteristics of patients diagnosed with MM and to contribute these data to the literature.

Keywords: Melanoma, Cutaneus, Skin neoplasm, Survival, Metastasis

1. INTRODUCTION

Malignant melanoma (MM) is an aggressive cancer originating from melanocytes—pigment-producing cells located in the basal layer of the epidermis—accounting for approximately 1% of all skin cancers yet responsible for nearly 80% of skin-cancer–related deaths.[1] While MM most commonly arises in the skin, it may also develop in other melanocyte-containing sites, including mucosal surfaces, the eye, and the central nervous system.[2]

MM results from the interplay of genetic predisposition and environmental factors, of which ultraviolet exposure is the most important environmental risk factor.[3] Although the incidence of MM increases with age, it is relatively frequent in individuals aged 20–45 years.[4] It is more common in women under the age of 40, whereas men are more frequently affected after 40 years of age.[5] When detected at an early stage, local excision achieves cure rates exceeding 90%; however, in advanced-stage melanoma, 5-year overall survival following treatment is approximately 20%.[2]

In Türkiye, although data suggest the incidence of MM is increasing, available studies are limited in number and focus primarily on cutaneous melanoma; data regarding mucosal melanoma are even scarcer.[6] In this study, conducted in our regional tertiary hospital, we aimed to describe the epidemiologic, clinicopathologic, and overall survival characteristics of patients diagnosed with MM and to contribute these data to the literature.

2. MATERIAL AND METHOD

This retrospective study reviewed the archived files and electronic records of cases diagnosed with MM in our hospital's Department of Pathology between 2003 and 2013. Demographic

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variables documented at diagnosis included age, gender, and tumour localization. Histopathologic parameters assessed were histologic subtype, Breslow tumour thickness, Clark level, presence of satellite nodules, and regression. Both primary and metastatic cases were evaluated; for metastatic cases, the involved anatomic sites were recorded. Overall survival was obtained via the hospital information system. Cases with missing data for the predefined parameters were excluded. As MM may arise from the skin, eye, meninges, and all mucosal surfaces—and because treatment, staging, and prognosis differ across these sites—cutaneous, ocular, and mucosal MM were analyzed as separate groups.

Our study was designed as a descriptive research. Descriptive statistics were used to summarize the data; in this context, the ratio, percentage, arithmetic mean, median, and standard deviation values were calculated. The chi-square test was applied to evaluate the relationships between the group.

3. RESULTS

A total of 157 patients were included (80 men and 77 women), with an average age of 62.61 years (range 3–88 years). Of these, 123 were primary cutaneous melanoma, 16 were metastatic melanoma of unknown primary, 15 were primary mucosal melanoma, and 3 were ocular melanoma cases. The distribution of cases is shown in table 1.

Table 1.

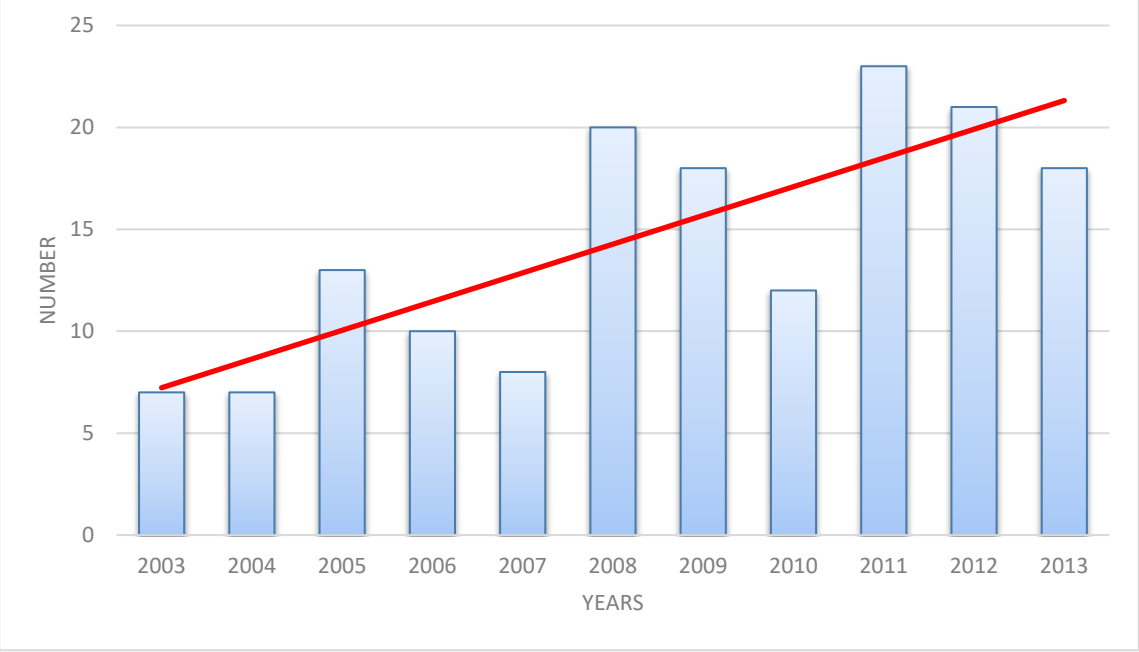
Overall case distribution

Case Distribution	(n)	Age	Gender		Overall Survival
			Female	Male	
Skin	123	NA	66(53.65%)	57(46.35%)	2-84 months
Mucosal	15	70	NA	NA	2-84 months
Ocular	3	NA	2(66.6%)	1(33.3%)	2-12 months
Metastatic	16	NA	NA	NA	NA
Total	157	62.61(3-88)	77	80	2-84 months

NA: Not available

Figure 1.

Distribution of melanoma cases over the years



Among mucosal MM cases (n=15), the mean age was 70 years; 10 patients (66.6%) were women and 5 (33.3%) were men. Primary sites were the nasal cavity in 12 cases, rectum in 2 cases and cervix in 1 case. The vital status of 2 patients could not be ascertained; the remaining patients had died. Overall survival ranged from 2 to 84 months, with a mean overall survival of 10 months.

Ocular MM comprised 3 cases (2 women and 1 man); all patients had died, with overall survivals of 2 and 12 months documented, representing the poorest overall survival among melanoma subgroups.

For metastatic melanoma of unknown primary (n=16), the distribution of metastases was as follows: lymph node (n=7), brain (n=6), liver (n=2), and lung (n=1). In cases where the primary lesion is unknown, the sites and numbers of metastases are shown in table 2.

Table 2.

Metastatic sites and numbers in cases with unknown primary site

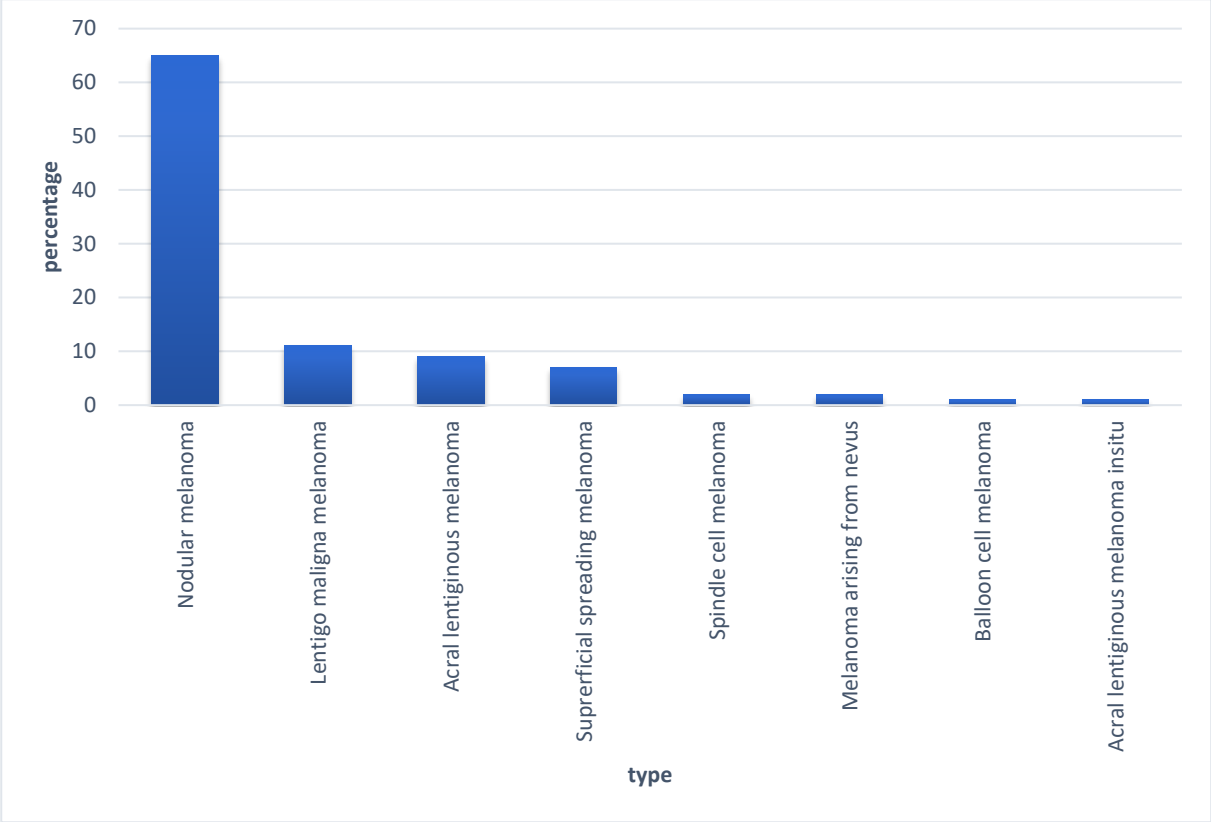
Area of metastasis	(n)
Lymph node	7
Brain	6
Liver	2
Lung	1

Among the 123 cutaneous MM cases, 66 (53.65%) were women and 57 (46.35%) were men. In both genders, the most frequent primary site was the head and neck, followed by the lower extremity.

Histologic subtypes among primary cutaneous MM were as follows: nodular MM 65 (66.32%), lentigo MM 11 (11.22%), acral lentiginous MM 9 (9.18%), superficial spreading MM 7 (7.14%), balloon cell MM 1 (1.02%), MM arising in a nevus 2 (2.04%), spindle cell MM 2 (2.04%) and acral lentiginous melanoma in situ 1 (1.02%). The histological subtypes and numbers in primary MM are shown in figure 2.

Figure 2.

Proportions of histologic subtypes among primary MM



When cases were stratified by Breslow thickness into "thin" (≤4 mm) and "thick" (>4 mm) melanomas, 45 cases (55.21%) were ≤4 mm and 38 cases (45.79%) were >4 mm. In thick melanomas, ulceration was present in 82% of cases and the mean mitotic count was 6.5/mm^2. In thinner melanomas (≤4 mm), ulceration was present in 50% of cases and the mean mitotic count was 5.15/mm^2.

With respect to invasion depth, 71 cases were Clark levels 4–5, and 24 cases were Clark levels 1–3. Among patients with lower Clark levels (1–3), 23% had died and their mean overall survival was 20 months. Among those with higher Clark levels (4–5), 42% had died and their mean overall survival was 15 months.

Of 43 cases in which the presence of satellites, microsatellites, or in-transit metastases was recorded, 8 had satellites, 8 had microsatellites and 1 had an in-transit metastasis. Sentinel lymph node positivity was present in 7 of the satellite-positive cases, in 2 of the microsatellite-positive cases, and in the single in-transit metastasis case. Among cases with satellites or microsatellites, 42% had died; mean overall survival was 16 months.

Ulceration was present in 42 cases (26.75%). Ulceration was most frequent in nodular melanoma and least frequent in lentiginous melanoma.

Among cases with reported mitotic activity, 17 (10.19%) had ≥6 mitoses/mm^2 and 30 (19.74%) had <6 mitoses/mm^2. In cases with ≥6 mitoses/mm^2, the mean Breslow thickness was 8.17 mm and ulceration was present in 53%. In cases with <6 mitoses/mm^2, the mean Breslow thickness was 4.56 mm.

Tumor-infiltrating lymphocytes (TILs) were reported in 43 patients: 28 cases were TIL-positive and 15 were TIL-negative. Among TIL-positive cases, 12 were alive and 16 had died; overall survival ranged from 3 to 36 months (mean, 10.93 months). Among TIL-negative cases, 6 were alive and 7 had died; overall survival ranged from 6 to 72 months (mean, 21.57 months).

Sentinel lymph node metastasis was identified in 44 cutaneous MM cases; their Breslow thicknesses ranged from 0.05 to 22 mm (mean, 7 mm). Of these 44 patients with nodal positivity, 33 had died; overall survival ranged from 2 to 84 months (mean, 15.25 months).

Overall survival data were available for 127 patients; 50 were alive and 77 had died, with overall survival ranging from 2 to 84 months (mean, 16.92 months). Among the deceased, 40 were men and 37 were women. Overall survival in men ranged from 2 to 49 months (mean, 13.17 months), and in women from 2 to 84 months (mean, 19.81 months).

4. DISCUSSION

Globally, the incidence of MM has risen markedly in recent years.[5] In our 10-year cohort, melanoma cases increased over time, broadly mirroring global patterns: in the first five years there were 45 cases, whereas 112 cases were observed in the latter five years.

In prior studies from Türkiye, the mean age at diagnosis of MM ranges from 51.6 to 59.5 years.[7-9] In the 104,784-case series by Zheng et al., the modal age range was 55–64 years.[10] In our cohort, the mean age of 62.61 years is slightly higher than the national averages, a difference that may reflect the sociodemographic characteristics of our region.

In men, the most frequent MM site is the back, whereas in women it is the lower extremity.[11] In prior Turkish series, the most common primary site has been the lower extremity, the face or the head and neck.[12-14] In our study, the head and neck region predominated, followed by the lower extremity, upper extremity, and trunk. Given the relatively low number of sunny days in our region and the role of ultraviolet radiation as the principal environmental risk factor in MM, certain distributional statistics may reasonably differ from other reports.[1,15] Nodular melanoma is the most common histologic subtype of cutaneous MM in our cohort, nodular melanoma was likewise predominant (66.2%).[14,16-18]

Clark level describes the depth of invasion from level 1 (confined to the epidermis) to level 5

(involving subcutaneous fat). Higher Clark level correlates with an increased risk of metastasis and poorer prognosis.[19] Prior Turkish series frequently reported Clark level 4 as the most common, and levels 4–5 constituting ~82% of cases.[13,14,17] In our subset of 95 cases with recorded Clark level, level 4 was most frequent (44.21%); levels 4–5 comprised 51% of cases, and all patients in this group died after a mean survival of 16.21 months. Levels 1–3 constituted 29.1% of cases. These results are consistent with the literature.

Mucosal MM has a poorer prognosis than cutaneous MM, with 5-year rates of 10–15%.[20] In our mucosal MM cases, the median survival was 10 months, shorter than cutaneous cases, in keeping with the literature.

Both cutaneous and mucosal MM tend to metastasize to regional lymph nodes early in the course of disease.[16] In the series by Külahçı et al., among 30 patients with nodal metastases the mean Breslow thickness was 1.24 mm.[13] In our cohort, sentinel lymph node metastasis occurred in 35.7% of cutaneous cases, with a mean Breslow thickness of 7 mm; 75% of node-positive patients had died, with a mean overall survival of 15.25 months. In the study by Morton et al., 5-year overall survival for stage-matched melanoma was 53% in sentinel node-positive patients and 83% in node-negative patients.[21]

Breslow thickness is the most important independent prognostic factor.[14] According to the AJCC, thresholds for tumor thickness are 1.0 mm, 2.0 mm, and 4.0 mm. Tumors ≤1.0 mm are "thin melanomas" with relatively favorable prognosis, whereas those >4.0 mm are "thick melanomas" with poor prognosis.[22] Multiple studies have demonstrated an inverse relationship between Breslow thickness and overall survival (Ramnath et al., 480 cases; Levi et al., 1,229 cases).[23,24] In both univariate and multivariate analyses, Breslow thickness remains the principal risk factor (Marashi-Pour et al.).[25] In our series, when categorized as ≤4 mm and >4 mm, 55.21% were thin and 45.79% were thick melanomas. Ulceration occurred in 50% of thin melanomas and in 82% of thick melanomas; as in other Turkish cohorts, increasing Breslow thickness was associated with higher mitotic counts and a higher frequency of ulceration.[12-14]

Regression is observed in 10–35% of primary cutaneous melanomas.[26] A prior Turkish study reported partial regression in 30.1%.[14] In our cohort, regression was noted in 11.62%, similar to published rates.

Microsatellitosis is strongly associated with regional lymph node metastasis and thus with prognosis.[27] Büyükpınarbaşılı et al. reported microsatellites in 3.2%, local recurrence in 7.5%, in-transit metastases in 1.1% and an associated nevus in 20.4%.[14] In our cohort, among 43 cases with recorded data, satellites were absent in 65.1%; satellites and microsatellites were each present in 18.6%, and in-transit metastasis in 2.3%. Sentinel node positivity was present in 87.5% of cases with satellites, 25% with microsatellites, and 100% with in-transit metastasis. Sixty percent of patients with satellites or microsatellites died, with a mean overall survival of 16 months.

Ulceration is a negative prognostic factor at all thicknesses.[28] In the AJCC TNM system (T, tumor invasion depth; N, nodal involvement; M, distant metastasis), 10-year overall survival in stage I–II melanomas is 78% in the absence of ulceration and 50% when ulceration is present.[29] Devrim et al. reported ulceration in 54% of cases, 73.7% of which were nodular melanoma.[17] Büyükpınarbaşılı et al. observed ulceration in 53.8% and demonstrated significant associations with Breslow thickness and with overall survival.[14] In our cohort, ulceration status was recorded in 63 cases; ulceration was present in 42 (66.66%). Breslow thickness in ulcerated tumors ranged from 0.6–18 mm (mean, 6.13 mm), versus 0.3–19 mm (mean, 4.14 mm) in non-ulcerated tumors. By site, ulcerated tumors involved the lower extremity in 20 cases (50%), head and neck in 13 (32.5%), trunk in 5 (12.5%), and upper extremity in 2 (5%). Nineteen ulcerated cases developed metastases (13 to lymph nodes, 3 to brain, and 3 to liver). These findings are concordant with the literature.

A higher mitotic count not only shortens overall survival but is also associated with sentinel lymph

node metastasis.[30] The risk of metastasis is 12-fold higher in patients with ≥6 mitoses/mm^2 compared with those without mitoses.[31] Büyükpınarbaşılı et al. identified mitotic activity of <6/mm^2 in 47 cases and ≥6/mm^2 in 27 with significant correlations among mitotic activity, Breslow thickness and ulceration; mitotic activity increased with Breslow thickness.[14] In our series, mitotic activity was reported in 47 patients (29.93%); 17 cases (10.19%) had ≥6 mitoses/mm^2 (Breslow 0.3–19 mm; mean, 8.17 mm) and 30 cases (19.74%) had <6 mitoses/mm^2 (Breslow 0.6–16 mm; mean, 4.56 mm). Ulceration was present in 53% of cases with ≥6 mitoses/mm^2. These observations are similar to other Turkish cohorts.

More than a century has passed since lymphocytes were first recognized within malignant tumors; these were later termed tumor-infiltrating lymphocytes (TILs).[32] Initially believed to reflect chronic inflammation, TILs were subsequently debated as either facilitating tumor growth or indicating a host antitumor response. In 1969, Clark et al. first described lymphocytic infiltration in primary cutaneous melanoma, and its prognostic significance was later established: patients with moderate to brisk lymphocytic infiltration had a three-fold increase in 5-year overall survival.[33] Elder et al. classified lymphocytic infiltration as "brisk," "non-brisk," or "absent," demonstrating prognostic value for TILs specifically in the vertical growth phase.[34] Conversely, TILs spread in the radial growth phase—regardless of in situ or invasive status—did not contribute to prognosis. TILs briskness was prognostic in T2–T4 primary cutaneous melanoma but not in very thick (T4) lesions; both long-term overall survival (5–10 years) and nodal metastasis probability were inversely related to TILs counts.[35] In the study by Clemente et al., 5-year overall survival rates were 55% with brisk TILs, 45% with non-brisk TILs, and 27% with absent TILs; among histologic factors, only tumor thickness and TILs were independent prognosticators.[36] In our series, TILs status was recorded in 43 patients: 28 were TIL-positive and 15 TILs-negative. Among TILs-positive cases, 12 were alive and 16 had died (overall survival 3–36 months; mean, 10.93 months). Among TIL-negative cases, 6 were alive and 7 had died (overall survival 6–72 months; mean, 21.57 months). Lymph node involvement was present in 5 TIL-positive and 5 TIL-negative cases. These findings are consistent with prior reports.

Despite the theoretical opportunity for cure when detected at a fully treatable stage, mortality from MM remains high. In a Norwegian cohort of ~3,000 patients in 1977, 5-year overall survival was ~60%. Levi et al. identified male sex as one of two principal determinants of poorer overall survival.[24] In the large series by Balch et al. (17,600 MM patients), men had shorter overall survival than women, and Marashi-Pour et al. similarly reported shorter overall survival in men.[25,37] In the series by Aydın et al., 1, 2, and 5 year overall survival rates were 96%, 92.1%, and 82.7%, respectively; mean overall survival was 89.74±6.9 months, with significantly longer overall survival in women (108.8 months) than in men (72.7 months).[38] In our cohort, overall survival data were available for 127 patients: 50 were alive and 77 had died (overall survival 2–84 months; mean, 16.92 months). Among the deceased, 40 cases were men and 37 cases were women. Although the incidence of MM in Türkiye is relatively low and stable, MM ranks among the ten most common tumors in both genders in developed countries.[39,40] The increasing preference for tanned skin is considered a major contributor; similar trends are evident in Türkiye. Public education campaigns addressing intentional tanning are therefore warranted.[39]

MM is a tumor in which cure rates exceed 90% when detected and treated at an early stage; however, despite promising therapeutic advances, overall survival remains poor in advanced disease.[40] In light of these facts, enhancing public awareness to facilitate early detection and treatment of cutaneous MM is of paramount importance.

5. CONCLUSION

This study demonstrates that malignant melanoma cases in our clinic are frequently diagnosed at advanced stages with high-risk clinicopathological features. The negative impact

of delayed diagnosis on survival highlights the importance of increasing awareness of early detection and preventive strategies. The findings are expected to contribute to the limited data on malignant melanoma in our country.

Article Information Form

Author Contributions

Conceptualization: G.Y.A., S.A.M.; Methodology: G.Y.A., S.A.M.; Formal analysis: G.Y.A., S.A.M; Investigation: G.Y.A.; Resources: G.Y.A.; Data curation: G.Y.A.; Writing – original draft: G.Y.A.; Writing – review & editing: G.Y.A., S.A.M.; Visualization: G.Y.A.; Supervision: S.A.M.; Project administration: G.Y.A.

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by authors.

The Declaration of Ethics Committee Approval

In 2015, ethical committee approval was obtained by the Karadeniz Technical University Clinical Research Ethics Committee with the registration number 24237859-227.

Artificial Intelligence Statement

No artificial intelligence tools were used while writing this article.

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