Abstract

Introduction
Melanoma diameter represents a controversial parameter in the diagnosis of melanoma. The ABCDE rule considers it an important diagnostic parameter, whereas some authors consider its relevance to be less important. Also, its measurement is not always reliable as histological methods are usually used. The current study aims to assess histological and digital measurements of melanoma diameter and to evaluate the relationship between the diameter and thickness of head versus trunk-limbs melanomas.

Methods
The study population was divided into subgroups based on melanoma diameters, considering head lesions and trunk-limbs lesions separately. Digital diameters measured by an automatic software referring to 477 melanoma images were compared with diameters reported on the pathologist’s records. Clinical and histological information was also considered, and the relationship between diameter and thickness was assessed. Odds ratios were computed for different diameter subgroups.

Results
Mean digital diameters of head melanomas and trunk-limbs melanomas exceeded histological measurements by 11% and 20%, respectively. In head melanomas, no relationship between diameter and thickness was observable, whereas in the trunk-limbs group, a direct relationship between thickness and diameter was noticed. Odds ratios for non-in situ versus in situ and for ≥1 mm versus <1 mm thick melanomas were lower for smaller lesions and larger for larger lesions, indicating that the latter are more likely to be thick.

Conclusion
Melanoma diameter should be assessed digitally to avoid tissue shrinkage after biopsy and imprecise in vivo measurements. Although nearly 10% of melanomas might escape an early diagnosis based only on the D parameter of the ABCD rule (diameter), melanoma diameter maybe related to its thickness. Evaluation with a computer vision system should be recommended for small pigmented lesions (<6mm) in order to reduce the percentage of misdiagnosed smaller melanomas and to better evaluate the parameter E of the ABCDE rule (evolving lesion).

Introduction
In the last decade, diagnostic efforts have focused on early identification of melanomas (MM) in order to reduce mortality related to invasive and potentially metastasizing tumours and the consequent social and economic impact on the public health system. Thus, in 1985, a clinical rule was elaborated to help identify suspicious lesions. The mnemonic ABCD stands for asymmetry, border irregularity, colour variegation and diameter greater than 6 mm. Later, a fifth criterion E was added, where E stands for evolution, enlargement or elevation of the lesion. The ABCDE rule is helpful to alert general practitioners and to induce patients to seek early medical advice, thus reducing the morbidity and mortality rates of MMs. The diameter component of the ABCDE rule has been the focus of previous studies that reported contradictory results. Some conclude that the ABCDE criteria are useful parameters that should always be used in the selection of atypical lesions, whereas others stipulate that the diameter criterion is not absolute and that the frequency of small MMs is high, thus making the evaluation of the lesion size irrelevant.

It is well known that there are discrepancies between diameter assessment performed in vivo on relaxed skin prior to excision and histologic measurement. Moreover, in spite of the availability of software for automatic measurement, MM diameter is generally not evaluated by digital video microscopy in clinical practice, because it is not generally considered for assessment of MM prognosis.

In our study, for the first time, a comparison between two measurement methods of MM diameter; the dermoscopic method and the histological method, was performed. Different diameter cut-offs were established to evaluate the occurrence of MMs of different sizes and
to correlate MM diameter with MM thickness at different body sites.

Materials and methods

Database
The database belongs to the Department of Dermatology, University of Modena and Reggio Emilia. The study is based on a retrospective analysis of digital dermoscopic images of 623 MMs of the head and trunk-limbs, recorded during 2003 to 2010, employing a 20-fold and a 50-fold magnification. Acral lesions were excluded from the evaluation.

Instrument
Dermoscopic images were collected by means of a digital epiluminescence microscope (FotoFinder®, TeachScreen Software GmbH, Bad Birnbach, Germany). It consists of a probe, comprising a CCD-chip colour video camera with an integrated handle and optics for epiluminescence microscopy, a processing unit and a colour monitor. Optics are set in a removable conic structure with a cylindrical transparent spacer and a contact plate at the end, and with six bright white light-emitting diodes, positioned at the bottom of the structure, for constant illumination of the viewing area. The digitised images offer a spatial resolution of 768 × 576 pixels and 16 million colours. For the epiluminescence observation, a drop of contact medium, such as alcohol in water solution, is applied between the contact plane and the skin, enabling the recognition of subsurface structures. The calibration method has already been described elsewhere10.

Diameter measurement
The instrument is equipped with a software enabling the automatic measurement of the lesion diameters. The lesion’s maximum diameter is obtained by positioning the start and the end of a line at the two most distant points on the border of the lesion. Some lesions were totally included within the screen when employing the 20-fold magnification and were immediately measurable, whereas some lesions required two images which were overlapped before measurement. Larger lesions requiring the assembly of >2 images, 65 lesions of the head area and 81 lesions of the trunk-limbs area were not considered. On the whole, the digital diameter was obtained on images corresponding to 477 lesions (Figure 1).

Study design
Digital values were compared with diameters reported on the pathologist’s records assessed employing the micrometer. For larger images, where automatic measurement was not possible, only the histological diameter was considered.

MMs were divided according to localisation into two main areas: 1) the ‘head’, including face and scalp lesions and 2) the ‘trunk-limbs’, comprising lesions in the trunk, neck and upper and lower extremities. For each main area, the total number of patients, sex ratio, mean patient age, mean Breslow thickness, percentage of MMs smaller than 6 mm and mean dermoscopic and histologic diameters were considered. Moreover, MMs were divided into 7 groups according to diameter intervals: 0–3.5 mm, 3.51–4 mm, 4.01–6 mm, 6.01–10 mm, 10.01–15 mm, 15.01–20 mm and ≥20.01 mm. Mean thickness and the ratio between in situ and invasive MMs were calculated in each group in order to study the relationship between diameter and thickness at different body sites.

Statistics
A statistical analysis was carried out using the Statistical Package for the Social Science (SPSS), version 9.02 for Windows®. Data are expressed as mean and standard deviation. Differences between age and thickness values in the different groups were calculated by means of Student’s t-test. The relationship between diameter and thickness was determined by employing the 20-fold magnification and were immediately measurable, whereas some lesions required two images which were overlapped before measurement. Larger lesions requiring the assembly of >2 images, 65 lesions of the head area and 81 lesions of the trunk-limbs area were not considered. On the whole, the digital diameter was obtained on images corresponding to 477 lesions (Figure 1).

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The head group comprised 64 men and 43 women. In this group, the mean patients’ age was 73.42 ± 12.40 years and the mean Breslow thickness was 1.02 ± 2.3 mm. The mean digital diameter in the head group, which was calculated on 42 cases, was 13.02 mm, whereas the corresponding histological diameter was 11.55 mm.

The characteristics of the trunk-limbs group, comprising lesions of the trunk, neck and upper and lower extremities, were: male/female patient ratio of 53.29%, mean patient age of 56.98 ± 16.03 years and mean Breslow thickness of 1.01 ± 1.7 mm. MMs were localised on the trunk in 263 (50.96%) cases, on the upper limbs in 97 (18.79%) cases and on the lower limbs in 156 (30.23%) cases. The mean histological diameter; which was calculated on 435 cases, was 10.55 mm, whereas the corresponding digital diameter was 13.26 mm.

Considering the complete database (623 head + trunk-limbs lesions, also including large lesions where only histological measurement was possible), the mean diameter was 13.86 mm.

Comparing lesions where both the dermoscopic and histological diameters were available, the latter exceeded the former by 11.29% for head lesions and by 20.44% for trunk-limbs lesions.

Table 2 describes 69 MMs that were ≤6 mm in diameter, representing 11.1% of the total number of MMs localised on the head (9 cases, 8.4% of 107 head lesions) and trunk-limbs (60 cases, 11.63% of 516 trunk-limbs lesions). Small head MMs were found in male patients in 2/3 of cases, with a mean age of 72 years; mean thickness was 1.12 mm, and 55% of these were in situ. Small trunk-limbs MMs were found mainly in women with a mean age of 47 years and a mean thickness of 0.21 mm. Differences between thickness values and age of the two groups were statistically significant.

Figure 2 shows the mean thickness values and percentage of in situ lesions according to diameter subgroups in head MMs. As shown in the figure, MMs of ≤4 mm in diameter comprised only in situ lesions (5 MMs); MMs that were 4.01–6 mm large showed a mean thickness value of 2.03 mm and included only one in situ lesion. For MMs of >6.01 mm in diameter, the mean thickness values in the head region ranged from 0.75 to 1.15 mm and comprised 38%–57% of in situ lesions. In head

| Table 1. Description of 623 MMs localised on head and trunk-limbs. SD, standard deviation. |
|---------------------------------|-------------------|-----------------|----------|
|                                | Head group        | Trunk-limbs     | Total    |
|                                |                   | group           |          |
| Total number                   | 107               | 516             | 623      |
| Males; n (%)                   | 64 (59.81%)       | 275 (53.29%)    | 339 (54.41%) |
| Mean age ± SD (years)          | 73.42 ± 12.4      | 56.98 ± 16.03   | 59.81 ± 16.66 |
| * p = 0.000                    |                   |                 |          |
| Mean thickness ± SD (mm)       | 1.02 ± 2.3        | 1.01 ± 1.70     | 1.01±1.82 |
| Digital diameter (mm)          | 13.02 ± 7.40      | 13.26 ± 5.16    |          |
| (42 cases)                     | (435 cases)       | (477 cases)     |          |
| Histological diameter (mm) on digital cases | 11.55 ± 7.39  | 10.55 ± 5.89   | 10.63 ± 6.02 |
| (42 cases)                     | (435 cases)       | (477 cases)     |          |
| Diameter > 6 mm; n (%)         | 98 (91.6%)        | 456 (88.4%)     | 554 (88.9%) |
| * Significant versus trunk-limbs group | ** Significant versus diameters measured on histological specimens |

The Pearson correlation coefficient (r) using a linear regression line. Odds ratios (OR) were computed for a lesion to be in situ versus non-in situ and <1 mm thick versus >1 mm thick for different diameter subgroups. A p value < 0.05 for all tests was considered statistically significant.

Results
The study population consisted of 339 male and 284 female patients with a mean age of 59.81 ± 16.66 years and a mean MM thickness of 1.01 ± 1.82 mm (Table 1).

The head group comprised 64 men and 43 women. In this group, the mean patients’ age was 73.42 ± 12.40 years and the mean Breslow thickness was 1.02 ± 2.3 mm. The mean digital diameter in the head group, which was calculated on 42 cases, was 13.02 mm, whereas the corresponding histological diameter was 11.55 mm.

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MMs, no relationship between diameter and thickness was observable ($r = 0.065$).

Figure 3 shows mean thickness values and percentage of in situ lesions according to diameter subgroups in trunk-limbs MMs. In contrast with the head group, a direct relationship between thickness and diameter was observed in trunk-limbs MMs. Mean thickness of MMs ≤ 3.5 mm in diameter was 0.06 mm, whereas MMs ≥ 20.01 mm showed a mean thickness value of 2.18 mm. Relationship between diameter and thickness for the entire trunk-limbs group was 0.322 ($p = 0.000$), whereas for the trunk alone, it was 0.558 ($p = 0.000$), and for the limbs alone, it was 0.229 ($p = 0.000$).

Discussion

In this study, we showed that with respect to an accurate digital estimation, diameter measurement of ex vivo specimens provides under-valued data and that no correlation exists between diameter and tumour thickness for head MM.

The ABCDE mnemonic rule, which is used to assist a non-experts’ diagnosis of MM, is widely promoted.

Table 3. ORs for non-in situ versus in situ and ≥1 mm thickness versus <1 mm thickness (including in situ lesions), according to MM diameter.

<table>
<thead>
<tr>
<th>Diameter (mm)</th>
<th>OR for non-in situ vs. in situ</th>
<th>95% CI</th>
<th>Diameter (mm)</th>
<th>OR for ≥1 mm vs. &lt;1 mm</th>
<th>95% CI</th>
</tr>
</thead>
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<tr>
<td>≤3.5 (reference)</td>
<td>1.00</td>
<td></td>
<td>≤6 (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&gt;3.5–≤4</td>
<td>0.49</td>
<td>0.12–2.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;4–≤6</td>
<td>2.85</td>
<td>0.92–8.82</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;6–≤10</td>
<td>3.84</td>
<td>1.33–11.06</td>
<td>&gt;6–≤10</td>
<td>1.84</td>
<td>0.91–3.69</td>
</tr>
<tr>
<td>&gt;10–≤15</td>
<td>6.49</td>
<td>2.18–19.34</td>
<td>&gt;10–≤15</td>
<td>3.75</td>
<td>1.87–7.53</td>
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<tr>
<td>&gt;15–≤20</td>
<td>13.75</td>
<td>3.23–58.59</td>
<td>&gt;15–≤20</td>
<td>8.00</td>
<td>3.31–19.34</td>
</tr>
</tbody>
</table>

Figure 2: Head MMs: mean thickness and frequency of in situ lesions according to diameter subgroups. a) Mean thickness; b) Frequency of in situ MMs. Number of lesions for each diameter subgroup were as follows: ≤3.5 mm, 2; 3.51–4 mm, 2; 4.01–6 mm, 5; 6.01–10 mm, 21; 10.01–15 mm, 33; 15.01–20 mm, 21; ≥20.01 mm, 23.

Figure 3b shows the percentage decrease of in situ MMs according to lesion diameter. MMs < 3.5 mm in diameter included 72.7% of in situ lesions, whereas those ≥20.01 mm in diameter included 15.6% of in situ lesions.

Table 3 shows ORs for a lesion to be non-in situ versus in situ and ≥1 mm thick versus <1 mm thick according to MM diameter. ORs for non-in situ versus in situ lesions were very low (0.49) for smaller lesions, whereas they increased to 13.75 for 15–20 mm diameter lesions. Similarly, ORs for ≥1 mm thickness versus <1 mm thickness gradually increased to 7.33 for lesions >20 mm, indicating that larger lesions are more likely to be thick.
Although the ABCDE criteria show low reproducibility among untrained novices\(^1\), the diameter parameter can be based on an objective assessment, and can thus be studied with higher reliability. In this study, we evaluated the occurrence of MMs of different sizes to estimate the frequency of small-diameter MMs and to correlate MM diameter with MM thickness at different body sites.

Our study is innovative as we used computer technology to measure the diameter of MMs with greater accuracy and precision, thus avoiding inter-observer variability introduced by human measurements on skin lesions or \textit{ex vivo} specimens. An automatic measurement method has already been proposed by Abbasi et al., who employed a computerised skin imaging system to assess 1,657 pigmented lesions, which were suggestive of MM\(^9\). In their study, however, a comparison between the computer and the histological diameter was not provided. It was reported that \textit{ex vivo} specimen measurements may result in an underestimation of lesion diameter by as much as 20%\(^{12,13}\). This is caused due to shrinkage of a biological tissue after fixation with formalin; surgical specimens from patients younger than 50 years of age are especially prone to develop this alteration\(^{12,13}\).

In this survey, on comparing digital diameter measurements with those from pathology reports, we observed that tissue shrinkage varied according to different body sites by approximately 11% for head lesions and by 20% for trunk-limbs lesions. The results of this study, based on the comparison of a double assessment, stress the importance of accurate measurements when performing studies on MM diameter, which are relevant for practical reasons including diagnosis and surgical management as well as for speculating the biological potential of melanocytic neoplasms.

With regard to the frequency of small MMs, we found that 11.6% of trunk-limbs MMs and 8.4% of head MMs were ≤6 mm in size. The former were found mostly in young women (66% in women with a mean age of 47 years).

The frequency of small MMs in a clinical context differs significantly between studies. Bono et al. found that 17% of 270 MMs measured <6 mm\(^{14}\). Helsing and Loeb reported that 11.4% of 158 MMs, included in a multicentre prospective study in Norway, were <7 mm\(^8\). In contrast, an Australian study in 1992\(^3\), based on measurements made on histopathological specimens, found a very high frequency of small-diameter MMs. The authors explained this by the very high public awareness of MMs in Australia and the routine performance of prophylactic mole checks. Among 383 MMs considered by Fernandez and Helm, employing the pathology reports, 38.21% were found to be ≤6 mm\(^7\). The authors themselves observed that this percentage may be falsely elevated because size measurement was based on pathological specimens with a consequent underestimation of the diameter\(^1\).

The accuracy of our study design, based on accurate lesion measurements rather than rough estimates based on a ruler or a clinical

*Figure 3*: Trunk-limbs MMs: mean thickness and frequency of \textit{in situ} lesions according to diameter subgroups. a) Mean thickness; b) Frequency of \textit{in situ} MMs. Number of lesions for each diameter subgroup were as follows: ≤3.5 mm, 11; 3.51–4 mm, 8; 4.01–6 mm, 41; 6.01–10 mm, 155; 10.01–15 mm, 162; 15.01–20 mm, 76; ≥20.01 mm, 64.
assessment, allows much greater insight into the relationship between lesion diameter and MM thickness. Our data showed that MMs on the head and trunk-limbs areas behave in two different ways, and a separate description of these two populations was provided for the first time. A significant relationship between diameter and thickness was observed for lesions located on the trunk-limbs area, with small-diameter (<6mm) MMs showing a mean thickness value of 0.21 mm and comprising 62% of in situ lesions. The highest correlation coefficient was observed on the trunk, reflecting a higher risk of being a thick MM when the diameter grows larger. This was confirmed by the observation that ORs for 1.5–2 cm large lesions to be thicker than 1 mm are 8 times higher than those for <6 mm large lesions.

Exceptions to the rule that ‘small corresponds to thin’ have been reported14. Bono et al. described 11 small nodular MMs (<6mm) with a Breslow thickness ranging from 0.53 to 2.35 mm. In spite of the vertical growth, no patient showed a relapse after a 6-year follow-up period, and the authors hypothesised that besides the mitotic rate, the lesion dimension itself may represent an independent prognostic factor. In fact, the observation that very small lesions may show vertical growth is also confirmed by our data revealing that one third of trunk-limbs MMs <3.5 mm were not in situ.

On the other hand, no relationship between diameter and thickness was observed for MMs of the head area, with MMs 4.01–6 mm large showing a mean thickness value of 2 mm and those above 1 cm showing a thickness of around 1 mm. These data indicate that MMs of the head region include two different populations: one consisting of lesions developing in situ and persisting as lentigo maligna with long lasting horizontal growth and the other comprising of lesions that show vertical growth from the beginning in spite of their small size. In this study, we found that 4 out of 5 MMs of the head, 4.01–6 mm large, were already invasive.

In conclusion, to collect comparable literature data, MM diameter must be assessed in vivo, employing appropriate technology, before tissue shrinkage after biopsy. In particular, a computer-based method for determining MM diameter should be routinely used in clinical practice. Considering the cut-off at 6 mm, clinicians must be aware of the fact that nearly 10% of MMs will escape the D assessment, although anamnestic data on change and dermoscopic atypia may provide hints to correct diagnosis. Keeping this limitation in mind, the D rule is worth using as a simple patient educational guideline capable of saving lives.

At least in areas other than the face and scalp, MM diameter may predict its thickness; although invasive MM can also be found among very small lesions, a lesion with a diameter < 1 cm is more likely to be a thin MM. Small MMs have a biological potential to metastasize and, although literature on small-diameter MMs and their prognosis is sparse15,7, most authors believe that they are associated with a good prognosis; this makes a possible misdiagnosis less worrisome.

For small face and scalp lesions, a digital measurement may enable an objective follow-up to identify minor diameter variations possibly underlining a trend versus invasiveness.

Abbreviations list

MM, melanoma; OR, odds ratio.

References