Elastic scattering spectroscopy for detection of prostate cancer: preliminary feasibility study

Irving J. Bigio[a*], Ousama A amar[b] and Michelle S. Hirsch[c]
[a,b]Department of Biomedical Engineering and [a]Department of Electrical and Computer Engineering, Boston University, 44 Cummington St., Boston, MA 02215;
[c]Brigham & Women s Hospital, Harvard Medical School, 75 Francis St., Boston, MA 02115

ABSTRACT

We have conducted a preliminary study of the potential for diagnostic spectroscopy based on elastic light scattering to serve as a method for optically-guided biopsy to reduce sampling errors and thereby improve sensitivity, in detecting prostate cancer. This method also has the potential to provide real-time diagnostic assistance in surgical and treatment procedures.

Keywords: optical biopsy, scattering spectroscopy, diagnostic spectroscopy

1. INTRODUCTION AND BACKGROUND

Approximately 66% of patients, who have an elevated prostate-specific antigen (PSA) > 4ng/ml, will have a negative biopsy following an ultrasound guided sextant sampling [1, 2]. It is thought that the basis of the sampling error is that an 18-gauge biopsy core samples a 1-mm diameter of tissue over the prostatic rectal interface whose surface area is approximately 30 mm x 30 mm in the case of a normal size gland (prostate gland volume: 25-30 cm^3). Therefore, despite 6 samples a very small fraction of the surface is sampled. In addition, the core length is typically 1.0-1.5 cm, which at best samples <50% of the anterior to posterior extent of the cancer bearing region of the prostate gland (i.e. peripheral zone). It has been estimated that the false negative rate of a standard sextant sampling ranges from 15-31% [3-5]. Most important, however, is the observation that a significant percentage (10%-35%) of these prostate cancers diagnosed at a second or later attempt are high grade (Gleason score 7 or higher) and therefore, potentially lethal [6]. This delay in diagnosis due to sampling error can reduce curability in some men.

Modalities such as transrectal ultrasound (TRUS) have had limited success in guiding biopsy. A multicenter clinical trial [7] in which 6,630 men were screened with PSA and transrectal ultrasound (TRUS) where an abnormality on TRUS defined as a hypoechoic region corresponded to prostate cancer in only 18% of the cases. Conversely, 65% of non-malignant appearing regions on TRUS (i.e. isoechoic) were found to contain adenocarcinoma of the prostate. The study concluded that 52% of men diagnosed with prostate cancer would have been missed if only the hypoechoic lesion was biopsied. As a result, biopsy of the hypoechoic lesion alone is not sufficient. Therefore, directed biopsies are sometimes obtained when a palpable nodule is noted on digital rectal examination, and more biopsies have been suggested to generate a higher yield in men with larger (> 30 cm^3) prostate glands [8-10].

Optical technologies can be used to perform optical biopsy to assess tissue pathology *in-situ* and in real time, without the need for excision and processing as in conventional biopsy and histopathology. While optical techniques alone are not sufficient for diagnosis (at this time), by coupling optical guidance with core biopsy, the sample errors inherent in core biopsy could be significantly reduced, improving the sensitivity and reducing false negatives.

* bigio@bu.edu

Diagnostic Optical Spectroscopy in Biomedicine II, Georges A. Wagnières, Editor,
Proceedings of SPIE-OSA Biomedical Optics, SPIE Vol. 5141 (2003)

Optical Spectroscopy

Optical spectroscopy using fiber-optic probes can be used to perform noninvasive, or minimally-invasive, real-time assessment of tissue pathology *in-situ*. The most common approach has been based on UV-induced fluorescence spectroscopy, although Raman spectroscopy and reflectance spectroscopy have also been investigated [11]. Our group at the Boston University (continuing earlier work by IJB and colleagues, at Los Alamos National Laboratory) has developed elastic-scattering spectroscopy (ESS), which is sensitive to the sub-cellular architectural changes, such as nuclear grade or nuclear to cytoplasm ratio, that correlate with features used in histological assessment. The ESS method senses those morphology changes in a semi-quantitative manner, without actually imaging the microscopic structure [12,13]. Our group and others have performed clinical studies to ascertain the efficacy of ESS-base optical biopsy for distinguishing a variety of indications in a variety of organ sites [14-17].

Since optical biopsy can be performed through optical fibers, several potential benefits are obvious for organ sites that are endoscopically accessible, such as the upper or lower GI tract, the pulmonary tract, or the urinary tract, in addition to organ sites that are directly accessible, such as the skin, oral cavity or cervix. However, fiber optic devices also enable assessment of solid organs, such as the breast and prostate. Most recently, our clinical collaborators at University College London have conducted clinical trials to demonstrate the use of ESS-based optical biopsy to ascertain the tumor margins during breast surgery with the potential to significantly reduce the incidence of positive resection margins during partial mastectomies or lumpectomies. [17]

Significance for prostate cancer

Optical biopsy measurement can be conducted through very fine needles (smaller than 27-gauge) and thus can be integrated with core biopsies to reduce sampling error and improve sensitivity. This could result in reduced trauma from multiple excision of core specimens. Moreover, continuous measurement can be performed over the entire insertion track of the needle, from the entrance surface to the opposite side of the capsule. Thus, a much larger range of sites can be assessed in the gland, with reduced trauma compared with TRUS-guided core biopsies.

The potential benefits include:

1. To guide core biopsy and improve sensitivity by reducing sampling errors.
2. To aid brachytherapy, to verify the placement of insertion guide-needles into diseased tissue before releasing the radioactive seeds.
3. To aid surgical prostatectomy. To determine tumor margins, especially to verify whether the capsule is involved (i.e., whether or not malignancy is confined to the parenchyma). To provide a real-time *in-situ* assessment of extra-capsular malignancy (metastases) in nearby areas.
4. To assess the response of the prostate to novel treatment modalities such as photodynamic therapy and hyperthermia.

2. METHODS

As an initial guide to feasibility we have made the first measurements on tissue of a freshly-excised prostate gland. Within minutes of surgical excision the gland was sectioned in the pathology lab, exposing different volumes of the gland, and ESS measurements were taken on various locations of each slice. The site of each measurement was marked precisely, and those sites were the subject of careful histological assessment following standard fixation and staining procedures.

The clinical instrumentation based upon elastic-scattering spectroscopy is essentially similar to that described in earlier publications on clinical studies.[17] The system (see Figure 1) consists of a pulsed xenon-arc lamp (EG&G) for the light source, a PC-compatible spectrometer, (a modified version of a spectrometer manufactured by Ocean Optics, Dunedin, Florida), which employs a linear CCD array for detection, an optical-fiber based probe, and a laptop computer for system control and data display. The wavelength range of the system is from 300 to 900 nm, but the range used for these studies is 330-800 nm. The probe is designed to be used in (gentle) optical contact with the tissue and incorporates two optical fibers. For this study, both the illumination fiber and the collection fiber had core diameters of 150 microns, and the center-to-center separation of the fibers was 140 microns. A small piece of linear polarizer was affixed to the tip of the fiber probe, to enhance the sensitivity to large-angle scattering events near the surface, compared to the diffuse multiply-

scattered background. Prior to any measurements the ESS system response is calibrated with a reflectance standard (Spectralon™, Labspere, Inc.). During a measurement procedure an automated, real-time background subtraction is effected for every measurement by first taking a measurement without firing the pulsed light source, followed immediately by a measurement for the same detector integration time but with the lamp firing. The full sequence, including recording to hard disc and display on the computer monitor takes about 100 msec. Given the short detector integration time (typically about 10 msec.) and the use of a pulsed light source, all measurements can be made in the presence of full room light, with little effect on the overall signal-to-noise ratio.

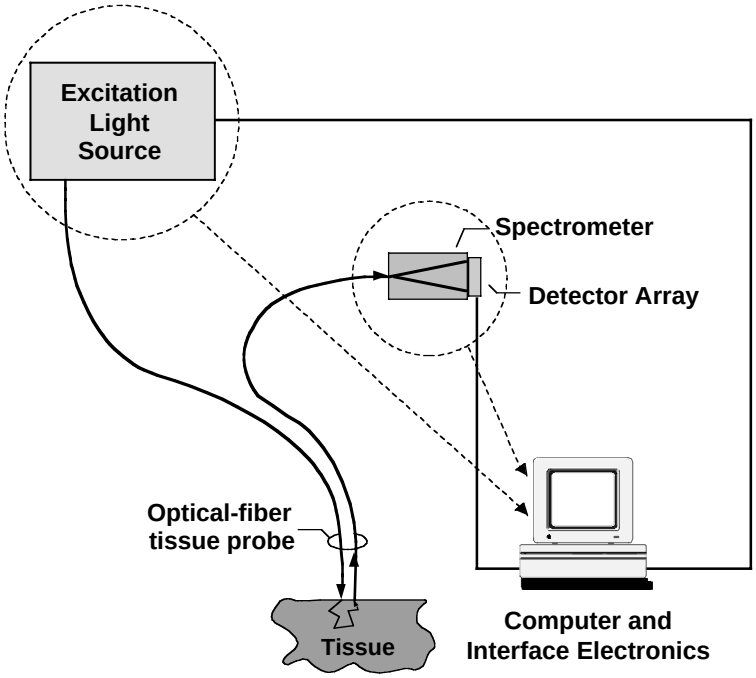

Fig. 1 Schematic of the system components for elastic-scattering spectroscopy.

3. RESULTS

Figure 2 shows the normalized ESS spectra for the 12 tissue sites for which there were corresponding histopathology reports. The gray traces correspond to histologically benign tissue sites (either normal or hyperplastic) and the black traces correspond to histologically malignant or pre-malignant sites (either prostatic adenocarcinoma or high-grade PIN).

Clear differences between the two diagnostic categories are visible by inspection of the spectra, although statistical analysis is not yet warranted for such a small data set (12 correlated spectra). Some of the distinguishing spectral features are consistent with increased perfusion of malignant and pre-malignant sites, and longer-scale slope variations are consistent with an increase in the size distribution of the scattering centers for malignant conditions (nuclei, organelles, etc.).

We also note that, on average, there is an absorption feature centered at 480 nm, which is larger for the spectra of malignant sites. To the naked eye the tumor sites had a slight yellow tinge compared with hyperplastic and normal zones of the gland. The shape of this spectral feature is consistent with the absorption spectrum of beta-carotene, a frequent constituent of lipids and cholesterol. We intend to further investigate this observation in future studies.

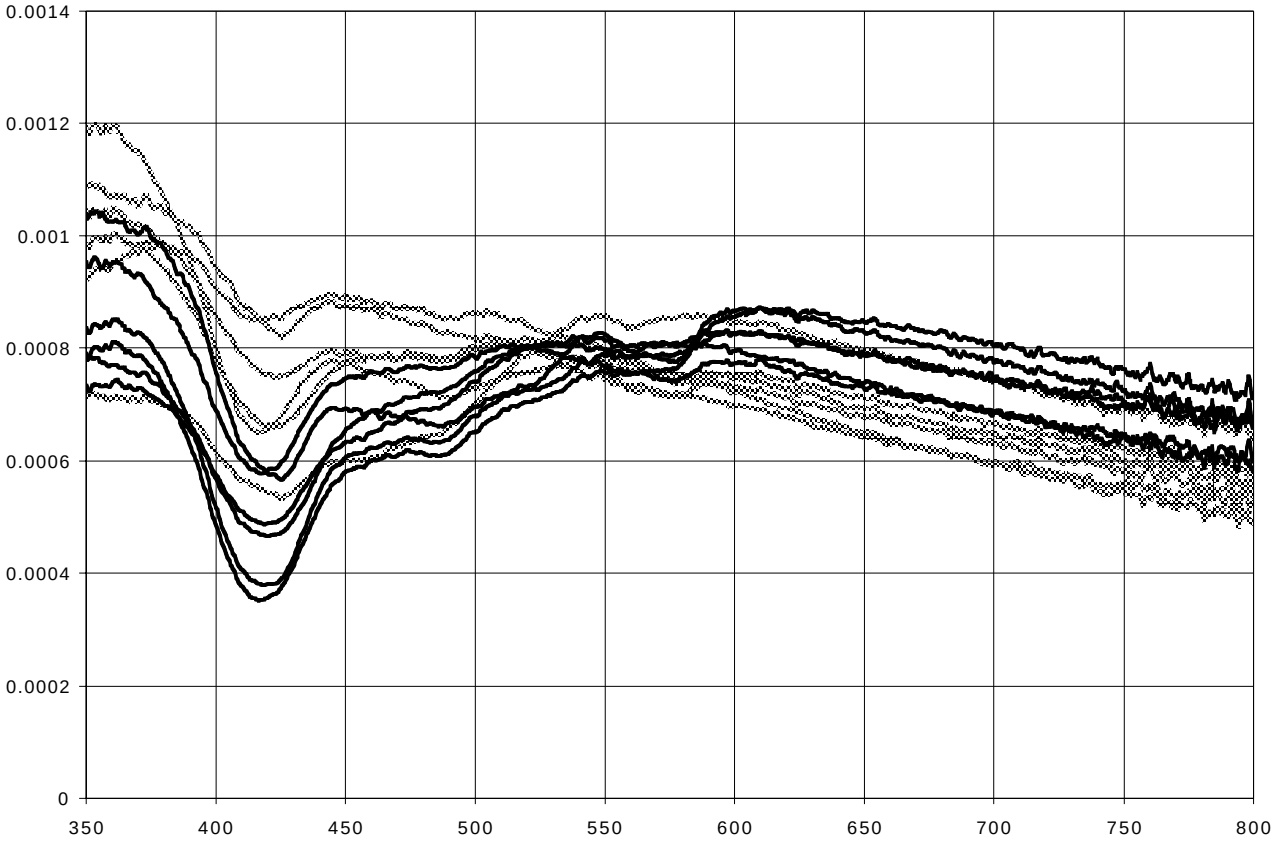

Figure 2. ESS spectra obtained form prostate specimens *ex vivo* using a fiber optical probe. Grey traces correspond to benign or hyperplastic sites, and black traces correspond to malignant or high-grade dysplasia sites.All traces are normalized to the same total integral intensity, so that only spectral shape is relevant. The probe had a 140-micron-separation of the excitation and collection fibers.

DISCUSSION & CONCLUSIONS

The data are encouraging and suggestive, but the study reported here does not invoke a statistically large enough data set to derive any firm conclusions. Nonetheless, we hope to demonstrate in the next set of studies that the spectral signatures from ESS measurements on prostate tissue will exhibit repeatable differences for normal and hyperplastic glandular tissue vs. and dysplastic conditions, up to adenocarcinoma. The potential impact of such spectral signatures will be the benefits to diagnostic and surgical applications as discussed above. We also expect that the successful development of optical methods such as these will lead to improved detection sensitivity and to techniques to assist in treatment and surgical guidance.

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