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MELANOMA OF THE LOWER EXTREMITIES: FOOT SITE IS AN INDEPENDENT RISK FACTOR FOR CLINICAL OUTCOME

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Abstract
Background Despite the better prognosis of melanomas localized on lower extremities, some studies have suggested that melanomas on the foot are related to a poorer survival and should be considered eparately.
Objective To review our case series of cutaneous melanomas on the lower extremities and to analyze the clinicopathological association, time course, types of progression, and survival differences.
Methods We included 1671 patients (stage 0–II) with a cutaneous melanoma on the lower extremities subungual melanomas were excluded). Of these, 327 were localized on the foot. Multivariate analyses were erformed to evaluate disease-specific survival and disease-free interval.
Results Distribution of known prognostic factors and patterns of progression of foot and leg melanoma differ across genders. The foot site was confirmed as a negative independent prognostic factor on disease-specific survival and disease-free interval.
Conclusion Foot melanoma could represent a particular subgroup, which could require specific anagement in the future.

Introduction

Several studies established the anatomic site of primary melanoma as a prognostic factor.1,2 Melanomas arising in regions barely noticed during self-inspection are often diagnosed with delay and, therefore, are related to a worse prognosis.1 It has also been speculated that lymphatic drainage may be responsible for differences in the clinical course of melanomas in different anatomical sites.
The length of lymphatic tracts and number of lymph nodes could influence the ability of the immune system to detect and neutralize metastasizing cells. This could explain the better prognosis of lesions on the lower extremities: tumor cells metastasizing from these regions have to pass through longer lymphatic tracts and a higher number of lymph nodes to reach the blood circulation when compared to cells derived from other skin sites.2

Some retrospective studies have suggested that, among melanomas of the lower extremities, the ones arising on the feet could be related to a poorer survival and should be considered separately.3,4 However, most of the literature data report limited size and non-homogeneous series; therefore, these results could be misleading. Some of these studies5–7 consider cutaneous melanomas together with subungual lesions, but subungual melanoma is known to be associated with a worse prognosis.5 Moreover,

the few studies that confirmed the negative independent prognostic factor of foot site in multivariate survival analyses were conducted on case series of limited size.3,4

Our aim was to review our case series of cutaneous melanomas of the lower extremities to analyze clinicopathological association, time course, types of progression, and survival differences between lesions on the feet and on other sites.

Methods

The case series of patients with melanoma arising on the lower extremities diagnosed and treated from 1975 to 2011 at the Department of Dermatology in Turin was reviewed. Patients with histologically proven primary cutaneous melanoma at the diagnosis stage 0–II, according to the American Joint Committee on Cancer (AJCC),8 were included in this study. Patients with incomplete histopathological data, unknown primary melanoma, or stage III and IV were excluded. Subungual melanomas (31 patients) were also excluded. Thus, a total of 1671 patients, with a median follow-up of 7.6 years (1–39 years), were analyzed. The clinical–demographic variables recorded were sex, age, year of diagnosis, site of primary melanoma, site, and type of progression. The pathologic features considered were Breslow thickness, Clark level, histological type, and ulceration. Only these variables were selected because they were available for all patients and they were the most standardized despite the long investigation time. A melanoma is defined as a leg melanoma when it arises on the leg, knee, or thigh and a foot melanoma when it arises on the ankle, sole, dorsal foot, or toes.

Clinical and imaging follow-up was performed according to the guidelines in use at the time of diagnosis and as previously reported.9

Statistical analyses were performed using Stata 12.0 Statistical Software (StataCorpLP, College Station, TX, USA). Pearson's chi-squared test and t-test were preliminarily performed to evaluate potential differences in the variables distribution between groups.

Disease-free interval (DFI) was calculated from the surgical excision of primary melanoma to the date of first disease relapse or last check-up. Disease-specific survival (DSS) was calculated from the surgical excision of primary melanoma to the date of death or last check-up. Survival estimates were derived by the Kaplan–Meier method, and the statistical comparison was done by the log-rank test. Univariate and multivariate Cox regression analyses were carried out to evaluate the influence of different variables on DFI and DSS. The proportionality assumption was assessed by Schoenfeld residuals. Log-likelihoods ratio test was performed to define linear or categorical nature of Breslow thickness and age. Akaike information criterion has been performed to select the model in terms of number of variables included and discriminates the best outcome. In the univariate/multivariate analyses, gender (male, M vs. female, F) and ulceration (present vs. absent) were categorical variables; site (foot vs. leg) and histological type of primary (nodular melanoma vs. others) were dichotomized; age at diagnosis and Breslow thickness were continuous variables.

Results

Clinicopathologic characteristics

In this study, of the 1671 patients with a diagnosis of cutaneous melanoma on the lower extremities, 327 of them had a melanoma on the foot (218 F, 109 M) and 1344 had a melanoma on the leg (1038 F, 306 M) ($P < 0.001$). The anatomic distribution of 327 patients with foot melanoma is as follows: 24 on the ankle (18 F, 6 M), 58 on the dorsum of the foot (43 F, 15 M), 72 on the heel (46 F, 26 M), 85 on the plantar (60 F, 25 M), and 88 on the toe (51 F, 37 M). The clinicopathologic features of the population are listed in Table 1.

Foot melanomas had a higher Breslow thickness ($P < 0.001$) than leg melanomas. When considering gender disparities, males with foot melanoma had a higher Breslow thickness than males with leg melanoma ($P = 0.045$) and females with foot melanoma higher than females with leg melanoma ($P < 0.001$). Among patients with leg melanoma, males were characterized by higher Breslow thickness than females ($P < 0.001$). On the other hand, among patients with foot melanoma, there was no difference in Breslow thickness across gender.

Ulceration was more frequently observed in foot melanoma than in leg melanoma ($P < 0.001$). Male patients with foot melanoma presented ulceration more frequently than males with leg melanoma ($P = 0.036$); females with foot melanoma presented more frequently than females with leg melanoma ($P <$

0.001). Among patients with leg melanoma, ulceration was more represented in males (P = 0.041); among foot melanoma, there was no difference across gender.

Patients with foot melanoma were older than patients with leg melanoma (P < 0.001), and this difference was maintained when we matched the two groups by gender (P < 0.001). Among patients with leg melanoma, females were older than males (P = 0.020), but there is no age difference across gender in patients with foot melanoma.

Females were characterized by more in situ melanomas on the leg than on the foot, while males did not show this difference. Stage I was more frequent than stage II in leg melanoma when compared to foot melanoma; across gender this difference was maintained only for females. There was a significant difference across gender only among patients with leg melanoma.

Nodular melanoma was more frequently observed in leg melanoma than in foot melanoma (P = 0.032). Male patients with leg melanoma presented nodular melanoma more frequently than females with leg melanoma (P = 0.030). Among foot melanoma, there was no difference across gender.

Of the 327 patients with a melanoma localized on the foot, 198 had an acral lentiginous melanoma (ALM). This histotype was significantly more frequent among males (75, 68.8%) than among females (123, 56.4%) (P < 0.031).

Pattern of metastasis

Patients with in situ melanoma were excluded from metastasis pattern analyses, so our population included 1503 patients (Table 2). During follow-up, 489 (29%) patients developed a disease progression (DP). Patients with foot melanoma developed DP more frequently (153 patients, 50%) than patients with leg melanoma (336 patients, 28%; P < 0.001). Males with foot melanoma progressed more frequently than males with leg melanoma (P < 0.001). The same pattern was observed in females (P < 0.001). Males developed DP more frequently than females (P = 0.002, P < 0.001) in both leg and foot groups. Among foot melanoma, no association was observed between the DP and the specific anatomic location of melanoma (34 of 85 plantar melanoma vs. 119 of 242 other foot regions, P = 0.09).

The most frequent first site of progression was regional in both the foot and leg melanoma groups. No differences were observed when we matched all groups. To analyze the type of regional progression, we compared skin involvement versus other sites of regional metastases (lymph nodes or concomitant lymph nodes and skin involvement). Among patients with foot melanoma, skin involvement was significantly more frequent in females (40%) than in males (24%) (P = 0.04). No difference was observed when we matched the remaining groups. Similarly, no difference was observed in the pattern of distance metastasis.

Survival analyses

Patients with foot melanoma had a worse prognosis than patients with leg melanoma, as they were when stratified by gender (Fig. 1). Breslow thickness, ulceration, nodular melanoma histotype, age, and gender showed a significant correlation on DFI and DSS in univariate analyses (Table 3). In particular, the foot site was related with a hazard ratio (HR) of 2.53 on DSS and 2.20 on DFI; ulceration was related with an HR of 5.48 on DSS and 3.89 on DFI. Among patients with foot melanoma, we did not observe a different prognosis in terms of DFI and DSS when we compared ALM to other histotypes.

Multivariate analyses (Table 4) confirmed the foot site as a negative independent prognostic factor on DSS and DFI as male gender, older age, higher Breslow thickness, and presence of ulceration; nodular histotype maintained a significant role only on DFI. In particular, the foot showed an HR of 1.52 on DSS and 1.59 on DFI, and ulceration showed an HR of 2.65 on DSS and 1.91 on DFI.

Discussion

In our experience,10,11 according to data in the literature, 2,12 patients with lower limb melanoma have a better prognosis compared to patients with non-lower limb involvement and they are more frequently females. The potential causes of this gender disparity include several hypotheses: hormonal influences,13 differences in sun exposure habits,14 or lower awareness and resistance to screening of men.15

Most of the data regarding melanoma arising on the foot are derived from case series, which are non-homogeneous (including subungual lesions and patients in different stage of diseases) and limited in

sample size.3–7 Therefore, it is still not clear whether among melanomas of the lower extremities, the ones on the foot should be considered as a separate entity with a worse prognosis.

Only a few studies reported analyses restricted to patients with foot or leg melanomas.3,4,16 Hsueh et al.3 demonstrated a correlation between the prognosis of lesions of the lower extremities and the distance of the melanoma from the trunk. Moreover, they confirmed in multivariate analyses that the foot site is an independent unfavorable variable for overall and disease-free survival as male gender, older age, higher Breslow thickness, and Clark level as demonstrated in our study. Even if these authors showed interesting results, the sample size of the study was limited to 652 patients, in particular only 92 of them have primary melanoma on the foot. Furthermore, these authors did not include ulceration in multivariate analyses, but in our study, it resulted in an important prognostic indicator in melanoma of the lower extremities (HR: 2.65 on DSS, HR: 1.91 on DFI).

Barnes et al.16 compared 262 patients with a lesion on the foot versus 736 patients with a melanoma located on the leg or thigh, but they also included subungual lesions and patients with different stages at diagnosis. Their multivariate analyses did not prove the role of anatomic location as an independent factor on survival (no DFI analyses was reported) when controlled for histologic type, thickness, and Clark level. However, in a limited case series, these results were probably affected by the presence of patients with advanced stage melanoma. To avoid this possible confounding element, we included only patients in stage I and II AJCC, who have comparable outcomes.

Talley et al.6 performed a case–control study between 119 patients with foot melanoma and 238 patients with leg melanoma, matching them for prognostic factors (thickness, ulceration, surgical treatment, gender, year of diagnosis, and age). They demonstrated that the foot site is an independent risk factor for survival. This study was performed only on stage I or II patients, but it also included toenail cases and consisted of only univariate analyses.

Our study represented the largest single institution case series of cutaneous melanoma of the lower extremities, without including subungual lesions, which compared foot to leg melanoma.

Patients with foot melanoma developed a DP and died more frequently than patients with leg melanoma. We found a significant association of foot lesions with some known unfavorable prognostic factors: male gender, older age, higher Breslow thickness, and presence of ulceration. However, despite this evidence, the foot site also maintained an independent prognostic role when corrected for other prognostic factors in multivariate analyses. Therefore, there should be other intrinsic differences related to foot site to explicate this phenomenon. A possible explanation could be the variable thickness of the skin and the variable density of vascular and lymphatic networks between these sites.17 In addition, plantar compression (due to walking) may promote the passage into lymphatic tracts of tumor cells derived from the foot, increasing the incidence of disease recurrence.3

Previous publications18,19 reported a poor prognosis for ALM. Among our patients with a diagnosis of foot melanoma, we did not find any differences in DSS and DFI when we compared ALM to other histotypes. This finding is in accordance with data already reported by Hsueh et al.3 Therefore, the worse prognosis of ALM seems to be more related to the foot site than the histotype.

Looking at the gender distribution of clinicopathological features, we found that among patients with leg melanoma, males are more frequently related to some unfavorable prognostic factors: higher Breslow thickness, ulceration, and older age. On the other hand, among foot melanoma, the distribution of the same prognostic factors did not show any gender-related differences. However, male patients progressed more frequently than females in both the leg and foot group. Considering the pattern of progression, and in particular the type of regional involvement, we also found an interesting difference according to gender in foot melanoma. In this group, females are more frequently related to skin involvement, while lymph node involvement is more frequent in males. This could in part explain the better prognosis of females in foot melanoma. In addition, this difference could be related to the different efficacy of lymphatic drainage in the foot in males and females.

In conclusion, we performed univariate and multivariate survival analyses on the largest single institution case series of patients with melanoma on the lower extremities. To have homogeneous data, we only included patients with stage I or stage II AJCC at diagnosis and cutaneous melanoma (subungual lesions, which are related to a known worse prognosis, were excluded). We were able to confirm that foot lesions are independently related to a worse prognosis when compared to leg melanoma in terms of DFI

and DSS. The different lymphatic drainage could explain the disadvantage of patients with foot melanoma compared to leg melanoma and the different pattern of regional progression when we compare females to males in patients with foot melanoma. Foot melanoma represents a particular subgroup of cutaneous melanoma, which could require specific management in the future. Further studies and other prognostic factors20,21 should be investigated to understand the biology of this rare but potentially severe type of cutaneous melanoma.

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Table 1 Clinicopathologic features of patients

	Foot melanoma (n = 327)			Leg melanoma (n = 1344)		
	Total (A)	Male (B)	Female (C)	Total (D)	Male (E)	Female (F)
Breslow thickness						
Mean	2.79 ± 2.52	2.84 ± 2.41	2.76 ± 2.58	1.83 ± 2.12	2.28 ± 2.53	1.70 ± 1.96
P^a	A vs. D, E vs. F, C vs. F <0.001; B vs. E 0.045; B vs. C NS					
Ulceration						
No	252 (77%)	82 (75%)	170 (78%)	1197 (89%)	261 (85%)	936 (90%)
Yes	75 (33%)	27 (25%)	48 (22%)	147 (11%)	45 (15%)	102 (10%)
P^b	A vs. D, C vs. F <0.001; B vs. E 0.036; E vs. F 0.041; B vs. C NS					
Age at diagnosis						
Median	61 (21–89)	62 (26–83)	60 (21–89)	52 (11–91)	50 (11–89)	53 (15–91)
P^b	A vs. D, C vs. F, B vs. E <0.001; E vs. F 0.006; B vs. C NS					
<65 years	204 (62%)	61 (56%)	143 (66%)	1058 (79%)	256 (84%)	802 (77%)
≥ 65 years	123 (38%)	48 (44%)	75 (34%)	286 (21%)	50 (16%)	236 (23%)
P^b	A vs. D, B vs. E, C vs. F <0.001; E vs. F 0.020; B vs. C NS					
AJCC stage						
In situ	20 (6%)	5 (5%)	15 (7%)	148 (11%)	24 (8%)	124 (12%)
P^b	C vs. F 0.04; A vs. D, E vs. F, B vs. C, B vs. E NS					
I	139 (43%)	48 (44%)	91 (42%)	761 (57%)	152 (50%)	609 (59%)
II	168 (51%)	56 (51%)	112 (51%)	435 (32%)	130 (42%)	305 (29%)
P^b	A vs. D, E vs. F, C vs. F <0.001; B vs. C, B vs. E NS					
Histotype						
NM	30 (9%)	11 (10%)	19 (9%)	173 (13%)	52 (17%)	121 (12%)
Other	297 (91%)	98 (90%)	199 (91%)	1171 (87%)	254 (83%)	917 (88%)
P^b	A vs. D 0.032, E vs. F 0.030, C vs. F, B vs. E, B vs. C NS					

AJCC, American Joint Committee on Cancer classification; NM, nodular melanoma.
[a]t-test.
[b]Pearson's chi-squared test.

Table 2 Pattern of progression of patients (in situ melanomas were excluded)

	Foot melanoma (n = 307)			Leg melanoma (n = 1196)		
	Total (A)	Male (B)	Female (C)	Total (D)	Male (E)	Female (F)
DFI status						
DF	154 (50%)	42 (40%)	112 (55%)	860 (72%)	181 (64%)	679 (74%)
PD	153 (50%)	62 (60%)	91 (45%)	336 (28%)	101 (36%)	235 (26%)
P^a	A vs. D, B vs. E, C vs. F, E vs. F <0.001; B vs. C 0.020					
DSS status						
Alive	205 (67%)	63 (61%)	142 (70%)	1008 (84%)	215 (76%)	793 (87%)
Dead	102 (33%)	41 (39%)	61 (30%)	188 (16%)	67 (24%)	121 (13%)
P^a	A vs. D, C vs. F, E vs. F <0.001; B vs. E 0.004; B vs. C NS					
Type progression						
Regional	139 (91%)	55 (89%)	84 (92%)	303 (90%)	91 (90%)	212 (90%)
Distant	14 (9%)	7 (11%)	7 (8%)	33 (10%)	10 (10%)	23 (10%)
P^a	A vs. D, C vs. F, E vs. F, B vs. E, B vs. C NS					
Regional progression						
Skin	47 (34%)	13 (24%)	34 (40%)	112 (37%)	27 (30%)	85 (40%)
Lymph node	79 (57%)	37 (67%)	42 (50%)	181 (60%)	60 (66%)	121 (57%)
Skin ± lymph node	13 (9%)	5 (9%)	8 (10%)	10 (3%)	4 (4%)	6 (3%)
P^a	[b]B vs. C 0.05; A vs. D, C vs. F, E vs. F, B vs. E, NS					
Distant progression						
Skin ± lymph node	4 (29%)	2 (29%)	2 (28.5%)	11 (33.3%)	3 (30%)	8 (35%)
Visceral	7 (50%)	5 (71%)	2 (28.5%)	12 (36.4%)	3 (30%)	9 (39%)
Miscellaneous	3 (21%)	0	3 (43%)	10 (30.3%)	4 (40%)	6 (26%)
P^a	A vs. D, C vs. F, E vs. F, B vs. E, B vs. C NS					

DFI, disease-free interval; DF, disease free; DSS, disease-specific survival; PD, progressive disease.
[a]Pearson's chi-squared test.
[b]Test was performed on skin vs. other regional metastases.

Table 3 Univariate analyses on DFI and DSS

	DSS				DFI			
	HR	*Z*	*P*	95% CI	HR	*Z*	*P*	95% CI
Gender	2.03	5.80	<0.0001	1.59–2.57	1.65	5.24	<0.0001	1.37–1.99
Age	1.03	6.74	<0.0001	1.02–1.04	1.03	9.01	<0.0001	1.02–1.03
Breslow thickness	1.32	17.48	<0.0001	1.99–3.22	1.28	20.55	<0.0001	1.25–1.31
Ulceration	5.48	13.94	<0.0001	4.31–6.96	3.89	13.53	<0.0001	1.82–2.67
Nodular histotype	2.14	5.51	<0.0001	1.64–2.82	2.50	8.61	<0.0001	2.03–3.08
Foot site	2.53	7.55	<0.0001	1.27–1.35	2.20	8.10	<0.0001	3.19–4.73

CI, confidence interval; DFI, disease-free interval; DSS, disease-specific survival; HR, hazard ratio.

Table 4 Multivariate analysis DFI and DSS

	DSS				DFI			
	HR	*Z*	*P*	95% CI	HR	*Z*	*P*	95% CI
Gender	1.69	4.23	<0.0001	1.33–2.16	1.41	3.51	<0.0001	1.16–1.71
Age	1.01	3.61	<0.0001	1.01–1.02	1.02	5.02	<0.0001	1.01–1.02
Breslow thickness	1.21	9.71	<0.0001	1.16–1.26	1.18	10.87	<0.0001	1.15–1.22
Ulceration	2.65	7.05	<0.0001	2.12–3.48	1.91	5.71	<0.0001	1.53–2.39
Nodular histotype	1.27	1.61	0.106	0.95–1.69	1.48	3.29	0.001	1.17–1.94
Foot site	1.52	3.27	0.001	1.18–1.97	1.59	4.51	<0.0001	1.30–1.94

CI, confidence interval; DFI, disease-free interval; DSS, disease-specific survival; HR, hazard ratio.

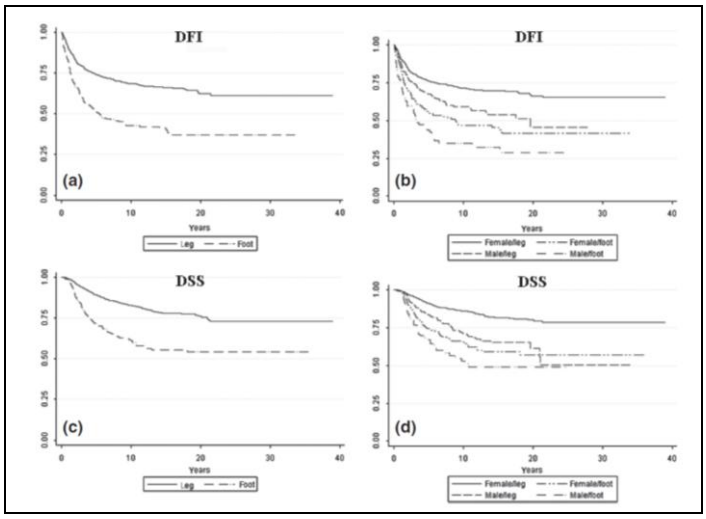

Figure 1 Kaplan–Meier estimated curves: DFI stratified by foot/leg site (a). DFI stratified by gender and site (b). DSS stratified by foot/leg site (c). DSS stratified by gender and site (d). DFI, disease-free interval; DSS, disease-specific survival