Novel Methods for the Treatment and Diagnosis of Skin Cancers and their Precursors

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Actinic keratosis (AK) is a common premalignant skin lesion carrying a risk of progression into invasive cutaneous squamous cell carcinoma (cSCC). Many international guidelines recommend field-directed therapy for multiple AKs and for field-cancerized skin.

Lentigo maligna (LM) is an *in situ* form of melanoma that grows very slowly radially and eventually can progress into invasive lentigo maligna melanoma (LMM). The gold standard treatment for LM is wide local excision but surgery is not always feasible due to elderly age of the patients and location on cosmetically sensitive head and neck area. Alternative, non-surgical therapies have been investigated with varying results.

Basal cell carcinoma (BCC) is the most common skin cancer among whites in Western countries and approximately 7% of all BCCs contain melanin, being clinically pigmented. Pigmented BCCs may be difficult to distinguish from melanoma and other melanocytic tumours even for an experienced dermatologist.

The dissertation consists of 3 separate studies. Study I was a randomized double-blind trial intended to compare clinical efficacy, tolerability and costeffectiveness of two photosensitizers, 5-aminolaevulinic acid nanoemulsion (BF-200 ALA) and methyl-5-aminolaevulinate (MAL) in daylight photodynamic therapy (DL-PDT) for AKs. Altogether 69 patients with 767 mild to moderate AKs were given a single DL-PDT treatment in a randomized split-face setting. In a follow-up of 12 months, BF-200 ALA was more effective than MAL, clearing 79.7% vs. 73.5% of all AKs. The tolerability of both treatments was very good, with no difference in pain, cosmetic outcome or patient preference, but BF-200 ALA caused more intense local skin reactions.

From left to right: Emerita Professor Erna Snellman (main supervisor), Professor Veli-Matti Kähäri (opponent), Professor Teea Salmi, MD Janne Räsänen and Docent Noora Neittaanmäki.

Study II was a prospective study intended to investigate the efficacy of ablative fractional laser (AFL)-assisted PDT in the treatment of LM. BF-200 ALA was used as a photosensitizer. Ten biopsy-verified LM lesions were treated with AFL-assisted PDT 3 times at two-week intervals. Four weeks after the last PDT treatment all LM lesions were surgically excised for histopathological evaluation. The complete histopathological clearance rate was seven out of ten lesions (70%). Some severe and unanticipated skin reactions occurred after PDT sessions.

Study III was a prospective diagnostic study piloting hyperspectral imaging (HSI) and convolutional neural network (CNN) for differential diagnosis of pigmented skin lesions. A total of 26 pigmented lesions were imaged with HSI *in vivo* and then surgically excised for histopathological evaluation. HSI images were divided into two halves, one of which was used for the training of the CNN and the other for the clas-

sification task. For two-class classifier (melanocytic tumours vs. pigmented BCCs) using majority of the pixels to predict the class of the lesion, we obtained high sensitivity of 100%, specificity of 90% and positive predictive value (PPV) of 94% for diagnosis of melanocytic tumours.

The results of this thesis permit the following conclusions:

- BF-200 ALA is more effective than MAL in DL-PDT for mild to moderate AKs and is slightly more cost-effective than MAL. BF-200 ALA caused more intense local skin reactions, which could affect the tolerability of the treatment.

- AFL-assisted PDT showed good efficacy of 70% for lentigo maligna in terms of histopathological clearance. It could be considered a minimally invasive alternative treatment for LM in cases where surgery is not an option.

- A CNN classifier can accurately and pixel-wise differen-

tiate melanocytic tumours from pigmented BCCs in hyperspectral images. A larger sample dataset with multiple tumour types and a separate training dataset is warranted in the future to confirm these preliminary results.

List of original publications

I. Räsänen JE, Neittaanmäki N, Ylitalo L, Hagman J, Rissanen P, Ylianttila L. et al. 5-aminolaevulinic acid nanoemulsion is more effective than methyl-5-aminolaevulinate in daylight photodynamic therapy for actinic keratosis: a nonsponsored randomized double-blind multicenter trial. Br J Dermatol 2019; 181: 265–274.

II. Räsänen JE, Neittaanmäki N, Jeskanen L, Pölönen I, Snellman E, Grönroos M. Ablative fractional laser-assisted photodynamic therapy for lentigo maligna: a prospective pilot study. J Eur Acad Dermatol Venereol 2020; 34: 510–517.

III. Räsänen J, Salmivuori M, Pölönen I, Grönroos M, Neittaanmäki N. Hyperspectral imaging reveals spectral differences and can distinguish malignant melanoma from pigmented basal cell carcinomas: a pilot study. Acta Derm Venereol 2021; 101: adv00405.