NEW PROSTATE BIOPSY STRATEGY OF 3-DIMENSIONAL CANCER MAPPING FOR ACTIVE SURVEILLANCE AND FOCAL THERAPY

BY OSAMU UKIMURA, MD., PHD.

In the U.S.A. during the wide-spread use of the PSA (Prostate Specific Antigen) blood test and current prostate biopsy practice with the sampling of increased core numbers of biopsy tissues, men with elevated PSA have been subject to under-diagnosis of clinically important cancer and over-diagnosis and over-treatment of early prostate cancer, unnecessarily exposing them to treatment-related side effects and financial costs [***Welch 2009***]. The search for the optimal prostate biopsy technique still continues in accounting the balance between the benefits and harms of prostate cancer detection, debating various issues including the indication of initial screening biopsy, the indication of repeat biopsy after a previous negative biopsy, the intra-prostatic location of biopsy sampling, anesthesia technique, the optimal number of biopsy samples, image-guidance, biopsy-related complications and anxiety, and cost.

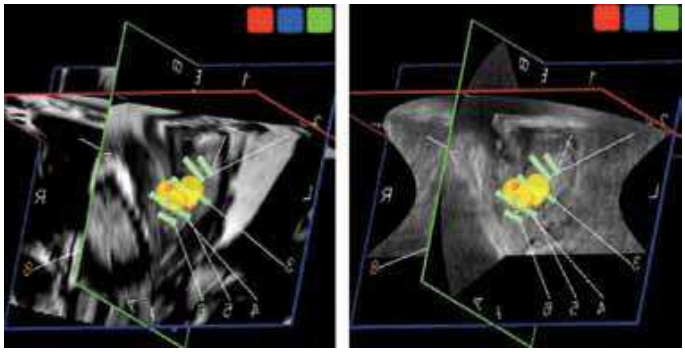
Prostate biopsy is generally performed transrectally by TRUS (transrectal ultrasound) guidance. Since the 1980s, the introduction of TRUS guidance for needle delivery into the prostate substantially improved the accuracy of prostate biopsy [***Lee 1986***]. Importantly, researchers reported that even in the current PSA era, the image-targeted biopsy (taken from abnormal TRUS findings) can provide the specimens with a significantly greater percentage of cancer involvement as well as higher grade cancer, in comparison to systematic random biopsy (taken from normal TRUS findings). Therefore, image-guided targeted biopsy-proven cancers from TRUS-visible-lesions are more clinically significant to better characterize the cancer [***Toi 2007***]. Emerging image-targeted biopsy (using the novel techniques of Doppler ultrasound, elastosonography, enhanced ultrasound, or Magnetic Resonance Imaging) could also duplicate significantly better performances of image-guided targeting. These result in better characterization of the biopsy-proven cancer, to determine the higher-grade and greater-volume cancers as 'important,' as well as the lower-grade and smaller-volume cancers as 'indolent' [***Ukimura 2012***].

Unfortunately, however, today's prostate biopsies are likely 'not' to use image-based suspicious lesion-targeting techniques, but simply to deliver the needle toward the "rough" region of the so-called 'sextant' of the prostate. This may be called "image-blinded" biopsy because it involves no effort to precisely target and document the biopsy-proven cancer in the prostate. As such, if they are image-blinded, currently wide-spread prostate biopsy practices are unable to precisely determine the spatial localization of the cancer foci and also unable to characterize clinically important cancers very well.

We believe that the better characterization of the known cancer as well as intra-prostatic 3-dimensional (3D) localization/documentation (mapping) of the cancer foci seems a key in successful decision-making for undergoing novel therapeutic strategy options, such as the active surveillance of slow-growing/low-volume prostate cancer. Another potential option includes targeted focal therapy of the known cancer foci, which aims to cure or control the known cancer while minimizing the treatment-related side effects [***Ukimura 2011***, ***Ward 2012***]. Targeted focal therapy of the known-cancer foci is contemporary strategy in the way that most other solid organ cancers are treated.

The majority of contemporary prostate cancer patients are classified as having a low- or intermediate-risk form of the disease. The long natural history of low-risk prostate cancer and the presence of competing risks in an otherwise elderly male population all contribute to the problem of over-treatment of primary prostate cancer. The high incidence of clinically occult prostate cancer discovered at autopsy, the side effects of radical therapies, and the low risk of progression following radical therapies has led to development of less aggressive treatment strategies. "Active surveillance" is an approach incorporating regular clinical follow-up without intervention for select low-risk sub-groups of prostate cancer patients [***Bill-Axelson 2005, Klotz 2006***]. The issue is how to appropriately select and how to appropriately follow-up using the 'best technique for surveillance biopsy' under active surveillance practice. While

there are significant differences in how patients are deemed to have "progressed" from active surveillance, a general consensus has developed around factors such as pathologic progression in surveillance of biopsy specimens (indicating increases in Gleason score or number of cores involved with the cancer, or percentage cores involved with the cancer), rapid PSA progression, and/or clinical progression on digital rectal examination. However, if there was "no" documentation of the precise 3D mapping of the biopsy-proven cancer at the time of the previous positive biopsy session, to accurately re-visit the biopsy-proven cancer lesion foci only 1-2 mm in size to move towards appropriate decision-making seems similar to a game of chance. There exists a need to better define patients enrolled, by developing a "targeted active surveillance" strategy that incorporates monitoring on a "per lesion of the known cancer" basis, founded on sophisticated imaging as well as precise 3D-mapping/documentation of cancer location rather than the current image-blinded prostate biopsy approach [***Hoeks 2011, Ukimura 2011, 2012, Baumann 2011, Natarajan 2011***]. An approach using the 'best technique for surveillance biopsy' would possibly be based on spatially-directed 3D mapping biopsy techniques.



Real-time 3D ultrasound image-based mapping biopsy technique using MRI/TRUS fusion guided targeting
Geographical 3D locations of every single biopsy trajectory (green color-doded) are digitally recorded in a computer workstation in the USC clinic. The recorded biopsy trajectories can be superimposed on either 3dMRI volume data (left) or 3D TRUS volume data (right) to confirm the relation of biopsy with 3D image of the prostate. The yellow color-coded lesions represent MRI suspcious lesions, and the targeted biopsy (orange color-coded) precisely hits the cetner of the lesion. Since the coordinates of the distal end (x1,y1,z1) and proximal end (x2,y2,z2) of the biopsy trajctory are recorded in computer workstations, future revisiting intervention the the same location is possible.

We believe that, for patients with low-or-intermediate risk disease, a new paradigm centered around the concept of treatment on a precise "per-lesion in 3D space of the prostate" rather than a rough 'whole gland of the prostate' basis is attractive. Recent evidence suggests that a primary tumor focus, an "index lesion" (that is, a dominant cancer lesion with the highest grade and/or largest volume per patient), is present in most patients and ultimately drives the natural history of the prostate cancer in each individual [***Ahmed 2009***]. In most cases, this "index lesion" can be distinguished by its larger size (several-fold larger than secondary lesions) and the presence of aggressive pathologic features such as Gleason grade 4/5 or extra-prostatic extension or metastatic potential. If the index lesion contains a clone with metastatic potential, it could be targeted and destroyed to minimize the life-threatening risks. Conversely, cancerous areas which do not harbour these "lethal" clones (which are likely in lower-grade and smaller volume cancer foci) could potentially undergo surveillance without intervention. It seems clear that serial "per lesion" monitoring, based on geographically-mapped precise biopsies of cancer lesions could provide new insights.

We believe that the two main streams for optimizing prostate biopsy strategy to improve patient decision-making for contemporary treatment options for early prostate cancer are, first, to improve the accuracy of cancer visualization using emerging imaging techniques and, second, to enhance the precision of needle delivery using the geographical 3D mapping techniques for biopsy-proven cancer.

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By Osamu Ukimura, MD., PhD.
USC Institute of Urology, University of Southern California/Norris Cancer Center
1441 Eastlake Ave, Suite 7416, Los Angeles, CA 90089
TEL: 323-865-3700 FAX: 323-865-0120