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ADVANCES IN MRI IMAGING TECHNOLOGY:
New Technique of Fusing Multiparametric MRI Upon TRUS Data has the Potential To Upgrade the Diagnosis Of Prostate Cancer and Its Management.

Optimal prostate cancer management is currently limited by the difficulty of accurately identifying the location, volume, and maximal grade of cancer within the prostate gland. The transrectal ultrasound (TRUS) guided biopsy, the current standard for initial diagnosis, often fails to adequately define these important tumor characteristics. The root cause of the deficiency in TRUS biopsies is the inherent randomness of the technique. The result may be undergrading of tumors, falsely negative results initially or at the time of rebiopsy, and difficulty in detecting cancer when it is recurrent in the prostate at PSA relapse.

Biopsies specifically targeted to the location of greatest suspicion for cancer have been shown to improve upon the randomness of the standard 12-core TRUS guided method. Although systematic, the TRUS guided biopsy is in essence "blind." The limitations of this method are becoming recognized. Although, tumor biology is complex and unpredictable and will continue to thwart our quest for the most accurate information, advances in imaging technology can lessen the information gap and inform improved management.

This COMMENTARY will discuss findings based on an emerging radiological technique: **MRI/Ultrasound fusion**. This system permits information gained from a pre-biopsy multiparametricMRI (MPMRI) to be subsequently superimposed upon real-time TRUS images to guide a truly "targeted" biopsy.

Each of the following two sections will highlight a clinical problem where current practice has been shown to have limitations. Selected recent studies will be reviewed to indicate the improvements that can be achieved with this more advanced imaging technology.

SECTION I: MPMRI/ULTRASOUND FUSION COMPARED TO 12-CORE SYSTEMATIC TRUS PROSTATE BIOPSY: The Advantage for Targeted Biopsies.

Clinical problem: TRUS biopsies often provide incomplete information. Although the traditional 12-core TRUS biopsy systematically obtains 2 cores from the base, mid-gland, and apex on the right and left side of the prostate, the sampling is random relative to the location of tumor(s). Even a 24 or more core "saturation" biopsy, although acquiring more tissue, does not significantly improve cancer detection and must also be considered a random non-targeted sampling. (Jones JS, *J UROL*, 2006).

The TRUS based technique
- may provide falsely negative information
- miss the index tumor entirely
- sample only a satellite lesion with a lesser grade, or
- nip the index lesion in a way that suggests a tumor grade less than the highest grade

Missed lesions are frequently at the apex or the anterior portion of the gland, regions difficult to reach on a TRUS biopsy. The 20%-40% rate of tumor upgrade on repeat biopsies and prostatectomy specimens speaks to the extent that the initial biopsy results can be misrepresentative.

Emerging technology: Targeted biopsies with MPMRI-Ultrasound fusion guidance offer more complete data. Imaging systems are available that permit superimposition of stored information from a pre-biopsy MPMRI onto real-time ultrasound images guiding the clinician to specifically biopsy targets suspicious for cancer -- and this can be performed in an office setting.

Three particularly informative articles present the fusion technique in detail and report data comparing the accuracy of targeted biopsies using MPMRI-US fusion with results from the conventional 12-core technique. The fusion system can be employed for the initial prostate biopsy or in a search for cancer persisting in the prostate after primary therapy.

ARTICLE 1

"TARGETED BIOPSY IN THE DETECTION OF PROSTATE CANCER USING AN OFFICE BASED MAGNETIC RESONANCE ULTRASOUND FUSION DEVICE"

J UROL, January 2013, Marks, Sonn et al. (UCLA), compares the results of targeted MPMRI/US fusion biopsies with 12 systematic biopsies in 171 men conducted in a 20 minute procedure under local anesthesia in their clinic. MPMRI images were acquired at 3 Tesla without an endorectal coil.

Their summary: "Targeted biopsy was 3 times more likely to identify cancer than a systematic biopsy (21% vs 7%)."

Their findings: Of the tumors identified, 36% of tumors diagnosed on MPMRI-US were Gleason score >7 as compared to 24% identified on systematic cores. "In fact, 38% of men with Gleason 7 or greater had disease detected only via targeted biopsies of lesions identified on MRI."

 "The yield of targeted biopsies related directly to the ability of the radiologist to accurately identify targets on MRI."

> As is becoming customary in MRI interpretation, the results of imaging are graded as to the clarity of lesion identification by correlating the findings of the T2 weighted, the diffusion weighted, and contrast enhanced sequences.

> Gleason grade 3 lesions are the least conspicuous and are assigned an image grade of 2. "No target seen" is graded 1. Greater lesion conspicuity is associated with increasing Gleason grade creating a range of suspicion that spans 2 - 5.

The prostate cancer detection rate for image grade "no target," 2, 3, 4, and 5 was 32%, 43%, 48%, 56% and 94% respectively.

Conclusion: As a result of the greater accuracy of diagnosis of MPMRI-US fusion, "targeted prostate biopsies may be useful in 3 key situations: active surveillance, increased PSA but negative TRUS biopsy, and selection for focal therapy."

ARTICLE 2

"MAGNETIC RESONANCE IMAGING/ULTRASOUND FUSION GUIDED PROSTATE BIOPSY IMPROVES CANCER DETECTION FOLLOWING TRANSRECTAL ULTRASOUND BIOPSY AND CORRELEATED WITH MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING"

J UROL, Oct 2011, Pinto et al. (Molecular Imaging Program, NCI), further substantiates the superior diagnostic accuracy of targeted biopsies using MPMRI-US fusion over the conventional 12-core pattern biopsy. Once again, the method "fuses pre-biopsy magnetic resonance imaging with real-time transrectal ultrasound imaging to identify and biopsy lesions suspicious for cancer." The study involved 101 men, 90% with a negative DRE, and was conducted in a clinic setting. The 12-core TRUS sextant biopsy was performed first followed in the same setting by an MPMRI-US fusion guided biopsy of "suspicious lesions identified on pre-biopsy MRI."

Their Summary: The "MRI/US fusion guided biopsy **detected more cancerous cores** than standard 12-core TRUS biopsy alone."

Their Findings: "Cancer was detected in 12 of 43 (27.9%), 26 of 39 (66.7%) and 17 of 19 (89%) patients with low, moderate, or high suspicion, respectively. *"The current standard of care practice for an initial prostate biopsy involves taking 10 to 14 cores and has a cancer detection taste of 27% to 40.3%."* As with the Marks study (above), in this study the degree of suspicion on MRI regarding the presence of cancer was graded as low, moderate, or a high degree of suspicion.

ARTICLE 2 CONTINUED

In addition, the MPMRI/US fusion guided method detected **more cancer per core** than the standard 12-core TRUS biopsy. For low, moderate, and high suspicion on MRI the percent of cores positive for MPMRI/US vs. 12-core for low, moderate, and high suspicion was 4.8% vs 3.8%, 20.7% vs 12.3% and 53% vs 29%, respectively.

The authors state that "MRI is currently limited to identifying cancer greater than 3 mm." For tumors greater than 3 mm they cite studies reporting histopathological correlation of peripheral tumors with $\longrightarrow$ MPMRI showing sensitivity and specificity for T2 weighted images of 94% and 83%, and for dynamic contrast enhanced sequences, of 56% and 96% (Turkbey B, *Radiology,* 2010).

Conclusion: "MRI/US fusion biopsy may aid in the detection of higher-risk prostate disease compared to standard TRUS biopsy alone."

ARTICLE 3

"A NOVEL STEREOTACTIC PROSTATE BIOPSY SYSTEM INTEGRATING PRE-INTERVENTIONAL MAGNETIC RESONANCE IMAGING AND LIVE ULTRASOUND FUSION"

Hadaschik *et al, J UROL,* Dec 2011 (University Hospital, Heidelberg, Germany) presents this group's results employing template guided targeted transperineal biopsies. They find this technique especially effective for sampling apical and anterior lesions since the transperineal approach can easily target these areas sampled with difficulty using a transrectal penetration. The skill of a brachytherapist is quite compatible with this method since it employs a technique similar to the placement of radioactive seeds into the prostate. It does, however, require regional anesthesia.

Their Findings: Cancer was diagnosed in 31 of 46 men (67.4%). "The diagnostic improvement of 67.4% PC detection on initial biopsies compared to 40% detection rate of conventional 10 to 18 -core TRUS biopsies was most likely a result of integrating MRI information." Similar work by Taira, Merrick *et al.* yielded "a 76% detection rate in men undergoing transperineal template guided mapping biopsies… (*Prostate Cancer and Prostatic Diseases, 2010).*

Caveat: The randomness inherent in 12-core biopsies does have some advantages over MRI in detecting micro focal cancers as reported in a small French study (Belias O, *Prog Urol,* Sep 2012). Among 71 patients in whom the overall detection rate was 53%, both systems jointly identified 21 cancers. The 12-core pattern alone found 14 (71% micro focal) cancers compared to 3 tumors seen only by MRI, but in keeping with the advantages of MRI to target areas judged highly suspicion for cancer, 70% of MRI guided biopsies into the suspicious areas were positive. *"The Gleason score in the MRI-targeted area was the highest Gleason score in 90% of cases, i.e. >6 in 76%."* This is in keeping with the findings of the two articles quoted above in which targeted biopsies also performed better detecting cancers with the highest Gleason scores. The resolution of MRI detection is 3 - 4 mm and MPMRI poorly visualizes low grade cancer.

SECTION II: USING MPMRI TO REFINE SELECTION OF OPTIMAL CANDIDATES FOR MANAGEMENT BY ACTIVE SURVEILLANCE.

Clinical Problem: A significant number, 20% to 40%, of candidates for active surveillance (AS) management, even those meeting the strictest eligibility criteria, are misclassified on the initial biopsy and upgraded on a confirmatory biopsy. As a result of upgrading or PSA progression, within 2 to 3 years after program entry primary treatment is recommended for these men -- treatment that might have been better offered initially.
Most AS protocols prescribe a surveillance biopsy at one year (recommendations vary from 3-6 months to possibly at 2 or 3 years into the program). Repeated biopsies are troublesome, expensive, and when done repeatedly, may complicate nerve-sparing at subsequent surgery.

Emerging Technology MPMRI-US imaging performed initially can lessen misclassification and may also substitute for surveillance biopsies. The utility of MPMRI arises from its superiority over TRUS technology in localizing and estimating the volume of tumors. By combining information from the functional components of MRI, i.e. diffusion weighted and dynamic contrast enhancement sequences, an experienced uroradiologist can estimate the grade of cancer.

ARTICLE 1

"IMPACT OF MULTIPARAMETRIC ENDORECTAL COIL PROSTATE MAGNETIC RESONANCE IMAGING ON DISEASE RECLASSIFICATION AMONG ACTIVE SURVEILLANCE CANDIDATES: A PROSPECTIVE COHORT STUDY"

J UROL, Apr 2012, Margel et. al. (Princess Margaret Hospital, Toronto), describes the results of a small study of 60 men with biopsied low-risk cancer who underwent MPMRI prior to active surveillance. The MRI findings were stratified into 1) no cancer seen; 2) cancers <1 cm (i.e. 0.5 cc volume, one criterion for "insignificant " cancer); and 3) cancers >1 cc.

"Of the cases, 18 (32.14%) were reclassified." Concordant with the recognized low sensitivity of MRI to low grade cancer, among the 23 cases (38%) where the MRI did not visualize cancer only 2 (3.5%) were reclassified.

Their conclusion: "Upon confirmation of our results magnetic resonance imaging may be used to better select and guide patients before active surveillance."

ARTICLE 2

"MRI AND SURVEILLANCE"

Curr Opin Urol, Ouzzane et al., University Lille Nord de France, is a review enthusiastically supporting "multiparametric MRI and its role in the selection and monitoring of patients on active surveillance." The focus is on the limitations of the "Current diagnostic pathway … in selecting patients with insignificant prostate cancer for active surveillance." The authors express as their major concern the underdiagnosis by the current practice of systematic posterior TRUS biopsies of anterior cancers, "which represent 20% of cancers in an unselected population of men with suspicious prostate-specific antigen elevation."

Their recommendation: Perform a pre-biopsy MPMRI imaging before a referral of a patient for active surveillance.

Their Interpretation of the Literature: "… most reclassification of men fulfilling active surveillance criteria at initial biopsy occurs at immediate repeat biopsy or 1 - 2 years after diagnosis, suggesting under-sampling of significant tumors at the time of initial biopsy, rather than progression of indolent tumors."

MPMRI "yields high sensitivity and specificity for the detection of anterior and posterior cancers.
At tumor volumes greater than 0.5 cc, sensitivity and specificity was 86% and 94% … in correlation with radical prostatectomy pathology as reference standard."

A negative MPMRI has a 95% negative predictive value for ruling out clinically significant disease (Rouse *et al., Urol Int,* 2001).

The authors are impressed with the greater accuracy of transperineal template-guided prostate mapping biopsies in detecting anteriorly and apically located cancers (as also reported by Taira, Merrick *et al*., *Prostate Cancer and Prostatic Diseases,* 2010).

"In a series of radical prostatectomies in patients with failure of active surveillance, 10 of the 48 tumors on histopathology were greater than 1 cc in volume and were all anteriorly located (Duffield AS, *J UROL,* 2009).

The authors stress that the MPMRI approach requires a highly skilled team to achieve the required optimal performance.

Ouzzane's Conclusion: "Incorporation of mp-MRI into active surveillance selection criteria for patients with low-risk prostate cancer can reduce the number of patients reclassified … ."

BOTTOM LINE: Multi-parametric MRI and the targeted biopsies facilitated by MPMRI/US fusion have brought clinical practice to the cusp of a new era of prostate cancer management based on improved detection of the location, volume, and grade of cancer within the prostate.

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Your comments and requests for information on a specific topic are welcome at ecweber@nwlink.com