

Methods for Early Diagnosis and Preventive Treatment of Skin Cancers - Hyperspectral Imaging and Laser-Mediated Photodynamic Therapy

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Vivian Lindholm, MD, PhD, conducted her PhD studies at the Department of Dermatology and Allergology, Helsinki University Hospital and University of Helsinki, Finland, during the period 2018–2024. Associate Professor Sari Pitkänen was her main supervisor and MD, PhD Kirsi Isoherranen her co-supervisor. The opponent was professor Emerita Erna Snellman from Tampere University, Finland.

Skin cancer is the most common cancer worldwide. As its incidence continues to rise, preventive efforts are essential to reduce its burden on patients and healthcare systems. Early detection and preventive treatment for at-risk individuals can help alleviate this burden. Several imaging methods for direct skin cancer diagnosis are under development, with some already in clinical use; however, most require expertise in image analysis.

In terms of preventive treatment, conventional photodynamic therapy (PDT) is an effective field treatment for precancerous lesions such as actinic keratoses (AKs) and broader field cancerisation. However, its use is often limited by treatment-related pain. Daylight PDT (dPDT), which uses sunlight, is nearly pain-free but less effective for treating thicker, grade III AKs. Moreover, natural dPDT is not feasible in temperatures below 10°C, prompting the development of indoor artificial dPDT.

This dissertation investigates the feasibility of non-invasive 3D hyperspectral imaging (HSI) combined with automated analysis via convolutional neural networks (CNNs) to differentiate visually similar malignant and benign skin lesions (Studies I–II). Additionally, it evaluates the tolerability and six-month outcomes of two novel laser-mediated PDT methods for treating AKs or field cancerisation (Studies III–IV).

In the pilot studies (I–II), the diagnostic accuracy of HSI-CNN was assessed in differentiating cutaneous melanomas (CM) from benign pigmented nevi (PN), keratinocyte cancers (KCs) from benign intradermal nevi (ID), and premalignant Bowen's disease (BD) from benign seborrheic keratoses (SK), with a total of 172 lesions analyzed.

In Study III, outcomes and tolerability of pulsed dye laser (PDL)–mediated PDT were compared with conventional PDT (cPDT). Study IV compared ablative fractional laser (AFXL)–mediated dPDT (natural or artificial) to dPDT alone for treating AKs on the head. Both studies were intra-individual, half-side, randomized, controlled, and blinded trials involving 115 patients in total.

The HSI-CNN method achieved high diagnostic performance: CM vs. PN with 95% sensitivity and 97% specificity; KC vs. ID with 85–100% sensitivity and 92–100% specificity; and BD vs. SK with 84% sensitivity and 94% specificity. In addition to majority-vote lesion classification, pixel-wise analysis provided lesion maps for visual interpretation.

In Study III, PDL-PDT was significantly less effective than cPDT (48% vs. 73% lesion clearance; $p < 0.01$), though less painful ($p < 0.01$). In Study IV, AFXL-dPDT was more effective than dPDT alone (86% vs. 70% clearance; $p < 0.01$), with short-term but tolerable

pain. Thick AKs (grades II–III) cleared as effectively as thin (grade I) lesions ($p = 0.84$), and artificial daylight was as effective as natural daylight for illumination ($p > 0.09$). AFXL-dPDT achieved comparable or better results than cPDT ($p = 0.58$ for complete clearance; $p = 0.04$ for partial clearance).

This proof-of-concept HSI-CNN demonstrates high accuracy in distinguishing malignant from benign melanocytic and keratinocytic tumors. It shows promise for immediate, non-invasive, and operator-independent skin cancer detection, supporting both specialists in ambiguous cases and general practitioners without specialized training. Further validation with larger, more diverse datasets is required.

AFXL-dPDT appears to be an effective, well-tolerated, and weather-independent single-visit treatment option for AKs of all grades, potentially outperforming cPDT. It may be particularly beneficial for patients with extensive or severe photodamage. Adjusted parameters in PDL-PDT could offer an alternative for patients with low pain tolerance. Further studies are needed to optimize laser settings and enhance outcomes and tolerability.



Professor Emerita Erna Snellman (left), Professor Sirkku Peltonen, MD, Vivian Lindholm, Associate Professor Sari Pitkänen, and MD, PhD, Kirsi Isoherranen.

List of original publications

I Lindholm V*, Raita-Hakola AM*, Annala L, Salmivuori M, Jeskanen L, Saari H, Koskenmies S, Pitkänen S, Pölönen I, Isoherranen K*, Ranki A*. Differentiating Malignant from Benign Pigmented or Non-Pigmented Skin Tumours - A Pilot Study on 3D Hyperspectral Imaging of Complex Skin Surfaces and Convolutional Neural Networks. *J Clin Med* 2022; 30; 11: 1914.

II Lindholm V*, Annala L*, Koskenmies S, Pitkänen S, Isoherranen K, Järvinen A, Jeskanen L, Pölönen I[✉], Ranki A[✉], Raita-Hakola A-M[✉], Salmivuori M[✉]. Discriminating Basal Cell Carcinoma and Bowen's Disease from Benign Skin Lesions with a 3D Hyperspectral Imaging System and Convolutional Neural Networks. *Skin Res Technol* 2024;30:e13677.

III Lindholm V, Pitkänen S, Schröder M, Hahtola S, Sahi H, Halme H, Isoherranen K. Pulsed Dye Laser-mediated Photodynamic Therapy is Less Effective than Conventional Photodynamic Therapy for Actinic Field Cancerization: A Randomized Half-side Comparative Study. *Acta Derm Venereol* 2021; 10: adv00404.

IV Lindholm V, Salmivuori M, Hahtola S, Mäkelä K, Pitkänen S[✉], Isoherranen K[✉]. Ablative Fractional Laser Enhances Artificial or Natural Daylight Photodynamic Therapy of Actinic Field Cancerization: A Randomized and Investigator-initiated Half-side Comparative Study. *Acta Derm Venereol* 2023; 103: adv6579.

* Shared first authorship between authors of different professions in a multidisciplinary cooperation [✉] Equal contribution

Link to complete thesis: <https://helda.helsinki.fi/items/68e4a4bb-ba20-414f-8bb4-96a88deca7c6>