

Diagnostic Imaging Approaches to Prostate Cancer

a report by

Edouard J Trabulsi and **Leonard G Gomella**

Department of Urology, Kimmel Cancer Center, Thomas Jefferson University

DOI: 10.17925/EOH.2007.0.2.110

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death in American men, with an estimated 186,320 new cases diagnosed and 28,660 prostate cancer deaths expected in the US in 2008.¹ With the use of prostate-specific antigen (PSA)-based screening, the number of prostate biopsies performed to diagnose prostate cancer has risen sharply over the past two decades, with a majority of those biopsies being negative.² Conversely, the false-negative rate of standard transrectal ultrasound (TRUS)-guided prostate biopsy is significant, approaching 30–40%.³ Additionally, the clinical significance of low-volume, low-grade prostate cancer detected on needle biopsy is unclear. The controversy regarding the potential overtreatment of 'clinically insignificant' prostate tumours is balanced by the infrequent but concerning finding of higher volume, higher-grade tumours recognised on final surgical pathology after radical prostatectomy. Improved diagnostic methods are necessary to more accurately detect prostate cancer while minimising unnecessary biopsies. Several new diagnostic imaging modalities being explored to improve the accurate diagnosis of prostate cancer are presented here.

Transrectal Ultrasound

Contrast Enhancement

Use of ultrasound contrast agents to improve biopsy targeting accuracy and cancer detection of TRUS-guided needle biopsy of the

prostate has been an ongoing research interest at our institution and others. Prostate cancer, like many other neoplasms, demonstrates neovascularity and increased microvessel density, with important prognostic implications.⁴

Based on the pathological finding of increased vascularity in prostate cancer, there has been great interest in using Doppler ultrasound to increase sensitivity and specificity for the detection of prostate cancer. Colour and power Doppler imaging are sensitive for detection of flow in vessels as small as 1mm. Asymmetrically increased flow patterns around and into areas of tumour with increased number and size of vessels characterise prostate cancer on Doppler imaging. These vessels will show an irregular orientation in contrast to the typical radial pattern of normal prostate flow. Multiple studies have demonstrated increased sensitivity and the positive predictive value of prostate biopsy in combination with colour Doppler imaging.^{5–10} In addition, colour Doppler signal correlates positively with the grade and stage of tumour, as well as with biochemical recurrence after treatment.¹¹ Although Doppler-guided biopsy may improve the rate of detection of prostate cancer, systematic biopsy cannot be eliminated, as the sensitivity of Doppler imaging is not sufficient to detect many of the lesions found by systematic biopsy.^{12–14}

Halpern et al. at Jefferson published a study analysing the use of intravenous sonographic contrast agents injected during TRUS analysis of the prostate with colour and power Doppler.¹⁵ The intravenous contrast agent utilises microbubbles, which enhance the ultrasound identification of microvascular flow anomalies associated with prostate cancer. In the trial by Halpern and colleagues, an intermittent harmonic greyscale imaging technique was used. This method provides an inter-scan delay that allows the contrast media to accumulate in the microvascular spaces before the microbubbles are destroyed by the ultrasound wave.¹⁵

A total of 301 men had microbubble contrast agents infused during TRUS, and areas of increased vascularity identified with colour or power Doppler were targeted for needle biopsy. Additional modified sextant biopsies were taken after the targeted biopsies, and the cancer detection rate of each biopsy strategy was analysed. Cancer was detected in 35% of men; targeted biopsies had a cancer detection rate of 15.5% compared with a cancer detection rate in modified sextant biopsies of 10.4%. In men in whom cancer was detected, targeted biopsies were twice as likely to be positive as modified sextant biopsies ($p < 0.01$, odds ratio [OR] 2.0). While the overall performance characteristics of these modalities were marginal, with a receiver operating characteristic (ROC) curve for intermittent harmonic imaging with contrast enhancement of 0.65, this represented a significant improvement over standard greyscale TRUS alone.



Edouard J Trabulsi is an Assistant Professor of Urology at the Kimmel Cancer Center at Thomas Jefferson University in Philadelphia, Co-Director of the Multidisciplinary Genito-urinary Cancer Clinic at the Kimmel Cancer Center and Co-Director of the Jefferson Prostate Diagnostic Center at Thomas Jefferson University. He is Director of Minimally Invasive Urologic Oncology and Co-Director of the CR Bard Fellowship in Endourology and Laparoscopy in the Department of Urology at Thomas Jefferson

University. He obtained his medical degree from the School of Medicine and Biomedical Sciences at the State University of New York in Buffalo, after attending college at the University of Rochester in New York. He then completed his urology residency at Thomas Jefferson University and a fellowship in urological oncology at Memorial Sloan-Kettering Cancer Center in New York.

E: edouard.trabulsi@jefferson.edu



Leonard G Gomella is the Bernard W Godwin Jr Professor of Prostate Cancer and Chairman of the Department of Urology at Thomas Jefferson University, as well as Director of Clinical Affairs in the Kimmel Cancer Center at Thomas Jefferson University. He has been at Thomas Jefferson University since 1988, and was appointed Chairman in 2002. Dr Gomella completed his urology residency at the University of Kentucky and a fellowship in urological oncology at the National Cancer Institute/National

Institutes of Health in Bethesda, MD. He received his medical degree from the University of Kentucky in Lexington and attended Queens College, City University of New York.

E: leonard.gomella@jefferson.edu

These results are comparable to those from a similar collaborative study from Austria and Philadelphia. Pelzer et al. published a study examining the utility of adding prostate biopsies targeted to lesions identified with ultrasound contrast agents to a systematic biopsy approach.¹⁶ Three hundred and eighty patients with a serum PSA level between 4 and 10ng/ml received an intravenous ultrasound contrast microbubble agent, and contrast-enhanced colour Doppler (CECD) targeted biopsies were performed in areas of peripheral-zone hypervascularity. Additional standard systematic 10-core biopsies were then taken by another blinded examiner. The overall percentage of patients with cancer was 37.6% (143/380). The positive biopsy rates were comparable in the CECD biopsies and systematic biopsies (27.4 and 27.6%, respectively). The combination of CECD biopsies with standard 10-core systematic biopsies increased the overall positive biopsy rate to 37.6%, with the percentage of positive individual positive cores significantly higher in the CECD-targeted biopsies compared with standard systematic biopsies (32.6 and 17.9%, respectively; $p < 0.01$).

Elastography

Cancerous prostate tissue can be firm to palpation, with limited elasticity or compressibility. Elastography of the prostate using TRUS uses this lack of compressibility as a targeting strategy. In a pilot study from Germany of 404 patients, König et al. demonstrated that use of realtime elastography in conjunction with standard greyscale TRUS significantly improved prostate cancer detection on needle biopsy.¹⁷ A total of 151 men (37.4%) were diagnosed with prostate cancer in this study. The sensitivity of standard TRUS biopsy techniques in detecting prostate cancer was 64.2%, while use of realtime elastography improved the biopsy sensitivity to 84.2%. While only a pilot study, and lacking thorough statistical analysis, this study supports further investigation examining realtime elastography measurements in conjunction with standard TRUS prostate biopsy schemes.

Magnetic Resonance Imaging

Dynamic Contrast-enhanced Magnetic Resonance Imaging

The technique of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is designed to take advantage of the increased vascularity that occurs in and around malignant tumours. The study is performed by administering gadolinium-based contrast agent and evaluating the variability in amount and speed of uptake in various regions of the prostate. It has been previously shown that cancerous regions in the peripheral zone demonstrate a faster enhancement in comparison with normal tissue. A study by Noworolski et al.¹⁸ sought to further delineate the DCE-MRI imaging characteristics of different types of prostate tissues. In contrast to previous studies that relied exclusively on the results of transrectal prostate biopsy for tissue comparison, this study sought to ensure more accurate prostate tissue identification by identifying tissue utilising the combined techniques of MRI, magnetic resonance spectroscopic imaging (MRSI) and transrectal biopsy. In this study, 25 patients were evaluated utilising DCE-MRI. Of these 25 patients, 21 had undergone biopsy. In comparison with normal peripheral-zone tissue, cancerous peripheral-zone tissue demonstrated a greater peak enhancement (126 ± 11 versus 118 ± 7 ; $p < 0.006$), a faster enhancement rate (16.9 ± 8.7 versus 8.8 ± 5.5 ; $p < 0.0008$) and a faster washout slope (-0.53 ± 1.4 versus 0.37 ± 1.4). Stromal benign prostatic hyperplasia was found to have the highest peak enhancement (132 ± 9) and the fastest

enhancement rate (30.3 ± 8) in comparison with all other tissue types studied ($p < 0.003$). The ability to further delineate the contrast characteristics of various prostate tissues offers much promise in future endeavours to create more accurate maps of benign and malignant prostate tissue. Potential weaknesses of this study include the absence of prostate cancers with Gleason scores greater than seven in the study group and the absence of evaluation of transitional-zone or central-zone tumours.

DCE-MRI has also been studied as an alternative to biopsy for the diagnosis of prostate cancer in the setting of elevated PSA in a Japanese population. Hara et al.¹⁹ investigated men with an elevated serum PSA level (defined as > 2.5 ng/ml) and compared DCE-MRI as

It has been previously shown that cancerous regions in the peripheral zone demonstrate a faster enhancement in comparison with normal tissue.

a detection modality versus 14-core biopsy. DCE-MRI in this study detected 92.9% of clinically significant prostate cancers with a specificity of 96.3%. For men with PSA < 10 ng/ml, the accuracy was 80.5%. With further improvements in technology and software, this modality holds promise for improved cancer detection and the ability to perform more selective biopsies in men with elevated PSA.

Magnetic Resonance Spectroscopic Imaging

MRSI is an imaging technique that provides a metabolic analysis of prostate tissue. The utility of this technique is derived from the differences in metabolic profile that exist between normal and malignant prostate tissue. Specifically, areas of prostatic malignancy tend to exhibit higher relative concentrations of choline and reduced levels of citrate. Zakian et al. investigated whether these differences could be used to predict prostate cancer aggressiveness, i.e. Gleason score, in a study of 94 men imaged prior to undergoing radical prostatectomy.²⁰ Post-operative whole-mount histological analysis was compared with pre-operative MRSI. Transrectal biopsy correctly predicted Gleason score in 64.2% of the patients. In the 94 patients evaluated, 239 peripheral-zone lesions were identified. MRSI correctly identified 135 of these lesions and performed best in identifying higher-grade lesions (sensitivity 44.4% for Gleason score 3+3 versus sensitivity 89.5% for Gleason score 4+4). The improved performance in higher-grade lesions was due to the positive correlation between increasing choline plus creatine to citrate ratio (Ch plus Cr to Cit) and increasing tumour aggressiveness. In Gleason score 3+3 lesions, tumour size was a significant factor in MRSI tumour detection (average largest diameter for tumours not detected was 7.9 ± 4.9 mm compared with 11.6 ± 6.8 mm for tumours that were detected; $p < 0.001$). From the same group, a recent study examined pre-operative MRSI in comparison with whole-mount prostatectomy specimens to predict clinically insignificant prostate cancer tumours.²¹ Compared with standard pre-operative clinical parameters and endorectal MRI, the use of MRSI more accurately predicted which patients had small-volume, low-grade tumours that were likely to be

clinically insignificant. This approach could be used to counsel men electing for deferred therapy or 'watchful waiting'.

Compared with standard pre-operative clinical parameters and endorectal magnetic resonance imaging, magnetic resonance spectroscopic imaging more accurately predicted which patients had small-volume, low-grade tumours that were likely to be clinically insignificant.

Cancer Detection with Previous Negative Biopsies

Another setting in which MRSI has shown promise is in patients with elevated PSA and previously negative biopsies. In a group of 42 men at high risk of prostate cancer (mean PSA 12ng/ml; mean number of prior negative biopsies 2.04), Amsellem-Ouazana et al. utilised pre-biopsy combined MRI/MRSI to identify areas suspicious for cancer.²² MRI was followed by 10-core TRUS-guided prostate biopsy with additional cores taken in areas determined to be suspicious by MRI/MRSI. Prostate cancer detection rate in this population was 35.7%, which represents an improvement over saturation biopsy techniques. Overall, utilising a stringent threshold of 3SD Ch plus Cr to Cit ratio to label areas as suspicious achieved a sensitivity of 73.3%, a specificity of 96.3% and an accuracy of 88%. This is the second such study to show a benefit of the use of combined MRI/MRSI in the setting of previously negative prostate biopsies, confirming the 2004 study by Yuen et al. in Singapore.²³

Positron Emission Tomography

Several studies have examined the utility of positron emission tomography (PET) for prostate biopsy and initial staging of prostate cancer. A Hungarian study by Toth et al. examined the use of carbon-11 (C-11) methionine in patients with persistently elevated PSA and previous negative biopsies.²⁴ A

total of 20 patients were enrolled, with a mean PSA of 9.36ng/ml (range: 3.49–28.6ng/ml), with an average of 1.4 previous negative biopsies (range 1–5). C-11 methionine positron emission tomography (PET) scans concentrated on the pelvis were performed and correlated with pelvic MRI to anatomically localise areas of high standardised uptake values (SUVs) seen on PET. These areas were then targeted on repeat TRUS biopsy. Of the 20 patients, 15 had positive PET scans, and these areas were positive on repeat TRUS biopsy in seven patients (46.7%). Conversely, of the five patients with negative PET scans, all five (100%) had negative repeat biopsies. In a similar fashion, in a study by Yamaguchi in Japan the utility of C-11 choline PET scan was compared with MRSI to attempt to localise areas of tumour in men newly diagnosed with prostate cancer.²⁵ Twenty men underwent both MRSI and C-11 choline PET after the diagnosis of cancer was made and prior to any treatment. Sixteen of the men subsequently underwent radical prostatectomy. Comparison of the radical prostatectomy specimens with both PET and MRSI revealed that PET was concordant with the whole-mount pathological findings in predicting the laterality of the dominant tumour nodule in 13 of 16 patients (81%), while MRSI was concordant in only eight of 16 patients (50%).

Therefore, these studies suggest that PET scanning may help to localise suspicious areas within the prostate for both targeting on repeat biopsy to improve the detection of prostate cancer and for more accurately assessing the laterality of tumour prior to radical prostatectomy.

Conclusion

Histological identification of prostate cancer remains the gold standard and the only modality to provide a definitive diagnosis of the disease. The diagnosis and characterisation of prostate cancer remains a clinical challenge, with the ultimate goal being the diagnosis of potentially lethal cancers in younger men and the avoidance of detection of 'clinically insignificant' prostate cancers in older men. Enhanced TRUS techniques, MRSI and PET imaging techniques represent new avenues of inquiry to better diagnose prostate cancer. With further enhancements, the ability to identify those men with aggressive and potentially life-threatening cancers will improve. ■

- Jemal A, Siegel R, Ward E, et al., Cancer statistics, 2008, *CA Cancer J Clin*, 2008;58:71–96.
- Potosky AL, Miller BA, Albertsen PC, Kramer BS, The role of increasing detection in the rising incidence of prostate cancer, *JAMA*, 1995;273:548–52.
- Naughton CK, Smith DS, Humphrey PA, et al., Clinical and pathologic tumor characteristics of prostate cancer as a function of the number of biopsy cores: a retrospective study, *Urology*, 1998;52:808–13.
- Brawer MK, Quantitative microvessel density. A staging and prognostic marker for human prostatic carcinoma, *Cancer*, 1996;78:345–9.
- Rifkin MD, Sudakoff GS, Alexander AA, Prostate: techniques, results, and potential applications of color Doppler US scanning, *Radiology*, 1993;186:509–13.
- Kelly IM, Lees WR, Rickards D, Prostate cancer and the role of color Doppler US, *Radiology*, 1993;189:153–6.
- Newman JS, Bree RL, Rubin JM, Prostate cancer: diagnosis with color Doppler sonography with histologic correlation of each biopsy site, *Radiology*, 1995;195:86–90.
- Shigeno K, Igawa M, Shiina H, et al., The role of colour Doppler ultrasonography in detecting prostate cancer, *BJU Int*, 2000;86:229–33.
- Lavoipierre AM, Snow RM, Frydenberg M, et al., Prostatic cancer: role of color Doppler imaging in transrectal sonography, *AJR Am J Roentgenol*, 1998;171:205–10.
- Cornud F, Hamida K, Flam T, et al., Endorectal color doppler sonography and endorectal MR imaging features of nonpalpable prostate cancer: correlation with radical prostatectomy findings, *AJR Am J Roentgenol*, 2000;175:1161–8.
- Ismail M, Petersen RO, Alexander AA, et al., Color Doppler imaging in predicting the biologic behavior of prostate cancer: correlation with disease-free survival, *Urology*, 1997;50:906–12.
- Halpern EJ, Strup SE, Using gray-scale and color and power Doppler sonography to detect prostatic cancer, *AJR Am J Roentgenol*, 2000;174:623–7.
- Halpern EJ, Fauscher F, Strup SE, et al., Prostate: high-frequency Doppler US imaging for cancer detection, *Radiology*, 2002;225:71–7.
- Cornud F, Belin X, Piron D, et al., Color Doppler-guided prostate biopsies in 591 patients with an elevated serum PSA level: impact on Gleason score for nonpalpable lesions, *Urology*, 1997;49:709–15.
- Halpern EJ, Ramey JR, Strup SE, et al., Detection of prostate carcinoma with contrast-enhanced sonography using intermittent harmonic imaging, *Cancer*, 2005;104:2373–83.
- Pelzer A, Bektic J, Berger AP, et al., Prostate cancer detection in men with prostate specific antigen 4 to 10 ng/ml using a combined approach of contrast enhanced color Doppler targeted and systematic biopsy, *J Urol*, 2005;173:1926–9.
- Konig K, Scheipers U, Pesavento A, et al., Initial experiences with real-time elastography guided biopsies of the prostate, *J Urol*, 2005;174:115–17.
- Noworolski SM, Henry RG, Vigneron DB, Kurhanewicz J, Dynamic contrast-enhanced MRI in normal and abnormal prostate tissues as defined by biopsy, MRI, and 3D MRSI, *Magn Reson Med*, 2005;53:249–55.
- Hara N, Okuizumi M, Koike H, et al., Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a useful modality for the precise detection and staging of early prostate cancer, *Prostate*, 2005;62:140–47.
- Zakian KL, Sircar K, Hricak H, et al., Correlation of proton MR spectroscopic imaging with gleason score based on step-section pathologic analysis after radical prostatectomy, *Radiology*, 2005;234:804–14.
- Shukla-Dave A, Hricak H, Kattan MW, et al., The utility of magnetic resonance imaging and spectroscopy for predicting insignificant prostate cancer: an initial analysis, *BJU Int*, 2007.
- Amsellem-Ouazana D, Younes P, Conquy S, et al., Negative prostatic biopsies in patients with a high risk of prostate cancer. Is the combination of endorectal MRI and magnetic resonance spectroscopy imaging (MRSI) a useful tool? A preliminary study, *Eur Urol*, 2005;47:582–6.
- Yuen JS, Thng CH, Tan PH, et al., Endorectal magnetic resonance imaging and spectroscopy for the detection of tumor foci in men with prior negative transrectal ultrasound prostate biopsy, *J Urol*, 2004;171:1482–6.
- Toth G, Lengyel Z, Balkay L, et al., Detection of prostate cancer with 11C-methionine positron emission tomography, *J Urol*, 2005;173:66–9, discussion 69.
- Yamaguchi T, Lee J, Uemura H, et al., Prostate cancer: a comparative study of 11C-choline PET and MR imaging combined with proton MR spectroscopy, *Eur J Nucl Med Mol Imaging*, 2005;32:742–8.