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Ph.D. Thesis

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Line-Field Confocal Optical Coherence Tomography in Dermato-Oncology: Opportunities and Challenges

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DANSK RESUMÉ

Keratinocytkarcinom (KC) er den hyppigste hudkræft på verdensplan. Forekomsten af hudkræft stiger, og nye digitale teknologier er under udvikling. Guldstandarden for diagnose er histopatologi; dog er denne procedure invasiv, tidskrævende og afhængig af ex vivo-vurderinger, hvilket kan forsinke beslutningstagning. Derudover oplever mange patienter, herunder højrisko-organtransplanterede (OTR), en høj sygdomsspecifik byrde forbundet med gentagne biopsier og flere konsultationer for diagnose og behandling.

Line-field optisk kohærens tomografi (LC-OCT) er en noninvasiv billeddannelsesteknologi, der tilbyder realtidsvisualisering med høj opløsning af de øverste hudlag. LC-OCT har et klinisk potentiale inden for dermato-onkologi, men der findes begrænset viden om, hvilke billedkarakteristika man skal fokusere på, hvor lette disse er at observere, og hvordan disse kan anvendes til triagering af hudlæsioner hos OTR. Desuden er den biologiske basis for basalcelle karcinom (BCC)-specifikke LC-OCT-billedkarakteristika uklar.

Dette ph.d.-projekt inkluderer en systematisk litteraturgennemgang (studie I), et interobservatør-enighedsstudie (IOA, studie II), et klinisk triageringsstudie (studie III) og et associationsstudie mellem noninvasiv billedkarakteristika og transkriptomiske mønstre af BCC (studie IV).

Som det første skridt gennemgik vi i Studie I systematisk litteraturen om anvendelsen af LC-OCT i hudkræft. Flere studier med varierende evidensniveauer og LC-OCT-terminologi blev kombineret for at skabe et forenet katalog over billedkarakteristika samt et udvalg af dem, der svarer til histologiske diagnostiske kriterier for KC og forstadie læsioner (heraf nøglebilledkarakteristika).

IOA for 10 nøglebilledkarakteristika blandt fagbedømmere med tidligere erfaring med optisk noninvasive udstyr blev vurderet i studie II. Interobservatør-enighed blandt fagbedømmere var højere ved vurdering af lobules, spalter og svær dysplasi, og lavere ved vurdering af integriteten af den dermoepidermale junction.

For at estimere den kliniske anvendelighed af 10 nøglebilledkarakteristika blev der udviklet et simpelt firetrins LC-OCT-beslutningstræ til triagering af hudlæsioner hos OTR i studie III. Beslutningstræet inkorporerede fem billedkarakteristika, der kunne detektere KC, Bowen's sygdom (BD) og aktinisk keratose (AK), hvilket viste høj sensitivitet for KCs.

Ved at kombinere LC-OCT billedkarakteristika med genekspressionsmønstre fra tape-prøver fra BCC'er, gav studie IV nye indsigter i BCC's patobiologi og identificerede unikke differentielt udtrykte gener for to BCC-billedkarakteristika: millefeuille-mønsteret og kollagenændringer.

Sammenfattet indikerer litteratur og klinisk evidens fra studier I–IV, at LC-OCT har potentiale til at udvikle sig fra en morfologisk billeddannelsesteknik til et klinisk modent værktøj i dermato-onkologi gennem standardisering af terminologi, identifikation af nøgle billedkarakteristika, samt estimering af deres IOA og anvendelse til triage af hudlæsioner hos OTR-patienter. LC-OCT af BCC i kombination med transkriptomisk analyse tilbyder en flerdimensionel tilgang til forståelsen af sygdommen.

ENGLISH SUMMARY

Keratinocyte carcinoma (KC) is the most common type of skin cancer worldwide. The incidence of skin cancer is increasing, and new digital technologies are being developed. The gold standard for diagnosis is histopathology; however, this procedure is invasive, time-consuming, and dependent on ex vivo assessments, which can delay clinical decision-making. Additionally, many patients, including high-risk organ transplant recipients (OTRs), face a high disease-specific burden requiring repeated invasive biopsies and multiple consultations for diagnosis and treatment.

Line-field optical coherence tomography (LC-OCT) is a noninvasive imaging technology that offers real-time, high-resolution visualization of the upper skin layers. LC-OCT holds clinical potential in dermato-oncology, but there is limited knowledge regarding which skin cancer image features to focus on, how easily they can be observed, and how they can be utilized to triage skin cancers in OTRs. Moreover, the biological basis underlying BCC-specific LC-OCT image features remains unclear.

This PhD includes a systematic review (study I), an interobserver agreement (IOA) study (study II), a clinical triage study (study III), and an association study between noninvasive imaging features and transcriptomic (i.e., gene expression) patterns of BCC (study IV).

As a first step, we systematically reviewed the literature on LC-OCT imaging of skin cancer in Study I. Multiple studies with varying levels of evidence and LC-OCT terminology were combined to create a unified glossary of imaging features, as well as a selection of those corresponding to histological diagnostic criteria for KCs and precursor lesions (i.e., key image features).

The IOA of 10 image features among evaluators with previous noninvasive imaging experience was assessed in Study II. The IOA was higher among evaluators who assessed lobules, clefting, and severe dysplasia, and lower for the assessment of the integrity of the dermal-epidermal junction.

To estimate the clinical utility of 10 key image features, a simple four-step LC-OCT decision tree was developed for triaging skin lesions in OTRs in study III. The decision tree incorporated five high-yield features for detecting KCs, Bowen's disease (BD), and actinic keratosis (AK), showing high sensitivity for detecting KCs.

Finally, by combining LC-OCT with gene expression patterns from tape strips in BCC, study IV provided novel insights into BCC pathobiology, identifying unique differentially expressed genes for two BCC image features: the millefeuille pattern and collagen alterations.

In summary, literature and clinical evidence from studies I–IV indicate that LC-OCT has the potential to evolve from a morphological imaging technique into a clinically mature tool in dermato-oncology through standardization of terminology, identification of key imaging features, estimation of IOA for key features, and their utility to triage skin lesions in OTR patients. LC-OCT features of BCC in combination with transcriptomics analysis offer a multidimensional approach to understanding the disease.