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ELECTRICAL IMPEDANCE SPECTROSCOPY FOR PROSTATE CANCER DIAGNOSIS

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***Abstract*—Electrical impedance was recorded at 21 discrete frequencies (1 to 100 kHz) from 27 ex vivo human prostates. These electrical properties were measured by using custom designed Electrical Impedance Spectroscopy (EIS) sensing biopsy (Bx) needles. EIS-Bx needles gauge the electrical properties of tissue in tandem with the tissue extraction (used for histopathological assessment). The EIS-Bx probe has a signal-to-noise ratio (SNR) of 65 dB across the frequency range (1 kHz to 100 kHz). A total of 36 cancers and 288 benign regions were sampled from 27 human prostates. Mean resistance (R) of prostate decreased from 537.27 Ω to 126.74 Ω for benign tissues and 999.52 Ω to 340.67 Ω for malignant tissues across the 1 kHz - 100 kHz spectral range. Likewise, mean reactance (X) ranged from -391.41 Ω to -62.6 Ω for benign and -675.09 Ω to -162.28 Ω for cancer tissues over the same frequency range. Both R and X values are found to be significantly lower in normal prostate tissues than in malignant tissue (p<0.001). Further testing to evaluate the clinical efficacy of this coupled device is underway.**

I. INTRODUCTION

Prostate cancer is the second most common cancer found in American men after skin [1]. Diagnostic confirmation of prostate cancer is based on microscopic assessment of tissue samples extracted during a standard 12 core biopsy procedure. The conventional biopsy technique samples a very small volume of prostate gland (typically <1% of 24cm^3 prostate) leading to misdiagnosis and inaccurate assessment of disease severity [1] [2] [3]. Previous studies have shown the significant contrast between electrical properties of benign and malignant tissues [4] [5] [6] [7]. These contrasts are due to morphological differences present in the different prostatic tissue types. We have developed an electrical impedance spectroscopy (EIS) sensing biopsy (Bx) needle to record bipolar impedance measurements in tandem with tissue core extraction. We have demonstrated that this type of data has the potential to distinguish normal from abnormal tissue across a larger fraction of prostate volume than that sampled during conventional biopsy procedure [8] [9]. We present our most recent analysis of a 27 patient cohort evaluating how well these electrical properties discriminate cancer from non-cancer tissues in the prostate.

II. EIS-BX DEVICE OVERVIEW

Device Design

A typical biopsy needle is constructed of stainless steel and consists of an inner trocar and an outer cannula. BARD Maxcore Disposable Biopsy Instruments (MC1820, C.R. Bard, Murray Hill, NJ) extract a 22 mm long tissue core and are the standard biopsy needles used for prostate biopsy at our institution. These needles are modified into an EIS-Bx device by electrically isolating the two (inner and outer) needle elements; a thin insulating tube (polyimide) is adhered onto the surface of each of these elements, leaving just the tip of both needles exposed. The tips of inner and outer elements act as two electrodes, through which EIS based bipolar measurements are recoded. The two electrodes are interfaced to an impedance analyzer (HP4284A, Agilent Technologies) through a RCA plug and assembly of coaxial cables. A small current (<1mA) is applied between the tip electrodes. The impedance recorded is the ratio of induced voltage to the applied

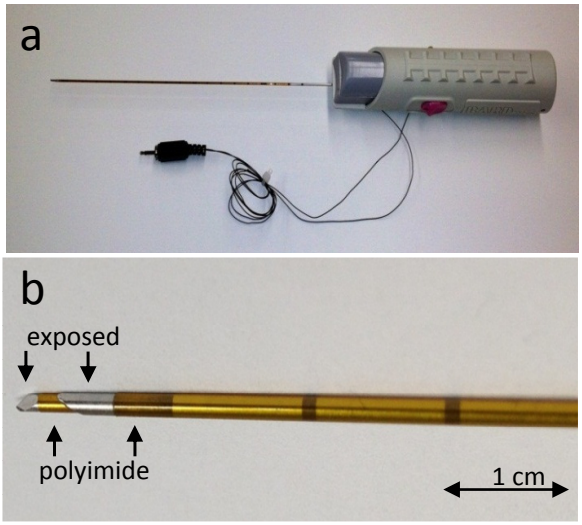

Figure 1: EIS-Bx probe design, with polyimide insulation used in clinical phase of the program: [reproduced from [10]]

current, at 21 discrete frequencies ranging from 1 kHz to 100 kHz. System control by a laptop computer is established through an USB-to-GPIB interface controller. A user interface was developed in Visual Basic to record resistance (R) and reactance (X) at 21 discrete frequencies ranging from 1 kHz to 100 kHz [6] [7] [8]. An example of the designed diagnostic device used in clinical EIS biopsy procedure is shown in Figure 1[10].

III. Device Characterization

A. *Signal-to-noise*

The signal-to-noise ratio (SNR) of the EIS-Bx device was evaluated by performing 100 repeated EIS measurements using a 470 Ω discrete resistor load. Mean impedance magnitudes were 471.4Ω ± 0.3Ω at all frequencies ranging from 1 kHz to 100 kHz, and mean phases were $-1.87\times10^{-5}\pm5.84\times10^{-6}$, $-2.97\times10^{-5} \pm 1.54\times10^{-5}$, and $-3.88\times10^{-4} \pm1.22\times10^{-4}$ (in degrees) at 1 kHz, 10 kHz, 100 kHz, respectively. SNR values computed over these repeated measurements were 65 dB, 64.8 dB and 65 dB for 1 kHz, 10 kHz, and 100 kHz, respectively.

IV. Preclinical Ex-vivo Evaluation

A total of 27 prostate specimens were extracted from men undergoing robot assisted radical prostatectomy procedures. Each ex-vivo prostate is held within a custom designed tank by a suspension mechanism. The tank is filled with saline solution of 0.1 S/m which imitates the electrical properties of the pelvic cavity surrounding the prostate. A 3D ultrasound image of the specimen is acquired from a transrectal ultrasound (TRUS) probe (TargetScan TS-360-P Envisioneering Medical Inc, St. Louis, MS). The position of TRUS probe is fixed in the tank using a rigid stand.

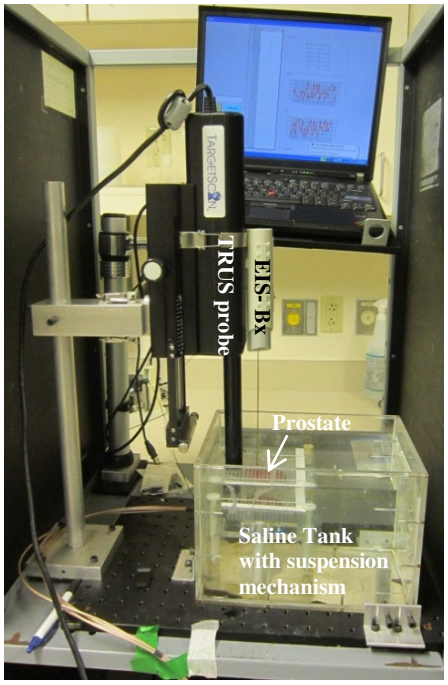

Figure 2: Experimental configuration for mounting a tissue specimen, imaging it with TRUS, and introducing the EIS-Bx device at specific locations.

Based on the acquired TRUS image, 12-core systematic biopsy was executed. A graphic user interface (GUI) was developed in matlab which provides the 12 biopsy locations in the prostate (right medial base, right medial mid, right medial apex, right lateral base, right lateral mid, right lateral apex, left medial base, left medial mid, left medial apex, left lateral base, left lateral mid, left lateral apex). The boundaries (top, bottom, right, and left) of the prostate are specified by user in the GUI. Within this bounded box, this program identifies 12 locations at the intersection of 4 equally spaced columns and 3 equally spaced rows where the EIS-Bx is introduced to the specimen.

a)

b)

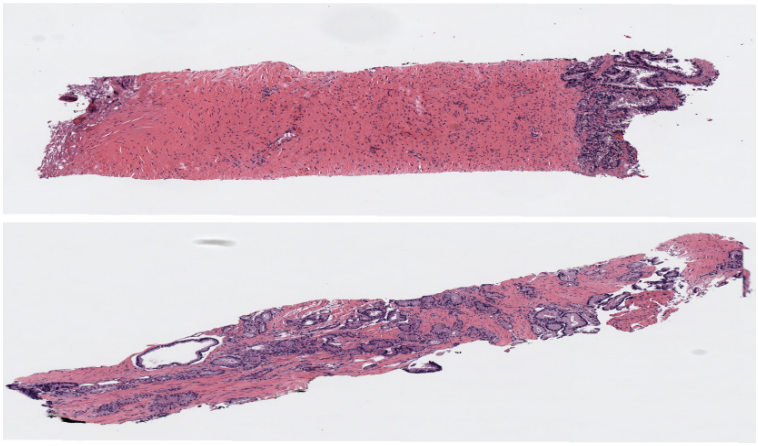

Figure 3: Photomicrographs showing; a) Benign tissue cores extracted by EIS-Bx protocol. b) Malignant tissue core.

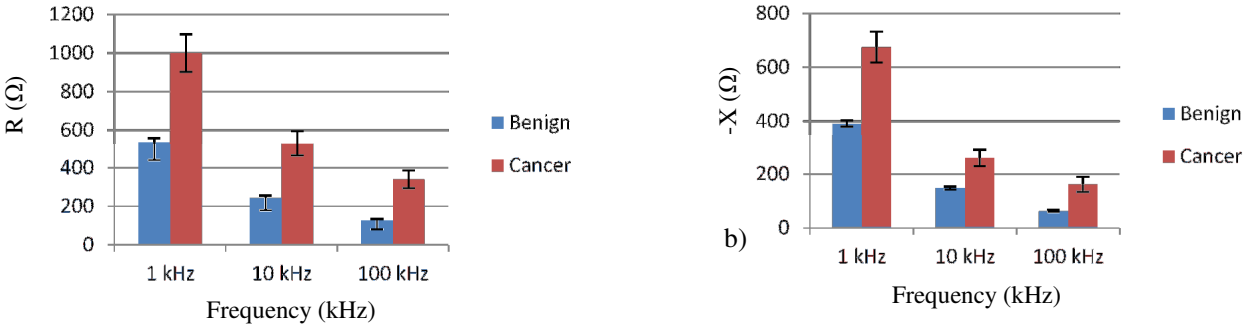

Figure 4: Shows mean impedance (R and X form) a) Mean resistance for 1, 10 and 100 kHz respectively. b) Mean reactance for 1, 10 and 100 kHz respectively. Error bar represents the standard error.

This systematic approach of identifying grid locations enables the core extraction from similar locations for all specimens independent of specimen size [10].

The needle was introduced into the prostate specimen at the specified locations, inserted to a depth at which both electrodes were below the prostatic surface, an impedance spectrum was recorded, and finally, the needle was fired to obtain the tissue core. The EIS-Bx has radial and axial sensitivities of ~4mm and ~3mm, respectively [9]; because the probe was inserted sufficiently deep into the prostate (>4 mm), the saline solution surrounding the tissue did not have a significant influence on the measurements. The extracted biopsy sample is microtomed, stained with H&E, and microscopically evaluated by a pathologist to determine if benign or malignant cells are present in tissue core (Figure 3).

V. RESULTS

The EIS-Bx device has been used to record electrical impedance spectra along with tissue extraction from a series of 27 ex vivo prostate specimens. A total of 324 prostatic tissue cores were extracted (12 cores per prostate × 27 prostates). Of these, 288 were found to consist of only benign tissues, while 36 had evidence of tumor. The mean lengths of these cores were reported to be 12.5 mm ± 5 mm.

Impedance magnitude was noted to decrease monotonically with frequency. Malignant tissues are observed to have significantly higher resistance and reactance than the benign tissues at all frequencies probed with the EIS-Bx needle ($p<0.001$) (Figure 4). Mean resistance decreased from 537.27 Ω (@ 1 kHz) to 126.74 Ω (@ 100 kHz) for benign tissues and from 999.52 Ω (@ 1 kHz)to 340.67 Ω (@ 100 kHz) for malignant tissues.

Similarly, mean reactance (X) ranges from -391.41 (@ 1kHz) Ω to -62.6 Ω (@ 100 kHz) for benign and -675.09 Ω (@1kHz) to -162.28 Ω (@100 kHz) for malignant tissues, respectively, over the same range of frequencies. p-values for R and X were evaluated by performing two tail t-tests, assuming unequal variances between malignant and benign tissue impedances. p-values, along with mean and standard deviations for resistance and reactance are reported in Table 1 and Table 2 respectively. Both were found to be statistically significant ($p<0.001$).

Resistance (Ω)	1 kHz	10 kHz	100 kHz
Mean Benign (Ω)	537.27	243.98	126.74
S.D. benign	361.20	203.71	116.6
Mean Cancer	999.53	529.79	340.67
S.D. cancer	583.67	389.58	275.19
p value	4.03×10^{-05}	1×10^{-04}	4.63×10^{-05}

Table 1: Mean resistance, standard deviation and p values reported for benign and malignant prostatic tissues.

Reactance (Ω)	1 kHz	10 kHz	100 kHz
Mean Benign (Ω)	-391.41	-148.28	-62.60
S.D. benign	184.26	96.04	62.09
Mean Cancer(Ω)	-675.09	-260.34	-162.28
S.D. cancer	343.38	185.77	169.14
p value	1.5×10^{-04}	1.0×10^{-03}	1.2×10^{-03}

Table 2: Mean reactance, standard deviation and p values reported for benign and malignant prostatic tissues.

VI. DISCUSSION

The statistical analysis of electrical impedance (R and X) gauged by EIS-Bx suggests the capability of distinguishing cancer from benign tissues. The impedance recorded using this device was found to

be larger for cancer tissues than for benign prostatic those reported in the literature for different tissues [5] [6] [11]. The standard deviation is found to have high values as reported in Tables 1 and 2. This may arise from actual variation in the tissue or in the probe construction. Moderate tissue impedance variation between multiple tissue samples has been previously reported to be on the order of 15% [6]. Probe construction took place in a laboratory setting. The exposed electrode lengths had variations on the order of 10% (1 +/- 0.1 mm in length). These variations will give rise to different effective impedances. One way to mitigate this is to calibrate the individual needles by recording impedance from known loads (such as saline solutions) and determining a geometry factor to convert impedances into needle-independent resistivities or admittivities.

The contrast in electrical properties of benign and malignant tissues is dependent on the pathology of the tissue probed, lesion size and Gleason grade. While it is difficult to predict the exact minimal lesion size detectable by the EIS-Bx device, the average lesion length noted here was 2.47mm. Lesions were binned into two categories based on their lengths (L) i) $L \leq 2$mm and ii) $L > 2$mm. The results tabulated in table 3 & 4 suggest that the contrast increases with length of lesion.

R (Ω)	1kHz	10 kHz	100 kHz	No. of lesions
L≤ 2mm	975.2	516.7	326	25
L>2mm	1054.8	559.4	374.2	11

Table 3: Variation of resistance (Ω) with the length of lesion (mm).

X (Ω)	1kHz	10 kHz	100 kHz	No. of lesions
L≤ 2mm	-660.1	-253.1	-159.2	25
L>2mm	-710	-276.4	-170	11

Table 4: Variation of reactance (Ω) with the length of lesion (mm).

Limitations to this study include: 1) impedance recorded with EIS-Bx at lower frequencies are significantly influenced by contact impedance due to bipolar configuration of the device, 2) variation in the homogeneity of tissue probed influence the impedance recorded and make it difficult to assign a single tissue type to a particular impedance spectra, 3) data was recorded from ex vivo prostates. Further studies involving a tetrapolar probe design, larger sample sizes, and in vivo measurements are suggested for better assessing clinical value.

VII. Conclusion

The differences observed between the electrical spectra of malignant and benign tissues are due to the morphological differences present in the architecture of tissues probed. The results presented here suggest that this coupled device has the potential to provide near real-time feedback for differentiating malignant from benign tissues in a clinical setting.

VIII. Acknowledgment

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