Clinical applications of functional optical coherence tomography

de Bruin, D.M.

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In this final chapter, the vision and recommendations of the author of this thesis on future research is given. This is partially based on the conclusions derived from this thesis which can be found in chapter 12 ‘Concluding Remarks’.

13.1 The potential of functional OCT in ophthalmology: optical properties from all layers

In this thesis, we described swept source OCT at 1050 nm and showed that it allows a) excellent visualization of the deeper tissue layers of the retina and b) visualization of age related macular degeneration with quantitative analysis of RPE detachment reduction by anti VEGF treatment. However, diagnosis of pathology that requires high resolution OCT (beyond 5 µm in axial direction) might be hampered by the limitations in available bandwidth caused by water absorption and technological thresholds in laser source design. Nevertheless, because of all the benefits, it is expected that 1050 SS-OCT technology will benefit the current state of the art retinal OCT imaging.

Ophthalmic applications of functional OCT present an additional challenge. Retinal layers, typically ~5 to ~55 micrometer thin, are often insufficient to support accurate fitting of the attenuation coefficient. The solution of this problem lies in developing high resolution (adaptive optics) OCT systems to increase the data density in these small layers; and in developing methods to extract functional information from e.g. speckle statistics (that can be obtained from thinner, but laterally extended volumes).

Furthermore, implementation of quantitative flow analysis in all directions combined with compensation for eye motion artifacts could result in a detailed description of the retinal micro vasculature.[1] If visualization and functional analysis of this vasculature is fully implemented in an ophthalmic OCT device which operates at 1050 nm, flow and possible perfusion of the surrounding tissue can be studied even until the deepest vascular part of the eye, the choroid. This could have possible consequences in the management of several ophthalmic diseases.[2–4]

13.2 The potential of functional OCT in cancer management: development of the optical biopsy

Due to improvements in diagnostic techniques, small solid tumors occupying less than 5-10% of any organ can now be detected with traditional imaging modalities like CT, US and MRI. Many of these tumors are confirmed with physical biopsy and subsequent histo-pathological grade (aggressiveness) evaluation. Because of unclear information on grade and stage of the lesion on presently available imaging techniques, a biopsy-sampling protocol is required in which (core-needle) biopsies are taken. Current treatment of solid tumors and epithelial tumors is based on systemic medication using chemotherapy and/or immunotherapy, radiation therapy (all using a balanced combination of necrosis and apoptosis to kill a tumor) or radical surgical procedures in which an organ is (partially) removed which comes with considerable side effects. These concerns have led to the development of focal (i.e. localized) therapies such as laser-ablation, cryo-ablation or brachy therapy, a selective radiation or ablation technique, reducing lifetime morbidity and side-effects without compromising life expectancy. The success of these treatment strategies relies on accurate demarcation, using smart treatment planning protocols and real time identification (grading) and follow-up of the lesion.[5] Both follow-up strategies and real-time identification of a lesion are unmet challenges using the current diagnostic techniques and OCT has the potential to fulfill this challenge. Additionally, the management of several cancers also allows a watchful waiting strategy in which a found suspected lesion is checked time to time in order to monitor the temporal changes. (Functional) OCT is an ideal candidate for this because it allows minimal invasive analysis of lesion grade related change of optical properties and stage related changes of layered tissue architecture i.e. visual detection of the basal membrane in the OCT image, an important factor in epithelial tumor staging and or tissue.

13.3 Needle based optical biopsy of solid tumors

The optical fiber based design of most OCT systems allows for integration with diffuse reflectance spectroscopy, another fiber based technology which have proven to be sensitive for physiological and biochemical changes in tissue. Combined in a single device, both state-of-the-art fiber optic technologies can i.e. be delivered through a 3 French (Ø = 1mm) needle, minimizing damage to the probed organ. This optical biopsy shows the morphology and architecture of the tissue at micrometer scale resolution (OCT) complemented by information on tissue function, e.g. cellular organization derived from light scattering (OCT/DRS), micro vascular properties such as perfusion (OCT), vessel density, oxygen saturation (DRS) and biochemical composition, e.g. fractions of water, fat, bilirubin, beta-carotene and hemoglobin (DRS).[6–8] Using such an optical biopsy, the morphological and biochemical changes that occur during cancer development can be quantified, enabling real time lesion detection and tumor grading. Additionally, when a lesion is detected by an optical biopsy, the location information can be used as additional input for a more exact treatment planning protocol and a physical biopsy sample can be obtained by the operating physician to confirm final pathology.
13.4 Integration with cross-sectional imaging modalities
Integration with cross-sectional imaging technologies such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI) ultrasound (US), Single photon emission computed tomography (SPECT) and positron emission tomography (PET) will become increasingly important. This is because medical imaging, especially in the detection of cancer, is progressing towards real-time point of care solutions which require a diagnostic tool that can a) find a lesion and b) differentiate this lesion. Functional OCT, because all aforementioned opportunities in paragraph 13.2 and 13.3 will have a large contribution to novel approach of diagnosing a disease.

13.5 Consideration on study design
It was not always possible to see a change in attenuation coefficient when compared to lesion grade and normal tissue. During investigation of functional OCT to grade bladder cancer, we stumbled onto fundamental limitations that are representative for an ex-vivo investigation. To optimize control during OCT imaging during the first attempt to relate optical properties to lesion grade, ultra high resolution time domain OCT with focus tracking around 800 nm was employed. However, the very small ex vivo biopsies imposes a challenge on both the OCT imaging, OCT signal analysis and pathology analysis which impaired good judgment on sample geometry (upside vs bottom). Furthermore, we have shown that pathology analysis of low grade tissue samples is very difficult for pathologist. However, in the current design of these type of studies, pathology is defined, with good reason, as gold standard. Consequently, the challenging judgment of low grade tumors will always have an impact on the outcome of a study. To overcome this limitation, a study design needs to include a) a pilot study on large freshly excised specimens that allows optimal knowledge of tissue geometry and optimal histological analysis by a pathologist, b) a diagnostic accuracy study that includes a range of consecutive patients with a control group (which could be healthy tissue from an available but similar contra lateral organ side from the same patient) with counter-blinding for both pathology and OCT outcome during analysis and c) a trial design over a patient population which is powered by the diagnostic accuracy study.

The downside for this approach in study design is that is requires a significant amount of time to develop a full study. Technological advances are usually much faster and, in case of OCT research, significant changes in instrument and data analysis were and are made in a short amount of time. This will impose ethical challenges during the duration of a study. Several attempts are employed to overcome this fundamental challenge, [9] which will hopefully result in a more practical, yet still fully scientifically supported, solution to this.

Within this thesis, we did start (when possible) with an ex-vivo pilot which progressed into a small study cohort. In case of the renal study (chapters 8 and 9) this has resulted into a large multicenter study to evaluate the diagnostic accuracy of optical biopsy using OCT to discriminate between normal tissue and tumor tissue and to differentiate tumor subtypes (not in this thesis).

REFERENCES