Terahertz Imaging for Margin Assessment of Breast Cancer Tumors

Ahmed M. Hassan1, David C. Hufnagle2, Magda El-Shenawee1 and Gilbert E. Pacey3,4

1Department of Electrical Engineering, University of Arkansas, Fayetteville, AR 72701
2Department of Chemistry and Biochemistry, Miami University, Oxford, OH, 45056
3Ohio Wright Center for Innovation, IDCAST, Dayton, OH 45402
4University of Dayton Research Institute, Dayton, OH 45469

Abstract — This work presents experimental terahertz measurements of excised formalin fixed paraffin embedded (FFPE) human breast cancer tissues. The data are collected using a terahertz pulsed system operating from 0.1 THz to 3THz. The results represent preliminary investigation of terahertz imaging technique for assessing the tumor margins. The direct imaging method will be compared with inverse scattering imaging methods using the experimental data along with histopathological images as references.

Index Terms — Terahertz imaging, tomography, level set, tomography, inverse scattering methods, breast cancer

I. INTRODUCTION

Due to advances in breast cancer detection techniques, the majority of breast tumors of less than 2cm in diameter will most likely be detected [1]. For these cases, Breast Conserving Surgery (BCS), also known as lumpectomy, is a desirable surgical treatment where only the localized tumor is removed in addition to a minimal margin of healthy tissue. The localized tumor excision reduces disfigurement of the breast compared with radical mastectomy. Following the surgery, the margins of the excised tumor tissue are analyzed by a pathologist to judge if they are (i) positive margins where cancer cells extend to the edge of the excised tissue, (ii) negative margins where no cancer cells are found within a certain distance, 1-10 mm, from the edge of the excised tissue, and (iii) close margins which fall between the positive and negative margins.

Pathological analysis of excised tissue can take several days and in the case of positive margins, a second surgery is needed to remove more tissue [2]-[4]. The second operation increases the chance of infection, increases breast disfigurement, increases the cost of the treatment, and reduces the confidence of the patient in the surgeon [4]. The literature reported that 20-70% of the time, the excised malignant breast tumors contained positive margins [4]. Therefore, breast surgeons continuously look for a technique that can assess the margins of excised tissue intra-operatively, such that the malignant tumor with adequate negative margins can be removed in a single surgery.

Electromagnetic waves in the terahertz (THz) band are capable of differentiating between fresh excised healthy and cancerous tissue due to the contrast in optical properties between the two tissue types [5]-[8]. Also, a main advantage of THz imaging is its ability to perform on fresh tissue; therefore, it can provide a quick diagnosis. Ashworth et al. in 2009 [5] measured the refractive indices of freshly excised cancerous and healthy tissues. The study showed significant differences in the optical properties between cancerous and healthy fatty tissues whereas it showed a difference in the order of ~10% between cancerous and fibrous tissue [5]. Moreover, the study concluded that the contrast in optical properties between cancerous and healthy tissue was not solely due to the difference in water concentration [6].

Other factors could contribute to the contrast such as the increased vasculature of cancerous tissue, the decreased lipid content, the increased cell density, and the presence of certain proteins or biomarkers [6]. In fact, water concentration was not the only source of contrast between cancerous and healthy tissue as corroborated by other studies that involved tissue samples fixed in formalin, dehydrated, and embedded in paraffin (FFPE) [7]. Preliminary studies estimated that water accounts for only ~50% of the contrast in optical properties between cancerous and healthy cells [7]-[8].

However, in order to quantitatively assess the accuracy of the THz images, a comparison with histopathologic images is needed. Care must be taken regarding the thickness of tissue samples; they need to be thin enough for the histopathological photos but thick enough for THz imaging [7]. Brun et al. conducted tomography process followed by principal component analysis (PCA) to classify the pixel region type as healthy, cancer, or intermediate. Although, classification of the THz images using PCA was capable of clearly revealing the tissue type of each region of squamous cell carcinoma (lung cancer), the results were not as clear for the invasive carcinoma where the cancer regions were highly intermingled with healthy tissue.

The objective of this work is to demonstrate that THz images can be improved using rigorous inverse scattering techniques instead of only using direct reflection or transmission modes or using simple signal processing techniques. These methods do not account for several factors such as multiple reflections, attenuation, dispersion and diffraction. The impact of these factors could be significant for thick tissue samples and when the size of cancerous regions in excised tissue is comparable to the wavelength. For example,
tumor regions in invasive and ill-defined tumors are highly intermingled with healthy tissue as shown in [7]. If THz images are obtained using direct reflection or transmission, the highly intermingled cancerous with healthy regions may appear blurred and difficult to identify.

II. EXPERIMENTAL THZ MEASUREMENTS OF FFPE BREAST CANCER TISSUE

Four different breast tissue FFPE samples were purchased from a tissue bank (BioServe Biotechnologies, Ltd). These four samples were obtained from the same excised tumor from a 38 years old patient. The tumor was classified to be invasive ductal adenocarcinoma and it had a triple negative phenotype.

The THz imaging setup was conducted using the system TPI Imaga 1000 (Teraview Ltd). The TPI system utilizes a time domain THz picosecond pulse raster scanned to image a window of 25.4mm×25.4mm (Fig. 1a). In order to extract the signature of the tissue sample, two measurements were typically performed: (i) one scan with the tissue sample positioned on the quartz window (Fig. 1a), and (ii) one scan with a mirror, instead of the sample, also positioned on the quartz window. The mirror measurement acts as the reference used to calibrate the measurements [9]. Calibration is necessary to remove the background effect from the tissue signature [9]. The four FFPE tissue samples were selected with different thicknesses: 20 µm, 10 µm and 5 µm (2 samples); one is stained and one is unstained as shown in Fig. 1b and c.

During the THz scanning, the system is being purged with Nitrogen gas in order to remove any water vapor that can attenuate the THz waves. The incident and reflected THz beam is raster scanned to cover the area of the tissue sample on the window. The THz system can provide image resolution up to 80 µm; however, the tissue sample is first scanned at low resolution, e.g. 300 µm, which only takes few minutes to complete. Once the coarse images are examined, the spatial limits of the sample are determined and then scanned with the highest resolution of 80 µm.

Imaging the tissue samples of thickness 5 µm and 10 µm shown in Fig. 1b and 1c was unsuccessful because of the small thickness of these samples compared with the wavelength. The reasons is that the two signals reflected from the lower and upper interfaces of the sample overlap, arrived almost at the same time making it difficult to obtain a meaningful image of the tissue. On the other hand, when the 20 µm thick slide show in of Fig. 1a was scanned using the same system, meaningful images were obtained as shown in Fig. 2. In this case, the received signals from the sample interfaces do not overlap as much as in the thin samples case.

The data was collected in the time domain and then transformed to frequency domain using the FFT. THz images using direct reflection method were obtained and plotted at 2 THz and 3 THz, as shown in Fig. 2a and 2b. Upon comparing the images in Fig. 2a with 2b, it can be seen that at higher frequency, 3 THz, the image shows more fine features in the tissue that was not clear at the 2 THz image, as expected. In addition, the obtained images clearly show strong heterogeneity of tumor tissue which indicates to the capability of THz waves to identify different regions on the slide.

After the THz images were acquired, the slides were stained by an independent pathologist and histopathologic images of regions A and B in Fig. 1a are obtained as shown in Fig. 2c and 2d, respectively. The cancer regions appear bluish or purple whereas the fibrous regions appear pink. The dark red region in the bottom of Fig. 2d represents a region of folded tissue where it was hard, according to the pathologist, to classify the fibrous and cancer tissues. Also, the pathologist indicated that the slide was highly heterogeneous with several small nodes of cancer tissue embedded in fibrous tissue. Therefore, an image of the whole slide was not presented but instead multiple magnified images of different regions were obtained as shown in Fig. 2c and 2d.

The histo-pathological images of Fig. 2c and 2d are compared with the THz images of Fig. 2e and 2f, for the same regions A and B. The results show that region A, in Fig. 2c contains more tumor nodes (purple regions) than region B in Fig. 2d. This observation correlates well with the THz image where region A has a higher magnitude (red regions) of reflected THz waves than region B (blue region) indicating to cancerous tissues as shown in Fig. 2a and 2b. Also, the results of THz images in Fig. 2c and 2d, show strong scattering near the boundaries of the excised tissue, as in region A for example, indicating that the tumor margin is positive and that more tissue needed to be removed from the patient. This correlates well with the histopathologic images which also show cancer regions, purple in color, at the boundaries of the slide in Fig. 2c. However, the direct reflection method, used in...
Fig. 2, for THz image was incapable of resolving the small features, like the small tumor nodes.

III. CONCLUSION AND FUTURE WORK

In this work, THz images were acquired using terahertz pulsed subsystem from heterogeneous FFPE breast cancer slides. The THz images were obtained using the direct reflection method. However, to accurately assess tumor margins, rigorous imaging techniques are needed, in particular inverse scattering and tomography methods. We are motivated by the fact that the inverse scattering algorithms typically achieve at least one order of magnitude improvement in the resolution compared with Rayleigh resolution [10]. In the conference presentation, we will present results using the linear sampling method (LSM) to image the tumor margins [11]. The LSM method, although qualitative, will provide estimates of cancerous margins in real time. In the future, we will implement more quantitative imaging methods using inverse scattering algorithms, e.g. the distorted Born Iterative Method [10] and the level set method [12].

Fig. 2: Images of the 20µm FFPE slide. (a) THz image of the slide at 2THz, (b) THz image of the slide at 3THz, (c) Magnified histopathologic image of region A in Fig. 1a (Stained), (d) Magnified histopathologic image of region B in Fig. 1a (Stained), (e) Magnified THz image of region A at 2THz, and (f) Magnified THz image of region B at 2THz.

ACKNOWLEDGEMENT

This work was sponsored by the Army Research Laboratory and was accomplished under Cooperative Agreement Number W911NF-10-2-0093. The views and conclusions contained in this document are those of the authors and should not be interpreted as representing the official policies, either expressed or implied, of the Army Research Laboratory or the U.S. Government. The U.S. Government is authorized to reproduce and distribute reprints for Government purposes notwithstanding any copyright notation herein.

REFERENCES