INNOVATIVE MULTIMODAL IMAGING TECHNIQUES IN DERMATOLOGY

Ph.D. Thesis Booklet

Noémi Nóra Varga M.D.

Translational Medicine Program

Károly Rácz Conservative Medicine Doctoral School

SEMMELWEIS UNIVERSITY

Supervisors: Norbert Kiss, M.D., Ph.D.
Márta Medvecz, M.D., Ph.D.

Official reviewers: Prof. Lajos Kemény, M.D., Ph.D., D.Sc.
Roxana-Ioana Nedelcu, M.D., Ph.D.

Head of the Complex Examination Committee: Andrea Harnos, M.D., Ph.D.

Members of the Complex Examination Committee:
Prof. Alan Irvine, M.D., Ph.D., D.Sc.
Prof. Szekanecz Zoltán, M.D., Ph.D., D.Sc.

Budapest

2025

1. Introduction

1.1. What is the topic?

The focus of my research is to investigate the diagnostic performance of emerging non-invasive optical imaging techniques for melanoma diagnosis, with a particular focus on preoperative Breslow thickness assessment, to identify clinically useful tools that could enhance future screening protocols.

1.2. What is the problem to solve?

The issue lies in the lack of accurate and objective non-invasive imaging tools in melanoma diagnostics. If new imaging modalities addressing this gap were implemented in clinical practice, they could improve diagnostic accuracy, reduce interobserver variability, and support earlier and more precise clinical decision-making.

1.3. What is the importance of the topic?

The significance of this topic cannot be overstated, as melanoma remains a growing public health concern, with an estimated 325,000 new cases and nearly 57,000 deaths globally in 2020, and projections to 510,000 new cases and 96,000 deaths by 2040. Early-stage detection is highly effective, yielding five-year survival rates above 95%, but this drops sharply to 20–40% when distant metastases are present, emphasizing the importance of timely diagnosis and intervention.

1.4. What would be the impact of our research results?

Our outcomes have a significant impact on dermatological practice by improving the early and accurate diagnosis of melanoma through the clinical implementation of novel, objective, and non-invasive imaging tools. Our findings support the development of more precise, reproducible, and accessible diagnostic pathways. This could reduce diagnostic delays, guide surgical planning, and ultimately improve patient outcomes and survival. Furthermore, the introduction of these methods may lower healthcare costs by minimizing unnecessary excisions and optimizing resource allocation in melanoma care.

2. Objectives

2.1. Study I. – Comparing the efficacy of OG-HFUS and MSI in preoperative estimation of Breslow thickness

The aim of this study was to compare the diagnostic accuracy of optically guided high-frequency ultrasound (OG-HFUS) and multispectral imaging (MSI) for preoperative estimation of Breslow tumor thickness in primary melanoma. In a prospective clinical study, we applied each modality to a cohort of 101 melanoma patients and compared their Breslow thickness estimates against the gold-standard histology to determine which imaging method provides greater accuracy for preoperative decision-making in melanoma care.

2.2. Study II. – Comparing the diagnostic accuracy of novel non-invasive optical imaging techniques for melanoma diagnosis

The objective of this study was to perform a comprehensive systematic review and meta-analysis evaluating the diagnostic performance of all optical imaging methods for melanoma detection. Although numerous new imaging modalities have been introduced in dermatology in recent years, the performance of these technologies has not yet been compared. This meta-analysis aimed to clarify and compare the diagnostic accuracy of each optical imaging technique and provide evidence-based insights to guide clinical decision-making and future research priorities in melanoma diagnostics.

3. Methods

3.1. Study I.

This single-center, prospective validation study was conducted at the Department of Dermatology, Venereology, and Dermatooncology, Semmelweis University, and included 101 consecutive adult patients (≥18 years) with suspected primary cutaneous melanoma scheduled for excision. Preoperative imaging was performed using two handheld devices – MSI and OG-HFUS - by trained operators blinded to histopathology. Patients whose lesions were histologically confirmed as primary cutaneous melanoma with Breslow thickness <10 mm were included; exclusions were in situ or metastatic melanomas, difficult anatomical locations (e.g., acral, genital, mucosal), or lesions with extensive hair, bleeding, or scaling impeding imaging. OG-HFUS scans were performed with the Dermus SkinScanner device (33 MHz single-element transducer; max penetration depth 10 mm), acquiring optical and ultrasound images for thickness estimation. MSI was performed using a prototype device (University of Latvia/Riga Technical University) with LEDs at 405, 525, 660, and 940 nm; images were analyzed quantitatively (green, red, infrared channels) for intensity and shape descriptors using ImageJ software. A previously developed MSI-based algorithm classified melanomas into Breslow categories (<1 mm, 1–2 mm, >2 mm) based on circularity and intensity thresholds. Histologically determined Breslow thickness served as the reference standard. Statistical analysis included Pearson's correlation for agreement, multivariate linear regression for MSI thickness estimation, and calculation of sensitivity, specificity, positive/negative predictive values (PPV/NPV), mean squared error (MSE), and Cohen's kappa (κ) for concordance. Significance was set at $p<0.05$. Analyses were performed using Python (scikit-learn, scipy, statsmodels).

3.2. Study II.

We conducted a systematic review and meta-analysis following the Cochrane Handbook and PRISMA 2020 guidelines, with a protocol registered in PROSPERO (CRD42023480274). The search was performed across MEDLINE (via PubMed), CENTRAL, and Embase up to November 15, 2023, using predefined search terms. Eligible studies followed the PIRD framework: patients suspected of melanoma (P), examined with non-invasive optical methods (I), compared to histopathology (R), and diagnosed with melanoma (D). Inclusion required peer-reviewed studies reporting diagnostic accuracy data. Exclusions were case reports, reviews, meta-analyses, letters, studies with <5 melanoma cases, or insufficient data for analysis. Two reviewers independently screened records and extracted data; disagreements were resolved by a third reviewer. Data extraction included study characteristics, patient demographics, lesion counts, imaging modalities, diagnostic outcomes (sensitivity, specificity, predictive values, diagnostic accuracy, and area under the curve), and contingency table data where available. Risk of bias was assessed using the QUADAS-2 tool; publication bias was examined by funnel plots. Certainty of evidence was graded using the GRADE approach with GRADEpro software. For statistical synthesis, we applied the bivariate model of Chu and Reitsma to estimate pooled sensitivity and specificity, accounting for their potential correlation. We visualized summary estimates with 95% confidence and prediction intervals and weighted ellipsoids (Burke method). PPV and NPV were calculated assuming a melanoma prevalence of 30%, the average across studies. We calculated diagnostic odds ratios (DORs) with 95% confidence intervals as a summary indicator of test performance. Heterogeneity was assessed using I^2 statistics. Statistical analyses were performed in R (v4.1.2) with the meta and lme4 packages, incorporating methods from Freeman et al. and guidance from Harrer et al.

4. Results

4.1. Study I.

A total of 101 patients with primary cutaneous melanoma were enrolled (mean age: 64.2 ± 15.2 years; 53 males, 48 females). Lesions were located mostly on the trunk (60%), extremities (32%), with others on the cheek, forehead, and neck. The average histologic Breslow thickness was 1.61 ± 1.69 mm (range 0.135–8.12 mm). Superficial spreading melanoma was the predominant subtype (68.3%), followed by nodular melanoma (7.9%) and other subtypes. OG-HFUS demonstrated almost perfect agreement with histologic Breslow thickness ($\kappa = 0.858$ [0.763–0.952]; $r = 0.943$, $p < 0.0001$), with highest accuracy in the <1 mm subgroup ($\kappa = 0.937$ [0.867–1.000]) and lower accuracy in the 1–2 mm subgroup ($\kappa = 0.701$ [0.503–0.900]). Overall sensitivity and specificity were 91.8% and 96.0%, respectively. In contrast, MSI performance was modest, with fair agreement overall ($\kappa = 0.440$ [0.298–0.583]) and weaker correlation with histologic thickness ($r = 0.714$, $p < 0.0001$). The infrared channel alone showed the strongest individual correlation ($r = –0.659$, $p < 0.0001$). MSI achieved its best accuracy in the >2 mm subgroup ($\kappa = 0.680$ [0.517–0.842]), and its poorest accuracy in the 1–2 mm subgroup ($\kappa = 0.177$ [–0.052–0.406]). Overall sensitivity and specificity were 62.6% and 81.3%. Comparatively, OG-HFUS consistently outperformed MSI across all Breslow categories, with higher sensitivity, specificity, predictive values, and lower MSE.

4.2. Study II.

We initially identified 16,239 records through database searching, of which 136 studies were found eligible. Additionally, via citation searching, we found 5 more eligible studies. Overall, 141 articles were included in the qualitative analysis (systematic review), of which 138 studies were included in the quantitative synthesis (meta-analysis). The studies spanned 1989–2022 and were predominantly prospective single- or multicenter diagnostic accuracy studies from various countries. Dermoscopy combined with artificial intelligence (DSC+AI) and reflectance confocal microscopy (RCM) showed the highest sensitivities (both 0.93), with DSC+AI slightly outperforming RCM in specificity (0.77 vs 0.75). Multispectral imaging combined with artificial intelligence also performed well (sensitivity 0.92, specificity 0.80). Dermoscopy (DSC) and teledermoscopy exhibited moderate accuracy (sensitivities 0.87 and 0.84; specificities 0.82 and 0.85, respectively), while MSI had lower specificity (0.64) but good sensitivity (0.87). Dermatofluoroscopy achieved high sensitivity (0.91) but the lowest specificity (0.55). Optical coherence tomography demonstrated strong diagnostic performance overall (sensitivity 0.84, specificity 0.85, DOR 64.25). The qualitative synthesis included near-infrared and skin impedance spectroscopy (sensitivity 0.83, specificity 0.95), multimodal spectral diagnosis (sensitivity and specificity 1.00), and multiphoton microscopy (sensitivity 0.75, specificity 0.80). GRADE assessment indicated high to moderate certainty of evidence for most sensitivity estimates but lower certainty for specificity in several modalities.

5. Conclusions

1) Using shape descriptors and spectral intensity features, we developed a novel MSI-based melanoma classification algorithm.

2) We were the first to employ MSI for melanoma thickness assessment and to classify melanomas into clinically relevant subgroups.

3) In our comparative analysis, OG-HFUS significantly outperformed MSI in the preoperative estimation of Breslow thickness. OG-HFUS yielded lower MSE and higher sensitivity, specificity, PPV, NPV, and Cohen's kappa compared to MSI.

4) OG-HFUS maintained particularly strong accuracy in the Breslow <1 mm subgroup and was least precise in the Breslow between 1–2 mm category.

5) The benefits of MSI and OG-HFUS are that they are handheld, user-friendly, and cost-effective tools for non-invasively estimating Breslow depth, and the measurements can be completed within minutes.

6) Accurate preoperative prediction of Breslow thickness defines the required surgical safety margin, determines the need for concurrent sentinel lymph node biopsy and the selection of further imaging studies to expedite treatment.

7) To the best of our knowledge, our systematic review and meta-analysis was the first to provide a comprehensive analysis of all non-invasive optical imaging techniques for melanoma diagnosis.

8) RCM and DSC+AI achieved the highest sensitivity and the highest level of evidence for sensitivity, indicating their consistency as diagnostic tools. They also demonstrated the highest NPV values, indicating that these modalities became the most effective in excluding melanoma.

9) The reliability and wide availability of DSC still make it the leading optical method for melanoma screening.

10) RCM and DSC+AI may both be utilized as second-step evaluation methods of pigmented lesions initially suspicious under DSC.

11) Incorporating multimodal imaging techniques after initial DSC screening could potentially maximize diagnostic accuracy.

12) This could mean that the introduction of more precise and reliable techniques as second-step evaluation methods can lead to earlier detection of melanoma, accelerate therapy, and improve the survival rates of melanoma patients.

6. Bibliography

6.1. Publications related to the thesis

1. **Varga, N.N.**†; Boostani, M.†; Farkas, K.; Bánvölgyi, A.; Lőrincz, K.; Posta, M.; Lihacova, I.; Lihachev, A.; Medvecz, M.; Holló, P.; Paragh, Gy.; Wikonkál, N. M.; Bozsányi, S.; & Kiss, N.
Optically Guided High-Frequency Ultrasound Shows Superior Efficacy for Preoperative Estimation of Breslow Thickness in Comparison with Multispectral Imaging: A Single-Center Prospective Validation Study
CANCERS
2024; 16(1), 157. https://doi.org/10.3390/cancers16010157
Q1, IF: 4.4 (2024)

2. **Varga, N.N.**; Gulyás, L.; Meznerics, F.A.; Barkovskij-Jakobsen, K.S.; Szabó, B.; Hegyi, P.; Bánvölgyi, A.; Medvecz, M.; & Kiss, N.
Diagnostic Accuracy of Novel Optical Imaging Techniques for Melanoma Detection: A Systematic Review and Meta-Analysis
INTERNATIONAL JOURNAL OF DERMATOLOGY
(0011-9059 1365-4632): 2025.
Advance online publication. https://doi.org/10.1111/ijd.17828
Q1, IF: 3.2 (2025)