

# Preoperative Melanoma Thickness Determination by 20-MHz Sonography and Digital Videomicroscopy in Combination



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**Objective:** To identify accurately thick melanomas preoperatively by means of a combined approach based on sonography and clinical-videomicroscopic evaluation.

**Design:** Ultrasonographic thickness measurement, obtained by means of a 20-MHz B-scanner, and identification of clinical and videomicroscopic variables useful in distinguishing between thick and thin melanomas were performed on a training set of 40 melanomas. An algorithm based on echographic, clinical, and videomicroscopic criteria was constructed to develop a method for preoperative evaluation of melanoma thickness and was validated on a test set of 48 melanomas.

**Setting:** University medical department.

**Patients:** Eighty-eight patients affected by primary cutaneous melanoma.

**Main Outcome Measures:** Sensitivity and specificity of the algorithm, with the use of sonographic, clinical,

and videomicroscopic data, in thick melanoma identification.

**Results:** Echographic thickness was calculated for each lesion. On the training set, 2 clinical and 7 videomicroscopic features were identified for distinction between thick and thin melanomas: nonpalpability, central pigment network, central brown globules, and blotches were characteristic of thin melanomas; clinical regression, localized peripheral pigment network, veil, grayish polygonal areas, and blood vessels were characteristic of thick ones. A coefficient was attributed to each variable and a score was obtained for each lesion. The algorithm, developed for preoperative thickness prediction, was validated on the test set, enabling the distinction of thick melanomas with an 86.7% sensitivity and a 100% specificity.

**Conclusion:** The correct classification of all thin melanomas as such renders this approach suitable in clinical practice.

*Arch Dermatol.* 2003;139:293-298

**S**ENTINEL LYMPH node surgery is suggested for patients with primary melanomas 1 mm or greater in depth.<sup>1-3</sup> Melanoma thickness is usually determined according to the Breslow method after excision of the lesion.<sup>4</sup> Since surgical manipulation may cause scarring and damage to the lymphatic vessels, altering the pattern of tumor drainage, especially in sites with ambiguous lymphatic circulation such as the head, neck, and trunk,<sup>1,2,5</sup> performing sentinel lymph node mapping preoperatively would represent the ideal procedure.

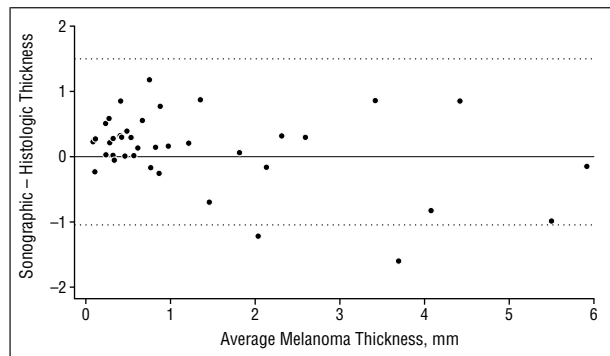
The use of 20-MHz sonography is helpful to study tissues close to the skin surface. By means of ultrasound, melanoma appears as a homogeneously echo-poor area in comparison with the surrounding echo-rich dermis, from which it can be easily distinguished. A sharp border between the hy-

pochogenic tumor structures and the hyperreflecting dermis is seen at the tumor base, permitting the determination of the maximum vertical tumor diameter.<sup>6</sup> A fair correlation between sonometric and histologic measurements of melanoma thickness was obtained by several authors, although a tendency to overestimate tumor thickness, owing to the impossibility of differentiating the lymphatic infiltrate from tumor tissue, has been reported.<sup>6-11</sup>

Clinical variables, such as palpability, have been suggested as criteria to determine melanoma thickness,<sup>12,13</sup> but their reliability was not confirmed.<sup>14,15</sup> Moreover, surface microscopic patterns<sup>16-19</sup> and scores<sup>20,21</sup> also in association with clinical examination<sup>18</sup> seemed insufficiently reliable for preoperative determination of melanoma thickness.

The aim of our study was to determine whether 20-MHz sonography, com-

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**Figure 1.** Bland-Altman plot showing differences between sonographic and histologic thickness against average of sonographic and histologic measurement, with 95% limits of agreement (broken lines), evaluated in 40 melanomas belonging to the training set.

combined with the evaluation of clinical features and microscopic patterns as assessed by digital videomicroscopy, allows accurate preoperative differentiation between melanomas thinner and thicker than 1 mm. A simple and reproducible method, based on thickness measurement and pattern description, was developed and applied to pigmented skin lesions, diagnosed as certain melanomas, to identify patients eligible for sentinel lymph node biopsy to be performed at the same time as the excision of the primary tumor.

## METHODS

A total of 88 consecutive patients with primary cutaneous melanoma (60 of which were 1 mm or thinner and 28 thicker than 1 mm) were studied. Two experienced dermatologists made a definite preoperative diagnosis by clinical and dermatoscopic examination of the lesion, also using a semiquantitative evaluation method. Only lesions definitely classified as melanoma by both examiners and with a total dermatoscopic score<sup>22</sup> greater than 5.75 were considered. No doubtful lesion was included in the study. All lesions selected on the basis of these criteria were classified as melanomas after histologic examination.

Before excision, ultrasonographic images of the tumor were recorded by means of a 20-MHz B-scanner (Dermascan C; Cortex Technology, Hadsund, Denmark), which produces images representing a cross section of the skin. The instrument, standardization procedures, and recording conditions have already been described in detail elsewhere.<sup>23</sup> Several sonographic scans were carried out for each tumor to find the plane with the highest vertical tumor thickness. Images were recorded with the gain curve enabling the best contrast between the tumor tissue and the surrounding tissue. Tumor thickness was immediately calculated by dedicated software measuring the maximum vertical distance between the entry echo and the inferior boundary of the echo-poor zone corresponding to the melanoma.

Subsequently, the clinical aspects of the lesions, including palpability ("not palpable" or "palpable and/or nodular") and the presence of regression areas (yes or no), were described.

Several images for each lesion were recorded by means of a videomicroscope (VMS-110A; Scalar Corporation, Tokyo, Japan),<sup>24</sup> with the use of an image acquisition program (Video-Cap 8.09; DS Medica, Milan, Italy), which runs under Microsoft Windows (Microsoft Corp, Redmond, Wash). Both 20- and 50-fold magnified images were used to assess the videomicroscopic aspects of thick and thin melanomas. The features referring to tumor images were described by 2 trained derma-

tologists filling in an appropriate electronic form. All of the variables established during the meeting of the Committee on Analytical Morphology of the Arbeitsgemeinschaft Dermatologische Forschung in Hamburg, Germany, in 1989, reported by Bahmer et al,<sup>25</sup> and modified during the First World Congress on Dermoscopy held in Rome, Italy, in 2000<sup>26</sup> were described, but for the creation of a reproducible algorithm, only variables enabling differentiation between nevi and melanomas were considered. All lesions underwent histologic examination for diagnostic confirmation and thickness determination.

Statistical evaluation was carried out with the SPSS statistical package (release 10.0.6, 1999; SPSS Inc, Chicago, Ill). Lesions were classified according to their histologic thickness in 2 groups: melanomas thicker than 1 mm (thick melanomas) and melanomas 1 mm or thinner (thin melanomas). To identify and validate a method for preoperative identification of thick melanomas, the study population was consecutively divided into a training set comprising 40 lesions (27 measuring 1 mm or thinner and 13 thicker) and a test set comprising 48 lesions (33 measuring 1 mm or thinner and 15 thicker). Only unambiguous melanomas, selected according to the criteria previously defined, were considered both for the test and for the training set.

The histometrically determined tumor thickness was compared with the measurements obtained by sonography by means of the Pearson correlation coefficient and the Bland-Altman plot for the limits of agreement.<sup>27</sup>

As basic statistical analysis, absolute and relative frequencies of each clinical and videomicroscopic criterion were calculated in thin and thick tumors both in the training and in the test set.

To identify variables useful for preoperative thickness determination, significant differences between thick and thin melanomas belonging to the training set were evaluated by the  $\chi^2$  test of independence (Fisher exact test was applied if any expected cell value in the  $2 \times 2$  table was less than 5). A *P* value less than .05 was considered significant. With the discriminant analysis approach and the odds ratio calculation, clinical and videomicroscopic variables useful for the distinction between thick and thin melanomas were identified and a coefficient for each variable was established. A total score was obtained for each lesion and a cutoff was established for classification into the 2 groups.

To develop a method for the preoperative evaluation of melanoma thickness, an algorithm based on sonographic, clinical, and videomicroscopic criteria was constructed on the data obtained from the melanomas belonging to the training set and validated on the lesions belonging to the test set. Melanomas were first subdivided into 2 groups according to sonography. Lesions evaluated as thin by sonography were considered as such and not further processed. On the contrary, melanomas with sonographic thickness greater than 1 mm underwent the clinical-videomicroscopic score calculation for the ultimate group attribution.

Sensitivity (intended as the number of thick melanomas identified as such) and specificity (intended as the number of thin melanomas identified as such) were calculated for the sonographic measurement, the clinical-videomicroscopic scoring system, and the integrated approach on the training set, the test set, and the total melanoma population.

## RESULTS

According to histologic examination, mean thickness of all melanomas was  $1.14 \pm 1.40$  mm; 28 lesions were thicker than 1 mm (mean thickness,  $2.69 \pm 1.56$  mm) and 60 were 1 mm or thinner (mean thickness,  $0.41 \pm 0.3$  mm).

**Table 1. Frequencies and Scores of the Clinical and Videomicroscopic Features Evaluated on a Training Set of 40 Melanomas and on a Test Set of 48 Melanomas**

Features	Training Set					Test Set	
	Thin MMs, No. (%) (n = 27)	Thick MMs, No. (%) (n = 13)	$\chi^2$	Odds Ratio, Thin/Thick	Score	Thin MMs, No. (%) (n = 33)	Thick MMs, No. (%) (n = 15)
Features characteristic of thin MMs							
Clinical aspects							
Nonpalpability	5 (19)	0	2.75	...*	-3	4 (12)	0
Videomicroscopic patterns							
Central pigment network	9 (33)	0	5.59†	...*	-3	9 (27)	0
Central brown globules	6 (22)	1 (8)	1.88	0.29	-2	6 (18)	1 (7)
Blotches	21 (78)	8 (62)	1.13	0.46	-2	23 (70)	8 (53)
Features characteristic of thick MMs							
Clinical aspects							
Regression	16 (59)	9 (69)	0.372	1.55	+1	14 (42)	7 (47)
Videomicroscopic patterns							
Localized peripheral network	0	3 (23)	6.74†	...*	+3	1 (3)	1 (7)
Veil	9 (33)	9 (69)	4.57†	4.50	+2	12 (36)	9 (60)
Grayish polygonal areas	2 (7)	9 (69)	16.8†	28.12	+2	3 (9)	10 (67)
Blood vessels	5 (19)	3 (23)	0.11	1.32	+1	6 (18)	6 (40)
Features not useful for melanoma thickness determination							
Pigment dots	15 (56)	6 (46)	0.31	0.69	...	19 (58)	7 (47)
Peripheral structures	9 (33)	5 (39)	0.10	1.25	...	11 (33)	5 (33)
Diffuse pigmentation	21 (78)	9 (69)	0.34	0.64	...	27 (82)	12 (80)
Hypopigmentation and/or regression structures	18 (67)	9 (69)	0.03	1.12	...	14 (42)	8 (54)

Abbreviation: MMs, malignant melanomas.

\*Odds ratio not evaluable because the examined feature is absent in 1 of the 2 groups.

† $P < .05$ .

## SONOGRAPHY

Mean thickness as assessed by 20-MHz ultrasonography was  $1.26 \pm 1.18$  mm. Comparison between histologic and sonographic thickness, evaluated on the melanomas belonging to the training set, showed a good correlation (Pearson  $r = 0.89$ ;  $P < .001$ ). According to the Bland-Altman statistical method, the 95% limits of agreement between the 2 measurement techniques were 1.57 and -1.13, with a mean difference (sonography minus histologic examination) of 0.06 mm and an SD of 0.78. The data are plotted in **Figure 1**. In the training set group, 23 (85%) of 27 thin melanomas and all thick ones were correctly classified by means of sonography. Thus, 15% of thin lesions were overestimated. In the test set, 28 (85%) of 33 thin melanomas and 14 (93%) of 15 thick ones were correctly classified, showing that only 7% of thick lesions were underestimated and 15% of thin ones were overestimated.

## CLINICAL DATA

Regarding the melanomas belonging to the training set, all lesions, except 5 thin melanomas, were palpable. On the other hand, nonpalpable lesions were always thin melanomas, corresponding to in situ lesions or to melanomas thinner than 0.2 mm. Clinical regression was more frequently observed in thick lesions (9 of 13 cases), although it was also present in a great number of thin ones (16 of 27 cases).

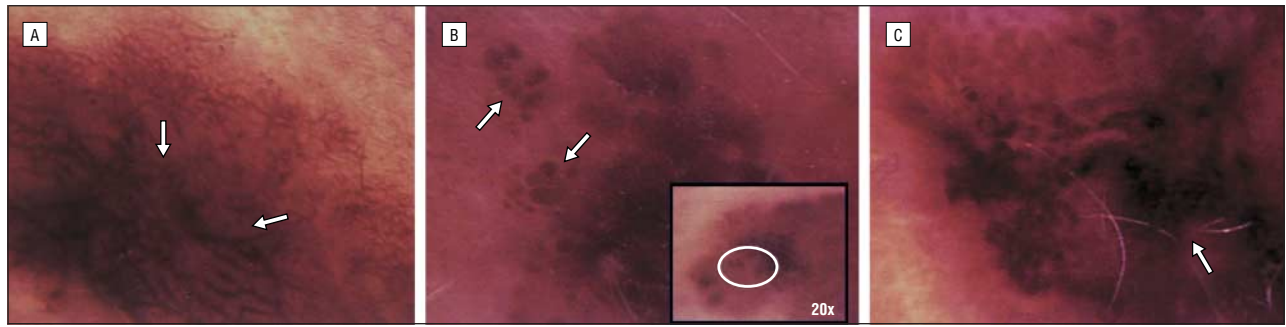
## VIDEOMICROSCOPIC EVALUATION

A significantly different frequency of some videomicroscopic patterns was observed between thick and thin melanomas (**Table 1**). Central pigment network, central brown globules, and blotches (areas of nonhomogeneous diffuse pigmentation) appeared as features characteristic of thin melanomas (**Figure 2**). Thick melanomas more frequently presented small and isolated network areas, occupying less than 2 of 8 sectors of the periphery (localized peripheral network). Moreover, these were characterized by the presence of veil and of grayish polygonal areas, corresponding to desquamation. Blood vessels were more often observed in thick melanomas than thin ones (**Figure 3**).

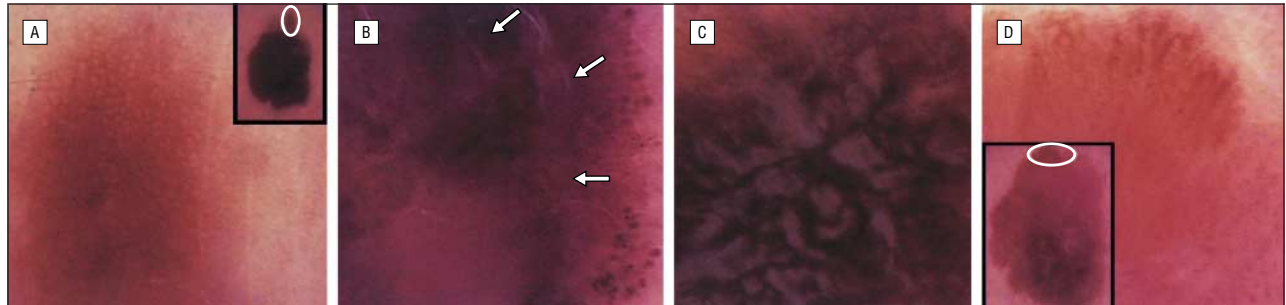
No significant differences regarding the presence, aspect, and distribution of pigment dots, peripheral structures (such as peripheral streaks or globules, and pseudopods), diffuse pigmentation, and hypopigmented areas were noticed.

## ALGORITHM FOR IN VIVO DISTINCTION OF THICK AND THIN MELANOMAS

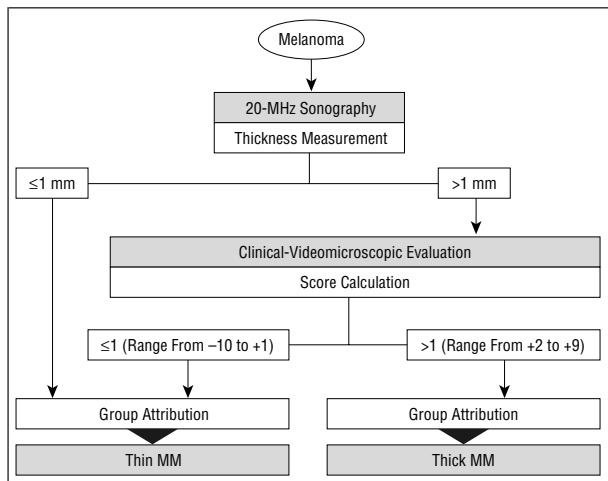
To predict tumor thickness preoperatively, a simple 2-step algorithm was developed on the lesions belonging to the training set, combining the data obtained from sonography and clinical-videomicroscopic scoring (**Figure 4**).



**Figure 2.** Images at  $\times 50$  magnification of melanomas presenting the patterns characteristic of thin lesions. A, Central pigment network (arrows). B, Central brown globules (arrows). The inset shows the whole lesion acquired at  $\times 20$  magnification, and the oval represents the  $\times 50$  magnified portion. C, Nonhomogeneous diffuse pigmentation (arrow).



**Figure 3.** Images at  $\times 50$  magnification of melanomas presenting the patterns characteristic of thick lesions. A, Localized peripheral network. The inset shows the whole lesion acquired at  $\times 20$  magnification, and the oval represents the  $\times 50$  magnified portion. B, Veil (arrows). C, Grayish polygonal areas. D, Blood vessels. The inset shows the whole lesion acquired at  $\times 20$  magnification, and the oval represents the  $\times 50$  magnified portion.



**Figure 4.** Flowchart for preoperative melanoma thickness determination. MM indicates malignant melanoma.

The first step is the echographic evaluation of tumor thickness. If this is 1 mm or less, we regard the lesion as a thin melanoma; if it is greater, we proceed to the next step. The second step is clinical and videomicroscopic evaluation. A score is assigned to the presence of predictive features, according to Table 1. A final score higher than 1 indicates tumors thicker than 1 mm. On the training set, all thin melanomas and 12 of 13 thick ones were correctly classified.

To validate this approach, the algorithm was applied in 48 melanomas belonging to the test set: 13 of 15 (87% sensitivity) thick melanomas and all thin ones (100% specificity) were correctly classified (100% posi-

tive predictive value and 94% negative predictive value). When the 2 approaches were combined, no thin melanomas were misclassified (**Table 2**).

#### COMMENT

The introduction of sentinel node biopsy in thick melanoma staging made the problem of preoperative determination of melanoma thickness crucial.<sup>1-3,5</sup> A melanoma thickness of 1 mm was chosen as the cutoff point to select cases for sentinel node biopsy because it is still debatable whether this surgical approach should also be used for lesions from 0.75 to 1 mm thick.<sup>3,28-30</sup> Since sentinel node identification is an invasive procedure and bears potential risks related to surgery and general anesthesia, only totally reliable methods that exclude the possibility of a misclassification of thin melanomas are useful in clinical practice, so as to avoid unnecessary surgical intervention. To date, none of the proposed methods seem reliable.

Sonography appeared promising in tumor thickness in vivo determination, as demonstrated by the high correlation between sonometric and histologic thickness measurements. However, the presence of an inflammatory infiltrate and of dermal nevus components underneath the melanoma tissue<sup>6-11</sup> gives rise to a great number of overestimated evaluations.<sup>31</sup> In our cases, the sonographic measurement was greater than the histologic one in 67 of 88 cases, with a mean overestimation of about 0.37 mm, and all thin melanomas misclassified by means of this method were 0.5 to 1 mm thick.



**Table 2. Comparison Between the Performances of Single Methods**

	Training Set, No. (%)		Test Set, No. (%)		Total Cases, No. (%)	
	Histologic Thickness		Histologic Thickness		Histologic Thickness	
	≤1 mm	>1 mm	≤1 mm	>1 mm	≤1 mm	>1 mm
Thickness on sonography, mm						
≤1	23 (85)	0	28 (85)	1 (7)	51 (85)	1 (4)
>1	4 (15)	13 (100)	5 (15)	14 (93)	9 (15)	27 (96)
<b>Total</b>	<b>27 (100)</b>	<b>13 (100)</b>	<b>33 (100)</b>	<b>15 (100)</b>	<b>60 (100)</b>	<b>28 (100)</b>
Clinical-videomicroscopic score						
≤1	24 (89)	1 (8)	32 (97)	2 (13)	56 (93)	3 (11)
≥2	3 (11)	12 (92)	1 (3)	13 (87)	4 (7)	25 (89)
<b>Total</b>	<b>27 (100)</b>	<b>13 (100)</b>	<b>33 (100)</b>	<b>15 (100)</b>	<b>60 (100)</b>	<b>28 (100)</b>
Group attribution by combined method						
Thin	27 (100)	1 (8)	33 (100)	2 (13)	60 (100)*	3 (11)
Thick	0	12 (92)	0	13 (87)	0	25 (89)†
<b>Total</b>	<b>27 (100)</b>	<b>13 (100)</b>	<b>33 (100)</b>	<b>15 (100)</b>	<b>60 (100)</b>	<b>28 (100)</b>

\*Specificity: thin melanomas identified as such.

†Sensitivity: thick melanomas identified as such.

Despite a significant overall correlation between palpability and histologic thickness<sup>32,33</sup> and Breslow level,<sup>12</sup> this clinical variable used as a single criterion enabled the correct distinction between thick and thin melanomas in only very few cases.<sup>14,15</sup> This is in accordance with our data concerning the low sensitivity of nonpalpability. In fact, although flat lesions invariably correspond to melanomas thinner than 1 mm, palpable ones may often be thin, probably because of irregular tumor growth, inflammatory infiltration, or the presence of an associated nevus.<sup>15</sup>

Epiluminescence techniques, enabling the observation of subsurface structures with variable magnifications, allowed the identification of features helpful in melanoma diagnosis.<sup>34-37</sup> Recently, the possibility of recognizing melanoma progression phases by dermatoscopy has been reported.<sup>16-19,38</sup> However, this approach too can lead to misclassification of thin melanomas, because specific aspects of thick lesions can also be present in thin ones.<sup>18</sup> Furthermore, the polymorphism of thin melanomas probably accounts for the nonreliability of the ABCD score for dermatoscopy in distinguishing between thick and thin lesions. The low specificity of this method leads to the misclassification of thin lesions into the thick group, resulting in unnecessary invasive surgery in many patients.<sup>20,21</sup>

Owing to their low cost, small size, and handiness, videomicroscopes are increasingly used in clinical practice. Unlike the epiluminescence technique, these instruments use a polarizing filter, to reduce reflected light and to gain access to the structures underlying the epidermis.<sup>24,36,37</sup> This may influence the aspect of the pigmented skin lesion image and may lead to the identification of melanoma thickness variables different from those previously identified by epiluminescence microscopy.<sup>16-19</sup>

In our cases, thin melanomas differed from thick ones by the presence of surface microscopic features in the center of the lesion. Tumor progression leads to the disappearance of pigment network, globules, and blotches from the center of the lesions, which are replaced by pinkish

white areas or by structureless areas frequently surmounted by the grayish polygonal structures constituted by thick horny scales, corresponding to the gray-blue areas observable by means of the epiluminescence technique.<sup>38</sup> Moreover, small localized areas of peripheral pigment network are characteristic of thick lesions. In accordance with previous data,<sup>39</sup> the veil was more frequently observed in thick melanomas, although we noticed this in fewer cases, probably because of the effects of the polarization of the light on color observation. A vascular pattern was detected in faintly pigmented lesions and in the regressive areas especially in thick melanomas, confirming previous observations.<sup>18,19</sup>

Our combined diagnostic approach for the identification of melanomas thicker than 1 mm appeared useful for clinical practice: in our series it allowed the distinction of the majority of thick melanomas without misclassification of thin ones. One of the 3 misclassified thick melanomas was a borderline lesion (histologic thickness, 1.1 mm), and the misclassification depended on a slight underestimation of the sonographic thickness (0.91 mm). The remaining 2 misclassified lesions appeared as thick melanomas by sonography, but the absence of features characteristic of thick lesions led to a low clinical-videomicroscopic score. We observed that, although some thin melanomas could be misclassified as belonging to the thick group solely on the basis of sonographic or clinical-videomicroscopic evaluation, combination of the 2 methods was highly specific for thick melanoma identification. Since echography represents the highest specificity rate method (Table 2), it is the first essential step to be used. Subsequently, only lesions appearing thicker than 1 mm require evaluation of the 2 clinical and 7 videomicroscopic criteria correlated to tumor thickness and combined in a simple linear equation for the definite classification of the lesions.

In conclusion, these data offer a new promising approach to preoperative determination of melanoma thickness, combining the use of ultrasound and the assessment of some selected clinical and videomicroscopic features of the lesion. The correct classification of all thin

melanomas (100% specificity) makes this approach particularly suitable in clinical practice, especially in centers where lymph node biopsy is routinely used for staging melanoma. In fact, the most widely applied treatment strategy for patients with melanoma is to excise the lesion without a safety margin and then, after histologic tumor thickness determination, decide on the safety margin and whether a sentinel node biopsy should be performed. However, the identification of the sentinel lymph node may be hampered by surgical manipulation of the skin site of the primary tumor. Our management strategy guarantees the advantages of certain identification of the sentinel lymph node by performing node mapping when the lesion is still in situ, and of a simultaneous surgical treatment.

Accepted for publication July 16, 2002.

This study was supported in part by grant 2001068929 from the Ministero dell'Istruzione dell'Università e della Ricerca, Rome.

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