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Abstract. We demonstrate a reflective, continuous-wave terahertz (THz) imaging system to acquire *ex vivo* images of fresh human colonic excisions. Reflection measurements of 5-mm-thick sections of colorectal tissues were obtained using a polarization-specific detection technique. Two-dimensional THz reflection images of both normal and cancerous colon tissues with a spatial resolution of 0.6 mm were acquired using an optically pumped far-infrared molecular gas laser. Good contrast has been observed between normal and tumorous tissues at 584 GHz frequency. The resulting THz reflection images compared with the tissue histology showed a correlation between cancerous region and increased reflection. We hypothesize that the imaging system and polarization techniques are capable of registering reflectance differences between cancerous and normal colon. However, further investigations are necessary to completely understand the source mechanism behind the contrast and confirm the hypothesis; if true, it likely represents the first continuous-wave THz reflection imaging technique to show sufficient contrast to identify colon tumor margins. Also, it may represent a significant step forward in clinical endoscopic application of THz technology to aid in *in vivo* colorectal cancer screening. [DOI: 10.1117/1.JBO.18.9.090504]

Keywords: terahertz; polarization; cancer detection; reflection; medical imaging; colon tissues.

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Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the world with more than 1.2 million new cases diagnosed each year and causing 0.6 million deaths (as per World Health Organization Data & Statistics 2008). Early diagnosis is an effective method of reducing cancer risk. The staging and subsequent treatment of CRC is dependent upon current imaging technologies, such as colonoscopy, computed tomography scan, positron emission tomography (PET), magnetic resonance imaging, and optical computed tomography.[1] During colonoscopy, the gold standard for CRC diagnosis, the decision to remove abnormal growths is based on the physician's experience. However, the terahertz (THz) frequency range, located midway between the microwave and infrared region, has become increasingly important for biological applications[2] due to its nonionizing nature and sensitivity to water content. As THz imaging offers intrinsic contrast between normal and abnormal tissue,[3] a THz endoscope can be used as a potential tool in the examination and detection of cancerous or precancerous regions of biological tissue.

The potential of THz imaging for colorectal studies was encouraged by the positive results obtained from dental tissue, skin burns, breast, liver, and skin cancer studies.[4–6] A recent pulsed THz transmission imaging study showed a contrast between cancerous and normal colon tissues in the frequency range of 0.5 to 1.5 THz (with the greatest difference at 0.6 THz), based on the increased absorption and refractive index.[7] This study states that the higher water content in the cancerous region is likely to be the main source of contrast, which necessitates a reflection-based imaging modality for *in vivo* applications. However, another colon study based on dehydrated samples[8] also showed the evidence of contrast, suggesting the possibility of other contributing factors such as increase in lymphatic systems, vasculature, and other molecular/structural changes in the diseased tissue.[9] In the current study, we demonstrate a continuous-wave (CW) THz reflection-based system to image fresh colon tissues and a polarization-specific detection technique to reject the unwanted Fresnel reflections from interfaces. In order to obtain maximum contrast, the imaging system operates at a frequency of 584 GHz (∼0.6 THz).

Fresh thick excess colorectal specimens used in this study were obtained within 2 h after the standard surgical procedures performed at University of Massachusetts Memorial Medical Center, under an institutional review board-approved protocol. A total of 10 specimens from six individuals were collected. The thickness of the specimens varied between 4 and 6 mm, with the lateral dimensions between 10 and 20 mm. For THz imaging, the tissue specimens were mounted in an aluminum sample holder with 7×2.5 cm aperture that was covered with a 1 mm z-cut quartz slide. In order to prevent tissue dehydration during the imaging procedure, the specimens were covered with wet gauze soaked in pH balanced (pH 7.4) saline.

In order to investigate the feasibility of CW THz imaging for CRC detection, the reflectance of normal versus cancerous tissue was obtained using a CO_2 optically pumped far-infrared gas laser operating at 584 GHz (513 μm). The schematic of the optical setup is depicted in Fig. 1. The THz beam exiting the far-infrared (FIR) cell is collimated using a 61-cm-focal-length Polymethylpentene (TPX) lens and then passed through a horizontal wire grid polarizer, a 50–50 Mylar beam splitter, and finally focused to 0.68 mm using a 9-cm-focal-length off-axis parabolic mirror (OAP1) with 0-deg angle of incidence. An automated XY scan stage was used to raster scan the sample holder, containing a set of normal and cancerous colon tissues mounted next to each other, in the imaging plane with a spatial resolution of 0.1 mm. The signal remitted from the sample was collected by a liquid helium-cooled silicon bolometer detector obtained from Infrared Laboratories, Tucson, Arizona.

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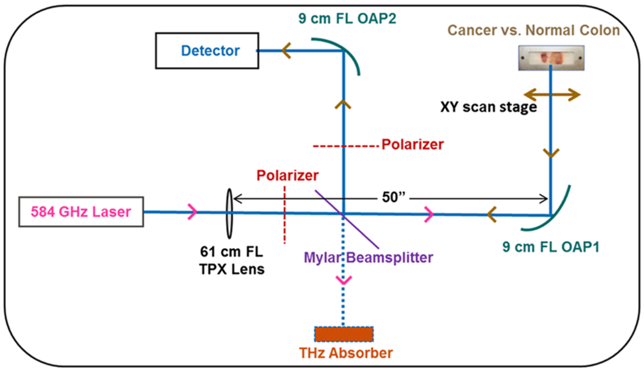

Fig. 1 Schematic of terahertz polarization imaging setup for colon cancer detection.

THz images were processed using a Labview® program that synchronized the sample position in the imaging plane with the return signal from the lock-in amplifier. The imaging system's signal-to-noise ratio was 65 dB. Both the co- and cross-polarized THz reflection images were obtained by collecting the signal remitted from the enface section of the colon specimens by placing an appropriate analyzing wire grid polarizer in the reflection arm. The data obtained from the tissue sample were then calibrated against the full-scale return from a flat front-surface gold mirror to determine the reflectance. The THz images were then plotted in logarithmic space, and the off sample areas were removed in postprocessing.

Unlike the time gating technique used in time-domain THz spectroscopic systems, the CW system that we used utilizes polarization to reject the Fresnel reflection from the air-glass interface. The copolarized THz response of the sample includes unnecessary reflection from the air-quartz and quartz-sample interfaces. In contrast, the cross-polarized THz response effectively rejects the specular reflections, as the Fresnel component is copolarized with the incident radiation and effectively samples the tissue volume. A recent study based on polarization imaging[6] showed the ability of cross-polarized THz imaging in delineating skin cancers.

In total, we measured 10 specimens from six subjects. Abnormal colon tissue and adjacent normal tissue were obtained from four individuals diagnosed with colorectal neoplasm, whereas normal tissue was acquired from each of the two normal subjects. The diagnoses were based on the analysis of hematoxylin and eosin-stained histopathology. Figure 2 shows a digital photograph and cross-polarized THz images of normal versus cancerous colonic tissue sets 1 and 2. The reflectance of the cross-polarized image varies between −21 and −23 dB. The off sample portion of the THz images was set to zero during postprocessing, so that only the THz response from the colon specimens was studied further. Contrast was observed between cancerous (C) and normal (N) colon tissue in each of two data sets, as shown in Fig. 2. Increased reflection of the cancerous region in the THz images of colon tissue indicates the altered THz response from tumor area. The data analysis confirmed that the reflectivity level for normal tissue was significantly different from cancerous region with a p value of 0.042 (<5% significance level). The THz images of normal tissues in Figs. 2(b) and 2(c) contained a solid white circle, representing high reflectance. These resulted from the air gaps that occurred between tissue and quartz slides during the mounting process,[10] which can be noticed clearly in the digital photographs of Figs. 2(a) and 2(d).

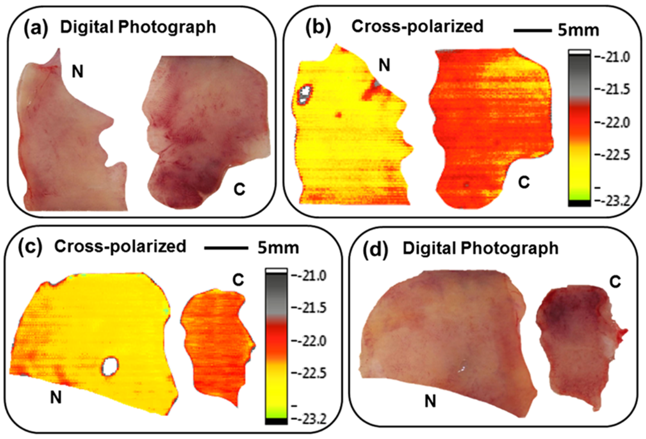

Fig. 2 Digital photograph, cross-polarized terahertz reflection images of fresh normal (N) versus cancerous (C) human colonic tissue set 1 [(a) and (b)] and set 2 [(c) and (d)].

For THz images, the percentage cross-polarized reflectivity of cancerous tissue was compared with adjacent normal tissue. Figure 3 displays column charts of averaged THz reflectivity values from fresh colon tissues, with the associated error bars. The reflectance difference between normal and cancerous regions of the colon tissue was observed at both polarizations with cross-polarized being more attenuated. Copolarized reflectance averaged over six normal and four cancerous tissues investigated was found to be 17.13 ± 0.28 and $19.28 \pm 0.31\%$, respectively. With cross-polarization, the averaged reflectance from normal samples was found to be $0.55 \pm 0.015\%$, while for cancer specimens it was $0.65 \pm 0.016\%$. Analysis of the reflectivity data from both co- and cross-polarized images showed that cancerous tissue had higher reflectivity than normal colon tissue. In addition, as shown in Fig. 3(a), an inconsistency in the copolarized reflectance difference between normal and cancerous regions of colon tissue was noticed for all data sets. This may have resulted from the fluctuations observed in the copolarized reflectance from normal colon tissue that contains the reflection from quartz-sample interface, which will vary for each data set (individual) as a function of tissue parameter such as refractive index, water content, etc. In contrast, from Fig. 3(b) it can be observed that the cross-polarized reflectance from normal and cancerous colon regions correlates well for all four data sets with a constant reflectance difference of 0.1%.

In general, comparing the cancerous areas to the adjacent normal areas of the same subject should yield good specificity. Hence, the relative difference in the reflected intensity between cancerous and normal areas was calculated for both co- and cross-polarized THz images using the background reflectance value obtained from saline soaked gauze with the formula

$$R_{\mathrm{rel}} = \left[\left(\frac{R_C}{R_B}\right) - \left(\frac{R_N}{R_B}\right)\right] / R_N = \frac{R_C - R_N}{R_N \times R_B}. \tag{1}$$

Here, R_C and R_N are the reflectance values of cancer and normal colon samples, whereas R_B represents the reflectance from background (saline-filled gauze).

Table 1 shows the calculated relative reflectance differences for colon samples measured at 584 GHz. It was observed that the relative reflectance values are >0 for all four data sets,

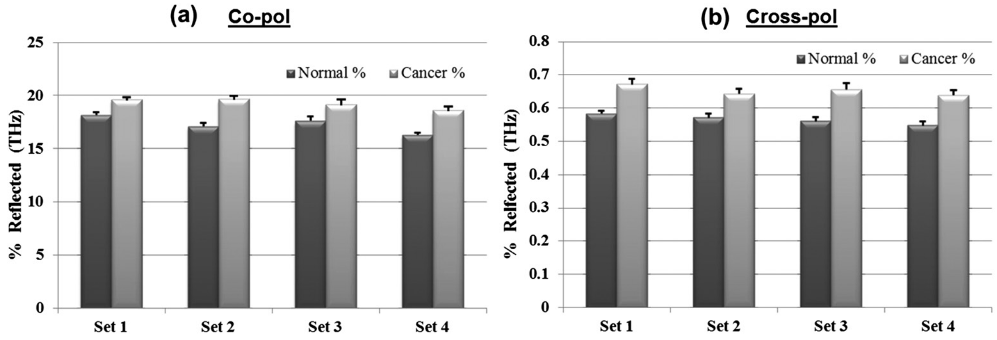

Fig. 3 Mean (a) copolarized, (b) cross-polarized terahertz reflectivity (%) from normal versus cancerous colon tissue at 584 GHz, which correlates well for all four data sets, with a calculated p value of 0.016.

Table 1 The relative reflectance difference between normal and cancerous colon tissues at 584 GHz.

Sample #	Copolarization ($\times 10^{-1}$%)	Cross-polarization (%)
Set 1	1.53	7.74
Set 2	3.03	7.74
Set 3	1.56	7.75
Set 4	2.44	7.30

representing the higher reflectivity values from abnormal tissues. This can be caused by the higher refractive index value associated with cancerous tissue as compared to normal. If true, the reflectivity from the tumor-quartz interface would be higher for abnormal regions as compared to normal. However, the signal from all interfaces was rejected in the cross-polarized images. Thus, their contrast is determined primarily by the refractive index fluctuations within the sample volume.

The high reflectivity values of cancerous colon tissues in cross-polarized imaging can possibly be attributed to the greater scattering resulting from increased vasculature, lymphatic systems, and other structural changes in diseased tissues. Given the wavelength of THz imaging, normal colon will look fairly homogeneous with minimal refractive index fluctuations. In contrast, abnormal tissues such as hyperplastic mucosa with larger crypt sizes (order of imaging wavelengths) cause greater mismatch in local refractive index and results in higher cross-polarized signal. From Table 1, it can also be observed that the relative reflectance difference for all the cross-polarized THz images were consistent. This suggests the possibility of using cross-polarized THz imaging in detecting CRC; however, the cause of the contrast needs further investigation.

To the best of our knowledge, this is the first study to use polarization-sensitive CW THz imaging for colon cancer detection. By implementing cross-polarized reflectance THz imaging, we were able to show a contrast between normal and cancerous colon tissue by rejecting specular reflections. The analysis indicates that the imaging system and polarization techniques are capable of registering reflectance differences between cancerous and normal colon. However, to obtain reliable statistics, a larger number of samples need to be studied. A pilot study is underway that will establish the sensitivity and specificity of the CW THz imaging of colorectal cancer demarcation.

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