QUANTITATIVE MULTISPECTRAL IMAGING FOR THE DIAGNOSIS AND TUMOR DEPTH ASSESSMENT OF MALIGNANT MELANOMA

PhD thesis booklet

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Introduction:

Melanoma (malignant melanoma, MM) is a malignant tumor that arises from melanocytes. It is responsible for the majority of skin cancer-related deaths (Matthews, Li et al. 2017, Nov. 2018 Sub (1973-2016)). Worldwide, approximately 232,100 new patients are diagnosed with melanoma annually and it accounts for about 55,000 deaths every year (Schadendorf, van Akkooi et al. 2018). Melanoma has four main subtypes: superficial spreading melanoma (SSM), nodular melanoma (NM), lenti There are many skin disorders which are similar to melanoma, including dysplastic nevus, lentigo maligna, congenital and acquired pigmented nevus, non-melanoma skin cancers, Bowen's disease, actinic keratosis, Spitz-nevus, blue nevus, hemorrhage, seborrheic keratosis and others (Elbaum, Kopf et al. 2001, Braun, Rabinovitz et al. 2002, Zalaudek, Ferrara et al. 2005, Braga, Scope et al. 2008, Fargnoli, Kostaki et al. 2012, Mun, Kim et al. 2013). There is a subgroup of malignant melanomas that are so similar to SKs that they make up even a new entity named SK-like malignant melanomas (Carrera, Segura et al. 2017). According to the American Academy of Dermatology, the National Institute of Health and the National Comprehensive Cancer Network, histopathological evaluation after surgical removal is the gold standard for the diagnosis of melanoma (Sober, Chuang et al. 2001, Swetter, Tsao et al. 2019).go maligna melanoma (LMM), and acral lentiginous melanoma (ALM). The treatment for primary malignant melanomas is surgical excision with an appropriate safety margin. In certain countries it is done as a two-step procedure when the primary resection is followed by a re-excision after the histopathological definition of the tumor thickness (Meyer, Lauwers-Cances et al. 2014). Melanoma in the early stages can be treated successfully with surgery alone (Davis, Shalin et al. 2019) where advanced cases need more complex treatment (Kandel, Allayous et al. 2018, Davis, Shalin et al. 2019). The Breslow tumor thickness or Breslow thickness is the maximum invasion depth of the melanoma, the distance is given in millimeters between the granular layer of the epidermis or the base of ulceration, and the deepest point invaded by tumor cells (Sladden, Balch et al. 2009, Swetter, Tsao et al. 2019) not including deeper follicular or adventitial extension (Swetter, Tsao et al. 2019). This is a vital element of the tumor staging (Gershenwald, Scolyer et al. 2017) which defines the required surgical safety margin (Coit, Andtbacka et al. 2012). Seborrheic keratosis (SK) is a common benign epithelial skin lesion which is very frequent among the elderly. In certain cases, when a younger patient is affected, and the number of simultaneous lesions is low, diagnostic challenges are more likely to occur (Izikson, Sober et al. 2002, Rubegni, Feci et al. 2015, Wollina 2019). There is a subgroup of melanomas that appear very similar to SKs and as a new

entity which is recently referred to as SK-like melanoma (Carrera, Segura et al. 2017). They cannot be distinguished from SKs with the naked eye nor with DS (Carrera, Segura et al. 2017). Among SKs there is also a subgroup, the MM-like SKs, which can only be differentiated by using DS.

Objectives:

The aim of the present study was to investigate spectral reflectance and autofluorescence properties of melanoma to achieve 2 main goals:

1) Estimate the depth of melanomas with the help of an MSI based device using G, R and IR light and compare it to the performance of clinical assessment by dermatologists and dermatology residents. The detailed description of this prototype device was previously published (Lihachev, Derjabo et al. 2015, Spigulis 2017). We have measured the mean gray value (integrated density/area), circularity(4π*area/perimeter^2), solidity (area/convex area) and roundness (4*area/(π*major_axis^2)). An additional first step was built in in this algorithm to rule out pigmented nevi using parameter *s'* (Equation 1) based on our previous studies (Diebele, Bekina et al. 2012, Lihacova, Bolocko et al. 2017, Lihacova, Bolochko et al. 2018, Lange, Kiss et al. 2019). The LED-based multispectral images were analysed with ImageJ v1.46 software (NIH, Bethesda, MD, USA) (Abràmoff, Magalhães et al. 2004).

$$parameter\ s' = lg \frac{I_G \cdot I_{R_{skin}}^2}{I_{G\_skin} \cdot I_{R\_skin}^2} \quad (1)$$

where I_G : intensity of lesion in green channel,

I_G _skin: mean intensity of skin in green channel,

I_R : intensity of lesion in red channel,

I_{R_skin} : mean intensity of skin in red channel.

2) Our second aim was to compare the MSI characteristics of melanomas to seborrheic keratoses to distinguish these two entities using a novel MSI based index operating with AF, G and R light, the SK index (Equation 2). For the intensity analysis we manually selected the skin lesions ROI using the AF, G and R channels. We analyzed the intensity including minimum and maximum, mean intensity value and standard deviation (SD), to compare melanomas with SKs regarding these parameters. We calculated ratios of the intensity values of the different channels including AF, G and R and used these ratios (AF/G, AF/R) to differentiate melanomas from SKs. We also measured the ratio of the pixels with the lowest and highest intensity values within each lesion (Min/Max). During this comparison we focused more on the more challenging lesions including melanoma (MM)-like SKs and SK-like MMs. Academic literature will be drawn upon to discuss these findings and the paper will close with recommendations for applications in the everyday practice. The LED-based multispectral images were analyzed with ImageJ v1.46 software (NIH, Bethesda, MD, USA) [76].

$$SK\ index = \frac{2 \cdot AF \cdot StDev \cdot (\frac{Min}{Max})}{G \cdot R} + (Particle\ number \cdot Area\ \%) \quad (2)$$

Materials and methods:

The handheld prototype used in this study was developed by the University of Latvia in collaboration with Riga Technical University (Riga, Latvia). The illumination source is a LED-ring which contains four types of LEDs (SML-LXL8047UVC, Lumex, Inc., Ronkonkoma, NY, USA) with wavelengths of 405 nm to induce skin autofluorescence (AF) and 525 nm green (G), 660 nm red (R) and 940 nm infrared (IR) (Zonios, Dimou et al. 2008, Borisova, Angelova et al. 2013) from which we used AF, G and R images for our further analyses. The lights penetrate to different layers of the skin with irradiating power density of 20 mW/cm^2. Images were collected with a color CMOS 5 megapixel IDS camera (MT9P006STC, IDS uEye UI3581LE-C-HQ, Obersulm, Germany) fixed at 60 mm distance from the illuminated skin with a field of view of 2x2cm^2 (Lihachev, Derjabo et al. 2015). A long pass filter (T515 nm > 90%) was inserted in front of the camera to block 405 nm excitation illumination. AF was captured in G and R spectral channels. In cases where the lesion surface was not flat (e.g. fingers, elbows, etc.) the image focus was slightly adapted by the adjustment of the region of interest (ROI). The acquired images were automatically transferred to a cloud server, as described earlier

(Bliznuks, Jakovels et al. 2015). The description of this prototype device can be found in (Lihachev, Derjabo et al. 2015, Spigulis 2017).This study was approved by the Ethics Committee of Semmelweis University and by the Scientific Research Ethics Committee of the University of Latvia.

Results:

- In the melanoma tumor depth analysis, we have examined one hundred patients with primary melanoma of the skin.
- In total, we have collected 128 image sets. Of the 100 melanomas, 69 were SSM (69%), 19 NM (19%), 2 ALM (2%), 3 LMM (3%), 1 naevoid (1%) and 6 unclassified (6 %). The mean age of melanoma patients was 62.64 ±14.29 years. The sex ratio of the affected patients was 37% women and 63% men. The mean Breslow tumor thickness was 1.777 ±1.728 mm, ranging from 0.12 mm to 7.5 mm.
- When the intensity values of various melanomas with different tumor depths were studied, we found significant differences in the green (G) and red (R) MSI channels that allowed us to efficiently differentiate the Breslow≤1 mm subgroup from the other two groups, the Breslow: 1-2 mm and the Breslow> 2 mm subgroups. In these tumors the intensity measured in these channels of Breslow≤1 mm melanomas were significantly higher than in the other two subgroups.
- Among the shape descriptors, both circularity and solidity proved significantly lower in the Breslow≤1 mm subgroup than in the other two subgroups. Pearson's correlation showed high correlation between solidity (r: 0.6324, 95% confidence interval: 0.4978 to 0.7372, p: <0.0001) and between circularity and Breslow thickness (r: 0.7109 95% confidence interval: 0.5980 to 0.7961, p: <0.0001).
- We have developed a novel MSI-based melanoma classification algorithm based on the shape descriptors and intensity values that allows us to classify melanomas into the above-mentioned three subgroups with a sensitivity of 78% and specificity of 89%, . The sensitivities for each subgroup were 80.85% (Breslow≤1 mm), 76.19% (Breslow: 1-2 mm) and 81.25% (Breslow>2 mm).
- The total sensitivity of the human expert categorization into the three subgroups described above was 60.38%, while the specificity was 80.86% with a moderate total agreement ($\kappa = 0.41$; 95% CI, 0.40 to 0.43), (Table 2.). The sensitivity of the assessment by dermatologists was 62.19% with a specificity 81.09% and a moderate

agreement ($\kappa = 0.44$; 95% CI, 0.42 to 0.47), where at the same time the sensitivity of the evaluation by dermatology residents was 58.44%, with a specificity of 79.76% and a fair agreement ($\kappa = 0.39$; 95% CI, From 0.36 to 0.41).

- We have examined total of 266 patients with melanoma or SK and taken one or more image sets of their lesions depending on the lesions' number and size. Many patients with SKs had several lesions increasing the number of image sets taken. Out of the total 127 patients (161 image sets) were histologically proven melanomas from which 66 were SSM (52 %), 18 NMs (14.1%), 21 in situ melanomas (16.5%), 3 ALM (2.3%), 1 LMM (1%) and 18 unclassified (14.1%). Six patients had SK resembling MMs (6 image sets). Comparison was made to 139 patients (319 SK lesions with 319 image sets) diagnosed with SK by dermatologists (2-3 SKs/patient) with the use of a commercial Heine Delta 20 (HEINE Optotechnik GmbH & Co. KG, Gilching, Germany) dermoscope. 30 patients had MM resembling SKs (52 image sets). The mean age of patients with melanoma and SK was 64.09 ±13.55 and 70.19 ±11.147 years, respectively. The gender ratio was 44 % women and 56 % men among patients with melanoma and 44.9% women and 55.1% men among patients with SK.
- In SKs, the AF/G, AF/R and Min/Max ratios proved to be all significantly higher compared to melanomas.
- We analyzed also the challenging cases including the melanoma (MM)-like SKs and SK-like MMs using the same method. In MM-like SKs all the intensity values were similar, yet significantly higher compared to SK-like melanomas including AF/G, AF/R, SD, Min/Max.
- Our algorithm could differentiate between SKs and melanomas. This algorithm counted significantly higher number of particles in SKs, which took greater part (Area%) of the lesion. We analyzed also melanoma (MM)-like SKs and SK-like MMs using the particle analyzing algorithm and the differences of the number of the particles detected and their area % of the lesions were not significantly different between the two groups using Welch's t-test. The percentage of melanomas excluded from the analysis amounted to no more than 5% of the total number of cases. The sensitivity of the SK index was 91.9 % with a specificity of 57.0 %. The positive predictive value proved to be 51.7% while the negative predictive value was

93.3 %. Among the melanoma-like SKs and SK-like melanomas, the sensitivity was 83.3 %, while the specificity was 51.9 %.

Discussion:

MSI allows the examiner to use different wavelength-dependent features and has been previously used to detect melanomas. Nonetheless, these studies mainly focused on how to differentiate melanomas from other skin lesions (Elbaum, Kopf et al. 2001, Tomatis, Carrara et al. 2005, Carrara, Bono et al. 2007, Diebele, Kuzmina et al. 2011, Kuzmina, Diebele et al. 2011, Diebele, Bekina et al. 2012); depth prediction is a field where we lack conclusive research publications (Marchesini, Bono et al. 2007, Diebele, Bekina et al. 2012). To the best of our knowledge, we were the first to analyze melanoma tumor thickness with multispectral imaging to classify melanomas into 3 subgroups of great clinical relevance.

The combination of shape descriptors and intensity values were sensitive and specific approach was enough for the melanoma classification algorithm to sort melanomas into the three categories with a sensitivity of 78.00 %, specificity of 89.00 % with a substantial agreement ($\kappa = 0.67$; 95% CI, 0.58-0.76). Circularity, the sphericity of lesions was the most applicable shape descriptor to classify melanomas into a low- and a high-risk group as the second step. Larger and thicker melanomas were more circular. Roundness showed no significant differences because roundness is less sensitive to variations in perimeter length compared to circularity (Kern, Schlomer et al. 2017). The third step of the analysis relied on to the dermal localization of melanoma cells. These data are in line with our previous findings as shorter wavelengths, like G and R penetrate the dermis only superficially and are absorbed and reflected by tumor chromophores mainly from the surface (Bozsányi, Farkas et al. 2021).

In this study, we also compared the performance of our MSI-based method to human observers. Clinical photographs and dermoscopic images of 100 melanomas were shown to dermatologists and dermatology residents to determine their dexterity to classify the lesion based on tumor thickness. Dermatologists and dermatology residents completed the form with a total sensitivity of 60.38%, of which the dermatologists reached a sensitivity of 62.19%, and the dermatologist residents operated at a sensitivity rate of 58.44%. Specificity reached 80.86%, with 81.09% and 79.76%, for dermatologists and dermatology residents, respectively. The total agreement was found to be moderate ($\kappa = 0.41$; 95% CI, 0.40 to 0.43). Compared to the melanoma classification algorithm, all human investigators achieved a lower sensitivity and

specificity in classifying melanomas into subgroups based on presumed histological tumor thickness. Humans had lower accuracy, and the agreement was higher using the algorithm (κ = 0.67; 95% CI, 0.58-0.76). However, it is important to note that palpation is an important guide to clinicians to supplement their vision when they estimate the tumor thickness during routine examinations, which was not possible in this study. This data was similar to earlier findings in the literature. Dermoscopy was recently described to be able to predict Breslow tumor thickness with a concordance of 0.52, and it could even differentiate between in situ melanomas and tumors thicker than 1 mm (Polesie, Jergéus et al. 2021) whereas we did not examine *in situ* melanomas because of their lack of Breslow thickness value.

This MSI technique and our novel algorithm is a potential modality to aid the clinicians in the evaluation of melanoma depth. It is comparable to other tools such as HFUS which could estimate the appropriate surgical margins of melanomas (1, 2 or 3 cm) in 26 of the 31 subjects (Machet, Belot et al. 2009). Reflectance confocal microscopy proved to be an accurate modality in the presurgical margin mapping of only LMMs (Chen, Elias et al. 2005, Yélamos, Cordova et al. 2017). Although these imaging modalities can be used to estimate Breslow tumor thickness, compared to MSI, their main disadvantage is that they are expensive, and their efficacy depends fundamentally on the examiner's skill and proficiency (Wolner, Yélamos et al. 2017, Levine and Markowitz 2018) (Schneider, Kohli et al. 2019).

In this study our second aim was to compare MMs to SKs with a LED-based modality, using multiple quantitative parameters. In the AF images of SKs, based on the comparison to dermoscopy images, high intensity values were mainly caused by the milia-like cysts and comedo-like openings, which are primarily consist of keratin (Bliznakova, Borisova et al. 2007). However, keratin is not solely responsible for the high intensity values, NADH, FAD, complex structures, lipid particles may also be responsible for higher AF signal (Takahama Jr, Kurachi et al. 2013, Pal, Edward et al. 2017). Compared to SKs, melanoma images had lower AF intensity values, in agreement with the data in the literature (Zonios, Dimou et al. 2008, Borisova, Angelova et al. 2013). The presence of melanin, which has a very specific absorption pattern, could be the explanation for the lower AF signal, (Borisova, Angelova et al. 2013), but the altered collagen structure caused by the tumor growth may also play a part. (Pratavieira, Andrade et al. 2011, Fang, Yuan et al. 2014). Melanin acts as a nonfluorescent pigment under UV and short wavelength visible light; it only bear with fluorescent characteristics under near-infrared light (Huang, Zeng et al. 2006). The latter has been confirmed with our measurements, where melanin appeared as a dark nonfluorescent pigment visualized with AF, G and R

channels without fluorescent emission. Both AF/G and AF/R ratios were significantly higher in SK, which is caused by mainly the high values in the AF channel. The average AF intensity of the SK lesion was significantly higher also compared to melanomas, which was in line with the Min/Max ratios, where the minimum values were significantly higher in SKs.

Our novel SK index could differentiate melanomas from SKs with a sensitivity of 91.9% and specificity of 57.0%. This method may have a great potential to screen melanomas in the everyday practice among general physicians (GPs), as it is capable of the differentiation of melanomas from benign SKs. Nowadays the computer assisted melanoma diagnosis is focusing on the differential diagnosis of melanoma from pigmented lesions, mostly nevi. There are many promising tools and applications, many of them has very high sensitivities and specificities (March, Hand et al. 2015), and they often use artificial intelligence based computer-assisted devices (CAD) to differentiate the lesions.

Conclusion:

It is easy-to-access, relatively cheap and can be used as a mobile-add-on device using the camera of a smartphone. Based on our findings:

1) MSI may be used in clinical practice for the prediction of appropriate safety margins for curative melanoma excisions. MSI is a potential tool to determine the required surgical margin based on the estimated Breslow thickness.

2) Parameter *s'* is a potential first step to differentiate nevi from melanomas to rule them out from the melanoma tumor depth determination

3) We found that melanoma can be differentiated from SK with the use of intensity descriptors and particle analysis.

4) SK index is a potential algorithm to differentiate melanoma from SK, and it is even able to differentiate the melanoma-mimicking MM-like SKs from melanoma and the SK-like MM's from SKs.

5) The collected data may serve as a training pool for machine learning algorithms for further improvements in order to achieve a more accurate estimation of Breslow thickness.

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