Optical Biopsies

More than a million men are screened for prostate cancer annually in the United States. An estimated 190,000 men will be diagnosed with prostate cancer and some 27,000 men will die of this disease. Transrectal ultrasound (TRUS) guided needle biopsy is the current standard to diagnose prostate cancer. While TRUS images can identify anatomical borders of the prostate gland, the procedure cannot discriminate between benign versus malignant prostatic tissue. Other prostate imaging modalities currently used such as magnetic resonance imaging (MRI), x-ray computed tomography (CT), positron emission tomography (PET), and single photon emission tomography (SPECT) do not provide any information regarding tissue morphology either. While combining imaging modalities such as MRI/CT, PET/CT, SPECT/MRI/CT have demonstrated some success in the diagnosis of advanced disease, they have consistently failed to identify small localized carcinomas (≤1cc) within the prostate. Consequently, many cancers are missed and often are spread beyond the prostate gland when finally diagnosed. Even when prostate cancer is clinically diagnosed at an early stage, prostate biopsies often fail to provide accurate grade and stage of the disease due to serious sampling errors. Currently, the only proven prognostic variable on biopsy for prostate cancer is its Gleason grade. Therefore, if prostatic carcinoma can be identified in real-time and in vivo, then additional prostate biopsies can be directed to these locations to determine the highest cancer grade as well as the extent of the disease.

Focal therapy requires accurate localization of the disease. Localization of disease requires histology and imaging either alone or in combination. An accurate localization strategy can clearly define patient population in terms of grade, stage, and disease burden. Hence, there is a need for new imaging modalities or to significantly improve existing modalities for accurate localization of the disease. We have developed a minimally invasive automatic optical biopsy needle (an integrated optical probe and an automatic biopsy needle) based on elastic scattering and fluorescence spectroscopy to obtain in vivo tissue morphology-guided prostate biopsies (see figure). Light interacts with biological tissue in a variety of ways

![Fluorescence Spectra - Benign Prostate Tissue](image)

![Fluorescence Spectra - Malignant Prostate Tissue](image)
including absorption, elastic scattering, and fluorescence. The optical properties of tissues are determined by their molecular composition and cellular morphology. As tissues undergo malignant growth, the optical properties change, offering the possibility of detecting disease state. Figure 2 illustrates fluorescence spectra obtained from optical biopsy needle. Fluorescence spectra of malignant tissue is relatively lower than for benign tissue. Utilizing this information, a classification method is being developed for real-time in vivo diagnosis of prostate cancer.

Multiparametric or multifunctional MRI using a combination of T2-weighted, dynamic contrast enhancement, diffusion weighting and spectroscopy either at 1.5 T or 3.0 T magnetic field strengths have demonstrated great potential to accurately localize prostate cancer. Recent study found that image quality for detecting prostate cancer is significantly better for MRI at 1.5 T using an endorectal-body phased-array coil as compared with the 3.0 T imaging using the torso phased-array coil. Gadolinium chelates are currently in clinical usage as a positive contrast enhancement agent for MRI to diagnose brain and breast cancer. In collaboration with Colorado School of Mines, we have developed a hybrid nanoparticle structure with gadolinium (Gd) and gold (Au) as a contrast enhancement agent for MRI and CT. By combining with targeting ligand specific for prostate cancer, these hybrid gadolinium-based nanoparticles can further improve sensitivity and specificity of MRI and CT to accurately localize the disease. Newer modalities of US are demonstrating promise but have yet to prove conclusive. Contrast-enhanced US, elastography and tissue-characterization technologies are demonstrating promise in locating clinically significant lesions and may be able to do so with a negative predictive value of over 90%. As it is the absence of disease in untreated areas that is paramount, a high negative predictive value for any diagnostic test would be the key to its adoption.

Accuracy of localization of the disease for any imaging modality needed to be validated by correlating to whole-mounted prostate pathology, currently the gold-standard for such validations. We have developed the most accurate and comprehensive 3D computer model of the prostate using whole-mounted prostate specimens. Figure illustrate the 3D model of a radical prostatectomy specimen with prostate carcinoma and various Gleason patterns are denoted in multiple colors. These 3D models provide valuable Biomorphometric information including tumor volume, location, Gleason grades, tumor multifocality, extra capsular extension, etc. We demonstrated potential clinical utility of 5mm-grid mapping biopsy procedure to accurately localize the disease using these 3D computer models. This groundbreaking research set the foundation to use mapping biopsies to identify clinical sub-populations as candidates for focal therapy. We expect our 3D computer models to play a vital role to validate imaging modalities for accurately localization of prostate cancer.