Contrast-Enhanced Ultrasound May Aid Prostate Cancer Detection

By Mike Fillon

Clinicians who suspect their patients have prostate cancer, may soon have a better way of validating their suspicions. In a recent phase III study, researchers from Thomas Jefferson University and Hospitals in Philadelphia found that a technique, known as contrast-enhanced ultrasound (CEUS), which uses “microbubbles” to measure change in blood flow, did a much better job detecting high-grade prostate cancer than conventional biopsy methods. The study appears in the Aug. 17, 2012, online edition of the Journal of Urology.

Lead author Ethan Halpern, M.D., codirector of Jefferson’s Prostate Diagnostic Center, said as a result of the study, they found almost three times as many high-grade cancers by using half as many needle biopsies compared with systematic biopsy methods. “Today, a physician may sample 12–18 tissue cores from the prostate in order to help diagnose a patient. But with contrast-enhanced, that number drops to six or even less,” said Halpern. “As a result, we believe CEUS could prove to be more efficient for screening clinically important cancers and monitoring low-risk ones with fewer biopsies.”

CEUS has been studied before. Two smaller studies, both conducted by researchers from the Medical University in Innsbruck, Austria—one in 2007 and the second in 2010—also concluded that CEUS improved prostate cancer detection. “Our study similarly confirms an increased frequency of positive cores in CEUS-targeted biopsy compared to systematic biopsy by nearly double,” said Halpern (16.4% vs. 8.5%).
Stacy Loeb, M.D., a urologist with the department of urology at the Joel E. Smilow Comprehensive Prostate Cancer Center at New York University School of Medicine also thinks CEUS might be the answer. “While prostate-specific antigen (PSA) is not a perfect test, and not all men are good candidates for screening, the results of this new study suggest that CEUS might be useful to selectively detect clinically significant prostate cancers during biopsy.”

Ultrasound is one of the two main imaging methods used for prostate cancer detection. Multiparametric magnetic resonance imaging (MRI) is also being tested in this context and has shown promise. Loeb said multiparametric MRI has been associated with both the presence and extent of prostate cancer on biopsy. “MRI has also been shown to predict the likelihood of short-term progression on active surveillance.”

By contrast, ultrasound imaging of the prostate is commonly used to assess the size of the gland and for needle placement during systematic biopsy, but it cannot easily distinguish benign from malignant tissue. Halpern believes CEUS could change that.

**Surprise Discovery**

History is replete with inadvertent discoveries that turn out better than what was originally sought. The same is true of the Jefferson study. “The result of this study was a pleasant surprise,” said Halpern, who explained that the original goal of the study was to investigate whether an oral dutasteride pretreatment improved the detection of prostate cancer. “It was a randomized study to look at that.” Although dutasteride had no effect, the researchers were pleased to find that CEUS-targeted biopsy provides a significant benefit for the detection of high-grade/high-volume prostate cancer.

A total of 272 men (210 white, 54 black, 6 Hispanic, and 2 Asian) completed the randomized, double-blind, placebo-controlled trial. Their mean age was 62 years (range, 36–83 years), with mean serum PSA levels of approximately 6.5 ng/dL.

Before contrast administration, grayscale ultrasound was performed to measure gland size and to evaluate for focal echo texture and contour abnormalities. The contrast agent along with 50 mL of normal saline was administered via an intravenous line in each subject’s arm for 10 minutes. The contrasting agent used was perfluoropropane microbubbles. “There are other agents that can be used as well,” said Halpern. Subjects were imaged in the lithotomy position to minimize perturbation of vascularity measurements.

Precontrast color and power Doppler imaging were performed to evaluate blood flow. During contrast infusion, continuous harmonic gray-scale imaging was performed, followed by color and power Doppler imaging, intermittent gray-scale harmonic imaging with a 2-second interscan delay, and finally flash replenishment imaging coupled with maximum-intensity projection imaging. Halpern said that prostate cancer, especially higher-grade cancers, have increased and disorganized pattern of microvessel density that can be observed using flash replenishment imaging. “It allows us to see if there is more blood flow and if there is an unusual pattern that could be associated with cancer.”

The contrast-enhanced ultrasound findings were graded and used to direct targeted biopsy (up to six cores per prostate). A blinded 12-core systematic biopsy was then performed on every subject on the basis of standard medial and lateral sampling of each sextant.

**While prostate-specific antigen (PSA) is not a perfect test, and not all men are good candidates for screening, the results of this new study suggest that CEUS might be useful to selectively detect clinically significant prostate cancers during biopsy.”**

Positive biopsy samples indicating prostate cancer were found in 43% of the men. The researchers found mean PSA of patients with and those without prostate cancer was not significantly different (7.1 vs. 6.4 ng/dL). For the detection of high-grade cancer (Gleason score 7 or greater,) receiver operating characteristic (ROC) analysis demonstrated improved accuracy for precontrast imaging and contrast-enhanced ultrasound. For the detection of high-grade cancer with greater than 50% biopsy core involvement, the researchers reported that excellent accuracy was demonstrated with precontrast and contrast-enhanced ultrasound.

Halpern has no illusions that CEUS is the be-all, end-all of prostate cancer detection. He noted that the combination of gray-scale with CEUS imaging provides an ROC area of only 0.64, suggesting that this technique misclassifies many cases. “Also, the paired analysis of CEUS targeted versus systematic biopsy confirms that CEUS misses many cancers.”

Still, Philip Kantoff, M.D., vice chair of department of medical oncology and professor of medicine at Harvard Medical School, said the study did a very good job of demonstrating the potential value of CEUS in the detection of high-grade prostate cancer, “which is the type of cancer we need to detect.” Kantoff added that the findings need to be confirmed in larger, multi-institutional studies.

Kantoff said the study has the potential to erase a lot of doubt over screening and monitoring. “Current biopsy techniques for the detection of prostate cancer are woefully inadequate,” said Kantoff. “They are essentially blind biopsies guided by ultrasound, which simply allows imaging of the configuration of the gland to allow systematic but random biopsy. Better imaging techniques are needed and will probably reduce the number of unnecessary biopsies and enhance the detection of potentially lethal prostate cancer.”

jnci.oxfordjournals.org

Without question, adding imaging studies before biopsy could increase costs. “However, these increased up-front costs might be warranted if the use of imaging ultimately reduces unnecessary biopsies and treatment,” said Loeb.

CEUS and Active Surveillance
It is widely accepted that older men, or men who have other serious health problems, may never need treatment for prostate cancer. This was a large part of the concern expressed by the U.S. Preventive Services Task Force. Instead, they may benefit from active surveillance, where their cancers are monitored with various tests to determine whether the cancer is beginning to be more aggressive.

“It stands to reason that the cost–benefit ratio for prostate cancer screening will improve if PSA screening is followed by a limited targeted biopsy based on CEUS,” said Edouard J. Trabulsi, M.D., codirector of the Prostate Diagnostic Center and associate professor of urology. “This also means contrast-enhanced ultrasound can act as another monitoring tool for active surveillance in low-grade cancer patients, potentially preventing unwarranted treatments.”

PDQ (Physician Data Query) is the National Cancer Institute’s source of comprehensive cancer information. It contains peer-reviewed, evidence-based cancer information summaries on treatment, supportive care, screening, prevention, genetics, and complementary and alternative medicine. The summaries are regularly updated by six editorial boards. The following PDQ summaries were recently updated:


The PDQ Genetics of Skin Cancer summary was recently updated to include the results of the Genes, Environment, and Melanoma (GEM) study, a multicenter, population-based, case-control study. The study showed that first-degree relatives of CDKN2A mutation carriers with melanoma had an approximately 50% increased risk of cancers other than melanoma compared with first-degree relatives of other melanoma patients. Cancers with increased risk in this population included gastrointestinal cancers (relative risk [RR], 2.4; 95% CI, 1.4–3.7), pancreatic cancers (RR, 7.4; 95% CI, 2.3–18.7), and Wilms tumor (RR, 40.4; 95% CI, 3.4–352.7). This study provides further evidence that CDKN2A mutations are associated with increased risk of several cancers other than melanoma.

To review the summary, please use the following link:

http://www.cancer.gov/cancertopics/pdq/genetics/skin/HealthProfessional/Page4#Section_644


The PDQ Chronic Myeloproliferative Disorders Treatment summary was recently updated to include information about ruxolitinib, an inhibitor of the Janus kinases JAK1 and JAK2 that helps reduce the splenomegaly and debilitating symptoms of weight loss, fatigue, and night sweats in patients with JAK2-positive or JAK2-negative primary myelofibrosis, post-essential thrombocythemia myelofibrosis, or post-polycythemia vera myelofibrosis. The summary was also updated to include results from two prospective, randomized trials with a total of 528 higher-risk patients who were randomly assigned to ruxolitinib or best available therapy or placebo. In the trial with best available therapy as the control arm, patients on ruxolitinib had a decrease of 56% in mean palpable spleen length at 48 weeks compared with an increase of 4% with best available therapy. In the placebo-controlled trial, 41.9% of patients on ruxolitinib had a >35% reduction in spleen volume at 24 weeks compared with 0.7% of patients on placebo. Ruxolitinib also improved overall quality-of-life measures, with low toxic effects in both studies but with no benefit in overall survival. Discontinuation of ruxolitinib resulted in a recurrence of systemic symptoms.

http://www.cancer.gov/cancertopics/pdq/treatment/myeloproliferative/HealthProfessional/Page4#Section_243

The PDQ Screening and Prevention Editorial Board recently completed a major update of the Ovarian Cancer Screening summary. The Board conducted a review of the published literature and revised the text of the summary and updated the citations. To review the summary, please use the following link:

http://www.cancer.gov/cancertopics/pdq/screening/ovarian/HealthProfessional

The PDQ Complementary and Alternative Medicine Editorial Board published a new summary about the use of high-dose vitamin C as a treatment for people with cancer. A comprehensive review of published literature was performed and the summary was reviewed by external experts in the field before final approval by the Editorial Board. The summary was posted on Cancer.gov on 02/08/2013. To review the summary, please use the following link:

http://www.cancer.gov/cancertopics/pdq/cam/highdosevitaminc/healthprofessional/page1/AllPages