MICROMACHINED “SIDE-VIEWING” OPTICAL SENSOR PROBE FOR NON-INVASIVE DETECTION OF ESOPHAGEAL CANCERS

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ABSTRACT

In this paper, we report the design, fabrication and testing of a new miniaturized optical sensor probe with “side viewing” capability for oblique incidence diffuse reflectance spectrometry. The sensor probe consists of three micromachined positioning substrates and source/collection fibers to achieve 45° light incidence and collection of spatial resolved diffuse reflectance. Diffuse reflectance of human esophageal surface has been successfully measured for classification of cancerous tissues from normal ones for the first time.

INTRODUCTION

In the United States, the American Cancer Society estimated that there were about 15,560 new cases of esophageal cancers with about 13,940 deaths in 2007 [1]. Esophageal cancer is 3 to 4 times more common among men than among women and 50% more common among African Americans than among whites.

Several different optical methodologies have been proposed to determinate the malignancy of tumors [2-4]. Among them, oblique incidence diffuse reflectance spectroscopy (OIDRS) is a novel non-invasive optical method for early diagnosis of epithelial types of cancer (e.g. skin and esophageal cancers), which utilizes a special optical fiber sensor probe to conduct comparative measurements of the diffuse reflectance spectra of interested tissues upon contact [5]. Unfortunately, OIDRS is currently limited to only skin applications by the available sensor probes, which are bulky and have only “front viewing” capability (Fig. 1a).

Figure 1: Schematic of OIDRS probe configuration: (a) front viewing and (b) side viewing.

To significantly extend OIDRS for the detection of a much wider variety of cancers inside human body, new sensor probes with much smaller size and more importantly “side viewing” capability are necessary for effective OIDRS measurement even in the narrow cavities (e.g. esophagus) (Fig. 1b). However, achieving

probe miniaturization and “side-viewing” capability requires dense placement and sharp bending of optical fibers, which would cause excessive light loss, cross-talk or even breaking of the fiber. To overcome these challenges, an entire new device design and structure need to be developed.

THEORY

As shown in Fig. 2, when light is incident on the surface of an inhomogeneous media (e.g. biological tissue), part of the incident light will be directly reflected (specular reflectance) and the remaining will transmit into and interacts with the media. After undergoing multiples times of scattering and absorption, part of the transmitted light will be “turned” back and escape from the surface the media, which forms the diffuse reflectance. The spatially resolved steady-state diffuse reflectance for particular wavelength and oblique incidence can be calculated by [6].

Figure 2: Illustration of OIDRS principle. After undergoing multiples times of scattering and absorption, part of the transmitted light is reflected back to form the diffuse reflectance.

$$R(x) = \frac{1}{4\pi} \left[\frac{\Delta z(1 + \mu_{eff} \rho_1) \exp(-\mu_{eff} \rho_1)}{\rho_1^3} + \frac{(\Delta z + 2z_b)(1 + \mu_{eff} \rho_2) \exp(-\mu_{eff} \rho_2)}{\rho_2^3} \right] \quad (1)$$

where ρ_1 and ρ_2 are the distances between the source point and the observation point on the skin surface. Δz is the distance between the virtual boundary and the tissue depth, and z_b is the distance between the virtual boundary and the surface of the sample (Fig. 3). The distance from the point of incidence to the positive point source $d_s = 3D$. For oblique incidence the diffusion coefficient is $D = (3(0.35\mu_a + \mu_s'))^{-1}$, where μ_a is the absorption coefficient and μ_s' is the reduced scattering coefficient. The effective attenuation coefficient $\mu_{eff} = (\mu_a/D)^{1/2}$. The shift of the point sources in the x direction $\Delta x = \sin(\alpha_t)/(3(0.35\mu_a + \mu_s'))$, and α_t is the angle of light transmission into the tissue. The absorption and reduced scattering coefficients can be calculated by [7]

$$\mu_a = \frac{\mu_{eff}^2 \Delta x}{3 \sin(\alpha_t)} \quad (2)$$

$$\mu_s' = \frac{\sin(\alpha_i)}{\Delta x} - 0.35\mu_a \quad (3)$$

Figure 3: Schematic of the diffusion theory model for oblique incidence.

The diffusion equation assumes that the reduced scattering coefficient is much larger than the absorption. The source and detector must also be separated in space so that the light is diffuse when it reaches the detector. When the distance between the source and the detectors is comparable to the transport mean free path (~ 1 mm), diffusion theory does not apply. In this case, Monte Carlo simulation can be applied for the extraction of optical properties from the measured diffuse reflectance [8].

PROBE DESIGN AND FABRICATION

To conduct OIDS measurement, it is necessary to accurately deliver light of particular wavelength at a desirable oblique incidence angle on the tissue surface and also collect the one-dimensional linear distribution of the diffuse reflectance $R(x)$. While this can be achieved by placing the biological sample under an imaging setup, it will not be convenient and feasible to conduct in-vivo OIDS measurements under ordinary clinical settings. To address this issue, we have investigated the idea of building a stand-alone fiber optic sensor probe for skin applications [9]. This skin probe takes a “front viewing” configuration, in which the sensor head is in line with the direction of the fiber bundle. Except the oblique incidence fibers, all other fibers remain straight without any need of bending, such that they can be arranged in a dense manner without possibility of fracture. However, the measurements from tissue inside human body, (such as esophagus) require a different configuration that allows the further miniaturization of the sensor and more importantly the side-view capability or the sensor, in which all the collection fibers have to undergo a sharp 90° turn within a tight space within 2~5 mm. This inevitably would cause significant light loss and leakage and also possible mechanical fracture of the collection fibers.

To address this problem, we have come up with a new probe design, which consists of three micromachined silicon substrates (Fig.4). The first substrate consists of a guiding structure made of $100\ \mu\text{m}$ thick SU-8 (MicroChem, MA) layer, which serves as a position device for the source fiber to provide light incidence at an oblique angle (45°) (Fig. 5a). The source fiber with a diameter of $200\ \mu\text{m}$ can be accommodated using a matching pair of two positioning substrates. The second substrate carries ten SU-8 waveguides ($100\times 100\ \mu\text{m}^2$) with a 90° turn for collecting the spatially resolved diffuse reflectance from the tested tissue surface

(Fig. 5b). The third substrate consists of a 1D array of bulk-etched V-groves to ensure precise position of the 10 interconnection fibers to interface the 90° collection waveguides to OIDS measurement setup (Fig. 5c). We choose SU-8 as structural materials for both the guiding structures of source fiber and also the curved waveguides for collecting the diffuse reflectance. SU-8 is preferable since it can be directly photolithographically patterned to form thick microstructures ($100\ \mu\text{m}$) without further etching process, which results in a straightforward and low-cost fabrication process. Also, SU-8 has excellent optical transmittance over the visible light spectrum (where OIDS works) (Fig. 6), which makes it a suitable optically conductive material for the curved waveguides. To prevent possible light leakage and cross-talk, the top/bottom surfaces and the two side walls of the SU-8 waveguides were coated with evaporated aluminum ($180\ \text{nm}$ thick). To ensure a good coverage of the two side walls and the top surface, the aluminum depositions were conducted with the substrate placed at an oblique $\pm 45^\circ$ with respect to the evaporation source.

Figure 4: Schematic design of the new “side-viewing” OIDS probe.

Figure 5: Micromachined silicon positioning substrates for the OIDS probe (a) Source fiber guide; b) Collection waveguide substrates; and c) Interconnection fiber guide.

After the fabrication of three substrates, both the source fiber and the interconnection fibers were carefully placed into their positioning substrates and fixed in place with black epoxy. Next, all the substrates were aligned and glue together to complete the assembly of the entire probe in an aluminum holder for protection (Fig. 7a). The outer dimension of the sensor head is $5\times 5\times 12\ \text{mm}^3$, which is small enough for esophagus inspection. The source and collection fibers of the sensor probe were then connected to the system via SMA connectors (Fig. 7b).

Figure 6: Optical transmittance of SU-8 in the visible spectrum (100 μ m thick film).

Figure 7: (a) OIDRS probe assembly. (b) Complete OIRS probe.

TESTING AND RESULTS

The testing set-up of the OIR is shown in Fig 8. It consists of halogen lamp, imaging spectrograph, CCD camera, and personal computer. Before an OIDRS measurement is conducted, the source fiber of the sensor probe is connected to the output of the light source via SMA connectors. The proximal end of each collection fiber is fitted with SMA 905 connectors and then connected to the input of the spectrograph through a custom-made interface. After the sensor probe gets into contact with the sample, white light is delivered through the source fiber and the diffuse reflectance is then captured by the collection fibers. The collection fibers are coupled with the imaging spectrograph that generates an optical spectrum for each fiber. The CCD camera collects the spectral-images from the wavelength range of 455 to 765 nm. The spectral images represent the steady-state diffuse reflectance spectra from each collection fiber, which are stored in the computer for further analysis. This system is capable of capturing one frame of spectral image in a fraction of a second.

Figure 8: Experimental setup for OIDRS probe testing.

Before the real measurement, the fabricated OIDRS probe and image capture system were calibrated using a standard liquid phantom, which consists of trypan blue dyes as the absorbers and polystyrene microspheres as the scattering elements [10]. After the calibration, the entire OIDRS system was used to conduct ex-vivo measurement of human esophagus specimens with cancerous tissues (adenocarcinoma) for the first time (one specimen shown as an example) (Fig. 9). The measurement results by the ten collection channels clearly show different diffuse reflectance spectra for the normal and cancerous tissues (Fig. 10). The general lower diffuse reflectance of the cancerous tissue is caused by its darker color (causing more light absorption). The stronger scattering of the cancerous tissue is believed to be caused by the relatively larger cell nuclei as stronger optical scatter in malignant tumor cells, which is expected to serve as a good indicator to effectively differentiate cancerous tissue from benign ones [11].

Figure 9: Esophagus cancer testing sample (adenocarcinoma).

Figure 10: Diffuse reflectance spectra of human esophagus from ex-vivo OIDS measurement: (a) Normal tissue; and (b) Cancer tissue.

CONCLUSIONS

A new miniaturized OIDS sensor probe has been successfully developed and used for ex-vivo testing of esophageal cancer for the first time. When used with medical endoscopes, the new sensor probe is expected to enable in-vivo non-invasive detection of esophageal cancer and many other epithelial types of cancers inside human body.

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