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ORIGINAL ARTICLE

De Novo and Nevus-Associated Melanomas: Different Histopathologic Characteristics but Similar Survival Rates

Faruk Tas [1] · Kayhan Erturk [2]

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Abstract

The clinical significances of de novo and nevus-associated melanomas are controversial. In this study, we investigated the correlations of these forms of melanomas in respect to their pathological and clinical features and patient outcomes. The data of 660 pathologically confirmed Turkish-Caucasian melanoma patients, whose tumors were either associated with a pre-existing melanocytic nevus or not, were analyzed retrospectively. They were treated and followed up at a single tertiary referral center. A total of 440 de novo (66.7%) and 220 nevus-associated melanomas (33.3%) were enrolled into the study. The median age of the patients was 51 years. The patients consisted of 341 men (51.7%) and 319 women (48.3%). There were significant correlations between de novo melanomas and advanced age ($p = 0.003$), tumor thickness greater than 2 mm ($p = 0.0001$), ulceration ($p = 0.01$) and high mitotic rate ($p = 0.03$). On the other hand, nevus-associated melanomas were found significantly associated with histological regression ($p = 0.03$) and BRAFV600E mutation ($p = 0.003$). Most of the nevus-associated melanomas were found on trunk and head/neck, whereas extremities were more frequently inflicted by de novo melanomas ($p = 0.0001$). Furthermore, none of other variables, such as sex, histopathology, lymph node involvement and presence of metastasis, showed statistically significant difference between de novo and nevus-associated melanoma patients ($p > 0.05$). The 5-year DFS rates were 62.4% and 72.7% for de novo melanoma and for nevus-associated melanoma patients, respectively ($p = 0.1$). The 5-year OS rate were 72.1% and 76.4% for de novo melanoma and nevus-associated melanoma patients, respectively ($p = 0.2$). In conclusion, even though de novo melanomas are more significantly correlated with aggressive histopathologic variables, such as tumor depth, ulceration and high mitotic rate, the survival rates of de novo and nevus-associated melanomas are similar.

Keywords Melanoma · de novo · Nevus-associated · Survival

Introduction

Cutaneous melanoma, the most lethal skin cancer worldwide, is the fifth (7%) and the sixth (4%) most common type of cancer in men and women, respectively, in the US [1]. In 2020, 100,350 patients will have been diagnosed with melanoma in the US, 6850 of whom will have lost their lives [1]. The incidence of melanoma continues to increase dramatically; the lifetime risk of developing melanoma is 1 in 28 and 1 in 41 for men and for women, respectively. Its incidence is increasing in men more rapidly than any other tumor; and in women more rapidly than any other malignancy, except lung carcinoma.

Cutaneous melanoma is a malignant melanocytic tumor and it arises either in association with a preexisting nevus (nevus-associated melanoma, NAM) or de novo, without any associated lesion (de novo melanoma, DNM) [2–5]. The epidemiologic and pathologic studies showed that the majority of the melanomas, nearly two thirds of patients, were DNMs [4, 5].

Because both NAMs and DNMs were negligible compared to well known other prognostic factors such as thickness, ulceration, mitotic rate and lymph node involvement in many trials, the clinical significances of these melanomas remain uncertain and controversial. Some found correlations with various clinic-pathological factors, but others disagreed and opposed to these suggestions [2–5]. Similarly, little is known about their prognostic significance on patient outcomes,

✉ Faruk Tas
faruktas2002@yahoo.com

[1] Institute of Oncology, Istanbul University, Capa, 34390 Istanbul, Turkey

[2] Department of Medical Oncology, Koc University, Istanbul, Turkey

owing to study limitations, such as small sample sizes, retrospective designs and unsatisfactory follow-up data [2, 6–13].

In this study, we questioned the correlations of these forms of melanomas in respect to their pathological and clinical features and patient outcomes.

Material and Methods

The data of 660 pathologically confirmed Turkish-Caucasian melanoma patients, whose tumors were either associated with a pre-existing melanocytic nevus or not, were analyzed retrospectively. They were treated and followed up at the Istanbul University Institute of Oncology, a single tertiary referral center.

The records were retrieved from the cancer registry and reviewed for clinical and pathological features and outcomes. American Joint Committee on Cancer (AJCC, 8th edition) system was used for staging the disease. Either sentinel lymph node (SLN) biopsy or lymph node dissection was performed so as to determine lymph node status. Patients with pathologically positive SLN underwent a completion lymphadenectomy. Patients were treated and followed-up according to the standard international guidelines, including National Comprehensive Cancer Network guidelines. The study was reviewed and approved by our Regional Ethical Committee.

Comparisons between patient/disease variables and melanoma groups were done using chi-square tests. Kaplan-Meier analysis was used for estimation of survival of patients. Disease-free survival (DFS) 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 determined from the date of pathologic diagnosis to death resulting from any cause. Statistical analysis was carried out using SPSS 21.0 software (SPSS Inc., Chicago, Illinois, USA). A p value ≤ 0.05 was considered significant.

Results

A total of 660 cutaneous melanoma patients, 440 DNMs (66.7%) and 220 NAMs (33.3%), were enrolled into the study. The median age of the patients was 51 years (range, 16–104). The patients consisted of 341 men (51.7%) and 319 women (48.3%). The demographic, pathological and clinical characteristics of the patients were given in Table 1.

Compared to NAMs, there were statistically significant correlations between DNMs and patients older than 51 years of age (58.6% *v* 46.4%, $p = 0.003$), tumor thickness greater than 2 mm (68.8% *v* 53.3%, $p = 0.0001$), ulceration (55.1% *v* 44.4%, $p = 0.01$) and mitotic rate higher than 3/mm^2 (51.3% *v* 42.4%, $p = 0.03$) (Table 1). On the other hand, NAMs were

Table 1 Distribution of the variables to DNM and NAM patients

Variable	DNM n (%)	NAM n (%)	p
Age of patient			0.003
>50 years	258 (58.6)	102 (46.4)	
≤50 years	182 (41.4)	118 (53.6)	
Sex			0.9
Female	212 (48.2)	107 (48.6)	
Male	228 (51.8)	113 (51.4)	
Site of lesion			0.0001
Axial	215 (48.9)	161 (73.2)	
Limbs	225 (51.1)	59 (26.8)	
Histopathology			0.1
Nodular	102 (24.5)	37 (18.8)	
Others	314 (75.5)	160 (81.2)	
Clark invasion level			0.4
I-III	123 (28.4)	66 (31.4)	
IV-V	310 (71.6)	144 (68.6)	
Breslow thickness			0.0001
<2 mm	135 (31.2)	99 (46.7)	
≥2 mm	297 (68.8)	113 (53.3)	
Ulceration			0.01
Yes	234 (55.1)	88 (44.4)	
No	191 (44.9)	110 (55.6)	
Mitotic rate			0.03
<3	205 (48.7)	114 (57.6)	
≥3	216 (51.3)	84 (42.4)	
Lymphovascular invasion			0.4
Yes	52 (12.3)	20 (10.2)	
No	370 (87.7)	177 (89.8)	
Vertical growth phase			0.2
Yes	272 (91.6)	141 (88.1)	
No	25 (8.4)	19 (11.9)	
Neurotropism			0.5
Yes	16 (4.7)	5 (3.4)	
No	321 (95.3)	142 (96.6)	
Tumor infiltrating lymphocytes			0.5
Yes	196 (45.5)	86 (43.0)	
No	235 (54.5)	114 (57.0)	
Regression			0.03
Yes	92 (22.1)	59 (30.3)	
No	324 (77.9)	136 (69.7)	
BRAFV600E mutation			0.003
Positive	27 (45.8)	21 (80.8)	
Negative	32 (54.2)	5 (19.2)	
Lymph node involvement (N)			0.2
No	275 (65.8)	150 (70.4)	
Yes	143 (34.2)	63 (29.6)	
Metastasis (M)			0.2
No	418 (95.0)	213 (96.8)	
Yes	22 (5.0)	7 (3.2)	
Relapse during follow-up			0.06
No	299 (71.5)	167 (78.4)	
Yes	119 (28.5)	46 (21.6)	
Last status			0.2
Dead	100 (22.7)	41 (18.6)	
Alive	340 (77.3)	179 (81.4)	

significantly correlated with histological regression (30.3% *v* 22.1%, $p = 0.03$) and BRAFV600E mutation (80.8% *v* 45.8%, $p = 0.003$) compared to DNMs. Most of the NAMs were found on trunk and head/neck, whereas extremities were more frequently inflicted by DNMs ($p = 0.0001$). Furthermore, none of other variables, such as sex, histopathology, lymph node involvement and presence of metastasis, showed statistically significant difference between DNMs and NAMs ($p > 0.05$) (Table 1).

During follow-up, 119 (28.5%) DNM and 46 (21.6%) NAM patients developed progression ($p = 0.06$) (Table 1). The median DFS times and 5-year DFS rates were 24.3 months (0.2–189.2) and 62.4% for DNM and 25.3 months (0.2–188.3) and 72.7% for NAM patients ($p = 0.1$) (Table 2, Fig. 1).

A total of 141 (21.4%) deaths occurred in the patient groups, 100 (22.7%) in DNMs and 41 (18.6%) in NAMs, at the time of the analysis ($p = 0.2$) (Table 1). The median OS times and 5-year OS rates were 30.5 months (0.2–195.0) and 72.1% for DNMs and 27.8 months (0.2–188.3) and 76.4% for NAMs ($p = 0.2$) (Table 2, Fig. 2).

Discussion

Even though the presence of underlying acquired nevus is an accepted indicator for increased risk of melanoma development, whether melanocytic lesions might also be considered as melanoma precursors is still controversial [3]. Epidemiological and pathological studies demonstrated a wide range of NAM prevalence, from 4% to 72% [3, 5]. A review of 25 studies showed that 36% of melanomas were associated with a preexisting nevus [6]. A Brazilian dermatopathology referral center concurred with our results in that one-third of melanomas were associated with NAMs (32.8%) [4]. Moreover, a prospective study conducted on a high-risk patient cohort found that 54.2% of primary melanomas were associated with melanocytic nevus [3]. Furthermore, a meta-analysis including 38 observational cohort and case-control studies concluded that 29.1% of melanomas arose from a preexisting nevus and 70.9% occurred de novo [5].

Similar to our conclusion ($p = 0.003$); Cymermann et al. [2] also showed that compared with NAMs, DNMs were significantly associated with older age at diagnosis ($p = 0.004$). Furthermore, a meta-analysis including 9 studies showed that patients with NAMs were younger than those with DNMs ($p < 0.001$) [5]. Otherwise, in agreement with our findings, no significant association was established between NAM and sex [4]. Moreover, no significant differences between men and women were reported in the 17 studies in which gender was indicated [5].

When considering the anatomic distribution of NAMs; most melanomas occur on intermittently sun-exposed areas, e.g. trunk and extremities. The finding that the trunk is the most frequently involved localization concurs with previous studies [3, 4]. Furthermore, DNMs were found to arise more frequently on extremities [2], yet in a meta-analysis trunk and

Table 2 Variables affecting survivals

Variable	DFS		OS	
	HR (95%CI)	P	HR(95%CI)	p
Age of patient	1.074 (0.790–1.460)	0.6	1.232 (0.881–1.721)	0.2
Sex	1.845 (1.344–2.532)	0.0001	2.245 (1.575–3.200)	0.0001
Site of lesion	0.805 (0.589–1.102)	0.1	0.749 (0.532–1.053)	0.09
Histopathology	1.834 (1.292–2.603)	0.001	2.323 (1.616–3.339)	0.0001
Clark invasion level	4.475 (2.668–7.506)	0.0001	4.688 (2.592–8.479)	0.0001
Breslow thickness	3.083 (2.083–4.565)	0.0001	3.566 (2.261–5.624)	0.0001
Ulceration	2.789 (1.992–3.904)	0.0001	2.587 (1.792–3.733)	0.0001
Mitotic rate	2.433 (1.753–3.377)	0.0001	1.944 (1.368–2.763)	0.0001
Lymphovascular invasion	2.255 (1.495–3.400)	0.0001	2.254 (1.466–3.467)	0.0001
Vertical growth phase	7.723 (1.907–31.267)	0.004	11.198 (1.560–80.401)	0.01
Neurotropism	1.920 (0.931–3.961)	0.07	2.844 (1.429–5.662)	0.003
Tumor infiltrating lymphocytes	0.787 (0.573–1.082)	0.1	0.582 (0.405–0.835)	0.003
Regression	0.909 (0.623–1.326)	0.6	0.656 (0.418–1.031)	0.06
BRAFV600E mutation	0.554 (0.327–0.997)	0.05	0.485 (0.239–0.986)	0.04
Lymph node involvement (N)	3.421 (2.513–4.658)	0.0001	2.793 (1.952–3.997)	0.0001
Metastasis (M)	–	–	11.971 (7.405–19.353)	0.0001
Relapse during follow-up	–	–	15.254 (9.427–24.682)	0.0001
Association with/without nevus	0.753 (0.536–1.059)	0.1	0.811 (0.564–1.167)	0.2

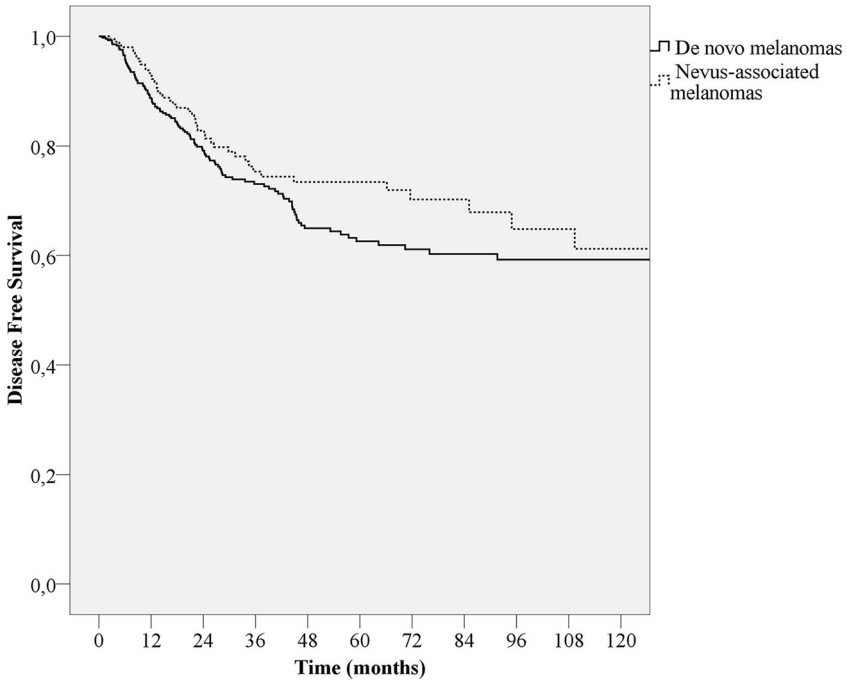

Fig. 1 DFS curves of the patients with DNM and NAM ($p = 0.1$)

extremities were reported as the most commonly inflicted locations for both groups; and this agrees with our findings [5]. In our study, NAMs were more frequently found on trunk and head/neck, whereas DNMs more likely occurred on limbs ($p = 0.0001$).

Many studies showed that superficial spreading melanoma was the prominent histotype in NAMs [3, 4], whereas DNMs were associated more frequently with nodular subtype [2]. Yet superficial spreading melanoma was reported in a meta-analysis as the most frequent histological subtype in both groups [5]. In our study there was no statistically difference between two melanoma types in terms of histopathology. Apart from that, tumor thickness was also examined and it was suggested that NAMs were associated with lower Breslow thickness [2–5, 7]. Haenssle et al. [3] found that the median Breslow thickness of invasive melanomas was 0.42 mm and nearly all showed a thickness of 1 mm or less. Similarly, the median Breslow thickness for DNMs was found

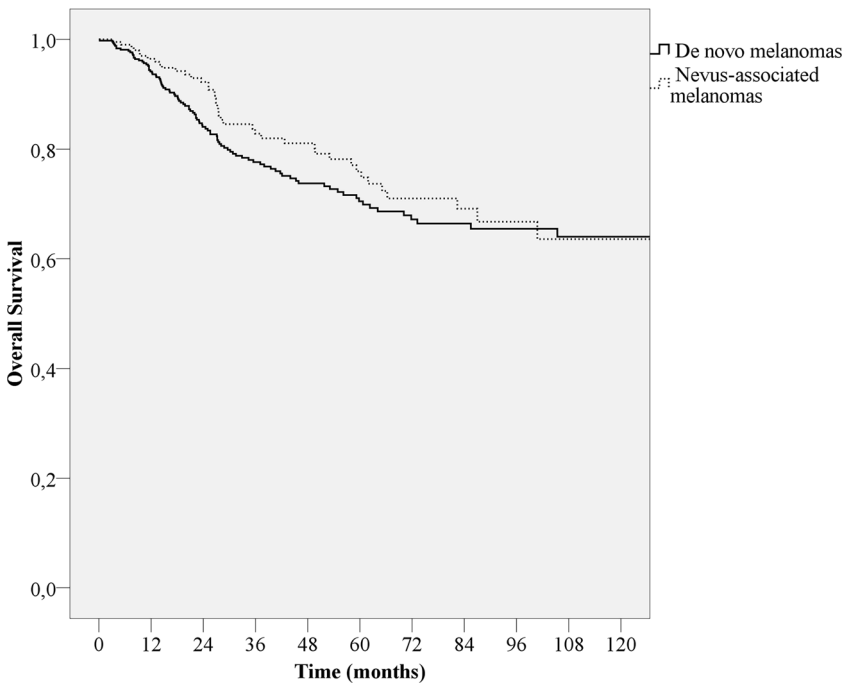

Fig. 2 OS curves of the patients with DNM and NAM ($p = 0.2$)

0.85 mm, which was greater than that for NAMs (0.7 mm) [4]. In another study DNMs were found to be associated not only with tumor thickness greater than 1 mm ($p < 0.001$), but also with other prognostic variables, such as ulceration ($p = 0.02$) and stages above stage I ($p < 0.001$) [2]. Accordingly, a meta-analysis reported that NAMs had a lower mean Breslow thickness than DNMs [5]. In our study, compared to NAMs, DNMs were significantly associated with poor prognostic indicators, such as tumor thickness ($p = 0.0001$), ulceration ($p = 0.01$) and high mitotic rate ($p = 0.03$). Conversely, histological regression ($p = 0.03$) and BRAFV600E mutation ($p = 0.003$) were found more frequently in NAMs than DNMs.

The prognostic significance of NAM is yet to be clarified [2, 6–13]. Weatherhead et al. [8] suggested in a prospective study that NAM had higher Breslow thickness and worse prognosis than DNM. However, some studies did not produce such a significant difference in prognosis between NAMs and DNMs [6, 7, 9–11]; and conversely other studies concluded that median Breslow thickness of NAMs was lower than that of DNMs suggesting a more favorable prognosis with NAMs compared to DNMs [12, 13]. It was shown that DNM was associated with poorer overall survival ($P < 0.001$) [2]; and in multivariate analysis DNM was determined as an independent poor prognostic indicator [2]. We found that even though NAMs were associated with more favorable survival rates than DNMs there was no statistically significant correlation between them. The possible explanation may be that even though there was the association between DNMs and tumor-related poor prognostic factors no correlation existed with the stage of disease, which is considered one of the most important prognostic factors.

There are limitations for this study. The retrospective hospital-based study design of the study is the most significant disadvantage. The data solely depend on the accuracy of the patient records at the Institute of Oncology and some data on clinicopathological features is missing. On the other hand, we acknowledge that the data from a single tertiary cancer center that comprised primarily patients with advanced diseases may not reflect overall national data. We may only assume that our findings are unlikely different from those of other centers. Further prospective studies with larger patient numbers are necessary to compare the results of this study.

In conclusion, we observed that even though DNMs are more significantly correlated with aggressive histopathologic variables, such as tumor depth, ulceration and high mitotic rate, the survival rates of DNMs and NAMs are similar.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

The study was reviewed and approved by our local ethical committee.

References

1. Siegel RL, Miller KD, Jemal A (2020) Cancer statistics, 2020. CA Cancer J Clin 70:7–30
2. Cymerman RM, Shao Y, Wang K, Zhang Y, Murzaku EC, Penn LA et al (2016) De novo vs nevus-associated melanomas: differences in associations with prognostic indicators and survival. J Natl Cancer Inst 108(10):djw121
3. Haenssle HA, Mograby N, Ngassa A, Buhl T, Emmert S, Schon MP et al (2016) Association of patient risk factors and frequency of nevus-associated cutaneous melanomas. JAMA Dermatol 152: 291–298
4. Shitara D, Nascimento MM, Puig S, Yamada S, Enokihara M, Michalany N et al (2014) Nevus-associated melanomas: clinicopathologic features. Am J Clin Pathol 142:485–491
5. Pampena R, Kyrgidis A, Lallas A, Moscarella E, Argenziano G, Longo C et al (2017) A meta-analysis of nevus-associated melanoma: prevalence and practical implications. J Am Acad Dermatol 77: 938–945
6. Lin WM, Luo S, Muzikansky A, Lobo AZC, Tanabe KK, Sober AJ, Cosimi AB, Tsao H, Duncan LM (2015) Outcome of patients with de novo versus nevus-associated melanoma. J Am Acad Dermatol 72:54–58
7. Purdue MP, From L, Armstrong BK, Kricker A, Gallagher RP, McLauhglin JR et al (2005) Etiologic and other factors predicting nevus-associated cutaneous malignant melanoma. Cancer Epidemiol Biomark Prev 14:2015–2022
8. Weatherhead SC, Haniffa M, Lawrence CM (2007) Melanomas arising from naevi and de novo melanomas—does origin matter? Br J Dermatol 156:72–76
9. Garcia-Cruz A, Florez A, de la Torre-Fraga C, Cruces PM (2009) Observational cross-sectional study comparing Breslow thickness of melanoma arising from naevi and melanoma de novo. Br J Dermatol 161:700–702
10. Kaddu S, Smolle J, Zenahlik P, Hofmann-Wellenhof R, Kerl H (2002) Melanoma with benign melanocytic naevus components: reappraisal of clinicopathological features and prognosis. Melanoma Res 12:271–278
11. Cochran AJ (1969) Histology and prognosis in malignant melanoma. J Pathol 97:459–468
12. Rhodes AR, Sober AJ, Day CL, Melski JW, Harris TJ, Mihm MC Jr et al (1982) The malignant potential of small congenital nevocellular nevi. An estimate of association based on a histologic study of 234 primary cutaneous melanomas. J Am Acad Dermatol 6:230–241
13. Friedman RJ, Rigel DS, Kopf AW, Lieblich L, Lew R, Harris MN, Roses DF, Gumport SL, Ragaz A, Waldo E, Levine J, Levenstein M, Koenig R, Bart RS, Trau H (1983) Favorable prognosis for malignant melanomas associated with acquired melanocytic nevi. Arch Dermatol 119:455–462