

Diagnostic Imaging Approaches to Prostate Cancer

a report by

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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.

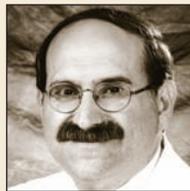
The controversy regarding the potential overtreatment of 'clinically insignificant' prostate tumors is balanced by the infrequent but concerning finding of higher-volume, higher-grade tumors recognized on final surgical pathology after radical prostatectomy. Improved diagnostic methods are necessary to more accurately detect prostate cancer while minimizing unnecessary biopsies. Several new diagnostic imaging modalities being explored to improve the accurate diagnosis of prostate cancer are presented here.



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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. Color 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 tumor with increased number and size of vessels characterize 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 color Doppler imaging.^{5–10} In addition, color Doppler signal correlates positively with the grade and stage of tumor, 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 analyzing the use of intravenous sonographic contrast agents injected during TRUS analysis of the prostate with color and power Doppler.¹⁵ The intravenous contrast agent utilizes microbubbles, which enhance the ultrasound identification of microvascular flow anomalies associated with prostate cancer. In the trial by Halpern and colleagues, an intermittent harmonic grayscale 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 color 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 analyzed. 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 grayscale TRUS alone.

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 10 ng/ml received an intravenous ultrasound contrast microbubble agent, and contrast-enhanced color 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 grayscale 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 tumors. 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 previously been 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 utilizing the combined techniques of MRI, magnetic resonance spectroscopic imaging (MRSI), and transrectal biopsy. In this study, 25 patients were evaluated utilizing 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

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tissues offers much promise in future endeavors 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 tumors.

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 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 tumor aggressiveness. In Gleason score 3+3 lesions, tumor size was a significant factor in MRSI tumor detection (average largest diameter for tumors not detected was 7.9 ± 4.9 mm compared with 11.6 ± 6.8 mm for tumors 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 tumors.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 tumors that were likely to be clinically insignificant. This approach could be used to counsel men electing for deferred therapy or 'watchful waiting.'

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 for prostate cancer (mean PSA 12ng/ml; mean number of prior negative biopsies 2.04), Amsellem-Ouazana et al. utilized 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, utilizing 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 biopsy, 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 localize areas of high standardized 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 localize areas of tumor 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 tumor 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 localize 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 tumor prior to radical prostatectomy.

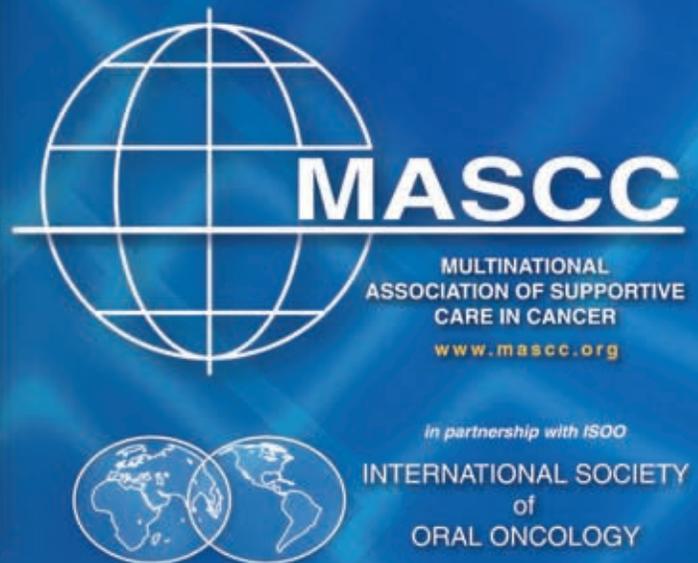
Conclusion

Histological identification of prostate cancer remains the gold standard and the only modality to provide a definitive diagnosis of the disease. The diagnosis and characterization 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. ■

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