Computer-aided clinical image analysis for non-invasive assessment of tumor thickness in cutaneous melanoma

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Abstract
Objective: Computerized clinical image analysis is shown to improve diagnostic accuracy for cutaneous melanoma but its effectiveness in preoperative assessment of melanoma thickness has not been studied. The aim of this study, is to explore how melanoma thickness correlates with computer-assisted objectively obtained color and geometric variables. All patients diagnosed with cutaneous melanoma with available clinical images prior to tumor excision were included in the study. All images underwent digital processing with an automated non-commercial software. The software provided measurements for geometrical variables, i.e., overall lesion surface, maximum diameter, perimeter, circularity, eccentricity, mean radius, as well as for color variables, i.e., range, standard deviation, coefficient of variation and skewness in the red, green, and blue color space.

Results: One hundred fifty-six lesions were included in the final analysis. The mean tumor thickness was 1.84 mm (range 0.2–25). Melanoma thickness was strongly correlated with overall surface area, maximum diameter, perimeter and mean lesion radius. Thickness was moderately correlated with eccentricity, green color and blue color. We conclude that geometrical and color parameters, as objectively extracted by computer-aided clinical image processing, may correlate with tumor thickness in patients with cutaneous melanoma. However, these correlations are not strong enough to reliably predict tumor thickness.

Introduction
Tumor thickness at the time of surgical treatment remains the most widely accepted and accurate predictor of prognosis in patients with cutaneous melanoma. It also defines the size of the surgical margin and helps determine which patients should undergo sentinel lymph node biopsy. For these reasons, much effort is being directed at obtaining reliable information regarding tumor thickness prior to the operation, as thick tumors have to be excised with a larger surgical margin.

Several tools have been implemented to support these efforts. Dermoscopy has become very popular the last 2 decades. It is not invasive and is proven to facilitate melanoma diagnosis of clinically suspicious pigmented lesions. However, its effectiveness as a thickness assessment tool is controversial. Some authors found specific dermatoscopic patterns, such as pigment networks, gray-blue areas and vascular patterns to be associated with thick lesions [1] or blue white veils, milky-red areas and shiny-white streaks to be associated with ulceration and mitotic rate [2], whereas other could not confirm these findings [3]. Several models to predict tumor thickness out of dermoscopic images have been proposed, but all require high expertise, as they are based in presence of absence of particular patterns. Interestingly, Pizzichetta...
et al. report that dermoscopical characteristics do not differ between patients with in situ melanoma and patients with invasive melanoma [4]. Finally, most dermoscopic criteria were described in the context of superficial spreading melanoma [5].

Other novel non-invasive methods, such as high-frequency sonography and epiluminescence light microscopy show promising results, but, apart from their cost, they also require training and are observer-dependent.

Computerized clinical image analysis is also shown to improve diagnostic accuracy for cutaneous melanoma [6]. It is non-invasive, cheap and obviates interpretative problems as it is based on mathematic analysis. Several color and geometric parameters are found to be associated with melanoma. However, to the best of our knowledge, a digital image processing analysis to demonstrate correlation of specific color and geometric variables with melanoma thickness has not been reported. The aim of this study is to explore how melanoma thickness correlates with computer-assisted objectively obtained color and geometric variables.

**Main text**

**Materials–methods**

**Patient recruitment, image collection, storage and image database**

Following the study approval by the institutional Ethics Committee of University Witten/Herdecke, we retrospectively reviewed and analyzed the computerized medical records of all patients, diagnosed with cutaneous melanoma in a tertiary university hospital in Germany during a 3-year period. The study included patients with histologically confirmed melanomas with available clinical images shot with a digital camera along with a ruler. Exclusion criteria included patients younger than 18 years old, in-situ melanomas, ulceration, extensive regression as reported in the pathologist report, mucosal tumors, acral melanomas and amelanotic lesions. All lesions were photographed at admission with the same commercial digital camera at the same high-resolution (1600×1200 pixels) and with a ruler being aligned beside the lesion to allow for correct scaling of the images. All photos were obtained from the same educated nurse to minimize inconsistencies in methodology. Any hairs on the lesion were removed with a razor prior to photography. The photos were then uploaded to a local server in the highest-quality jpeg format. After obtaining informed written patient consent, the lesions were excised under local anaesthesia and the diagnosis was histologically confirmed. Melanoma thickness was considered the one reported at the pathologist report.

**Image processing**

All color images obtained, underwent digital processing with an automated non-commercial software developed from one of the authors (AM) for study purposes. The software provided measurements for geometrical variables, i.e., overall lesion surface, maximum diameter, perimeter, circularity, eccentricity, mean radius, as well as for color variables, i.e., range, standard deviation, coefficient of variation and skewness in the red, green, and blue (RGB) color space. Each RGB component pixel was assigned an intensity value between 0 and 255 (8-bit accuracy). All 15 variables studied are explained in Table 1 [7].

**Statistical analysis**

Normal distribution was determined using histogram plots, box plots and the Shapiro–Wilk test. Continuous data were normal or approximately normal distributed.
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ysis provides measurements with the skin under tension,
entially and thus with higher reliability. Digital image anal-
represents the only criterion that can be studied objec-
tion form. Correlations were considered strong at $r \geq 0.6$, moderate
weak at $r < 0.2$. Data analyses were performed using SPSS 23.
Discussion
Tumor thickness remains the most important prognostic
factor in patients with cutaneous melanoma, with 1 mm
being the common cut-off value between thin and thick
tumors. The latter require broader excision and further
investigation with sentinel lymph node biopsy. Despite
this fact, correct thickness assessment can be a difficult
task, as even highly experienced dermatologists can cor-
correctly classify only about 90% of the cases [8].
Several studies analyzed digital dermoscopy images to
determine color and geometrical parameters observed in
thin and thick lesions [4, 8, 9]. Clinical image analysis is
considered a tool with high diagnostic accuracy for melano-
[6], but its effectiveness in non-invasive assessment of the
tumor thickness has not been studied. Our findings
demonstrate that specific geometrical and color
parameters correlate with melanoma thickness, the cor-
relations, though, are not strong enough to reliably pre-
dict tumor thickness.
The lesion diameter is part of the ABCDE criteria and
represents the only criterion that can be studied objec-
tively and thus with higher reliability. Digital image anal-
ysis provides measurements with the skin under tension,
which can differ from these of the ex vivo specimens pro-
vided from the pathologist, due to tissue shrinkage up to
20%, especially at patients younger than 50 years old [10].
Digital image processing prevents thus inter-observer
variability. We found that the largest lesion diameter
correlates strong with the tumor thickness. Seidenari
et al. also observed this relationship at lesions located on
the trunk and limbs, but not at head melanomas, attrib-
uting this finding to the large portion of head lesions
developing in situ and persisting as lentigo maligna with
long lasting horizontal growth [10]. Argenziano et al.
found this correlation being statistically significant only
in the case of thick lesions, but their interpretation was
based on ordinal rather than continuous data (i.e., diam-
eter was classified in categories) [1].
In our study, thickness was moderately correlated with
eccentricity. Eccentricity is considered a special case of
asymmetry. According to Lorentzen et al.: “with progres-
sion of the tumour, the cancerous tissue will be found not
only at the periphery but will also cause bulk asymmetry,
displacing the tissue with a less abnormal appearance”
[3]. Therefore, eccentric lesions are possible thicker.
Melanomas greater than 1 mm thick are reported to
have a larger area and a greater presence of blue [8]. Our
study confirms this finding, as the overall area as well as
the range and the standard deviation of the blue color
was found to increase with thickness (strong and moder-
ate correlation, respectively). The same study also reports

### Table 2

| Variable | Mean (SD) | r coefficient | p value |
|----------|----------|---------------|---------|
| Geometric variables | | | |
| Area (cm²) | 2.5 (3.7) | 0.72 | 0.000 |
| MaxD (cm) | 1.9 (1.1) | 0.65 | 0.000 |
| Perimeter (cm) | 5.5 (2.9) | 0.62 | 0.000 |
| Circularity (ratio) | 1.1 (0.07) | −0.05 | 0.56 |
| Rm (cm) | 0.8 (0.4) | 0.65 | 0.000 |
| Eccentricity (cm) | 0.03 (0.02) | 0.46 | 0.000 |
| Color variables | | | |
| Mean red | 156 (32) | −0.17 | 0.04 |
| SD red | 33 (11) | 0.11 | 0.19 |
| CV red | 23 (11) | 0.14 | 0.09 |
| Range red | 191 (35) | 0.15 | 0.06 |
| Skewness red | −0.3 (0.7) | 0.16 | 0.05 |
| Mean green | 97 (24) | −0.17 | 0.03 |
| SD green | 30 (6) | 0.28 | 0.000 |
| CV green | 33 (12) | 0.33 | 0.000 |
| Range green | 194 (32) | 0.23 | 0.003 |
| Skewness green | 0.43 (0.57) | 0.18 | 0.03 |
| Mean blue | 93 (23) | −0.04 | 0.64 |
| SD blue | 30 (6) | 0.21 | 0.01 |
| CV blue | 35 (12) | 0.18 | 0.02 |
| Range blue | 202 (33) | 0.21 | 0.009 |
| Skewness blue | 0.47 (0.54) | 0.08 | 0.31 |

All continuous variables are approximately normally distributed and therefore expressed in mean-deviation form. Statistical significance: p-value < 0.05.
a greater randomness in the disposition of pattern components in melanomas with thickness >1 mm, as shown by the presence of red, green and blue multicomponent patterns. According to the authors, such patterns express the number, dimensions and differences between objects color within the lesion and are correlated with the structural asymmetry and ‘disorder’ inside the lesion. However, a detailed description and definition of what should be considered a multicomponent pattern is not provided. In our analysis, we preferred to assess the color distribution in terms of color range for all three color intensities, rather than color percentiles inside the lesions.

There are different approaches regarding the assessment of color features. Several authors suggest assessment of all six colors that a pigmented lesion can present: black, dark brown, light, brown, blue-gray, red, and white [11]. This classification is common in dermoscopy, since the different colors are believed to represent different melanin locations: melanin appears black when it is located in the stratum corneum or upper epidermis, brown in the deep epidermis and gray or blue in the dermis. Red is associated with dilation of blood vessels and white with regression and/or scaring. Adopting this classification, one has to segment each lesion into their constituting colors [11]. We avoided this approach, as it is not fully objective and, moreover, is difficult to set the threshold of the covered lesion area for the color to be counted.

Argenziano et al. reported that the presence of blue-black color, i.e., a combination of blue and black pigmented areas involving at least 10% of the lesion surface, is associated with the presence of nodular melanoma, i.e., high-thickness melanoma. However, the assessment was based on qualitative observer-dependent evaluations, not on quantitative parameters [5].

We conclude that geometrical and color parameters, as objectively extracted by computer-aided clinical image processing, may correlate with tumor thickness in patients with cutaneous melanoma. However, these correlations are not strong enough to reliably predict tumor thickness.

Limitations
Our study has some limitations that should be considered. Firstly, it is a single-centre retrospective study and its results cannot be easily generalized. Secondly, we included only melanoma patients with available clinical images, made before the diagnosis was established. This could represent a selection bias, as patients with large abnormal pigmented lesions are more likely to seek medical advice. Similarly, particularly suspect cases were more likely to be photographed and therefore recruited. Thirdly, as the specimens were analyzed from different pathologists during the study period, the possibility of interpretation bias of tumors’ thickness cannot be ruled out, especially regarding regression. Last but not least, our analysis considered only the clinical bidimensional parameters of the lesion.

Abbreviations
RG: Red, green, and blue color space; SD: Standard deviation; CV: Coefficient of variation.

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Authors’ contributions
MP: Study design, data collection, Data analysis, literature review, manuscript drafting. AP: Data collection, AM: Data analysis, PL: Data collection, literature review, GM: Data analysis, HZ: Study design, Literature review. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
The study was approved from the Ethics Committee of University Witten/Herdecke and was performed in accordance with institutional guidelines. Written informed consent was waived for retrospective study participation.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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