The search for a more sensitive and specific diagnostic test for prostate cancer has led to the burgeoning field of proteomics, providing unprecedented opportunity to identify potential disease biomarkers. With support from the National Cancer Institute's Early Detection Research Network (EDRN), investigators have been examining and comparing protein patterns in the serum of prostate cancer patients and controls. The EDRN initiative makes use of surface-enhanced laser desorption ionization time-of-flight (SELDI-TOF) mass spectrometry.

"The first level of this work is pure proteomic profiling," said William Bigbee, Ph.D., a professor of epidemiology and director of the Proteomics Core Laboratory at the University of Pittsburgh Cancer Institute. "There are no predetermined proteins or biomarkers. We simply take unfractionated serum, put it on a proprietary SELDI preparative and analytical platform, and generate a protein expression fingerprint, profile, or pattern with as many features as we can discriminate on this instrument. Then we submit the profiles to pattern-searching algorithms to see whether we can find reproducible, stable features that distinguish cases from controls."

Initial results have been encouraging. In one representative study, investigators used SELDI mass spectrometry to evaluate serum samples from 167 men with prostate cancer, 77 with benign prostatic hypertrophy, and 82 age-matched controls. The results showed that a nine-protein pattern correctly classified 96% of the samples. Further evaluation of a blinded test set revealed a sensitivity of 83% and specificity of 97% (Cancer Res 2002;62:3609-3614).

The next phase of investigation involves evaluation of almost 1000 sets of serum from prostate cancer patients and controls from sites around the country. Headed by John Semmes, Ph.D., of Eastern Virginia Medical School and Dr. William Grizzle of the University of Alabama, Birmingham, the study could submit results for final statistical analysis by the end of the year.

At the University of California, San Francisco, MR spectroscopy imaging (MRSI) figures prominently in the decision-making process. The MRSI exam involves use of an endorectal coil, which is placed on top of the prostate, said John Kurhanewicz, Ph.D., an associate professor of radiology. The coil is connected to a pelvic phased array of four to eight external coils. The imaging technique provides a combined anatomic and metabolic scan.

Between 700 and 1000 prostate cancer patients are referred to UCSF for MRSI evaluation. Kurhanewicz estimates that about 60% of the studies are conducted to help guide treatment decisions. About 10% of the studies involve men who have a rising PSA but multiple negative biopsies.

The remaining referrals come to UCSF for post-therapy evaluation because of PSA abnormalities. Clues to whether the abnormalities are due to residual or recurrent cancer come from changes in three metabolic markers: choline-containing compounds, citrate, and polyamines. Choline compounds are elevated in prostate cancer. Levels of citrate and polyamines are reduced in the presence of cancer.

"We match the three [markers] up with anatomic change, as reflected by a decrease in T2 signal intensity," Kurhanewicz said. "The magnitude of the changes also correlates with the aggressiveness of cancer. With more aggressive cancer, the choline will be much higher, the polyamines will be virtually absent, and the citrate will be much lower.

PET imaging of androgen receptors has demonstrated potential for providing information about the extent of prostate cancer and possibly response to therapy. "When prostate cancer begins to grow into the lethal castrate-resistant form of the disease, that is characterized by abnormalities of biology of the tumor cells, one of which is expression of the androgen receptor," said Dr. Steven M. Larson, chief of nuclear medicine at Memorial Sloan-Kettering...
Cancer Center. "The androgen receptor appears to be very important in this disorder. New drugs that are being used can have a big effect on the androgen receptor, and we can image that."

Several groups have investigated PET imaging of androgen receptors with F-18 fluoro-5a-dihydrotestosterone (FDHT). One study of patients with metastatic disease showed that patients who have positive FDHT-PET studies had higher PSA levels, suggesting greater tumor burden. Patients with positive tests received the anti-androgen flutamide, and post-treatment PET scans revealed decreased tumor uptake of FDHT (Eur J Nucl Med Mol Imaging 2005;32:344-350).

"We would like to study patients with prostate cancer with this tracer [FDHT] and see if by this tracer we will know whether a patient will respond to hormone therapy," said Dr. Farrokh Dehdashti, a professor of radiology at Washington University in St. Louis.

MR imaging with the iron oxide-containing contrast agent ferumoxtran-10 has shown potential for noninvasive detection of clinically occult lymph node metastases in patients with prostate cancer. In an evaluation of patients who underwent lymph node dissection or biopsy, MR imaging with ferumoxtran-10 had a sensitivity of 90.5% and specificity of 97.8% compared with 35.4% and 90.4% for conventional MRI (NEJM 2003;348:2491-2499).

On the horizon, molecular imaging could play a major role in the development and evaluation of new therapeutic approaches to prostate cancer. At the 2005 American Society of Clinical Oncology Prostate Cancer Symposium, investigators reported the use of in vivo molecular imaging techniques to monitor suicide gene therapy in a prostate cancer model.

Using a viral gene delivery vector, the researchers targeted the herpes simplex thymidine kinase gene to prostate cancer cells. The experimental therapy was monitored by bioluminescence imaging, PET, and PET/CT, which revealed tumor cell destruction and minimal toxicity.

"The gene not only has killing capability, but it also enables PET imaging," said Dr. Lily Wu, an assistant professor of urology and pediatrics at the University of California, Los Angeles.

Disclosures:

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