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SPIE.

Event: European Conferences on Biomedical Optics, 2019, Munich, Germany

Terahertz time-domain spectroscopy for human gastric cancer diagnosis

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ABSTRACT

Non-invasive diagnostics methods are very helpful for cancer diagnosis and they are a research hotspot in the field of biomedicine. Terahertz (THz) photonics is an emerging technology that can be applied in the field of medical diagnostics. This is due to unique features of THz radiation such as harmlessness to biological tissues, strong absorption by water, ability to identify various biomolecules, etc. In this work we have investigated different types of normal and cancer fresh tissues of the stomach using terahertz time domain spectroscopy in reflection mode. Refractive indices of mucous, serous and tumor stomach tissues were obtained in the frequency range of 0,2 - 1 THz. These optical properties are higher for cancer tissue than for mucosa and lower than for serosa. Thus possibility of discrimination of tumor from normal stomach tissue was demonstrated. This study has practical significance for the field of clinical cancer diagnosis and will help to better understand the specifics of the method of pulsed THz spectroscopy applicable to this field.

Keywords: terahertz, spectroscopy, cancer diagnostics, gastric cancer, tissue, refractive index, patology, biophotonics

1. INTRODUCTION

In recent time terahertz (THz) technologies have been actively applied in many research areas particularly for biomedicine [1] such as therapy [2-4], glucose control in blood [5-6], water concentration determination in biotissues [7], as well cancer diagnosis [8-10]. This is due to the fact that THz radiation is sensitive to various biomolecules, non-ionizing and harmless to biological tissues. Also, THz radiation is strongly absorbed by intermolecular bindings, for example hydrogen compounds present in water, and NH-bonds present in proteins [1]. Different types of tissue can have different morphology and water content. Based on this fact normal and tumor tissues can be effectively distinguished as well as the boundary between them. Investigations of many cancer pathologies of different body parts were performed using THz time-domain spectroscopy and imaging methods. Thus cancer of skin [11], breast [12], colon [13, 14], brain [15 - 16] and liver [17] were studied by THz techniques. Also, the number of research works of gastric cancer diagnosis by THz techniques has been growing in recent years [8, 18 - 22]. Researchers try to apply these techniques in early gastric cancer diagnosis and develop THz endoscopic systems [23, 24]. Effective diagnostics is very important during treatment of stomach malignant tumors both by endoscopy and surgery methods. It can be safe more healthy tissue and increase survival rate after the treatment. Based on facts and researches mentioned before it is possible to use THz spectroscopy as a new effective method of gastric cancer diagnosis.

The aim of this study is investigation of normal and cancer fresh gastric tissues using THz time-domain spectroscopy method. We have investigated different types of normal and cancer fresh gastric tissues: inner (mucous) and outer (serous) stomach membranes and tumors from mucosa and serosa respectively. Results showed the possibility of discrimination of cancer from normal tissue in the both membranes.

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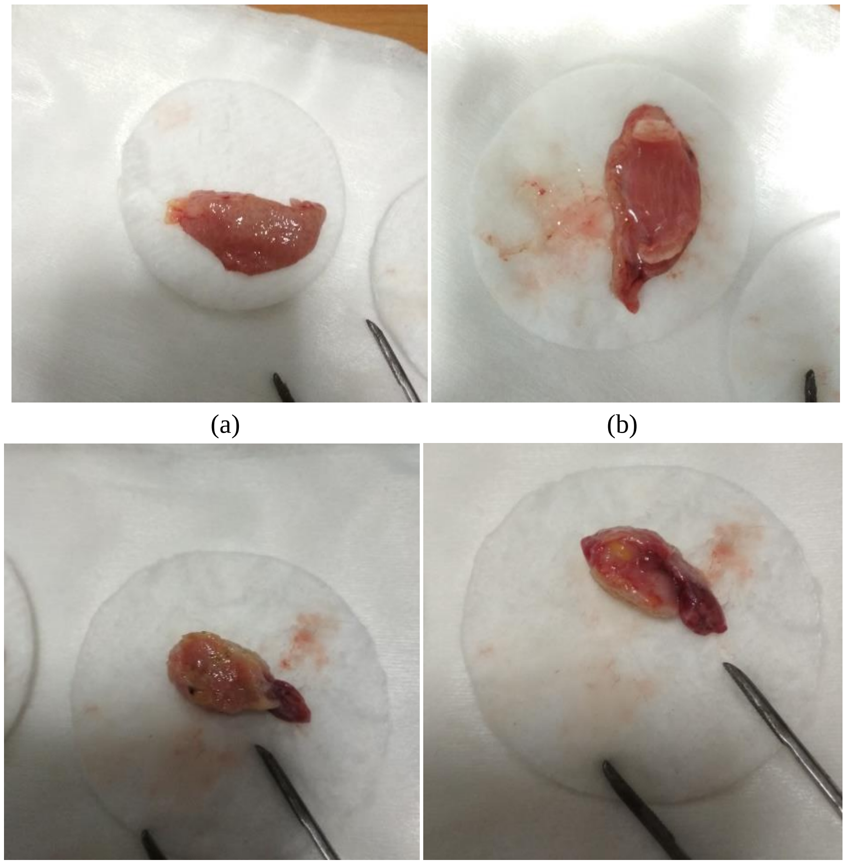
Clinical and Preclinical Optical Diagnostics II, edited by J. Quincy Brown, Ton G. van Leeuwen,
Proc. of SPIE-OSA, SPIE Vol. 11073, 110731X · © 2019 SPIE-OSA
CCC code: 1605-7422/19/$21 · doi: 10.1117/12.2526630

2. SAMPLE PREPARATION AND EXPERIMENTAL DETAILS

Mucous, serous and cancer tissues were obtained from Pavlov First St. Petersburg State Medical University (St. Petersburg, Russia) after surgery gastrectomy to patients with poorly differentiated (G3) gastric cancer (Figure 1). After extracting the samples were placed in physiological saline and delivered to the laboratory for the experiment. Samples were in solution no more than 3 hours. The experiment was performed at the temperature of 17 °C.



(c) (d)

Figure 1. The investigated samples of biological tissues. Mucous (a) and serous (d) side of normal tissue; tumor tissue localized in the mucous (c) and serous (d) membranes.

The samples were investigated by terahertz time domain (THz TD) spectrometer in the reflection mode. The schematic diagram of the whole experimental system is shown in Figure 2. The system had InAs and CdTe crystals as a generator and a detector of THz radiation respectively. The THz broadband pulsed radiation had the following parameters: the pulse duration of 2.7 ps, the average power of 30 µW, the power density 60 µW/cm^2. Optical excitation was performed by femtosecond laser (Yb:KYW) with the wavelength of 1040 nm, the pulse duration of 120 fs, the pulse repetition rate of 75 MHz and the power of 1 W. The working frequency range was from 0.2 to 1 THz. The experiment was performed using the method of a double-reflection measurement, also known as self-referenced geometry [25]. First, the THz pulses reflected from the silicon window were measured, and then the pulses reflected from the window-sample interface.

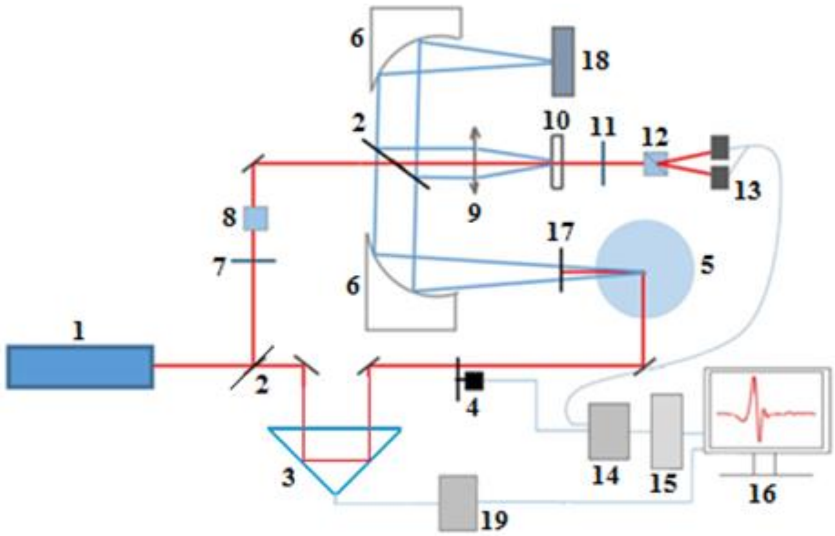


Figure 2. Schematic diagram of the THz TD spectrometer in the reflection mode. 1 - femtosecond laser "Solar" (power - 1.1 W, pulse duration - 200 fs); 2 - beam splitter; 3 - delay line; 4 - modulator; 5 - InAs crystal; 6 - parabolic mirrors; 7 - half-wave plate; 8 - Glan prism; 9 - collecting lenses; 10 - CdTe crystal; 11 - quarter-wave plate; 12 - Wollaston prism; 13 - balanced detector; 14 – lock-In amplifier; 15 - analog-to-digital converter; 16 - personal computer (PC); 17 - filter; 18 - sample; 19 - digital-to-analog converter.

3. RESULTS AND DISCUSSION

Pulses reflected from the top of the window (reference pulse) and delayed pulses reflected from the window-sample interface (sample pulse) were measured. All pulses fell at the normal incidence angle. The obtained waveforms were transformed into frequency domain using Fast Fourier Transform with a Hemming window function. To obtain refractive indices of the samples, the transfer function was calculated [25]:

$$H(\omega) = \frac{\hat{E}_{sam}(\omega)}{\hat{E}_{ref}(\omega)} = \frac{\tau_{aw}\tau_{wa}}{\rho_{aw}} \exp\left[-2in_w\frac{\omega l}{c}\right]\frac{n_w-\hat{n}_s}{n_w+\hat{n}_s}, \quad (1)$$

where $\hat{E}_{sam}(\omega)$ is the sample spectrum, $\hat{E}_{ref}(\omega)$ is the reference spectrum, l is the window thickness, τ_{aw} and τ_{wa} are the transmission coefficients for the air-window and window-air interfaces, respectively, ρ_{aw} is the reflection coefficient of the air-window interface, $\hat{\rho}_{ws}$ is the complex reflection coefficient of the window-sample interface, n_w is the refractive index of the window, $\hat{n}_s = n_s - jk_s$ is the complex refractive index of the sample, c is the speed of light.

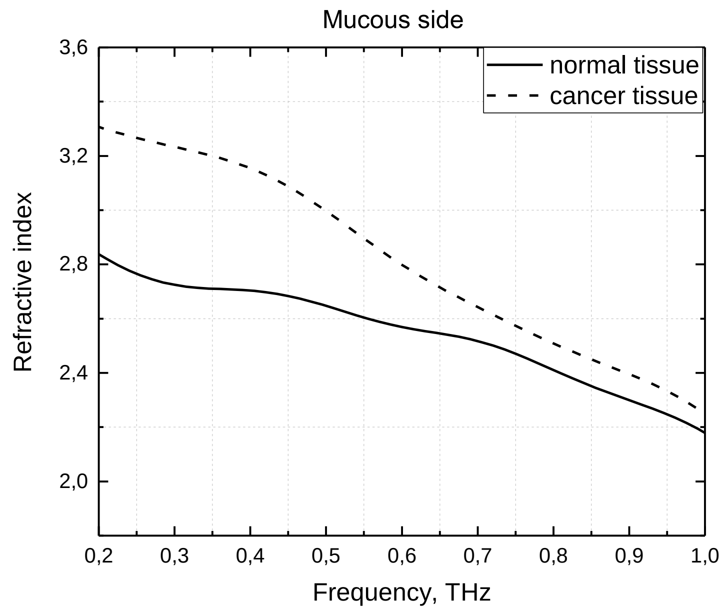
Rearranging (1) gives:

$$\frac{n_w-\hat{n}_s}{n_w+\hat{n}_s} = \frac{\rho_{aw}}{\tau_{aw}\tau_{wa}} \exp\left[2in_w\frac{\omega l}{c}\right]H(\omega) = Aexp(i\varphi)\,. \quad (2)$$

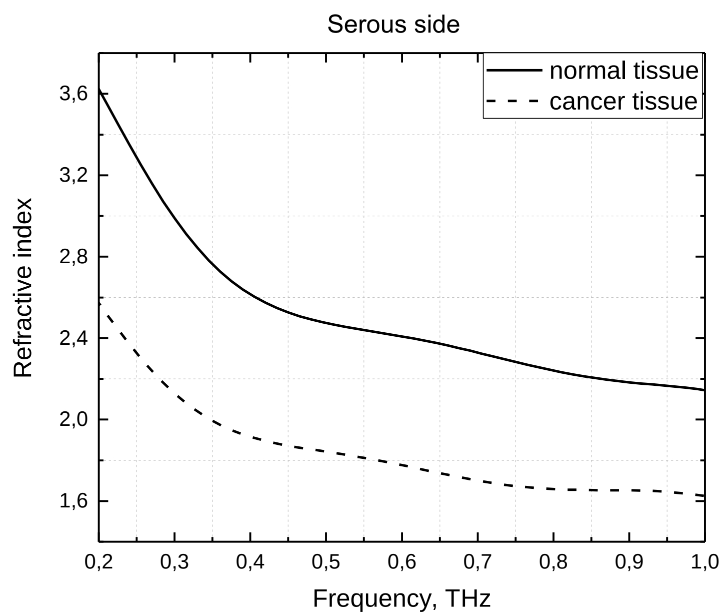
Then the refractive index can be calculated by:

$$n_s = \frac{n_w(1-A^2)}{1+A^2-2A\cos(\varphi)}\,. \quad (3)$$

As a result, the refractive indices of the mucous and serous stomach membranes, as well as tumor tissues localized in each of these membranes, were obtained. The dispersions of refractive indices of the samples are shown in Figure 3.



(a)



(b)

Figure 3. The dispersions of refractive indices of normal and cancer tissues from the mucous (a) and serous (b) stomach membranes

The observed difference in the refractive indices between normal and cancer areas can be explained by the different morphology of the gastric tissues. The mucosa consists of a tight epithelial layer under which a basement membrane and lamina propria locates [26]. The serosa includes connective tissue covered by a simple squamous epithelium, called the mesothelium, which reduces frictional forces during digestive movements [27]. Different morphology of the cells forming each tissue can change the optical density of the tissue. As seen in Figure 4, serosa has the highest refractive index. In this study the cancer tissues consisted of poorly differentiated adenocarcinomas that grew from the mucosa into the serous membrane. This tumor grade means that cancer tissue has abnormal-looking cells and may lack normal tissue structures [28]. Figure 3 shows that the tumor can be well discriminated from normal tissue by refractive indices from both the mucosa and the serosa sides. Also, optical properties of cancer tissue depend on its location.

4. CONCLUSION

In this work, we have studied normal and cancer fresh tissue of the stomach using terahertz time domain spectroscopy. The refractive indices of the inner (mucous) and outer (serous) membranes of the stomach, as well as poorly differentiated tumor localized in each of these membranes were obtained and compared for the first time. The results showed a difference between different types of tissues, as well as between cancer and normal tissues in both the mucous and serous membranes. The difference can be explained by the different morphology of the tissues. This work demonstrates the potential of the method of THz time-domain spectroscopy for gastric cancer diagnosis.

ACKNOWLEDGMENTS

This work was financially supported by Government of Russian Federation, Grant 08-08.

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