Overview of the status of the development of an OCT probe for the diagnosis of precursor cancer lesions in the uterine cervix

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Abstract. Optical Coherence Tomography (OCT) is used to generate images of uterine tissue capable of being compared with those obtained by light microscopy in post processed slides. Based on commercial instruments, the paper shows OCT images of the precursor lesions of cervical cancer. SD-OCT images were taken on cervical *ex vivo* samples and compared with histology images of the same samples in order to optimize the images obtained to maximize ease of classification. For the application of the technique in the real time exam (*in vivo*) at the doctor's office, a probe has been developed which is capable of being adapted to commercially available instruments to be inserted as an auxiliary tool in the colposcopic and stereoscopic examinations. In-vivo measurements using this probe are being planned.

1. Introduction

Optical coherence tomography (OCT) is a low-interferometry technique providing high-resolution images from internal microstructure of tissues in real time and is recognized as a very suitable technology for several applications related to biomedical imaging [1–4] for example for detection and classification of precancerous lesions of uterine cervix tissues using software image analysis [5–7]. OCT creates images from the magnitude and time delay of reflected light. A plot of this magnitude vs depth (calculated from the time delay) as known as an axial scan (A-scan). A two dimensional image (B-scan) is created from a series of A-scans captured while scanning the beam of light in a transverse direction. A three-dimensional volumetric image (C-scan) is created by repeated B-scans slightly offset one from the other [8].

This paper shows the results of using the OCT methodology with cervical tissue samples (with and without cervical intraepithelial neoplasia - CIN) using Spectral Domain OCT (SD-OCT). Two probes were constructed and are being analyzed and characterized. For this, two types of fiber lens prism (FLP)

assemblies were designed, and constructed, one with a reference reflection at the entrance to the prism and the other with the reflection at the exit of the prism. 20 FLP assemblies were built, 10 of each type, and after testing, the second type was shown to be better as the reference at the exit of the prism placed the oct measurements near the middle of the OCT A-scan range. Also shown was that the manufactured FLP assemblies either were acceptable to use or did not work at all (18 acceptable out of 20), which points to a simplified acceptance test in the future.

A SD-OCT instrument was used to perform B-scan measurements on *ex vivo* cervical samples from 30 different gynecological surgical patients, comparing OCT measurements with histology images on the same excised tissue.

In order to better compare the two image types we created a combination of image processing operations to improve the quality of the OCT images. The enhanced OCT images show a significant improvement in their quality, with details that do not appear in the original OCT images.

A collection of the raw, untreated OCT images, as well as the improved OCT images were used in an initial study to evaluate the specificity and sensibility of using the improved images to determine areas of higher grade CIN.

To facilitate *invivo* measurements, an OCT probe was developed and integrated with the existing SD-OCT instrument. Two types of FLP assemblies were designed internally and built by a third party. All built assemblies were tested and evaluated with respect to the design specifications.

2. Experimental setups and results

A motion control stage for precise movement of the samples under the OCT optics was added to the commercial SD-OCT system. The SD-OCT system took C-scan measurements in 2 mm sections at a time. Each section was swept generating 100 2D images.

The motion control facilitated precise positioning of the sample from one 2 mm section to the next rapidly enough to complete all the measurements in the approximately 40 minutes allowed to avoid degrading the sample before preservation for histology. The location of the focal point was highly relevant to evaluate possible lesions.

A technique of repeating scans at different focal depths at a single location was developed and with training became fast enough to terminate all the measurements in time. Each sample had different tissue structure with differing heights that made the relation of relevant tissue and depth of measurement complicated. It was needful to optimize the parts of the measurement which were automized and the parts which remained manual.

Figure 1 shows a sample taken from a gynecological patient and attached to a piece of styrofoam to be measured in the OCT system.

Figure 1. *Ex vivo* sample being aligned for OCT measurements

Histology techniques were applied to the same areas of the same samples, and microscopy images obtained with an Axio Z1 (Leica, Germany) microscope with a motorized plate. After the OCT measurement, the sample was dyed with different colors for the ectocervix and endocervix and fixed by submerging it in 10% buffered formaldehyde. It was then cut into 2 mm parallel sections from left to right. Each section was placed in a cassette and sequentially labeled to facilitate pairing with the OCT images. The sections were not as precisely repeatable as were the 2 mm OCT spacings due to variations in the cutting angles and thicknesses of the tissue due to the manual cleaving process. (Figure 2).

Figure 2. Sample being cleaved and inserted into numbered plastic cases where they will be embedded in paraffin.

The cassettes were processed automatically in a Leica TP1020 processor with sequential baths of alcohol, xylene, and paraffin. A Leica microtome was used to shave 5 µm at a time off of the block, each of which was stained in hematoxylin and eosin and mounted on a slide. These histological slides were scanned with a motorized platinum microscope and the resulting images were paired with the corresponding OCT image block.

Figure 3 shows a comparison of the images obtained with OCT (left) and histology (right). As can be seen, the images have a certain angle between themselves because of the cleaving process. Because of this, the process of pairing was important in order to identify the same regions in both images. Each OCT slice contained 100 contiguous images which permitted us to find the ones that best paired with each surface microscopy image from the actual tissue slice.

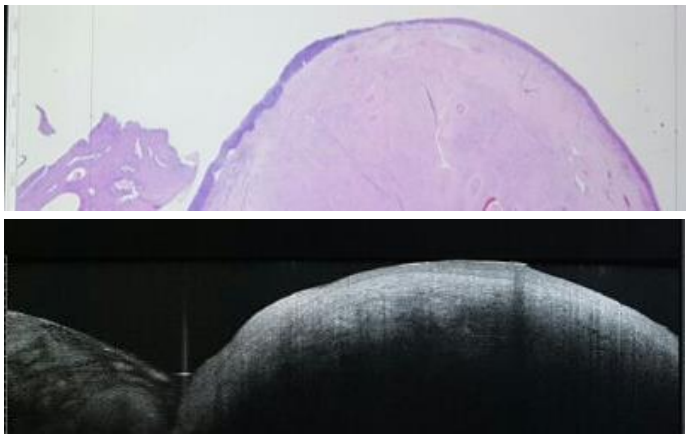

Figure 3. Comparison between OCT and Histology images of the same sample at the same location with the histology image at an angle due to variation in the cleaving angle.

A digital filter was developed and applied to the OCT images to facilitate identification of areas with lesions as shown in Figure 4 [9].

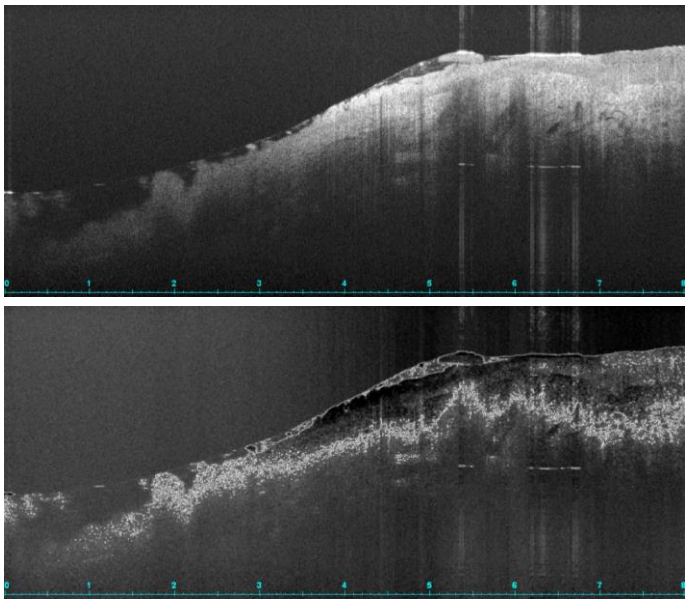

Figure 4. A) Original OCT image B) Filtered image. In the OCT image maximums are white while in the filtered image maxims are black with the intent to emphasize borders.

In order to take *in vivo* measurements, a hand held OCT probe is necessary. Figure 5 shows the FLP assembly and the prototype. The prototype was designed to be small enough to be inserted into the cervical canal (2 mm diameter) and to observe 90 degrees to the axis of the probe in order to measure within the cervical canal walls which remain hidden from standard colposcopy exams and thus rely on surgical excision and histology to determine the presence or absence of high grade CIN. The optics were connected to the commercial SD-OCT system and a field programmable gate array (FPGA) was built to provide A-scan triggers and to initiate movement of a small motion control stage which performs the B-scan movement of the probe [10, 11]. Figure 6 shows the protype in the test fixture measuring a *Taraxacum officinale* leaf (dandelion). Figure 7 shows a measurement of the underside of a human finger.

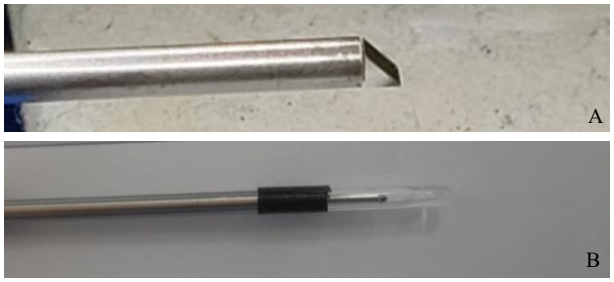

Figure 5. A) the FLP assembly with the prism showing B) the completed probe prototype with the FLP inside the metal sheath and quartz cap.

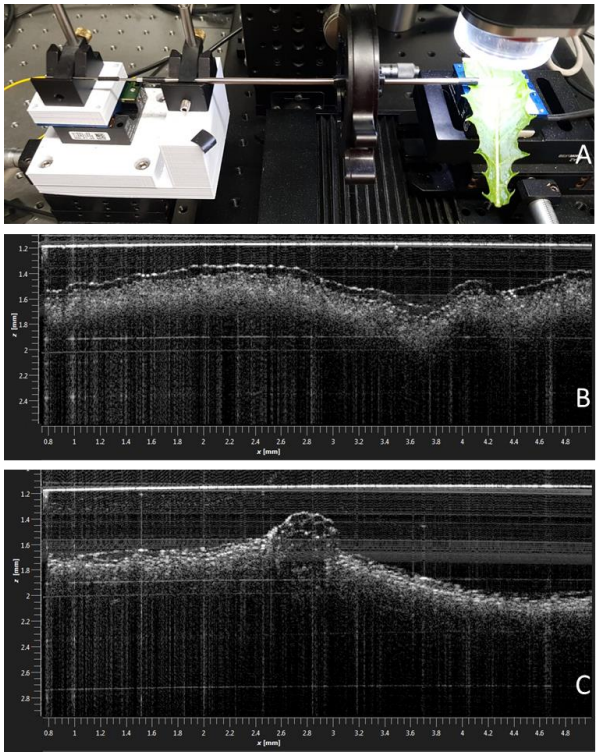

Figure 6. A) The probe prototype in the test fixture with a *T. officinale* leaf (front being measured). B) Front side measurement C) Back side measurement with central vein.

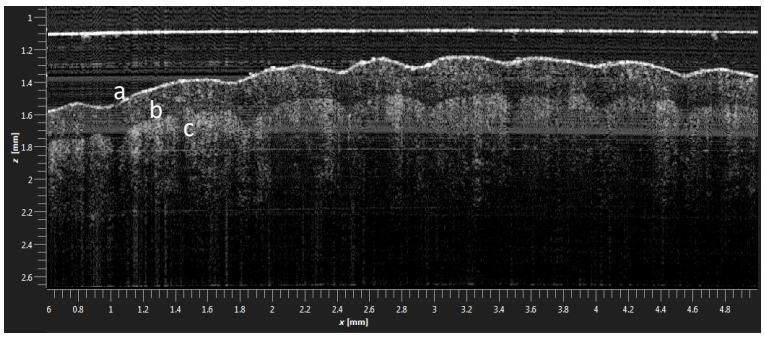

Figure 7. B-scan measurement using the prototype probe of the underside of a human finger showing the epidermal ridges (finger prints). The a) thin stratum corneum (bright) and the b) thicker stratum spinosum (darker) of the epidermis layer are very visible as is the start of the c) dermis layer (brighter again).

We are currently redesigning the probe to be used for *in vivo* measurements as shown in Figure 8.

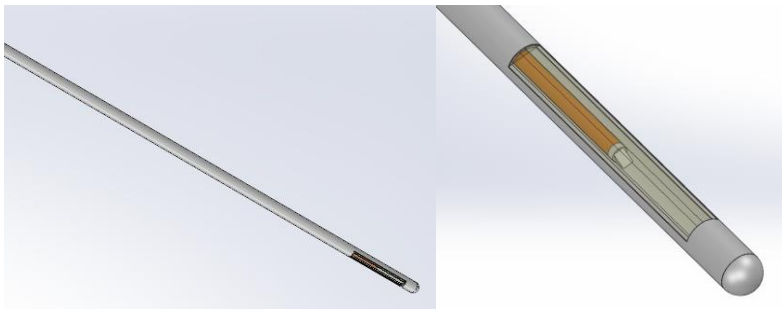

Figure 8. Redesign of the probe to be used in in-vivo measurements.

3. Conclusion

In this paper we describe the progress of the construction and characterization of an optical OCT prototype probe to be used to make cervical canal measurements in patients with possible cervical cancer lesions hidden from standard colposcopy exams. The initial protype was constructed and final evaluations are ongoing. Measurements of samples from 30 patients were completed and compared with histological results. A digital filter was designed and applied to the OCT images and compared with the originals in terms of readability of the tissue state. Measurements with the current prototype probe are being made and a new probe is being designed for *in vivo* measurements.

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