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ORIGINAL ARTICLE

Relevance of multiple basin drainage and primary histologic regression in prognosis of trunk melanoma patients with negative sentinel lymph nodes

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Abstract

Background Lymphatic drainage to multiple basins (MLBD) is frequently observed in patients with primary melanoma located in the trunk. Conflicting data regarding the prognostic impact of MLBD are reported.

Objective and methods We reviewed our case series of 352 patients with trunk melanoma to evaluate the pattern of basin drainage and to analyse whether different basin drainages may have different significance in negative sentinel lymph node (SLN) patients. The presence of single/multiple basin drainage, the status of SLN, the presence of melanoma regression, Breslow thickness, ulceration and type of melanoma were recorded for each patients and correlated to Disease Free Survival (DFS) and Overall Survival (OS).

Results MLBD occurred in 77 patients (21.9%) and single basin lymphatic drainage (SLBD) occurred in 275 patients (79.1%). The presence of metastases in SLN was not significantly different in patients with MLBD compared to those with SLBD (26% vs. 19.6%). No differences in OS and DFS were found in SLBD/MLBD independently from SLN status. However DFS was higher in patients with MLBD and negative SLN ($P = 0.0001$), in addition, in patients with negative SLN and SLBD disease recurrence was 19% while was only 7% in patients with negative SLN obtained from MLBD ($P = 0.03$). Multivariate analysis showed that Breslow thickness <2 mm, MLBD pattern and regression of melanoma were favourable variables for DFS of patients with negative SLN.

Conclusions An accurate study of the drainage basin and of all the SLNs obtained from MLBD is recommended because of the impact in prognosis of melanoma of the trunk.

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Conflict of Interest

None declared.

Introduction

Breslow thickness, ulceration and mitotic rate are well-recognized prognostic features of cutaneous melanoma incorporated into the current American Joint Committee on Cancer (AJCC) staging system.[1] After the introduction of lymphoscintigraphy and sentinel lymph node (SLN) biopsy, the histologic status of the SLN has been found to be the strongest prognostic factor for survival and recurrence in patients with primary melanoma and clinically negative lymph nodes.[2,3]

The location of the primary tumour has been considered as another prognostic factor. In particular numerous studies documented a worse prognosis in patients with primary melanomas of the trunk when compared with those located of the extremities.[4–6] The truncal location is characterised by lymphatic drainage to multiple basins (MLBD) in about one third of cases.[7] Conflicting data regarding the prognostic impact of MLBD are reported. Some authors showed that MLBD for truncal melanoma was associated with an increased risk of nodal metastases[7] or worse survival.[8] On the other hand, other studies did not confirm these findings,[9,10] suggesting that this phenomenon was only related to an overlapping drainage from the area of skin injected.[10]

Given the limited number of studies evaluating multiple drainages, its association with recurrence and the controversial results on survival, we retrospectively reviewed our case series of truncal melanomas with the aim of evaluating the prognostic impact of MLBD on Disease Free Survival (DFS) and Overall Survival (OS).

[1]Both authors contributed equally.

Methods

Patient population and follow up

A total of 815 consecutive patients with primary cutaneous melanoma underwent lymphatic mapping and SLN biopsy from May 1998 to July 2011 at our institutions. Among them 352 (43.2%) patients had a melanoma of the trunk.

Sentinel lymph node biopsy (SLNB) criteria were: Breslow thickness ≥1 mm or Breslow thickness <1 mm and at least one of the following histopathologic features: presence of regression, ulceration and/or Clark level IV–V and/or mitotic rate ≥1; no clinical or radiological evidence of regional and/or distant metastases. The follow up was performed according to the guidelines in use at the time of diagnosis[11,12] and extended until July 2011.

Sentinel node biopsy

Sentinel lymph node (SLN) biopsy was performed as previously described by Morton *et al.*[13] The SLNs were detected using a standardised preoperative protocol that included both lymphoscintigraphy and intradermal injection of patent blue dye around surgical scar. All single or multiple basins identified by lymphoscintigrafy were dissected. All radiolabeled lymph nodes and/or those which appeared blue stained were considered to be SLNs and were excised.

Sentinel lymph nodes (SLN) were immediately fixed in buffered formalin, bisected along the long axis of the ilar region and embedded in one or more paraffin blocks depending on SLN size. Sections were cut and immunostained with S-100 and HMB45 according to the European Organisation for Research and Treatment of Cancer (EORTC) recommendations[14] for working up of SLN of melanoma.

The slides were examined independently by two investigators (LM and AS) both blinded to the clinico-pathological data.

Statistical analysis

Statistical analyses were performed using the Stata 11.0 Statistical Software. Both parametric and non-parametric tests were used; only "*P*" values of parametric tests were reported, as the results of the two tests were similar. Univariate logistic regression was used to test for the significance of the predictor variables. For all patients, DFS was calculated from the surgical excision of SLN to the date of first disease relapse, OS was calculated from the surgical excision of SLN 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 analyses were carried out to evaluate the influence of different variables on DFS and OS.

Results

Clinico-pathologic characteristics and associated SLN findings

The clinico-pathologic characteristics are listed in Table 1.

Almost two thirds of the patients were male (245/352, 69.6%). In the majority of patients, the SLN was identified in the axillary basin (80.7%). Overall 74 patients out of 352 (21%) had a positive SLN biopsy result. No differences in the SLN status were found according to the basin site.

A complete lymph node dissection (CLND) was performed in all patients with positive SLN, 13 out of 74 showed lymph node metastases (17.6%).

Drainages to more than one lymphatic basin are identified in 77 patients (21.9%). The identification of MLBD was significantly associated with female gender (29% vs. 18.8% in males; $P = 0.03$). Age, Breslow thickness, Clark, histological characteristics, front/back site of the primary melanoma and ulceration demonstrated no significant association with the likelihood of drainage to more than one basin. Patients with MLBD did not show a higher incidence of positive SLN than those with single nodal basin drainage (SLBD) (26% vs. 19.6%, respectively).

Association of lymphatic basin drainage pattern with DFS and OS in all patients

The median follow-up time calculated from the date of surgical excision of SLN to the last contact date was 3.4 years (range 6 months–11.3 years). Out of 352 patients, 72 developed a disease recurrence (20.5%) and 57 patients (16.2%) died during the follow up.

No significant differences in DFS and OS were found in the two categories SLBD/MLBD (Fig. 1a,b) independently from the status of SLN.

As expected patients with SLN positive presented a worse prognosis. DFS and OS were influenced by both the number of drainage basins and SLN results, as shown in Fig. 2a,b. In particular the DFS was significantly more favourable in patients with negative MLBD as compared with that of other groups. In fact in patients without metastases 5-years DFS was 89.6% and 80.7% in MLBD and SLBD respectively; in SLBD positive DFS was 65.5% while it was of 61.2% in patients with MLBD and at least 1 positive basin or of 60% in patients with both positive basins respectively ($P = 0.0001$)

Similar results were observed in OS: in patients with SLN negative 5-years OS was 88.9% in MLBD and 82.1% in SLBD. On the contrary OS was of 63% in SLBD positive patient, 52.7% in cases with MLBD with at least 1 positive basin and 53.3% in MLBD with both positive basins ($P < 0.0001$).

Association of lymphatic basin drainage pattern with DFS and OS in patients with negative SLN

Features of patients with single or multiple drainage and negative SLN are reported in Table 2. A more frequent identification of MLBD was confirmed to be associated with female gender (28.2% F vs. 17.1% M). Age, Breslow thickness, Clark, histological characteristics, regression and ulceration demonstrated no significant

Table 1 Clinical and pathologic characteristics of the 352 patient with melanoma of the trunk

		All patients (*n* = 352)	SLBD (*n* = 275)	MLBD (*n* = 77)	*P*
Gender	Male	245 (69.6%)	199	46	0.03
	Female	107 (30.4%)	76	31	
Age		56 (16–86)	56 (16–86)	55 (22–78)	NS
Breslow		2.34 ± 1.97	2.37 ± 1.86	2.27 ± 2.36	NS
Trunk site	Front	122	97	25	NS
	Back	230	178	52	
Clark	I	1 (0.3%)	1	0	NS
	II	27 (7.7%)	20	7	
	III	170 (48.3%)	129	41	
	IV	143 (40.6%)	117	26	
	V	11 (3.1%)	8	3	
Histological characteristic	SSM	268 (76.1%)	208	60	NS
	Nodular	66 (18.8%)	54	12	
	Other	18 (5.1%)	13	5	
Ulceration	Absent	261 (74.2%)	204	57	NS
	Present	91 (25.8%)	71	20	
SLN	Negative	278 (74.4%)	221	57	NS
	Positive	74 (26.6%)	54	20	
SLN basin	Cervical	6 (1.7%)	5	1	NS
	Axillary	284 (80.7%)	228	56	
	Inguinal	48 (13.6%)	42	6	
	Mixed	14 (4%)	–	14	

MLBD, multiple lymphatic basin drainage; NS, not significant; SLBD, single lymphatic basin drainage; SLN, sentinel lymph node; SSM, superficial spreading melanoma.

association with the likelihood of drainage to more than one basin in SLN negative patients. A significantly higher percentage of disease recurrence characterized the SLBD patients (19%) as compared to the MLBD ones (7%, $P = 0.03$).

The prognostic relevance of MLBD in SLN negative patients was analysed by multivariate Cox regression. MLBD maintained a significant favourable prognostic role on DFS as independent factor (HR: 0.28) together with the presence of regression and low Breslow thickness (Table 3). On the other hand, no difference in OS was found between SLBD and MLBD in SLN negative patients. Thus, taking into consideration the significant results from the multivariate analysis we combined the three parameters that maintained a protective role on DFS.

Patients with negative MLBD, presence of regression and Breslow thickness <2 mm (20 out of 77 MLBD), presented a significantly longer DFS (Fig. 3) than patients without the 3 favourable parameters (10-years DFS: 100% vs. 46.6% respectively).

Discussion

This study provides an analysis of the prognostic impact of MLBD on DFS and OS in patients with diagnosis of primary truncal melanoma stratified on the basis of SLN status.

The presence of a single or multiple basin drainage does not affect significantly the disease course in patients with metastatic SLN. The new finding we report is that patients with negative SNL obtained from MLBD show a significantly better prognosis than patients with negative SLN obtained from SLBD. Specifically this result together with the presence of regression and Breslow thickness <2 mm identifies a subgroup of patients with lower risk of progression.

We focused our analysis on trunk melanoma which is indeed responsible for the majority of MLBD, to be able to collect a homogeneous patients' cohort and thus avoiding biases related to the controversial prognostic significance of melanoma localisation.[4–6] Despite the trunk is the principal site of melanoma in male,[4,5] MLBD was most frequent in females. This correlation was maintained even when we considered only negative SLN patients. Mc Hugh *et al.*[10] reported that gender was not associated with drainage typology, whereas other authors presented a population with a male prevalence in the MLBD group.[8]

The percentage of patients with truncal melanoma and evidence at preoperative lympho-scintigraphy of MLBD ranges widely between 17% and 46% according to different study series.[7–9,15] In our analysis 21.9% of 352 truncal melanoma patients had MLBD.

The prognostic relevance of MLBD is still a matter of controversy. Some studies did not find any relationship between SLBD and MLBD and DFS or OS.[9,10,15] Porter *et al.*[7] reported that MLBD is associated with an increased risk of SLN metastases. Our

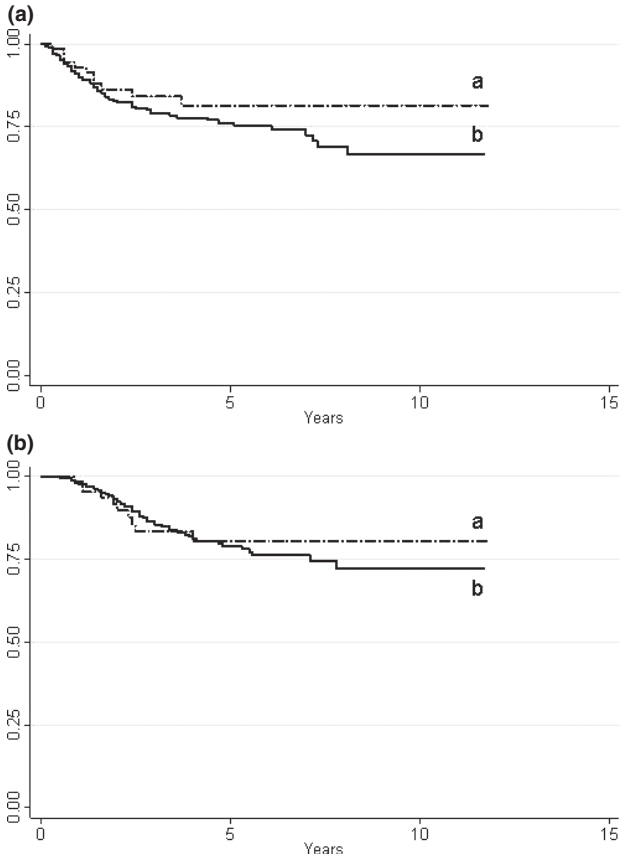

Figure 1 Disease Free Survival (a) and Overall Survival (b) of patients depending on the type of basin drainage independently from the status of Sentinel Lymph Node (a = MLBD, multiple lymphatic basin drainage; b = SLBD, single lymphatic basin drainage).

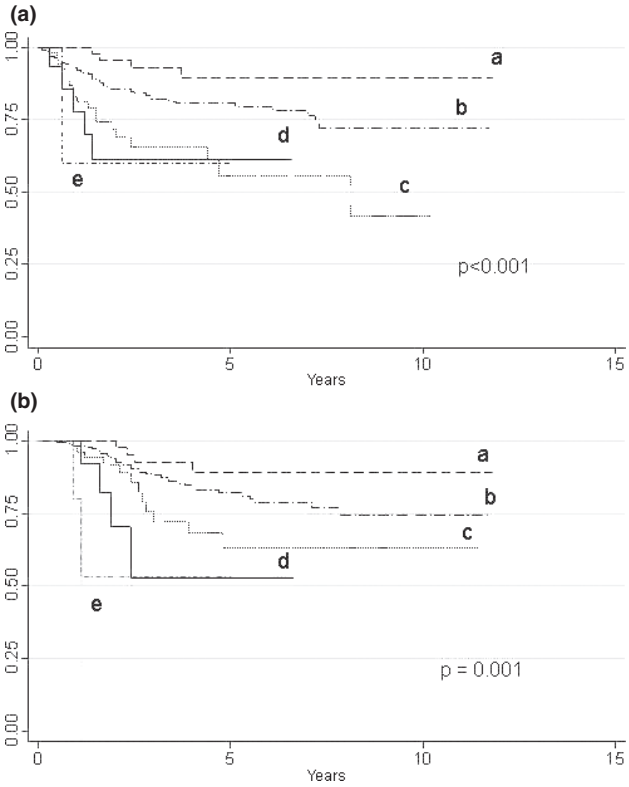

Figure 2 Disease Free Survival (a) and Overall Survival (b) of patients depending on the type of basin drainage and the status of Sentinel Lymph Node (SLN). Survival analysis on patients stratified or number of drainage and result of SLN (a) DFS; (b) OS (a = SLN negative MLBD, b = SLN negative SLBD, c = MLBD with at least 1 positive basin, d = SLN positive SLBD, e = SLN positive MLBD).

study did not confirm these results as no differences were found in numbers of SLN metastases between SLBD and MLBD patients (19.6% vs. 26%, respectively). Similar results were already reported by others.[8–10] Porter *et al.*[7] and Jimenez *et al.*[8] reported that MLBD patients have a less favourable prognosis than the SLBD ones, independently from the SLN status. The design of our study took into consideration the prognostic value of the SLN status within the SLBD and MLBD groups of patients (i.e. positive and negative SLN). The discrepancy as compared to the study by Jimenez *et al.*[8] could also be explained by a smaller cohort of patients and a shorter median follow-up (27 months vs. 42 months in our series). Piňero *et al.*[16] and Wall *et al.*[17] confirmed a worse outcome of MLBD in a retrospective cohort study with comparable follow-up, but they studied primary melanomas of both trunk and extremities with or without neck site respectively. MLBD involvement might identify a more aggressive behaviour and higher metastatic potential. Different alternative speculations may be considered for example development of collateral lymphatic vessels as a result of local tumour growth, congestion of the primary drainage pathway by tumour cells, postoperative development of new lymphatic channels around the original site of the tumour or a combination of these. The discrepancies in literature results could be related to the different technique for SLN identification as well as to a heterogeneous patients' population or different anatomic pattern of drainage. On the contrary in our experience the finding of a negative SLN in MDLB was associated with a favourable prognosis.

The association with regression and Breslow thickness strengthened this observation. Regression traditionally it has been considered as a marker of poor prognosis, mainly in thin melanomas, as it cannot be ruled out that the initial thickness of the melanoma in the area of regression might have been superior to that suggested by the Breslow depth of the remaining tumour. On the contrary recent data reported that the presence of regression was associated with a lower likelihood of a positive SLN and even better clinical outcome.[6,18–20] Probably regression may be considered as an indicator of an immune response of the host against the primary tumour and, consequentially, it might have a certain protec-

Table 2 Clinical and pathologic characteristics of patients with melanoma of the trunk and negative SLN

Variable		SLBD (*n* = 221)	MLBD (*n* = 57)	*P*
Gender	M	160	33	0.034
	F	61	24	
Age		57 (16–78)	53 (22–78)	NS
Breslow		2.18 ± 1.80	2.03 ± 2.42	
Clark	I	1	0	NS
	II	20	5	
	III	113	35	
	IV	82	15	
	V	5	2	
Histological characteristic	SSM	166	44	NS
	Nodular	42	9	
	Other	13	4	
Ulceration	Absent	166	44	NS
	Present	55	13	
Regression	Absent	143	35	NS
	Present	78	22	
Status	DF	179	53	0.030
	PD	42	4	
Site of progression	Regional	19	2	NS
	Distant	23	2	

DF, disease free; F, female; M, male; MLBD, multiple lymphatic basin drainage; NS, not significant; PD, progression disease;SLBD, single lymphatic basin drainage; SSM, superficial spreading melanoma.

tive effect. Although the biological pathways related to the favourable prognostic relevance of negative MLBD are not clear at present, it could be speculated that this phenomenon could be explained from an immunological point of view. Indeed, from one side, the association with regression reflects a potential capacity of the immune system to recognize and therefore enhance the immune response against tumour; from the other side, the multiple anatomic drainage could allow a better contact between tumour cells and the immune surveillance system, in according to recent findings.[6,18–20] Kaur *et al.*[20] demonstrated that primary regression is a favourable prognostic feature in melanoma patients and is not associated to a higher risk of metastatic SLN. More

Table 3 Multivariate Cox regression in patients with melanoma of the trunk and SLN negative. Significant values are highlighted in bold

DFS	HR	SE	*Z*	*P* > |*z*|	95% IC
Age	1.00	0.01	0.44	0.660	0.98 1.02
Gender	0.88	0.31	−0.36	0.717	0.43 1.77
Breslow	1.31	0.09	3.89	**0.000**	1.14 1.50
Ulceration	1.05	0.44	0.12	0.906	0.46 2.38
Regression	0.27	0.14	−2.61	**0.009**	0.10 0.73
Multiple drainage	0.28	0.16	−2.24	**0.025**	0.09 0.85
Nodular histotype	0.71	0.28	−0.85	0.395	0.33 1.55

DFS, disease free survival; HR, hazard rate; IC, interval confidence SE, standard error.

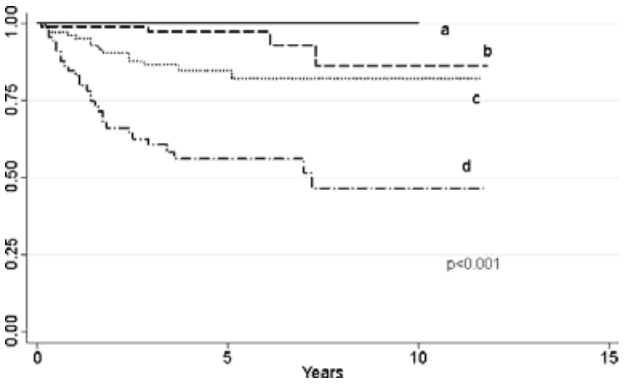

Figure 3 DFS analysis on patients stratified depending on the presence of: negative SLN in MLBD, regression and Breslow thickness <2 mm of primary. (a = all three protective parameters, b = two protective parameters, c = only one protective parameters, d = no protective parameters).

recently, Ma *et al.*[19] showed that melanoma regression and presence of dendritic cell increase in the primary lesion are associated to a significantly decreased incidence of SLN involvement. This theory is supported by the evidence of relevant amounts of regulatory T cells in metastatic SLNs when compared to the negative ones; this event potentially reveals a down-regulation of antitumour immune responses.

From a clinical point of view, our data show that the presence of negative MLBD may be a potential new parameter for the identification of patients with a more favourable disease course, thus an accurate study of the drainage basin and of all the SLNs obtained is recommended.

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