INVESTIGATION OF TELEDERMATOLOGY AND MULTISPECTRAL IMAGING AS NOVEL SKIN CANCER SCREENING MODALITIES

PhD thesis

Antal Jobbágy MD

KÁROLY RÁCZ DOCTORAL SCHOOL OF CLINICAL MEDICINE
Semmelweis University

Supervisor: Norbert M. Wikonkál, MD, DSc,
András Bánvölgyi MD, PhD

Official reviewers: Orsolya Németh, MD, PhD,
Nóra Belső, MD, PhD

Head of the Complex Examination Committee:
Ádám Domonkos Tárnoki, MD, PhD

Members of the Complex Examination Committee:
Magdolna Gaál, MD, PhD, András Terebessy, MD, PhD

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1. Introduction

Skin cancer is the most common malignancy worldwide. Furthermore, incidence curves suggest that the incidence will continue to increase. Early detection is pivotal in skin cancer management if we consider high mortality rates and costs of medical treatment. Despite advances in dermoscopic imaging, there is a great need to develop other screening techniques that are easy to use and accessible to other health care professionals. Teledermatology (TD) can be defined as the use of telecommunication technologies to provide medical information and services from a distance in dermatology care. The most widely used form of TD is asynchronous, which is also called as "store-and-forward" modality. Clinical history and digital images of skin lesions are obtained by patients or the requesting clinician and then referred to a dermatologist. Nowadays, high-resolution digital images taken by digital cameras, mobile phones or tablets could ensure simplified use and advanced visualization of the lesions. After the outbreak of the COVID-19 pandemic, the role of telemedicine has undergone explosive growth all around the world in every field of medicine. As for oncodermatology, TD had been already used for skin cancer screening before the pandemic yet it gained unprecedented importance after restrictions were introduced in public health care systems. Multi-modal spectroscopy or multispectral imaging (MSI) is another emerging non-invasive technique that combines spectroscopic and other digital imaging methods. The analysis of reflected light helps to determine the morphological features of different skin lesions.

2. Objectives

2.1. Project I.

The primary outcome measure was to investigate the efficacy of store-and-forward TD system for skin cancer screening during the first wave of the COVID-19 pandemic. We aimed to assess the overall diagnostic agreement of TD care among patients referred for dermoscopic examination. We also evaluated the diagnostic parameters of different malignant and non-malignant lesions and compared them with the result of other studies before the pandemic. Another goal was to investigate the effectiveness of TD as a triage tool to refer patients with potential skin cancer for face-to-face (FTF) examination.

2.2. Project II.

Our objective was to set the most suitable threshold of a light-emitting diode (LED)-based MSI device to optimize the identification of MM from SK and SK-like MM from MM-like SK. Based on the investigation of the lesions' spectral reflectance and autofluorescence properties, an algorithm was created to calculate the SK index. Receiver operating characteristic (ROC) curves were performed to determine the appropriate value of the SK index as a threshold for screening.

3. Methods

3.1. Project I.

3.1.1. Patient data

This retrospective and single-center study focused on patients who submitted their cases via an asynchronous TD system (MedInnoScan, etc.) for consultation between 25 March 2020 and 13 July 2020 at the Department of Dermatology,

Venereology and Dermatooncology, Semmelweis University (Budapest, Hungary). Medical records of TD consultations were reviewed in the local hospital information system (HIS) to obtain information on patients who were invited for a personal examination with a dermoscope. Later, follow-up of patients was performed between 1 March and 30 April 2021 to collect the results of FTF or potential histopathological examinations. Data were collected from the HIS and the National eHealth Infrastructure system of Hungary (EESZT). If no data was found, patients were contacted by phone.

3.1.2. Diagnostic groups

All types of MM were categorized into one diagnostic group. Similarly, all forms of BCC and SCC were divided into two separate groups. Actinic keratoses (AKs) were also listed as malignant lesions, while the diagnostic group called "other malignancies" included skin cancers that could be classified other than the previous ones. As for non-malignant pigmented lesions, dysplastic naevi were represented as a separate group, while all other naevi were grouped together as "naevi". SK's, haemangiomas and warts were also defined as different groups. All additional diagnoses with a lower number of cases were grouped into the "other lesions" group.

3.1.3. Triage groups

All cases were classified into three triage groups by the immediacy of the findings during TD consultations: high-urgency, moderate-urgency and low-urgency group. If more than one lesion was referred to teledermatology consultation by the same patient, these cases received only one triage status. In these cases, the same triage status was assigned to both lesions, equally.

3.1.4. Statistical analyses

Histopathology was the reference standard in case when lesions were excised. Where no histology was performed, the reference meant the result of the FTF examination. In all cases, the outcome of the TD consultation was matched with the result of subsequent FTF or histopathological examinations. Diagnostic parameters such as sensitivity (Sen), specificity (Spe), predictive values and Cohen's kappa coefficient (κ) were assessed for each diagnostic group, separately. Overall diagnostic accuracy and κ value of the system were calculated. Diagnostic agreement of all malignant and non-malignant lesions was also measured, separately. All diagnostic performances were calculated based on primary and aggregated diagnoses, as well. Pearson's chi-square test (two-tailed) was used for categorical variables. The proportion of true positive and false negative diagnoses was compared among different triage groups. The distribution of confirmed malignancies and non-malignant lesions was also compared among various triage groups.

3.1.5. Inclusion Criteria

All patients whose photographs were deemed of sufficient quality by teledermatologists and later attended personal examination with dermoscopy. The availability of at least results from the FTF examination was an additional criterion in case of confirmed benign lesions. Diagnostic verification of MMs, BCCs, SCCs and other malignancies was established by histological examination.

3.1.6. Exclusion Criteria

If teledermatologists could not determine the diagnosis due to lack of adequate photographs or absence of medical history.

Patients were also excluded from the study if no follow-up information could be obtained.

3.2. Project II.

3.2.1. Patient data

MSI measurements were carried out at the Department of Dermatology, Venereology and Dermatooncology, Semmelweis University (Budapest, Hungary) and at the Oncology Centre of Latvia (Riga, Latvia). Patients with lesions such as MM, SK, SK-like MM and MM-like SK were involved in the study. In many cases, more than one image sets were taken because of the lesions' number and size.

3.2.2. LED-based multispectral imaging device

The handheld MSI device employed an illumination source of four types of LEDs with wavelengths of 405 nm to induce skin autofluorescence (AF), 525 nm green (G), 660 nm red (R) and 940 nm infrared for diffuse reflectance imaging. The lights penetrate different layers of the skin with irradiating power density of 20 mW/cm2. Images were collected with a color CMOS 5 megapixel IDS camera and were automatically transferred to a cloud server.

3.2.3. Intensity and Particle Analysis

Quantitative parameters of intensity such as minimum and maximum, mean intensity and standard deviation (SD) were analyzed in different channels (AF, G, R) to investigate spectral reflectance and autofluorescence properties of the lesions. Images were analyzed with the use of ImageJ v1.46 software (NIH, Bethesda, MD, USA). Regions of interest (ROI) were selected manually for intensity analysis. The ratio of the pixels with the lowest and highest intensity values (Min/Max) of all

lesions were also measured within the AF channel. AF images were converted into 8-bit form to analyze the fluorescence values of particles. After that automated thresholding process of the ImageJ software was used. Subsequently, the number and size of the particles were determined between the range of 10 and 100.000 pixels. Circularity was set between 0.4 and 1.0, while the edges were excluded. If more than one SK was in one field of view or hair affected the measurement, ROI was selected manually to specify the lesion for particle analysis. The area percentage (%) was calculated from the ratio of the area of the particles with fluorescence values above the threshold and the area of the lesion. Quantitative parameters and particle analysis results were combined to calculate the SK index of each lesion:

$$\text{SK index} = \frac{2 \cdot \text{AF} \cdot \text{SD} \cdot \left(\frac{\text{Min}}{\text{Max}}\right)}{\text{G} \cdot \text{R}} + \left(\text{Particle number} \cdot \text{Area \%}\right)$$

3.2.4 Statistical analysis

Rare forms with morphological overlaps of both MM (SK-like MM) and SK (MM-like SK) were separated from typical forms of the lesions. SK index value of all lesions was calculated, then logarithmic transformation was performed. Welch's t-test was used to compare the SK index value of MMs with SKs and SK-like MMs with MM-like SKs. Receiver operating characteristic (ROC) curves were used based on the SK index values to count the area under the curves (AUC) and characterize the diagnostic performance of the LED-based MSI device. Finally, sensitivity and specificity pairs of different cut-off points were spotted to determine the equivalent threshold.

3.2.5. Inclusion criteria

Lesions on body parts accessible to the MSI device were involved in the study. Only histologically confirmed MMs were included, while all SKs had to be verified by clinical and dermoscopic examinations by a board-certified dermatologist.

3.2.6. Exclusion criteria

MM were excluded without histological validation. All ulcerated lesions were also excluded from the study.

4. Results

4.1. Project I.

4.1.1. Inclusion and patient data

749 patients with 779 lesions were included our study. The mean age of the included patients was 43.54 ± 21.03 years. The median number of lesions per patient was one (interquartile range: 1–2). 45 patients (6%) had skin cancer in their personal history, 18 patients (2.4%) had it in their family history, while two patients (0.3%) had it in both. The remaining 684 patients (91.3%) had no skin cancer in their medical history. During TD consultation sessions, 639 (82%), 132 (17%) and eight lesions (1%) received a single, two and three diagnoses, respectively.

4.1.2. Triage groups

206 lesions (26.5%) were triaged as high-urgency, 227 lesions (29.1%) as moderate-urgency, and 346 lesions (44.4%) as low-urgency by teledermatologists, respectively. 156 lesions (75.7%) were diagnosed correctly in the high-urgency group, 195 (85.9%) lesions in the moderate-urgency group and 334

lesions (96.5%) in the low-urgency group, respectively. Considering misdiagnosed cases, 50 lesions (24.3%) were categorized in the high-urgency group, 32 lesions (14.1%) in the moderate-urgency group and 12 (3.5%) lesions in the low-urgency group, respectively ($p < 0.0001$). After the follow-up, 87 malignancies (42.2%) and 119 benign lesions (57.7%) were confirmed in the high-urgency group, 49 malignant (21.6%) and 178 benign lesions (78.4%) in the moderate-urgency group, while 16 malignant (4.6%) and 330 benign lesions (95.4%) in the low-urgency group, respectively ($p < 0.0001$).

4.1.3. Overall primary and aggregated diagnostic agreement

Primary diagnosis of 633 lesions during TD consultations matched with the reference standard, while 146 lesions were misdiagnosed. When all differential diagnoses were included, 685 lesions matched with the reference standard, while 94 lesions failed to do so. In total, significant difference was assessed between overall aggregated and primary diagnostic accuracy ($p <0.0001$).

-Primary diagnostic (PD) parameters of malignant lesions: κ= 0.647, accuracy= 86.3%; Aggregated diagnostic (AD) parameters of malignant lesions: κ= 0.644, accuracy= 85.3%

-Primary diagnostic (PD) parameters of non-malignant lesions: κ= 0.811, accuracy= 81.3%; Aggregated diagnostic (AD) parameters of non-malignant lesions: κ= 0.790, accuracy= 86.5%

-Primary diagnostic (PD) parameters of all lesions: κ= 0.769, accuracy= 81.2%; Aggregated diagnostic (AD) parameters of all lesions: κ= 0.754, accuracy= 87.9%

4.1.4. Diagnostic parameters of malignant diagnostic groups

According to the primary diagnoses, the possibility of malignancy was raised in 198 lesions, while it increased to 228 lesions by involving another differential (aggregated) diagnoses during TD consultations. Later, 152 patients (female-male ratio: 48.7%-51.3%; mean age: 62.26 years ± 16.13) were diagnosed with malignancy. Histological examination confirmed the diagnosis of MM in 15 cases, BCC in 78 cases, SCC in 21 cases, other malignancies in seven cases and AK in three cases. In case of the other 28 AKs, result of the FTF examination was considered the reference standard. In the other malignancies group, all diagnoses were confirmed by histological examination: primary cutaneous follicle center lymphoma (3 lesions), invasive mammary carcinoma, dermatofibrosarcoma protuberans, metastasis of Merkel cell carcinoma, metastasis of adenocarcinoma.

-Primary diagnostic (PD) parameters of MM: κ= 0.410, Sen= 66.7%, Spe= 97.1%, Positive predictive value (PPV)= 31.3%, Negative predictive value (NPV)= 99.3%; Aggregated diagnostic (AD) parameters of MM: κ=0.476, Sen= 93.3%, Spe= 96.3%, PPV= 33.3%, NPV= 99.9%

-PD parameters of SCC: κ= 0.437, Sen= 61.9%, Spe= 97.0%, PPV= 36.1%, NPV= 98.9%; AD parameters of SCC: κ= 0.560, Sen= 90.5%, Spe= 96.6%, PPV= 42.2%, NPV= 99.7%

-PD parameters of BCC: κ= 0.770, Sen= 89.7%, Spe= 96.0%, PPV= 71.4%, NPV= 98.8%; AD parameters of BCC: κ= 0.714, Sen= 91,00%, Spe= 94.2%, PPV= 63,4%, NPV= 99,00%

-PD parameters of other malignancies: κ= 0.663, Sen= 71.4%, Spe= 99.6%, PPV= 62.5%, NPV= 99.7%; AD parameters of other malignancies: κ= 0.663, Sen= 71.4%, Spe= 99.6%, PPV= 62.5%, NPV= 99.7%

-PD parameters of actinic keratosis: κ= 0.704, Sen= 64.5%, Spe= 99.3%, PPV= 80.0%, NPV= 98.5%; AD parameters of actinic keratosis: κ= 0.739, Sen= 77.4%, Spe= 98.8%, PPV= 72.7%, NPV= 99.1%

4.1.5. Diagnostic parameters of non-malignant diagnostic groups

The result of the FTF examination was the gold standard in 481 cases, while histological evaluation confirmed the diagnosis in the remaining 146 cases of non-malignant lesions.

-PD parameters of dysplastic naevi: κ= 0.437, Sen= 80.0%, Spe= 96.6%, PPV= 31.6%, NPV= 99.6%; AD parameters of dysplastic naevi; κ= 0.375, Sen= 80.0%, Spe= 95.50%, PPV= 26.10%, NPV= 99.6%

-PD parameters of naevi: κ= 0.848, Sen= 87.0%, Spe= 96.6%, PPV= 93.6%, NPV= 92.8%; AD parameters of naevi: κ= 0.848, Sen= 91.2%, Spe= 93.9%, PPV= 89.7%, NPV= 94.9%

-PD parameters of SK: κ= 0.810, Sen= 78.3%, Spe= 98.3%, PPV= 91.10%, NPV= 95.30%; AD parameters of SK: κ= 0.780, Sen= 85.3%, Spe= 95.0%, PPV= 79.2%, NPV= 96.6%

-PD parameters of haemangiomas: κ= 0.944, Sen= 92.9%, Spe= 99.7%, PPV= 97.0%, NPV= 99.3%; AD parameters of haemangiomas: κ= 0.961, Sen= 95.7%, Spe= 99.7%, PPV= 97.1%, NPV= 99.6%

-PD parameters of warts: κ= 0.880, Sen= 78.9%, Spe= 100%, PPV= 100%, NPV= 99.5%; AD parameters of warts: κ= 0.943, Sen= 89.5%, Spe= 100%, PPV= 100%, NPV= 99.7%

-PD parameters of other lesions: κ= 0.731, Sen= 66.3%, Spe= 98.7%, PPV= 87.5%, NPV= 95.5%; AD parameters of other lesions: κ= 0.676, Sen= 77.9%, Spe= 94.6%, PPV= 66.7%, NPV= 96.9%

4.2. Project II.

4.2.1. Patient data

A total of 266 patients were included in our study. The diagnosis of MM was proven in 127 cases (161 image sets). 66 out of all were diagnosed with superficial spreading melanoma (52 %), 18 with nodular melanoma (14.1%), 21 with in situ melanoma (16.5%), 3 with acral lentiginous melanoma (2.3%), 1 with lentigo maligna melanoma (1%), while 18 remained unclassified (14.1%). Six patients had SK-like MM (6 image sets). The mean age of patients with melanoma was 64.09 ±13.55 years (female-male ratio: 45.6%-54.3%). 139 patients (319 lesions with 319 image sets) were involved in the study with the diagnosis of SK. 30 patients had MM-like SK (52 image sets). The mean age of patients with SK was 70.19 ±11.147 years (female-male ratio: 44.6%-55.4%).

4.2.2. Threshold optimization

Based on logarithmic transformation of the data, SK index values of SKs (Means ± SD:1.565 ± 0.729) were proved to be significantly higher (p<0.0001) compared to MM (Means ± SD: 0.649 ± 0.528). There was no significant difference (p= 0.06) between MM-like SK (Means ± SD: 1.607 ± 0.884) and SK-like MM (Means ± SD: 0.745 ± 0.747). Threshold determination was based on the results of ROC analyses. The Area Under the Curve (AUC) was 0.844 (95% CI: 0.8085 – 0.8811, p < 0.0001) on the MM and SK ROC curve. AUC was 0.826 (95% CI: 0.5681 – 1.000, p = 0.0092) on ROC curve of the MM-like SK and SK-like MM comparison. The selection method of the equivalent threshold was chosen to provide appropriate diagnostic parameters for the differentiation of both MM from SK and SK-like MM from MM-like SK. Consequently, the 30 value of SK index proved to be the most optimal threshold. To differentiate MM from SK, sensitivity reached 91.88% (95% CI: 86.60% - 95.19%), while specificity was 57.05% (95% CI: 51.57% - 62.37%). PPV reached 51.76% (95% CI: 45.96% - 57.51%), NPV was 93.33% (95% CI: 88.93% - 96.06%). The 30 threshold was also suitable with a sensitivity of 83.3% (95% CI:43,65% - 99,15%) and specificity of 51.9% (38,69% - 64,90%) to identify MM-like SK from SK-like MM. The PPV reached 16.67% (95% CI: 7.34% - 33.56%), while NPV was 96.43% (95% CI: 82.29% to 99.82%).

5. Conclusion

Project I.

During the first wave of the COVID-19 pandemic, a mobile phone-based store-and-forward teledermatology system was set up at the Department of Dermatology, Venereology and Dermatooncology of Semmelweis University in Budapest,

Hungary. Based on our findings the following statements can be said:

1. Teledermatology serves as an effective triage tool to refer patients with skin cancer for personal examination when outpatient care is restricted for any reason.
2. Teledermatology can ensure effective detection of MM in real crisis situations when macroscopic images are not taken by health care professionals.
3. Teledermatology enables reliable BCC and SCC screening, when access to personal visits is limited.
4. Teledermatology may be considered as an appropriate alternative of personal examination to detect benign skin lesions, such as SKs, haemangiomas and warts.

Project II.

The handheld LED-based MSI device has the potential to serve as an accurate screening tool. We have come to a conclusion:

1. Determination of the appropriate threshold of the SK index algorithm is needed to optimize the differentiation of both MM from SK and SK-like MM from MM-like SK.

6. Bibliography of the candidate's publications

Publications directly related to this thesis

1. Jobbágy A, Kiss N, Meznerics F A, Farkas K, Plázár D, Bozsányi S, Fésűs L, Bartha Á, Szabó E, Lőrincz K, Sárdy M, Wikonkál NM, Szoldán P, Bánvölgyi A. (2022) Emergency Use and Efficacy of an Asynchronous Teledermatology System as a Novel Tool for Early Diagnosis of Skin Cancer during the First Wave of COVID-19 Pandemic. *Int J Environ Res Public Health*, 19(5):2699. **IF: 3.390**

2. Bozsányi S, Farkas K, Bánvölgyi A, Lőrincz K, Fésűs L, Anker P, Zakariás S, **Jobbágy A**, Lihacova I, Lihachev A, Lange M, Bliznuks D, Medvecz M, Kiss N, Wikonkál NM. (2021) Quantitative Multispectral Imaging Differentiates Melanoma from Seborrheic Keratosis. *Diagnostics*, 11(8):1315. **IF: 3.706**

3. Jobbágy A, Meznerics F A, Farkas K, Plázár D, Bozsányi Sz, Fésűs L, Róbert L, Schveibert Á, Kuzmanovszki D, Szoldán P, Lőrincz K, Kiss N, Wikonkál N, Sárdy M, Bánvölgyi A. (2022) Teledermatology: the new era of digitalization in dermatology care. *Bőrgyógyászati és Venerológiai Szemle,* 98(3):100-107. **IF: -**

Publications not related to this thesis

1. Polak K, **Jobbágy A**, Muszyński T, Wojciechowska K, Frątczak A, Bánvölgyi A, Bergler-Czop B, Kiss N. (2021) Microbiome Modulation as a Therapeutic Approach in Chronic Skin Diseases. *Biomedicines*, 9(10):1436. **IF: 6.081**

2. Lőrincz K, Meznerics F A, **Jobbágy A**, Kiss N, Madarász M, Belvon L, Tóth B, Tamási B, Wikonkál N M, Marschalkó M, Bánvölgyi A. (2022) STIs during the COVID-19 Pandemic in Hungary: Gonorrhea as a Potential Indicator of Sexual Behavior. *Int J Environ Res Public Health*, 19(15):9627. **IF: 4.614**

3. Virág D, Kremmer T, Lőrincz K, Kiss N, **Jobbágy A**, Bozsányi S, Gulyás L, Wikonkál N, Schlosser G, Borbély A, Huba Z, Dalmadi Kiss B, Antal I, Ludányi K. (2021) Altered Glycosylation of Human Alpha-1-Acid Glycoprotein as a Biomarker for Malignant Melanoma. *Molecules*, 26(19):6003. **IF: 4.412**

4. Bozsányi S, Varga NN, Farkas K, Bánvölgyi A, Lőrincz K, Lihacova I, Lihachev A, Plorina EV, Bartha Á, **Jobbágy A**, Kuroli E, Paragh G, Holló P, Medvecz M, Kiss N, Wikonkál NM. (2021) Multispectral Imaging Algorithm Predicts Breslow Thickness of Melanoma. *J Clin Med*, 11(1):189. **IF: 4.242**

5. Fésűs L, **Jobbágy A**, Kiss N, Horváth E, Avci P, Lukács A, Mayer K, Bergler-Czop B, Wikonkál N, Bánvölgyi A. (2021) Dermatologic aspects of bed bug epidemic: an atlas of differential diagnosis. *Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii*, 38:184-192. **IF: 1.837**

6. Jobbágy A, Fésűs L, Kiss N, Lőrincz K, Sárdy M, Wikonkál N, Bánvölgyi A. (2020) Hyperhidrosis: clinical classification and treatment options. *Bőrgyógyászati és Venerológiai Szemle*, 96(1):36-43. **IF: -**

7. Fésűs L, Kiss N, **Jobbágy A**, Farkas K, Meznerics F, Bozsányi Sz, Bánvölgyi A, Wikonkál N, Lőrincz K. (2022) Innovative in vivo imaging techniques in dermatology. *Bőrgyógyászati és Venerológiai Szemle,* 98(3):133-141. **IF: -**

8. Szalai K, Farkas K, Gergely H, Varga N N, Magyar M, Nagy Z Zs, Fésűs L, Bozsányi Sz, **Jobbágy A**, Medvecz M, Bánvölgyi A, Lőrincz K, Wikonkál N, Kiss N. (2022) Clinical application of high-frequency ultrasound, optical coherence tomography and magnetic resonance imaging in dermatology, Bőrgyógyászati és Venerológiai Szemle, 98(3):125-132. **IF: -**