Clinical and Dermoscopic Criteria Related to Melanoma Sentinel Lymph Node Positivity

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Abstract. *Background: The early detection of lymph node metastases may have important prognostic and therapeutic implications in melanoma patients. The purpose of this study was to investigate whether specific clinical and/or dermoscopic features could be "in vivo" predictors of sentinel lymph node (SLN) positivity in melanomas >1 mm thick. Materials and Methods: Five Italian centres (Istituto Dermopatico dell'Immacolata, IDI, Rome; Skin Cancer Unit, Oncologia Dermatologica, CPO, Ravenna; Istituto Europeo Oncologico, Milan; Centro di Riferimento Oncologico, Aviano; Istituto Nazionale Tumori, Naples) carried out a blind retrospective study on 508 melanomas observed from January 1994 to December 2002. The clinical and dermoscopic features of 78 melanomas >1 mm thick with the SLN biopsied were reviewed. Results: The tumour palpability was the only factor correlated to SLN positivity in melanomas >1 mm thick. Palpability was found in 46.2% of nodal positive melanomas and in 18.5% of nodal negative melanomas (p=0.03). The patients with palpable melanomas showed a higher risk of nodal metastasis (OR=3.8). Dermoscopy failed to recognize predictive criteria for SLN positivity. Some clinical and dermoscopic features, although not statistically significant, showed interesting differences between nodal-negative and nodal-positive melanomas. Conclusion: Melanoma palpability may suggest the presence of nodal metastasis in >1 mm thick tumours.*

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In 2002, the American Joint Committee on Cancer revised the TNM staging system for cutaneous melanoma on the basis of important emerging prognostic evidence in melanoma patients (1). The new TNM classification included some fundamental changes: the Breslow thickness was considered to be the most important survival indicator in patients with localized melanoma; a new thickness threshold of 1.0 mm defined the T1/T2 stage, set at 0.75 mm in the previous (1997) version; the presence of ulceration (evidenced histopathologically) or a Clark level IV/V, upstaged the tumour to the next T level; the number of lymph nodes involved rather than their dimension was considered to be the primary determinant in N staging; the lymphatic mapping and the sentinel lymph node (SLN) biopsy were established as highly accurate techniques in pathological regional nodal staging that allow the selective application of SLN dissection only in node-positive melanoma patients (2).

Historically tumour thickness (3) and more recently the SLN involvement (2) have been considered as the most powerful prognostic indicators in melanoma patients.

Dermoscopy (dermatoscopy, epiluminescence microscopy, incident light microscopy and surface microscopy) is a useful and non-invasive technique for early melanoma detection (4). Dermoscopy reveals skin features, otherwise invisible to the naked-eye, correlated to specific histological characteristics (5). Since some dermoscopic criteria, such as the pigment network, blue-grey areas and vascular patterns have been related to different tumour thicknesses, dermoscopy may have a role in the pre-operative assessment of melanoma thickness and may be an indication for SLN biopsy (6-8).

The purpose of this study was to investigate whether specific clinical and/or dermoscopic features could be "*in vivo*" predictors of SLN positivity in >1 mm thick

melanoma patients. A secondary objective was to identify melanoma patients, currently not routinely considered for SLN biopsy, at sufficient risk of metastasis to justify extended indications for SLN biopsy.

Patients and Methods

The five Italian centres included in this multicentric retrospective study (Istituto Dermopatico dell'Immacolata, IDI, Rome; Skin Cancer Unit, Oncologia Dermatologica, CPO, Ravenna; Istituto Europeo Oncologico, Milan; Centro di Riferimento Oncologico, Aviano and Istituto Nazionale Tumori, Naples) reviewed a total of 508 melanomas observed in 494 patients (221 males and 273 females) between January 1994 and December 2002. Three hundred and ninety-one melanomas were ≤1 mm (77%) and 117 melanomas >1 mm (23%) thick. Fourteen patients had two or more melanomas. The patients with multiple and/or ulcerated melanoma, as well as the patients with incomplete clinical and/or dermoscopic data were not included in the study. The Clark level was not used for SLN biopsy selection. Seventy-eight melanoma cases (42 males and 36 females) thicker than 1 mm which had undergone SLN biopsy were included in this study.

A clinical data sheet for each patient was completed and reported age (<40, 40-49, 50-59 and >60 years), gender (M/F) tumor site (trunk, lower limbs, upper limbs), previous melanoma (yes or no), thickness (flat or palpable), shape (symmetric/asymmetric), borders (sharp or partly sharp), colour (one colour, two or more colours, colourless), and presence of regression (yes or no). Melanoma dermoscopic images were acquired and stored on a compact disc as jpeg files; 438 images were taken with a digital stereomicroscope and 70 with a Dermaphot camera (Heine Optotechnik; Herrsching, Germany) (x10 magnification) and then digitalized with the Kodak PhotoCD system. The digital stereomicroscope system consisting of a stereomicroscope and a Sony 3CCD DXC-930P colour video camera, produced digital images with a magnification range from 16x to 25x. Three experts in dermoscopy (M.A.P., R.B. and I.S.) evaluated and registered the dermoscopic features of each melanoma, including pigment network (absent/typical or atypical), radial streaks (absent or present), pseudopodes (absent or present), pigmentation (absent/regular or irregular), brown globules (absent or present), pink globules (absent or present), black dots (absent or present), blue-whitish veil (absent or present), regression (absent or present), hypopigmentation (absent or present) and vascular pattern (absent/regular or irregular). The presence or absence of clinical and dermoscopic criteria were defined by a 2/3 or unanimous agreement.

Chi-square test was used to evaluate differences for the qualitative parameters (9). The differences between subgroups were also computed by odd ratios (OR) and corresponding 95% confidence interval (CI) (10). The results were considered to be statistically significant at $p \leq 0.05$ (two-sided).

Results

The distribution of 78 melanomas >1 mm thick by negative (65 cases) and positive (13 cases) SLN histopathological diagnosis according to age, gender and site is reported in Table I. The percentage of nodal metastasis was 16.6%. The median age was 55 years (range: 22-83) for the patients with negative SLN and 54 years (range: 33-84) for the patients with nodal metastasis. There were no differences in the age, gender and site distribution percentages.

Table I. *Age, gender and sites of 78 melanomas subjected to SLN biopsy according to histological diagnosis of sentinel lymph node.*

	Histological diagnosis of sentinel lymph-node			
	Negative (n=65)		Positive (n=13)	
	N.	(%)	N.	(%)
Age (years)				
<40	16	(24.6)	1	(7.7)
40-49	9	(13.9)	3	(23.0)
50-59	17	(26.1)	4	(30.8)
≥60	23	(35.4)	5	(38.5)
Gender				
Male	34	(52.3)	8	(61.5)
Female	31	(47.7)	5	(38.5)
Site				
Trunk	37	(56.9)	9	(69.2)
Lower limbs	21	(32.3)	3	(23.1)
Upper limbs	7	(10.8)	1	(7.7)

Table II compares the clinical features of melanomas with and without nodal metastasis. Palpable thickness was more likely to be present in melanomas with positive SLN than in those with negative SLN (46.2% and 18.5% respectively). Moreover patients with palpable melanomas had a significantly higher risk (OR=3.8; 95% CI: 1.1-13.3; $p \leq 0.03$) for nodal metastasis than those with flat melanomas. The other clinical features, such as a previous melanoma, the melanoma shape, borders, colour and the presence of regression did not show any significant differences between tumors with negative and positive SLN.

Table III compares the dermoscopic features of melanomas with and without nodal metastasis. Although some features such as the presence of pseudopodes and regression showed interesting differences between these groups of cases, they were however not significant.

Discussion

The most important aim of the non-invasive methods used to measure melanoma thickness is to differentiate thin (≤1 mm) from thick (>1 mm) lesions and then to perform SLN biopsy only on the latter. The current use of SLN biopsy is considered appropriate only for patients with non-palpable lymph nodes and melanoma thickness of more than 1 mm, or ulcerated, or Clark level IV/V (11). For thin melanomas

Table II. *Clinical features of 78 melanomas subjected to SLN biopsy according to histological diagnosis of sentinel lymph node.*

	Histological diagnosis of sentinel lymph-node			
	Negative (n=65)		Positive (n=13)	
	N.	(%)	N.	(%)
Previous melanoma				
No	57	(87.7)	12	(92.3)
Yes	8	(12.3)	1	(7.7)
Thickness				
Flat	53	(81.5)	7	(53.8)
Palpable	12	(18.5)	6	(46.2)[1]
Shape				
Symmetric	21	(32.3)	3	(23.1)
Asymmetric	44	(67.7)	10	(76.9)
Borders				
Sharp	30	(46.2)	8	(61.5)
Partly sharp	35	(53.8)	5	(38.5)
Colour				
One colour	34	(52.3)	7	(53.9)
Two or more colours	30	(46.2)	6	(46.2)
Colourless	1	(1.5)	--	
Regression				
No	39	(60.0)	10	(76.9)
Yes	26	(40.0)	3	(23.1)

[1]In comparison with the negative histological diagnosis of SLN *p* value of the Chi-square test was 0.03, odds ratio (OR) was 3.8 (95% CI: 1.1-13.3).

Table III. *Dermoscopic criteria of 78 melanomas subjected to SLN biopsy according to histological diagnosis of sentinel lymph node.*

	Histological diagnosis of sentinel lymph-node			
	Negative (n=65)		Positive (n=13)	
	N.	(%)	N.	(%)
Pigment network				
Absent/typical	40	(61.5)	10	(76.9)
Atypical	25	(38.5)	3	(23.1)
Radial streaks				
Absent	46	(70.8)	10	(76.9)
Present	19	(29.2)	3	(23.1)
Pseudopodes				
Absent	49	(75.4)	13	(100.0)
Present	16	(24.6)	--	--
Pigmentation				
Absent/regular	5	(7.7)	3	(23.1)
Irregular	60	(92.3)	10	(76.9)
Brown globules				
Absent	23	(35.4)	7	(53.9)
Present	42	(64.6)	6	(46.2)
Pink globules				
Absent	53	(81.5)	13	(100.0)
Present	12	(18.5)	--	--
Black dots				
Absent	17	(26.2)	3	(23.1)
Present	48	(73.8)	10	(76.9)
Blue-whitish veil				
Absent	17	(26.2)	2	(15.4)
Present	48	(73.8)	11	(84.6)
Regression				
Absent	25	(38.5)	7	(53.8)
Present	40	(61.5)	6	(46.2)
Hypopigmentation				
Absent	54	(83.1)	9	(69.2)
Present	11	(16.9)	4	(30.8)
Vascular patterns				
Absent/regular	49	(75.4)	10	(76.9)
Irregular	16	(24.6)	3	(23.1)

the risk of regional lymph node metastasis is very low (12) and the SLN biopsy is not commonly performed. Patients with thick melanoma have a 20-25% incidence of microscopic regional disease (13) and SLN biopsy is performed in order to estimate the prognosis and the need for adjuvant therapy.

Several factors have been reported to have a predictive value for SLN metastasis (3, 14, 15), including Breslow thickness, Clark level, ulceration, mitotic rate, microsatellitosis, angiolymphatic invasion, primary tumour location and patient age. The Breslow thickness is the only reproducible factor predictive of SLN status in all studies (16) and is still considered to be the most powerful independent prognostic factor in localized cutaneous melanoma (17-20). The Clark level is an independent predictive feature in thin melanoma but not for thicker lesions (21). Ulceration was not included in the previous staging system, but in the new version it is considered to be the second strongest prognostic factor in primary melanoma and the only primary tumour factor to modify the prognosis of node-positive disease (1). Ulceration can be clinically difficult to distinguish from artifactual or traumatic disruption of the epidermis, but it is easy to recognize with histopathology (1). It has not been considered in our study because of the impossibility of defining the dermoscopic features of ulcerated melanomas and its well-estabilished importance in melanoma prognosis.

A high mitotic rate, calculated as >5 mitosis per square millimeter (22), has been reported as an independent prognostic predictor of lymph node positivity in melanoma patients (23-25).

Microsatellites, reported as tumor nests >0.05 mm separated from the original melanoma by normal tissue (26), have been associated with an increased frequency of regional lymph node metastasis, although they rarely occur in tumours of <1.5 mm.

Angiolymphatic invasion is rarely present in non-metastatic melanomas, while it has been reported in 57% of nodular melanomas with SLN positivity (27).

Some studies have shown that a young age is an independent factor associated with an increased likelihood of nodal melanoma metastasis (23). Conversely some data have emphasized old patients as being more likely to present with thicker and ulcerated melanomas and generally the survival rate decreases as the patient's age increases(28). Many studies have reported that women have a better prognosis, even in patients with nodal metastasis (18, 29-31). In another study the male gender has been correlated to nodal disease in thin melanoma patients (32). Some primary tumour locations, such as head, neck and trunk have been correlated to a worse prognosis when compared with a melanoma of the extremities (18, 29, 30).

Our results from patients with melanoma thickness >1 mm showed that the patient's age and gender, and the location of the primary tumour did not significatively influence the SLN status, although in the middle-aged patients (40-49 years) the percentage of positive SLN (23.0%) was higher than in those with negative SLN (13.9%), and males seems more likely to present SLN metastasis (61.5% *vs.* 38.5% in females).

To date relatively few studies have examined the relationship between clinical palpability and melanoma thickness, and very few between clinical palpability and SLN status. Although previous reports have demonstrated a direct correlation between palpability and melanoma thickness (33-35), other authors did not confirm it (36). In most of these studies a 0.75 mm thickness threshold from the "old" TNM staging system has been used to distinguish the "thin" from "thick" melanoma. Melanoma palpability has recently been reconsidered by Argenziano *et al*. for the construction of an algorithm of combined clinical and dermoscopic criteria which would allow a predictive value for melanomas >0.75 mm in 89% of cases. The predictive value of palpability alone was correct in 62% (37). According to Argenziano *et al*., a lesion was considered to be palpable in the present study when it was obviously discernable by touch, nodular or at least papular. In our study palpability showed a statistically significant correlation with SLN positivity and was found in 46.2% of SLN positive melanomas and in 18.5% of SLN negative tumours.

Although regression is frequently observed in primary melanomas and especially in thin lesions, accounting for 10 to 35% of all melanoma cases (38) and up to 58% of those with a thickness <0.75 mm (39), its prognostic significance is still controversial. Histopathology may understimate the real Breslow thickness of a melanoma with regression because of tumour cell replacement by inflammatory cells and fibrosis (40). On the other hand regression may reflect a good host immune response to tumour cells. Many authors have claimed that regression has no adverse effect on the SLN positivity (41, 42), others regard it as a sign of poor prognosis (43, 44) and in a recent study the SLN status seems more favourable in the presence of regression(45). Our study results seem to validate the latter since evidence of clinical regression was present in 40% of >1 mm melanomas with negative SLN and in 23.1% of those with positive SLN and dermoscopic signs of regression were found in 61.5% of negative SLN melanomas and in 46.2% of positive SLN tumours.

In our experience dermoscopy failed to recognize statistically significant predictive criteria for SLN positivity in melanomas >1 mm thick. Specific melanoma criteria strongly associated with a higher Breslow thickness such as grey-blue areas or an atypical vascular pattern (6) were not correlated to SLN positivity. The blue-whitish veil was found in 84.6% of SLN positive melanomas and in 73.8% SLN negative tumours, an atypical vascular pattern was present in 23.1% of SLN positive melanomas and in 24.6% SLN negative tumours. The low prevalence of malignant epidermal structures such as an atypical pigment network, radial streaks and pseudopods in melanomas >1 mm thick was closely related to the dermal proliferation activity (8). The pigment network and the relative peripheral extension expressed by radial streaks and pseudopods appeared to be inversely proportional to the Breslow thickness, most likely due to increased infiltration, dis-aggregation and compression of the rete ridges (6, 8, 46). In our experience the malignant epidermal structures were more frequent in SLN negative melanomas when compared to SLN positive melanomas (atypical pigment network in 38.5% *vs.* 23.1%, radial streaks in 29.2% *vs.* 23.1%, respectively). Furthermore, no SLN positive melanoma showed pseudopods, while they were present in 24.6% of SLN negative melanomas. Nevertheless no statistically significant differences were recorded.

Palpability was the only factor correlated to SLN positivity, among the clinical and dermoscopic features considered in the present study, in melanomas >1 mm thick. Furthermore, in patients with palpable melanoma there was a 3.8 higher risk of finding SLN metastasis when compared with non-palpable melanoma patients. Our results seem to rehabilitate the role of melanoma palpability as a useful and simple clinical indication of SLN positivity in melanomas >1 mm thick. It is easy to recognize, reproducible and objective.

Further investigation on a larger number of cases is needed to verify our results and to confirm the role of palpability as an indipendent prognostic factor in thick melanomas.

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