Session IV: Prostate

Prostate cancer and imaging

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Prostate cancer's incidence, prevalence, etiology, and risk factors, and the influence of clinical trials on imaging technology development are discussed.

One in seven Western men older than 70 will develop prostate cancer. The advent of prostate-specific antigen (PSA) screening means most men will now be diagnosed with early disease (85% not palpable on digital rectal exam (DRE), fewer grade 8–10 Gleason score tumors, *etc.*). An infection/inflammation event may be the basis for transforming events within the prostate, perhaps driven by an infectious agent or by dietary or environmental exposure to oxidative stress-producing substances which can cause chronic carcinogenic inflammatory infiltrates. A number of prostate cancer susceptibility genes control or regulate pathways associated with cellular defense; intervention with protective agents such as NSAIDs or free-radical scavenging drugs hold promise for localized disease control or treatment. Managing more advanced extraglandular disease remains problematic, as does biochemical failure after radical prostatectomy or external beam radiation; imaging disease stage and progression associated with these distinct classes of cases is challenging. Fundamental data soon to be available from large screening trials (e.g., European Organization of Research and Treatment of Cancer, or Prostate, Lung, Colorectal, and Ovarian Cancer Trial), and implications for prevention science from recent studies of hormone antagonists such as finasteride in the Prostate Cancer Prevention Trial or toremifene, should stimulate new ways of thinking about treatment and diagnosis in urology and imaging communities.

Prostate atrophy, inflammation, and dietary charred meat carcinogens in prostate carcinogenesis

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Why is prostate cancer so common? Epidemiological data points to aging and genetics with a potential role for diet and inflammation/infection as well. Prostate atrophy is an extremely common histological alteration in the human prostate. Although most investigators over the last several decades have assumed that it is not relevant to prostate cancer, as early as the 1930s pathologists suggested that prostate cancers might arise from prostate atrophy. Chronic inflammation is a major contributing cause of cancer in many organ systems. Only in the last few years have investigators begun to examine whether chronic inflammation, which is virtually always associated with atrophic prostate tissue, may also be involved in the pathogenesis of prostate cancer. Data regarding histological features, as well as cellular and molecular biology of prostate atrophy, is examined in relation to a stem cell model of prostate cancer development. New information indicates that the dietary "charred meat" carcinogen, 2-amino-1-methyl-6-phenylimidazo(4,5,6)pyridine (PhIP), acts as both a tumor initiator and a tumor promoter in the rat ventral prostate. Our updated model of human prostate carcinogenesis is that inflammation and/or dietary carcinogens interact to injure the prostatic epithelium by producing DNA damage, either from oxidants and nitrosative agents from the inflammatory cells, or from activated electrophilic compounds from the diet. This injury manifests morphologically as proliferative inflammatory atrophy (with inflammation) or "proliferative atrophy" (with little or no inflammation). These regenerative lesions then undergo somatic DNA alterations including telomere shortening, methylation of CpG dinucleotides in the promoter region of the *GSTP1* and other genes, and other somatic genome alterations to produce either high-grade prostatic intraepithelial

neoplasia (PIN) or small carcinoma lesions which then progress, under continued genome-damaging conditions, to invasive carcinoma and eventually to metastatic disease. This work has implications for chemoprevention and/or dietary changes that may eventually help to prevent prostate cancer.

Dynamic contrast-enhanced magnetic resonance imaging of prostate cancer at 3.0 Tesla

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Prostate cancer is the second most prevalent cancer among men. The American Cancer Society estimates that 234,460 men will be diagnosed with prostate cancer and 27,350 men will die of it in 2006. Though up to one in six men will receive a diagnosis of prostate cancer within their lifetime, only 3% of those will die as a direct result of the disease. This discrepancy highlights the heterogeneous nature of the disease, which can range from very aggressive to relatively indolent in nature. Prostate cancer can be treated with chemotherapy, radiotherapy, or surgery, though all these treatments have potentially debilitating side effects, such as radiation proctitis, impotence, and/or incontinence. Therefore, it is important to develop diagnostic techniques that can accurately diagnose prostate cancer early, as well as predict prognosis.

MRI is widely accepted as the best imaging modality for diagnosis and staging of prostate cancer. The higher field strength of 3.0 Tesla MRI produces an increase in the signal-to-noise-ratio. In addition, the combined use of a body phased-array coil and endo-rectal coil can further increase the spatial resolution. T2-weighted MR images have long been used in the diagnosis of prostate cancer; however, they lack adequate sensitivity and specificity. This results from the difficulty in distinguishing prostate cancer from areas of prostatitis, post-biopsy hemorrhage, and even benign prostatic hyperplasia. Dynamic contrast-enhanced (DCE)-MRI uses contrast enhancement patterns to derive functionality within the prostate gland. Wash-in and wash-out curves are generated from regions of interest, and application of a computer model can then produce several parameters of permeability. Quantitative analysis of DCE-MRI and three-dimensional MR spectroscopy at 3.0 Tesla is promising in terms of diagnosis and staging of prostate cancer. This may help stratify patients into standard treatment, more aggressive treatment, or "watchful waiting."

Latest developments in tissue-type imaging of prostate cancer: Ultrasonic and magnetic resonance approaches[1]

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Ultrasonic spectrum (USS) analysis applied to radiofrequency ultrasonic echo signals has proven to provide a promising basis for distinguishing among different types of tissue based on sometimes subtle differences in tissue microarchitecture and scattering properties. In the prostate, USS combined with artificial neural network (ANN) classification tools has enabled encouraging differentiation between cancerous and noncancerous tissue. These methods have produced a receiver operating characteristic (ROC) curve area of 0.84 compared to an area of 0.64 for conventional B-mode based determinations of suspicion levels for identical regions of the gland. Based on the areas and shapes of these ROC curves, USS alone seems to be potentially capable of improving the sensitivity of ultrasound-guided biopsies by more than 50% using tissue-type images (TTIs) derived from ultrasound spectra and ANNs to target the biopsy needle. Such TTIs potentially can depict regions showing cancerous properties in two or three dimensions for biopsy guidance, disease evaluation, treatment planning and targeting, and therapy monitoring.

Like conventional ultrasound B-mode images, conventional MRIs cannot reliably depict cancerous regions of the prostate. However, as in ultrasound spectral methods, magnetic resonance spectroscopy (MRS) shows an encouraging ability to distinguish cancerous from noncancerous prostate tissue based on its depiction of chemical constituents of tissue. In noncancerous prostate tissue, the level of citrate tends to be higher than that of choline or creatine. However, in cancer

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of the prostate, the situation is reversed, and creatine, choline, or both tend to be elevated with respect to citrate. MRS can depict the ratios of these constituents and, based on the ratios, can distinguish cancerous from noncancerous prostate tissue. As is the case with USS, classification of prostate tissue by MRS produces ROC curve areas having values ranging from 0.70 to 0.80.

Because these two modalities sense fundamentally different properties of tissue, i.e., mechanical properties for ultrasound and chemical properties for MRS, we anticipate that combining the two modalities and applying new, more powerful classification tools such as support-vector machines will markedly improve classification performance. Currently, efforts are underway to register ultrasonic and MRS data in 3-D and to correlate TTIs with prostatectomy histology.

Image guided intervention/magnetic resonance imaging guided diagnosis and therapy

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The recent emergence of minimally invasive therapeutic procedures has brought major advantages over conventional surgical procedures and has revolutionized certain surgical interventions. Many benefits derive from minimally invasive surgery. First, recovery time, and thus hospital stay, can be significantly shorter than in conventional open surgeries. Second, the risk of complications, e.g., infection and bleeding, is lower. Third, the procedure may require only local anesthesia or sedation instead of general anesthesia. Clearly, the above factors combined would lead to a significantly reduced cost for the intervention. Motivated by these potential benefits and our strong interest in prostate MRI and IGI, we established a MR-guided prostate intervention program more than five years ago. Our team of investigators designed and developed the program on site using the surgical planning laboratory and Signa SP 0.5T system from General Electric medical systems.

Currently, our institution employs MR-guided interventions for both prostate biopsy and cancer treatment. MR-guided prostate brachytherapy and prostate biopsy procedures are investigated along with current and future roles of imaging. New MR-based molecular imaging methods and other imaging modalities are changing prostate diagnosis and treatment; for instance, a totally non-invasive thermal ablation method, MR-guided focused ultrasound (MRgFUS) has the potential to be performed in prostate cancer.