An intra-operative THz probe for use during the surgical removal of breast tumors

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Abstract— **A portable intra-operative scanning terahertz (THz) probe has been developed for medical use by TeraView Ltd to aid surgeons in the removal of breast tumors by providing positive identification of diseased tissue in real-time. Initial *ex vivo* tests have been carried out using this system at Guy's Hospital, London, its ability to perform in a clinical environment has been tested by comparing THz data with histological diagnosis of localized areas of breast tissue from 27 patients as well as examination of sentinel node biopsies (SNB) of 37 patients. In this paper the system is described and findings of this initial study are discussed.**

I. Introduction And Background

One in eight women will be diagnosed with breast cancer at some point during their lives[1] and each year around 40,000 women die as a result of the disease in the US alone making breast cancer the second most common form of cancer among women and the third leading cause of cancer related death. About 60% of patients with early breast cancer undergo breast conserving surgery which involves removal of the primary tumor whilst preserving as much of the healthy tissue as possible. The difficulty with this technique is that often the existing methods used to define the margins of tumors intra-operatively such as specimen x-ray mammography and palpation are unreliable and can leave the surgeon making a "best guess" as to the extent of the tumor. The current practice to determine if a tumor has been completely removed requires histopathological examination of the removed tumor; this is a very time consuming means of diagnosis taking 5-7 days so it cannot be performed intra-operatively. As a result between 15-20% of these patients require secondary procedures[2], taking place sometimes weeks after their first operation, to remove potentially cancerous tissue which has been left behind after the initial surgery. This leads to further psychological and physical trauma, a need for additional medical care and increased risk of complications as well as resultant delays in adjuvant therapy. With the expansion of screening programs and an increase in the use of pre-operative chemotherapy and endocrine therapy (which is designed to downstage tumors), it is likely that the number of women requiring breast conserving surgery will significantly increase in relation to those undergoing mastectomies. As such there is a strong motivation to develop techniques that will reduce the number of re-excision procedures required.

The previously relatively unexplored THz region of the electromagnetic spectrum (0.1 – 10 THz) shows great potential as a tool for medical imaging through its' unique sensitivity to water[3] and non-ionizing nature[4]. In 2006 it was shown that THz Pulsed Imaging (TPI) could be used to distinguish between healthy fibrous breast tissue, adipose (fatty) tissue and cancer with a sensitivity and specificity of 92% and 91% respectively based on the use of support vector Machine (SVM) processing of THz data[5]. Furthermore it was shown that ductal carcinoma in situ (DCIS), a common form of breast cancer that is particularly difficult for surgeons to distinguish from normal tissue, could be resolved using TPI. Further spectroscopy work has shown that the contrast seen can primarily be attributed to a difference in the refractive index of adipose (fat), fibrous and tumor tissue[6].

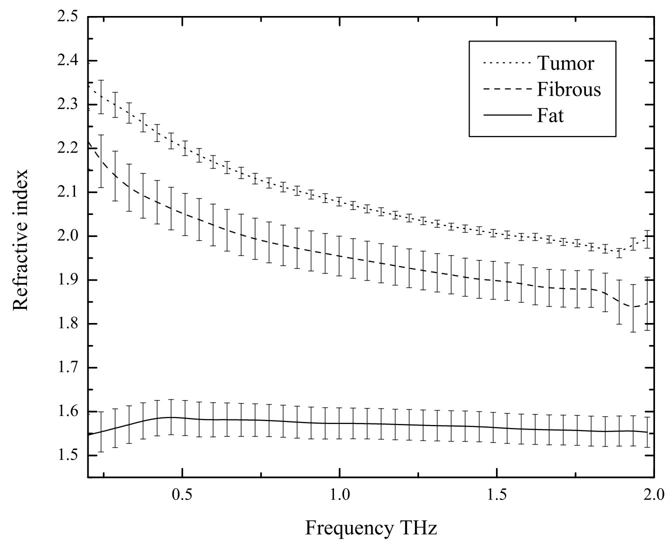

Figure 1: Graph showing refractive indices of 3 tissue types. Error bars represent 95% confidence intervals

II. Experimental Setup

TeraView Ltd. (Cambridge, UK) has developed a handheld THz probe designed to be used intra-operatively by surgeons when removing breast tumors. The system uses a Ti:Sapphire laser that produces 90fs 800nm pulses at a rate of 80MHz. These are guided down optical fibers, contained within an "umbilical" cord alongside electrical cables, to the probe (approximately 2 inches in diameter) where they are incident on a photoconductive emitter and receiver (gold electrodes on a GaAs Substrate) producing and detecting THz pulses of bandwidth 0.1 – 2 THz. The THz pulse beam is focused to the probe tip, a smooth edged z-cut quartz measuring window

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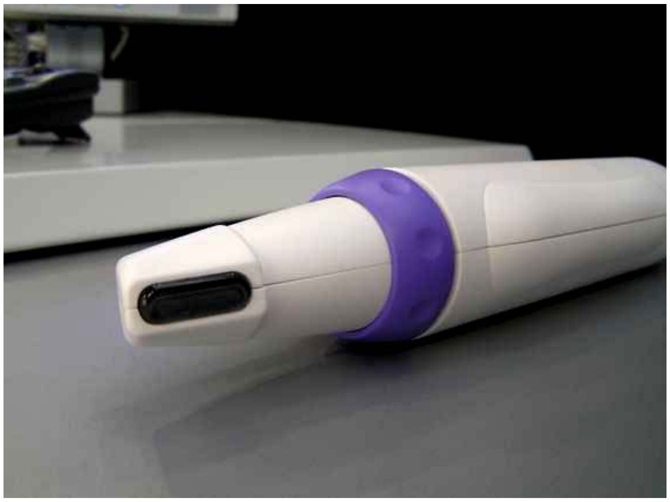

Figure 2: Picture showing the medical THz probe head and operational tip.

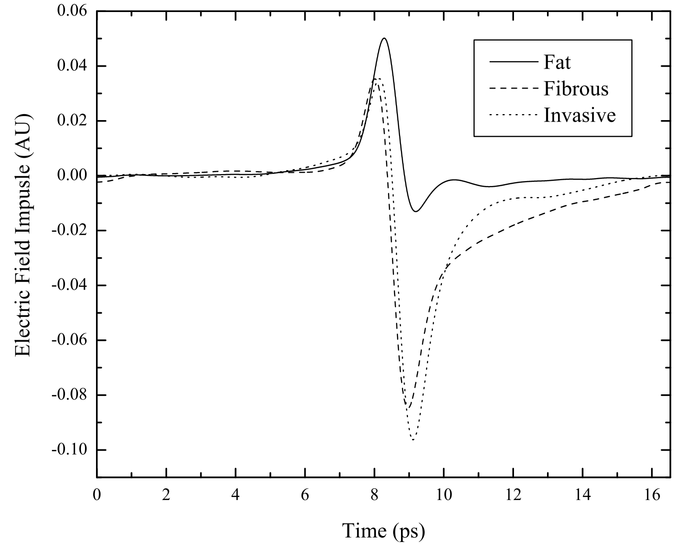

Figure 3: Typical Pulse responses to the 3 main tissue types seen in specimens from which parameters are calculated.

from which they are reflected back, through a silicon lens and a system of Risley beam steering prisms. The THz pulse beam is scanned back and forth across the active area by controlled rotation of the Risley prisms. The system has a lateral resolution of 0.7mm (~1mm at 1THz) and a scan speed of up to 8 lines per second. The scan length of individual lines was 7mm, adjustable to 15mm by use of replacement Risley prisms. The system has a measured axial resolution of better than 50μm and a signal to noise ratio on the receiver of 800:1 in amplitude (~10000:1 at 1THz). For the purpose of these measurements the probe was wrapped in a disposable protective sheath specifically designed to protect the instrument, and those handling it, against contamination and from potential biohazards, whilst allowing clear transmission of the THz signal to specimens.

Over a 2 month period 37 patients undergoing mastectomies, wide local excisions (WLEs) and sentinel node biopsies (SNB) took part in the study. All patients provided informed signed consent for their tissue to be used for THz research purposes and ethical approval was granted by the Local Research Ethics Committee (LREC). Tissue specimens removed from patients during mastectomy and WLE operations were immediately brought to the histopathology department in Guy's hospital; there localized areas of breast tissue that were excess to diagnostic requirements were measured for 20 seconds using the probe. All measurements of tissue were carried out within 30 minutes of the surgical procedures. Tissue specimens that had been used for the study were then marked for orientation purposes and subjected to standard histological methods to determine the percentage of tissue types (fat, fibrous and cancer) present in these areas. The measured reflected pulses from specimens were analyzed by removing a baseline, a measurement of z-cut quartz, in the time domain and comparing with a reference, measured against air, in the frequency domain to provide processed pulses or THz impulse responses of the tissue as shown in figure 3. A number of distinguishing features (or parameters) of the processed pulses were then identified, such as maximum amplitude and full width half maximum (FWHM) as had been found to be of relevance by Fitzgerald *et al.*[5] in SVM analysis. The calculated values of each of these parameters were then averaged for all reflected pulses measured from their respective specimens giving a single averaged value of each parameter for each specimen measured.

Specimens collected from patients undergoing SNB procedures were scanned on 2 opposing sides of the nodes before being dissected and scanned internally. Nodes were then sent for standard histological diagnosis. Nodes often had a large quantity of patent blue V dye, used by the surgeons to locate the nodes during the biopsy procedure, it should be noted that THz spectroscopy was performed on this dye using TPI spectra 2000 developed by TeraView Ltd[7] and no significant spectral features were found; it is therefore assumed this dye does interfere with our results. Parameters calculated from processed measured pulses for these specimens were averaged in the same way as described above.

III. Results and Discussion

Figure 4 shows the average of 4 parameters for areas of tissue from 27 patients that contained more than 75% of the respective tissue type where "Cancer" includes both invasive tumors and DCIS. "Fat" and "Fibrous" were averaged from specimens containing no cancer. The values are normalized with respect to fibrous tissue and the error bars represent 95% confidence intervals. Parameters that relied on information derived from the phase of pulses were found to be inaccurate and so have been excluded here. This inaccuracy was caused by a temporal shift in the pulses when moving the probe head as a result of stresses within the optical fibers. A solution to this problem has since been developed and implemented however no new data has been collected since that could be

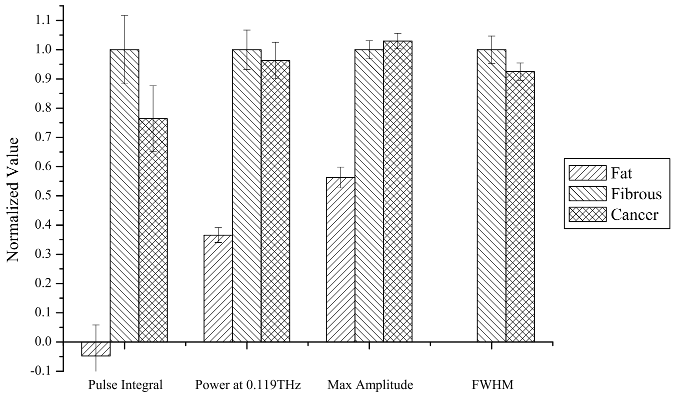

Figure 4: Graph showing average parameter values, normalized with respect to fibrous tissue, for different tissue types as measured by the probe. The error bars represent 95% confidence intervals.

included in these results. In the results shown in figure 4 slight differences can be seen between fibrous tissue and tumors in the parameters "Pulse Integral" and "FWHM". No difference can be seen between fibrous tissue and cancer in "Max Amplitude" and "Power at 0.119 THz" however a clear difference can be seen when compared with fat. This is an important result as it allows the fat content to be determined and that partial fat- fibrous mixtures may be distinguished from tumors when processing the results through SVM. The parameter "FWHM" does not have a value for fat presented here as the parameter was calculated based on the trough of the processed pulses, this was not a reliable algorithm when used in conjunction with fat as the troughs on the processed pulses were too small, as could be seen in figure 3, and were not consistent in shape. When the data collected from specimens reported to be DCIS were examined independently of invasive tumors in this way similar results were observed.

No results for the measurements taken on SNBs are presented here as although data was collected for 37 patients only 4 nodes were reported as being either affected by either micro (3 nodes) or macro metastasis (1 node). The results for these 4 nodes were very promising although may be misleading due to the small size of the data set. If results in future work agree with these early measurements it would imply that THz imaging is suitable for registering a change in the nodes taking place as a result of the presence of cancer rather than just imaging the cancer directly. This is because it was not expected that THz imaging would resolve small islands of cancer that occur in micro-metastasis yet the early results witnessed seem to imply that THz imaging can distinguish a difference between healthy nodes and nodes affected by micro-metastasis. If this is true then THz imaging could prove also to be a viable tool for surgeons to use to diagnose the state of sentinel nodes and improve patient care by reducing time between tests and further surgical procedures.

IV. CONCLUSIONS

Initial results show that differences are observed between cancer and healthy fibrous tissue, using THz imaging, consistent with previous studies as well as a suggestion from very preliminary results that involved lymph nodes may be diagnosed in real time. The system's ability to successfully perform as a real-time THz medical diagnostic device has been demonstrated and, as a result of inconsistencies, improvements were made so that phase information could be derived accurately from the data.

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