New Options for Non-invasive Imaging and Non-invasive Treatment of Skin Cancers

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Mari Salmivuori, MD, PhD, conducted her PhD studies at Department of Dermatology and Allergology, Päijät-Häme Social and Health Care Group, Lahti, Finland during the period 2014-2019. Emerita Professor Erna Snellman was her main supervisor and the co-supervisor was Docent Mari Grönroos. The opponent was Associate Professor John Paoli University of Gothenburg, Sweden. The thesis was defended on November 20, 2020 and can be found at http://urn.fi/URN:ISBN:978-952-03-1541-2.

Background

Basal cell carcinoma is the most common cancer in the world. The incidence of superficial basal cell carcinoma, a subtype of basal cell carcinoma, is rising at a far steeper rate than the other subtypes, and as a non-aggressive subtype, it can be treated non-invasively. Aggressive subtypes of basal cell carcinoma are often ill-defined, which poses a clinical problem in preoperative margin assessment. Another ill-defined skin cancer type is lentigo maligna. Lentigo maligna is an *in situ* melanoma, and a precursor of lentigo maligna melanoma. These two forms are clinically challenging to distinguish from each other, which is crucial as melanoma has the worst prognosis of all skin cancers. Non-invasive imaging is an option for increasing the accuracy of preoperative diagnosis and the assessment. Hyperspectral imaging is a novel, fast, and computer-aided imaging modality with a wide field of view. In non-invasive treatment of non-aggressive basal cell carcinomas, photodynamic therapy has many advantages: an excellent cosmetic outcome as well as a shorter application time and recovery period. Notwithstanding these advantages, the efficacy of photodynamic therapy is lower when compared to topical pharmacological options such as imiquimod and 5-fluorouracil.

Objectives

This dissertation focuses on non-invasive imaging and non-invasive treatment. In non-invasive imaging, the aim is to study the performance of a hyperspectral imaging system in separating lentigo maligna melanoma from lentigo maligna and assessing the preoperative margins of ill-defined basal cell carcinomas compared to clinical delineation assessments performed with a dermoscope. In non-invasive treatment, the aim is to compare the efficacy of three different photosensitisers in photodynamic therapy of non-aggressive basal cell carcinomas.

The main supervisor Erna Snellman with the defendent Mari Salmivouri. The opponent John Paoli to the right on top and the co-supervisor Mari Grönroos at the boottom.

Methods

There are two pilot studies with hyperspectral imaging: one on lentigo maligna and lentigo maligna melanoma, and another on ill-defined basal cell carcinoma. Tumours were preoperatively visually inspected utilising a dermoscope, and thereafter imaged with the hyperspectral imaging system. Next, surgical excision was performed. Hyperspectral images were created with computer-aided mathematical models. Additional mathematical models were subsequently developed. In the results analysis, the findings of the hyperspectral imaging and clinically assessed margins were compared to the histopathology results, where assessment was performed blind to the hyperspectral imaging findings. A non-sponsored, prospective, randomised, controlled and double-blinded trial focused on non-invasive treatment. In this trial, two novel photosensitisers, 5-aminolevulinic acid nanoemulsion and low-concentration hexylaminolevulinate, were compared to

the commonly used methylaminolevulinate in photodynamic therapy of non-aggressive basal cell carcinomas, i.e. thin nodular or superficial subtypes. The primary outcome was histological clearance at three months.

Secondary outcomes included adverse events such as pain associated with the treatment while using a long-lasting local anaesthetic as pain management, post-treatment reaction, as well as cosmetic outcome, and fluorescence and photobleaching during the illumination. We used an experimental fluorescence imaging system. Punch biopsies were performed prior to treatment and during follow-up. Both patient and observers of outcomes were blind to the photosensitiser that was used.

Results

Hyperspectral imaging exhibited a unique hyperspectral graph for lentigo maligna melanoma, lentigo maligna, and healthy skin. Based on these results, hyperspectral images were created where hyperspectral data was represented in several abundance maps. The maps showed differing abundances for lentigo maligna melanoma and lentigo maligna, and it was possible to localise the invasion site inside the lesion. For ill-defined basal cell carcinoma, the margins of the tumour were delineated more accurately than by clinical assessment, and the results were confirmed with histopathology. The results of the clinical trial in photodynamic therapy showed that the histological clearance of hexylaminolevulinate was similar compared to 5-aminolevulinic acid nanoemulsion and methylaminolevulinate, with no differences in cosmetic outcome, pain or post-treatment reaction between the arms. In our fluorescence and photobleaching analyses the results were widely spread.

Conclusions

Hyperspectral imaging seems to be a promising and useful new imaging modality with a wide field of view: it is fast, easy to use and it seems to be capable of visualising subclinical findings. In non-invasive treatment, hexylaminolevulinate is an interesting option for photodynamic therapy of nonaggressive basal cell carcinomas. Hexylaminolevulinate at low concentrations achieves a comparable efficacy to 5-aminolevulinic acid nanoemulsion and methylaminolevulinate at higher concentrations. No differences were observed in adverse events or cosmetic outcome between the arms.

List of original publications

I. Neittaanmäki N, Salmivuori M, Pölönen I, Jeskanen L, Ranki A, Saksela O, et al. Hyperspectral imaging in detecting dermal invasion in lentigo maligna melanoma. Br J Dermatol 2017; 177: 1742–1744.
II. Salmivuori M, Neittaanmäki N, Pölönen I, Jeskanen L, Snellman E, Grönroos M. Hyperspectral imaging system in the delineation of ill-defined basal cell carcinomas: A pilot study. J Eur Acad Dermatol Venereol 2019; 33: 71–78.
III. Salmivuori M, Grönroos M, Tani T, Pölönen I, Räsänen J, Annala L, et al. Hexyl aminolevulinate, 5-aminolevulinic acid nanoemulsion, and methyl aminolevulinate in photodynamic therapy of non-aggressive basal cell carcinomas: A non-sponsored, randomized, prospective and double-blinded trial. J Eur Acad Dermatol Venereol 2020; 34: 2781–2788.