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Project title: **The first retrospective study to assess the diagnostic performance of the newly invented line-field confocal optical coherence tomography for basal cell carcinoma diagnosis and subtype classification**

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Background

Basal cell carcinoma (BCC) is the most frequent skin cancer in the general population and its incidence keeps on increasing worldwide, especially among caucasians.[1] BCC is classified together with squamous cell carcinoma (SCC) as a non-melanoma skin cancer, and is a complex disease in which ultraviolet radiation and individual genotypic and phenotypic factors interact.

Although BCC is not immediately life-threatening and is rarely metastatic, it can be mutilating if the diagnosis is not made properly, and the treatment not initiated quickly. Indeed, BCC's morbidity is significant as it mostly occurs on highly visible areas such as the head, face and neck and invades the surrounding tissues with consequent ulceration and bleeding

It is also important to know that BCC is classified into different subtypes [superficial BCC (sBCC), nodular BCC (nBCC), infiltrative BCC (iBCC), and mixed forms] which are not necessarily treated in the same way. sBCC can be treated non-surgically (topical therapies, destructive therapies and photodynamic therapy) unlike other forms of BCCs which require surgery.[2] Therefore, it is necessary to make an early BCC diagnosis and subtyping in order to have an adequate management.

In some cases, it is challenging to diagnose BCCs and to classify them just by clinical and dermoscopic assessment, partly because of the existence of BCC imitators such as actinic keratosis (AK), SCC, dermal naevus (DN), seborrheic keratosis (SK), sebaceous hyperplasia (SH), and certain inflammatory skin conditions.[2]

Histopathology remains the gold standard for the distinction between BCC and BCC imitators and for BCC subtype classification,[3] but new non-invasive skin imaging techniques have emerged in the last decade, which could improve dermatologists' diagnostic performance and reduce the need of biopsies or surgical excisions in order to confirm the diagnosis of BCC.

Line-field confocal optical coherence tomography (LC-OCT) represents one of the newest non-invasive *in vivo* skin imaging techniques. It is an interferometry-based imaging modality that measures the time of flight and amplitude of the light backscattered from the skin microstructures. It is based on previous non-invasive imaging techniques: optical coherence tomography (OCT) and reflectance confocal microscopy (RCM).[4] While OCT allows to have cross-sectional images of the skin with a high penetration depth (1-2 mm), its disadvantage consists in its low lateral resolution (7,5 µm) that renders impossible the visualization of cytological details useful for the diagnosis. On the other hand, weak penetration (~200 µm) and imaging on the horizontal plane represent the disadvantages of RCM, while its advantage lays in the high lateral resolution (1 µm).[5] The LC-OCT technology is highly innovative as it allows to combine the advantages of OCT and RCM and to minimize their respective shortcomings: indeed, LC-OCT displays high isotropic resolution (just above 1 µm) and high penetration depth (around 500 µm), it permits imaging both on the horizontal and vertical

planes, and features the unprecedent characteristic of instantaneous 3D reconstructions of the physiological and pathological skin.[3]

Even though the LC-OCT morphological aspects of the main BCC subtypes,[6,7] as well as of some BCC imitators have been recently described,[8-10] there is no data concerning the clinical use and the diagnostic performance of LC-OCT in the field of BCC.

Objectives

The aims of this project are to (i) determine the sensitivity, specificity, positive and negative predicted values (PPV, NPV) of LC-OCT for the diagnosis of BCC, and (ii) to describe LC-OCT features that allow the distinction between BCC and clinical/dermoscopic mimickers as well as (iii) the discrimination of BCC subtypes.

Proposed methodology

This will be a monocentric, retrospective study including skin lesions with a confirmed histopathological diagnosis of BCC (including the following BCC subtypes: sBCC, nBCC, iBCC, and mixed forms) and of BCC imitators (AK, SCC, DN, SK, SH, lichen planus, psoriasis, eczema). All lesions will be biopsied or surgically excised from patients (male or female older than 18 years old) of the Department of Dermatology of the *Hôpital Erasme*, ULB, Brussels.

Lesion selection will include the following criteria:

- patients' consent for their images to be anonymously included in the study (availability of a signed informed consent form);
- availability of good-quality clinical, dermoscopic and LC-OCT images taken prior to the lesion biopsy/excision, as judged by the project leader;
- availability of a complete histopathological diagnosis, including – in the case of BCC diagnosis – the BCC subtype classification;
- availability of histopathological images in order to perform a correlation between LC-OCT and histopathology, if needed.

A list of LC-OCT criteria will be prepared by the project leader and co-workers based on the available scientific literature on LC-OCT and previous non-invasive skin imaging techniques, as well as on the clinical expertise built within the last 3.5 years (a prototype of LC-OCT was first made available to the project leader in September 2018).

After completion of lesion selection, three independent observers, all blinded for the histopathological diagnosis, will analyse the clinical, dermoscopic and LC-OCT images for the presence or absence of LC-OCT criteria.

The foreseen statistical analysis will include the report of:

- absolute and relative frequencies of LC-OCT criteria according to lesion type;
- for each lesion type, diagnostic parameters of LC-OCT compared to clinical/dermoscopic examination, including sensitivity, specificity, PPV, and NPV;
- the diagnostic weight of each LC-OCT criterion, determined as the mean square contingency coefficient (phi): features with the highest diagnostic weight will be used to create a diagnostic algorithm for BCC distinction and subtype classification.

Pre-study sample size calculations established the ideal size of the study sample as being between 200 and 250 lesions. We expect that, after lesion selection, the total number of lesions included in the study will be comprised between 300 and 350.

References

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