www.medscape.com

2nd Annual Multidisciplinary Prostate Cancer Symposium
Planning and Assessment of New Prostate Cancer Therapies CME

Complete author affiliations and disclosures are at the end of this activity.

The materials presented here were prepared by independent authors under the editorial supervision of Medscape and do not represent a publication of the 2nd Annual Multidisciplinary Prostate Cancer Symposium. These materials and the related activity are not sanctioned by the 2nd Annual Multidisciplinary Prostate Cancer Symposium or the commercial supporter of the conference, and do not constitute an official part of that conference.

Release Date: April 26, 2006; **Valid for credit through April 26, 2007**

Target Audience

This activity is intended for oncologists, urologists, radiologists, and surgeons interested in learning about emergent approaches for managing early-stage prostate cancer, including new surgical, radiation therapy, and immunotherapy techniques, the role of molecular pathways, and imaging of prostate cancer.

Goal

The objective of this activity is to review the utility of surgical, radiotherapeutic, and imaging advances in the management of early-stage prostate cancer, define appropriate settings for the use of these new technologies, and offer a forum for an expert to outline the benefit of these approaches for the Oncology, Urology, Radiology, Surgery, and other relevant clinical audiences on Medscape.

Overall Learning Objectives

Upon completion of this activity, participants will be able to:

1. Describe advances in surgery, radiation therapy, chemotherapy, novel and hormonal agents, and immunotherapy for treating prostate cancer.
2. Review the imaging modalities used to evaluate prostate cancer.
3. Detail the relationship between molecular pathways and targeted molecular therapies in the treatment of prostate cancer.

Learning Objectives for this CME Activity

Upon completion of this activity, participants will be able to:

1. Describe advances in surgery, radiation therapy, and immunotherapy for treating early-stage prostate cancer.
2. Discuss the role of molecular pathways in planning targeted therapies for prostate cancer.
3. Review the role of imaging in the accurate assessment of prostate cancer.

Credits Available

Physicians - up to 1.0 *AMA PRA Category 1 Credit(s)*™ for physicians

All other healthcare professionals completing continuing education credit for this activity will be issued a certificate of participation.

Participants should claim only the number of hours actually spent in completing the educational activity.

Accreditation Statements

For Physicians

Medscape is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Medscape designates this educational activity for a maximum of **1.0 Category 1 credit(s)** toward the AMA Physician's Recognition Award. Each physician should claim only those credits that reflect the time he/she actually spent in the activity.

For questions regarding the content of this activity, contact the accredited provider for this CME/CE activity: CME@webmd.net. For technical assistance, contact CME@webmd.net.

This activity is supported by an independent educational grant from Sanofi Aventis.

Instructions for Credit

There are no fees for participating in or receiving credit for this online educational activity. For information on applicability and acceptance of continuing education credit for this activity, please consult your professional licensing board.

This activity is designed to be completed within the time designated on the title page; physicians should claim only those credits that reflect the time actually spent in the activity. To successfully earn credit, participants must complete the activity online during the valid credit period that is noted on the title page.

Follow these steps to earn CME/CE credit*:

1. Read the target audience, learning objectives, and author disclosures.
2. Study the educational content online or printed out.
3. Online, choose the best answer to each test question. To receive a certificate, you must receive a passing score as designated at the top of the test. Medscape encourages you to complete the Activity Evaluation to provide feedback for future programming.

You may now view or print the certificate from your CME/CE Tracker. You may print the certificate but you cannot alter it. Credits will be tallied in your CME/CE Tracker and archived for 6 years; at any point within this time period you can print out the tally as well as the certificates by accessing "Edit Your Profile" at the top of your Medscape homepage.

*The credit that you receive is based on your user profile.

Legal Disclaimer
The materials presented here do not reflect the views of Medscape or the companies providing unrestricted educational grants. These materials may discuss uses and dosages for therapeutic products that have not been approved by the United States Food and Drug Administration. A qualified healthcare professional should be consulted before using any therapeutic product discussed. All readers or continuing education participants should verify all information and data before treating patients or employing any therapies described in this educational activity.

Copyright © 2006 Medscape.

Contents of This CME Activity

1. Improving Prognosis for Patients With Early Prostate Cancer: Innovations in Surgery, Radiotherapy, and Immunotherapy
   Hossein Jadvar, MD, PhD
2. Using Molecular Pathways to Select Targeted Therapies for Prostate Cancer
   Hossein Jadvar, MD, PhD
3. Imaging of Prostate Cancer: Many Options, Paltry Progress
   Hossein Jadvar, MD, PhD

Improving Prognosis for Patients With Early Prostate Cancer: Innovations in Surgery, Radiotherapy, and Immunotherapy

Hossein Jadvar, MD, PhD

Prostate cancer is the most common cancer affecting men in the United States. In 2003, the estimated incidence of and deaths from this disease were 220,900 cases and 28,900 cases, respectively.[1] In this report, we summarize the research on the treatment of early and localized disease that was presented at the 2nd Annual Meeting of the Multidisciplinary Prostate Cancer Symposium held in San Francisco, California; February 24-26, 2006; and cosponsored by the American Society of Clinical Oncology (ASCO), the American Society for Therapeutic Radiology and Oncology (ASTRO), the Prostate Cancer Foundation (PCF), and the Society of Urologic Oncology (SUO).

COMPARE Results

There are several treatment options for early stage prostate cancer. A multi-institutional study assessed the choices of the initial definitive treatment strategies for prostate cancer in all regions of the United States through a database entitled COMPARE (Comprehensive Multicenter Prostate Adenocarcinoma Registry) that was started in October 2004.[2] As of September 2005, there were 146 physician sites (129 urology, 12 radiation oncology, 3 medical oncology, 2 miscellaneous) with most practices in the private setting rather than academic (132 vs 14, respectively). Overall, it was found that the most common current definitive treatment for early stage prostate cancer was radical prostatectomy (RP) followed by external beam radiation therapy (EBRT) and brachytherapy (BT). For patients younger than 70 years, use of RP was more common than in patients older than 70 years, who were most frequently treated with EBRT, BT, or both.

In low-risk prostate cancer (defined as prostate-specific antigen [PSA] < 10 ng/mL and biopsy Gleason sum ≤ 6), it was shown that immediate treatment (up to 180 days after diagnosis) may be unnecessary without untoward effect on outcome, although delays greater than 180 days were associated with an increased risk (relative risk 2.73) of biochemical progression.[3] In a related study by Kwan and colleagues, the effect of delay in RT on outcome was determined.[4] The time to treatment from diagnosis to RT was analyzed with respect to PSA control in 1024 hormone-naive patients. The authors found no significant impact on outcome with a longer interval between diagnosis and RT. The multivariate analysis revealed pretreatment PSA and Gleason score as the most significant parameters in predicting PSA failure in both the intermediate and the high-risk disease.

Watch and Wait vs New Surgical Approaches

An outcome report from investigators in Toronto and the Mayo Clinic in Minnesota followed patients younger than 55 years with insignificant disease (< 3 positive cores with sextant biopsies or ≤ 3 cores with 8-12 biopsies with no core having > 50% involvement) who were followed prospectively.[5] The cohort consisted of patients with favorable-risk prostate cancer (PSA ≤ 10, Gleason ≤ 6, T1c-T2), with a median follow-up of 4.5 years (range, 0.5-10 years). At 10 years, the overall actuarial survival was 85% and disease-specific survival was 99.5%. The study concluded that over a 10-year period, virtually all men with "favorable-risk" prostate cancer managed conservatively in this fashion may die of causes unrelated to prostate cancer.

Surgical management in relation to the extent of pelvic lymph node dissection was reported by the investigators from

the Memorial Sloan-Kettering Cancer Center in New York.[6] The authors of this study noted that a lymph node dissection including the external iliac, obturator, and hypogastric lymph node basins yields more positive nodes than the often-performed lymph node dissection limited to the external iliac nodes (relative risk of 21.2). It was concluded that although limited lymph node dissection may be safe in low-risk patients (based on Partin tables), this strategy will need to be validated by long-term biochemical failure data. In another related study, investigators from the Cleveland Clinic and University of California at San Francisco (UCSF) compared biochemical relapse-free survival rates in patients who underwent radical prostatectomy with or without pelvic lymph node dissection.[7] This study demonstrated that there was no effect on biochemical relapse-free survival rates at 5 years in low-, intermediate-, and high-risk prostate cancer patients. In fact, performing pelvic lymph nodal dissection was not a predictor of biochemical failure. Therefore, the findings of this latter study from the Midwest and the West coast was in line with the findings of the previous study from the East coast, namely that lymph nodal dissection (limited or extended) may not be related to eventual possible development of biochemical failure.

The surgical impact of pathologic evaluation of intraoperative frozen sections during laparoscopic radical prostatectomy was investigated by Pansadoro and co-workers.[8] This study showed that intraoperative frozen sections can identify an additional 11% of patients in whom it is possible to obtain negative margins potentially impacting their long-term outcome.

CAPRA: Prostatectomy and Prognosis

The results of the UCSF Cancer of the Prostate Risk Assessment (CAPRA) were also presented as a novel preoperative index designed to predict the risk of prostate cancer recurrence following RP.[9] The index was developed based on a national database of men treated at large community practices across the United States. The CAPRA score ranges from 0 to 10 and is determined based on Gleason score, clinical T stage, age, PSA, and percent positive cores of at least a sextant biopsy. Median follow-up in the dataset was 34%, and 26% of patients experienced recurrence (defined as 2 consecutive PSA values > 0.2 or any second treatment). The 5-year actuarial recurrence-free survival ranged from 86% for CAPRA 0-1 patients to 21% for CAPRA 7-10 patients. The authors concluded that UCSF-CAPRA can accurately predict outcome in men following prostatectomy for prostate cancer.

Comparing Radiotherapy and Brachytherapy Results

The favorable clinical results of high-dose BT were reported in 156 patients with T1 and T2 localized prostate cancer with a median Gleason score of 7, a median PSA of 9.3, and a median follow-up of 66 months.[10] The high-dose BT was associated with no seed migration, greater dose flexibility and precision of radiation dose delivery while avoiding bladder and rectal complications of EBRT. In another study, the effect of a modest escalation of EBRT of 5.4 Gy resulted in a more rapid decline in PSA in patients with localized prostate cancer and pretreatment PSA levels of 10 ng/mL or more. It also significantly lowered PSA values at 1 year follow-up, suggesting that small incremental radiation dose escalations may result in improved biochemical outcomes.[11]

In a study from Coen and colleagues, high-dose proton radiation therapy was compared with BT for localized prostate cancer.[12] The two groups of patients were well matched with regards to median PSA level, T-stage, and Gleason score. This study concluded that high-dose EBRT was equivalent to BT for control of localized prostate cancer, and that treatment decisions might be based on future quality of life comparisons.

In another multi-institutional investigation, salvage and adjuvant postoperative radiation therapy (RT) were compared in patients with pT3/4N0 prostate cancer.[13] Seventy-two patients received adjuvant RT within 12 months of RP. Two-hundred fifty-seven patients underwent salvage RT after biochemical failure. The patients were matched according to preoperative PSA, Gleason score, seminal vesicle invasion, surgical margin status, and length of follow-up. A PSA increase of 0.2 ng/mL was considered biochemical failure. The 5-year freedom-from-PSA-failure was 68% after adjuvant RT as compared to 42% for salvage RT at the time of PSA failure. Salvage RT, seminal vesicle invasion, and Gleason score above 7 were independent predictors of biochemical failure. The authors concluded that early post-prostatectomy, adjuvant RT for pT3/4N0 prostate cancer significantly decreases the risk of disease progression compared with delayed salvage RT. The effect of hypofractionated (ie, larger doses per fraction) RT in comparison to the conventionally fractionated cohort was studied by the Canadian researchers.[14] The study showed that hypofractionated RT is not only associated with very low rates of late bladder and rectal toxicity, but also the biochemical outcome during follow-up period (median follow-up 28-31 months with minimum of 14 months) was similar to dose-escalated conventional fractionated RT.

Intensity-modulated Radiotherapy With and Without Immunotherapy

Fonteyne and investigators presented 2 abstracts detailing their clinical experience with intensity-modulated radiotherapy (IMRT).[15,16] The first study summarized the data on the 5-year biochemical control of IMRT in 133 patients with T1-4 N0 M0 disease and a median PSA level of 10.9 ng/mL. The 5-year biochemical non-evidence of disease was 100%, 94%, and 74% for low, intermediate, and high-risk groups, respectively. The authors concluded that IMRT as primary therapy offers excellent biochemical control. In the second report from the same group of investigators, it was also noted that IMRT is associated with a low rate of late treatment-induced toxicity, with half of the cases of GI and GU toxicity resolving in less than 6 months.

The phase 2 clinical results of an immunotherapy approach were also presented.[17] The study was based on an adenoviral vector expressing the herpes thymidine kinase gene delivered to the prostate via transrectal ultrasound guidance, followed by 14 days of oral prodrug. The mechanism of biologic action was described as direct tumor cytotoxicity, recruitment and activation of antigen-presenting cells, and stimulation of T-cell immunity. This approach was combined with RT in 66 men with newly diagnosed prostate cancer in 2 study arms. The first arm of the study included 33 patients with low-risk disease (PSA < 10, Gleason < 7, T1c-T2a) and the second arm included 33 intermediate-high risk patients (PSA ≥ 10, Gleason ≥ 7, T2b-T3). Results showed that this adenoviral immunotherapy approach combined with RT may significantly reduce recurrence rate, particularly in patients with intermediate- to high-risk disease.

In another study, Shu and co-workers evaluated the efficacy of the immunotherapy approach using thalidomide and granulocyte macrophage-colony stimulating factor (GM-CSF).[18] Thalidomide augments the immune system and inhibits angiogenesis. GM-CSF is involved in enhancement of T-cell priming. The study enrolled 18 hormone-naive patients with prostate cancer who had failed definitive local therapy and demonstrated biochemical progression with no radiographic evidence of local disease. The data were encouraging, demonstrating median PSA response of 59% with reversible toxicity. The authors postulated that this approach may represent an alternative to hormonal therapy, which will need to be addressed in future comparative studies.

References

1. SEER: The Surveillance, Epidemiology, and End Results Program. Available at: http://seer.cancer.go. Accessed March 21, 2006.
2. McLeod DG, Schellhammer PF, Halabi S, et al. Initial definitive treatment choices for prostate cancer: results from the COMPARE registry. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 87.
3. Freeland SJ, Kane CJ, Amling CL, et al. Delay in receiving radical prostatectomy and risk of biochemical progression among men with low risk prostate cancer. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 71.
4. Kwan WB, Pickles T, Duncan G, et al. Does delay in radiotherapy result in poorer biochemical control for prostate cancer? Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 82.
5. Loblaw DA, Choo R, Zhang L, et al. Updated follow-up of active surveillance with selected delayed intervention for localized prostate cancer. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 37.
6. Touijer K, Rabbani F, Romero J, et al. Extended vs. limited laparoscopic pelvic lymph node dissection for prostate cancer: the value of Partin tables in selection of the need for and the extent of dissection. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 43.
7. Berglund R, Sadetsky N, DuChane J, et al. Limited pelvic lymph node dissection at the time of radical prostatectomy does not affect five-year biochemical failure rates for low-, intermediate-, and high-risk prostate cancer. Results from the Cancer of the Prostate Strategic Urologic Research Endeavor Database. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 46.
8. Pansadoro V, Emiliozzi P, Amini M, et al. Laparoscopic radical prostatectomy: intraoperative frozen sections-are they worth it? Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 65.
9. Cooperberg MR, Freedland SJ, Pasta DJ, et al. Multi-institutional validation of the UCSF Cancer of the Prostate Risk Assessment (CAPRA) for prediction of recurrence following radical prostatectomy. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 49.
10. Mark RJ, Vallabhan G, Anderson P, et al. High-dose rate (HDR) brachytherapy alone for localized prostate cancer. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 108.

11. Kuritzky N, Mehta R, Sherr DL, et al. The effect of modest external beam radiation therapy dose escalation on the rate and magnitude of PSA response in patients with localized prostate cancer. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 96.
12. Coen JJ, Zietman AL, Rossi CJ, et al. Comparison of high-dose proton radiation therapy vs. brachytherapy in localized prostate cancer: a case-matched analysis. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 38.
13. Valicenti RK, Hanton AL, Pisansky HM, et al. A multi-institutional matched-control analysis of adjuvant and salvage postoperative radiation therapy for pT3/4N0 prostate cancer. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 39.
14. Martin JM, Bayley A, Bristow RG, et al. Hypofractionated radiotherapy for prostate cancer: a prospective study compared with a conventionally fractionated cohort. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 72.
15. Fonteyne V, Vakaet L, Villeirs G, et al. Intensity-modulated radiotherapy (IMRT) as primary therapy for prostate cancer -- part 1: 5 years biochemical control. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 118.
16. Fonteyne V, Vakaet L, Villeirs G, et al. Intensity-modulated radiotherapy (IMRT) as primary therapy for prostate cancer -- part 2: late toxicity. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 121.
17. Butler EB, The B, Mai W, et al. Five-year follow-up of phase II cytotoxic immunotherapy study in combination with radiation in newly diagnosed prostate cancer. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 134
18. Shu T, Karediy M, Jones P, et al. A phase II trial of granulocyte macrophage-colony stimulating factor (GM-CSF) plus thalidomide for hormone-naive prostate cancer (HNPC). Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 135.

Using Molecular Pathways to Select Targeted Therapies for Prostate Cancer

Hossein Jadvar, MD, PhD

Prostate cancer is a heterogeneous disease with varying biologic behavior. In this article, we briefly discuss recent research focusing on molecular diagnostics and therapeutics for prostate cancer, which were spotlighted at the 2006 Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California; this symposium was cosponsored by the American Society of Clinical Oncology (ASCO), the American Society for Therapeutic Radiology and Oncology (ASTRO), the Prostate Cancer Foundation (PCF), and the Society of Urologic Oncology (SUO).

Biologic and Molecular Basis of Prostate Cancer

There were 2 relevant featured educational sessions, one emphasizing the stem cell biology of prostate cancer and the other a general discussion of the molecular diagnostics of prostate cancer.[1,2] In particular, the potential role of chronic inflammation, which is virtually always associated with atrophic prostate tissue, in the pathogenesis of prostate cancer was discussed.[1] There were also a number of abstracts that explored the biology of prostate cancer.

Bagala and co-workers studied the role of reverse transcriptase (RT) inhibitors in prostate cancer.[3] RT inhibitors induce reprogramming of gene expression in many cancer cell models. This study showed that RT inhibition can increase the sensitivity of androgen-independent prostate cancer to androgens and thus allow further application of androgen-deprivation therapy.

Of particular interest, this study demonstrated that RT inhibition resulted in inhibition of PC3 androgen-independent prostate cancer proliferation, and significant reprogramming of gene expression characterized by down-regulation of a number of genes (eg, vascular endothelial growth factor receptor), as well as upregulation of the androgen receptor and prostate-specific antigen (PSA). In another study from Lin and the group from Seattle, it was noted that surgical manipulation results in significant gene expression changes.[4] In this study, 12 patients with clinically localized

disease underwent immediate in situ prostate biopsy after induction of anesthesia for radical prostatectomy. Ex vivo prostate biopsies were then performed immediately after surgical removal of the prostate. There were 62 unique genes (1.5% of total measurable gene expression) that were altered due to surgery. The authors warned that this rapid change in gene expression (and potentially in the translated transcript and the protein product) should be considered when designing and analyzing molecular correlates in clinical trials. The exact basis and mechanism of this observed rapid gene expression alteration induced by surgical manipulation and its potential effect on diagnosis, treatment, and clinical outcome will need to be established.

Epidermal Growth Factor Receptor, Human Epidermal Growth Factor Receptor 2, and Prognosis

Schlomm and colleagues from Germany analyzed the alterations of the epidermal growth factor receptor (EGFR) family members in prostate cancer as potential targets for treatment.[5] EGFR and human epidermal growth factor receptor 2 (HER2) status were assessed in the tissues obtained from radical prostatectomy and correlated to tumor stage and clinical outcome. Both receptors were strongly linked to tumor recurrence, high Gleason grade, and advanced stage cancer. Specifically, coexpression of EGFR and HER2 was correlated with poor prognosis. The authors concluded that because EGFR and HER2 alterations are frequent in advanced prostate cancer and strongly linked to prognosis, clinical trials using an anti-EGFR/HER2 drug would be justified.

Detecting Tumor Cells

In another interesting study, Fizazi and investigators reported that circulating tumor cells (CTC) in patients with prostate cancer can be isolated by measuring telomerase activity.[6] Peripheral blood mononuclear cells were isolated from whole blood and then epithelial cells were harvested using immunomagnetic beads coated with an epithelial-specific antibody. Telomerase activity was then assessed in these epithelial cells. CTC were detected in 75% of patients with advanced prostate cancer and in 79% of patients with localized disease, even in those with low PSA level (< 0.1 ng/mL). This study suggested that CTC can be detected using telomerase activity in the majority of patients with prostate cancer, including those with localized disease and those with low PSA level. Although potentially useful, this technique cannot localize and assess the extent of occult recurrent and/or metastatic disease.

Androgen Ablation

The role of 5alpha-androstane-3alpha, 17beta-diol (3alpha-diol) in the development of androgen-independent prostate cancer was reported.[7] 3alpha-diol has long been considered to have no androgenic function in prostate pathophysiology. This investigation used LNCaP cells as a model to study 3alpha-diol-mediated androgenic effects. It was found that 3alpha-diol can stimulate prostate cell proliferation using androgen receptor independent pathways and hence may contribute to promoting cancer growth despite androgen deprivation. Another report concentrated on protocadherin-PC (PCDH-PC), which is a male-specific member of the delta protocadherin gene family whose expression is highly regulated in prostate cancer cells by androgen withdrawal.[8] Expression of PCDH-PC leads to apoptosis and increased p53 degradation. This study suggested that prostate cancer cells switch from dependence on androgens to dependence on PCDH-PC expression following androgen ablation, which may then provide a potential target for therapy.

Tumor Progression and Angiogenesis

The role of tumor hypoxia in tumor progression was also highlighted in a study by Simons and co-workers.[9] Hypoxic tumors have elevated rates of mutagenesis and genetic instability. Hypoxia-inducible factor (HIF) is principally responsible for the survival of cancer cells in the hypoxic state by utilizing glucose for energy and by fostering angiogenesis. Blocking HIF therefore provides an opportunity for treatment. Canadian investigators showed that hypoxia reduces expression of DNA repair genes in prostate cancer, which may give rise to genetic instability and tumor progression.[10] They concluded that hypoxia can modify DNA repair gene expression in prostate cancer.

Wnts are secreted glycoproteins that bind to receptor complexes, including the low-density lipoprotein receptor-related protein (LRP)-5/6 and the Frizzled proteins.[11] An investigation of the expression profile of the four Wnt family members in prostate cancer was reported by British investigators. This study showed that overexpression of Wnt-2 and reduced expression of Wnt-3 and Wnt-10b may play contributory roles in an invasive phenotype in prostate cancer. The role of the tumor suppressor gene PTEN and the other downstream constituents in the pathway was investigated by Gottschalk and colleagues.[12] In this study, it was noted that increased pAKT staining (loss of PTEN

causes activation of AKT, which is associated with increased proliferation, resistance to death, and increased angiogenesis) in tumors is associated with higher Gleason score and pathologic T stage.

Molecular Markers, Apoptosis

The role of apoptosis-inducing factor (AIF) in prostate cancer cell apoptosis induced by cisplatin was investigated by researchers from Nebraska, who showed that cisplatin can lead to AIF translocation and apoptotic cell death in prostate cancer.[13]

In a report from Peru, the relationship between several molecular markers (Bcl-2, C-erb-2, p53) and overall survival was studied.[14] It was determined that about two thirds of prostate tumors express 1 or more of these markers and that the higher the Gleason score, the higher the expression of these markers. Furthermore, the expression of these markers was correlated with poor survival. In another study by Andren and co-workers, the role of anti-adhesion mucins, such as MUC-1, was studied in prostate cancer.[15] This joint Swedish and Harvard study tested the hypothesis that altered tissue expression of MUC-1 is associated with the risk of dying from prostate cancer. It was determined that 23% of patients with abnormal MUC-1 intensity died of prostate cancer compared with only 7% of patients with normal tissue expression of MUC-1. In fact, men whose tumors demonstrated either overexpression or underexpression of MUC-1 had a more than 4-fold higher risk of dying from prostate cancer, independent of tumor extent and the Gleason score. The authors of this article concluded that altered expression of MUC-1 plays a role in the progression of prostate cancer independent of other clinical parameters.

Alteration of proto-ontogenesis (ETS-related gene or ERG as one of the most frequent gene overexpressions) in prostate cancer is not well understood. It was shown that ERG has significant diagnostic and prognostic implications in prostate cancers by its significant role in regulation of cell growth, differentiation, and tumorigenesis.[16]

It was clear to the participants in these sessions that, as our understanding of the specific molecular pathways involved in prostate cancer pathogenesis and progression grows, there may be significant opportunities for development of molecularly based treatments.

References

1. DeMarzo A. Prostate cancer stem cell biology. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. p. 41.
2. Gelmann EP. Molecular diagnostics of prostate cancer. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. p. 47.
3. Bagala C, Landriscina M, Quirino A, et al. Reverse transcriptase inhibitors induce an androgen-dependent phenotype in undifferentiated androgen-independent prostate carcinoma cells. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 307.
4. Lin DW, Coleman I, Hawley S, et al. The influence of surgical manipulation on prostate gene expression: Implications for molecular correlates of treatment effects and disease prognosis. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 309.
5. Schlomm T, Erbersdobler A, Simon R, et al. Epidermal growth factor receptor family members (EGFR and HER2) are prognostic markers and potential therapeutic targets in prostate cancer. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 310.
6. Fizazi K, Morat L, Chauvenic L, et al. Circulating tumor cells can be detected using telomerase activity with a high rate in patients with prostate cancer. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 313.
7. Vemulapalli S, Lin H, Wong C, et al. 5alpha-androstane-3alpha, 17beta-diol protects prostate cancer cell survival and promotes cell proliferation using androgen receptor independent pathway. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 314.
8. Benson MC, Olsson CA, Mckiernan J, Buttyan R. Protocadherin-PC and prostate cancer. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 357.
9. Simons J. HIF-1 alpha and angiogenesis as a target. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. p. 83.
10. Bristow RG, Meng A, Jalali F, et al. Hypoxia reduces expression of DNA repair genes in prostate cancer:

Implications for mutation and tumor progression. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 316.

11. Davies G, Mason MD, Maintland NJ, et al. The differential expression of Wnts and associated family proteins in prostate cancer. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 320.
12. Gottschalk AR, Weinberg VK, Carroll PR, Simko J. The association of the phosphatidyllinositol-3-kinase (PI3K) pathway to Gleason score, prostate-specific antigen, and pathologic stage in prostate cancer. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 322.
13. Balaji KC, Zhang W. Role of apoptosis inducing factor in prostate cancer cell apoptosis induced by cisplatin. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 328.
14. Alarcon-Rozas AE Sr. New molecular prognostic factors for overall survival (OS) in patients with prostate cancer (PCa). Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 333.
15. Andren O, Fell K, Andersson S, et al. MUC-1 gene is associated with prostate cancer progression: A 20-year follow-up of a population-based study in Sweden. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 334.
16. Shaheduzzaman S, Petrovics G, Srikantan V, et al. ETS-related gene (ERG), a frequent proto-oncogene expression alteration in prostate cancer with potentials in diagnosis and prognosis. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 340.

Imaging of Prostate Cancer: Many Options, Paltry Progress

Hossein Jadvar, MD, PhD

Imaging evaluation of prostate cancer includes the use of ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy, Indium-111 capromab pendetide (*ProstaScint*; Cytogen; Princeton, New Jersey), and positron-emission tomography (PET). Despite this array of imaging modalities, the imaging assessment of prostate cancer remains challenging in many important clinical situations.[1,2] This article offers a snapshot of research presented at the 2006 Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006, San Francisco, California, which was cosponsored by the American Society of Clinical Oncology (ASCO), the American Society for Therapeutic Radiology and Oncology (ASTRO), the Prostate Cancer Foundation (PCF), and the Society of Urologic Oncology (SUO).

Evaluating Recurrent Disease

One challenge in the imaging evaluation of prostate cancer is the detection of recurrent disease in men with biochemical failure after definitive therapy.[3] Advances in imaging technology such as the development of hybrid imaging systems (eg, PET-CT, SPECT-CT), which depict both structural and metabolic information, has contributed to more accurate imaging assessment by reducing false-positive and false-negative findings.

Use of tracers such as radiolabeled monoclonal antibodies to prostate-specific membrane antigen generated some initial interest; however, the literature shows mixed results, which is probably largely due to the differences in patient populations that have been studied as well as to use of different imaging techniques. The imaging protocol is somewhat cumbersome requiring multi-day imaging sessions, and the image interpretation can be challenging due to nonspecific tracer accumulation and delayed clearance.

PET in Advanced Disease

PET with fluorodeoxyglucose (FDG) has been quite successful in the imaging evaluation of a large number of tumor types. Prostate cancer, however, has variable accumulation of FDG, which is probably a reflection of the heterogeneous nature of the disease. Early studies of FDG-PET in prostate cancer have shown that FDG

accumulation in the primary prostate cancer may be low and overlap with the uptake in benign prostatic hyperplasia, in normal gland, and in postoperative scar or local recurrence.[4-6] However, animal and preliminary clinical studies have demonstrated that FDG-PET may be useful in the evaluation of advanced disease and in patients with high Gleason scores and serum prostate-specific antigen (PSA) levels, in the detection of active osseous and soft tissue metastases, and in the assessment of response after androgen ablation and treatment with novel chemotherapies.[7-11] Additional studies are underway to investigate the specific clinical situations in which FDG-PET may be useful in the imaging assessment of men with prostate cancer.[12]

The use of PET with other radiotracers such as C-11 acetate, C-11 choline, and 16beta-18F-fluoro-5alpha-dihdrotestosterone (FDHT) has also been explored.[13-25] Acetate participates in cytoplasmic lipid synthesis (believed to be increased in tumors) and in oxidative metabolism. The biologic basis for radiolabeled choline uptake in tumors is the malignancy-induced upregulation of choline kinase, which leads to the incorporation and trapping of choline in the form of phosphatidylcholine (lecithin) in the tumor cell membrane in proportion to the rate of tumor duplication. FDHT has been developed for PET of androgen receptor expression. Although promising, more work is needed to establish the exact clinical situations in which 1 tracer may be more applicable or preferred over others in the evaluation of prostate cancer. However, it is likely that optimal imaging of prostate cancer will involve PET (or PET-CT) in conjunction with a tracer or tracers appropriate for the specific clinical situation at hand, which will need to be defined.

Additionally, most treatment response assessments have typically been validated based on PSA response but not on objective imaging-based criteria for anti-tumor response to treatment. The challenge in prostate cancer is compounded by the frequent use of treatment (such as hormonal therapy) at the time of biochemical failure before the actual detection and localization of recurrent and metastatic disease (primarily due to insensitivity of current imaging tests). Likewise, imaging assessment of measurable disease based on bone scintigraphy or on CT is limited, due to the relatively less prevalent involvement of disease in the soft tissues.[26]

Oncologists Fear Overuse of Bone Studies, CT

Strum and colleagues expressed the cumulative clinical experience of a group of medical oncologists in their belief that a large number of men with low-risk disease undergo unnecessary bone or CT scans without regard to nomogram risk assessment results.[27] The authors of this study warned against the reflex ordering of bone and CT scans, which is costly and often does not produce a significant diagnostic yield. Another study, however, addressed a more practical question of the interchangeability of daily US and fiducial marker localization during prostate treatment planning in view of a lack of "gold" standard.[28] The study revealed that there was a substantial lack of agreement between US and fiducial marker software and therefore it was concluded that they may not be clinically interchangeable.

MRI and CT Applications

de Jong and investigators evaluated the utility of F-18 fluoride PET for the detection of osseous metastases in prostate cancer.[29] Men with prostate cancer at risk for bone metastases (PSA $\geq$ 15 ng/mL and Gleason $\geq$ 7) underwent F-18 fluoride scan, technetium-99m methylene diphosphate bone scan, and MRI of the spinal column and the pelvis. It was found that although F-18 fluoride scan was as accurate as bone scan in depicting osseous metastases, the PET scan demonstrated superior image detail in spite of the fact that both bone scan and PET missed some lesions shown on MRI. This study suggests that multi-modality imaging may be needed for detecting the extent of osseous metastatic disease, although the clinical impact of such detailed information will need to be addressed.

Thurairaja and co-workers evaluated MRI as a potential means for the early detection of bony metastases compared with bone scans.[30] The authors of this paper noted that, similar to the previous report, MRI depicted more lesions than did bone scan. However, the clinical significance of the improved sensitivity of MRI was not discussed. In another relevant investigation, researchers from the Memorial Sloan Kettering Cancer Center, New York City, evaluated the prognostic utility of MRI of the bone marrow as an outcome measure for patients with metastatic cancer.[31] This report concluded that MRI of the bone marrow can be an early indicator of treatment failure. Treatment-induced PSA response was found to be more concordant with the MRI findings than with bone scan findings in patients with progressive disease (73% vs 46%, respectively). Conversely, in patients with stable and improved PSA response, the concordance with PSA was slightly lower for MRI than that for the bone scan (64% vs 71%, respectively). This interesting observation supports the notion that different imaging modalities may be suited for different clinical situations and expected outcomes.

In the future, there will be greater opportunities for imaging research in prostate cancer as hybrid imaging systems reach widespread use and "smart" imaging agents in the developmental pipeline help to address the current challenges in this important clinical setting.

References

1. Yu KK, Hricak H. Imaging prostate cancer. Radiol Clin North Am. 2000;38:59-85. Abstract
2. Hricak H, Schoder H, Pucar D, et al. Advances in imaging in the postoperative patient with a rising prostate specific antigen level. Semin Oncol. 2003;30:616-634. Abstract
3. Wahl RL. Advances in imaging of prostate cancer support. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California.
4. Effert PJ, Bares R, Handt S, et al. Metabolic imaging of untreated prostate cancer by positron emission tomography with 18fluorine-labeled deoxyglucose. J Urol. 1996;155:994-998. Abstract
5. Hofer C, Laubenbacher C, Block T, et al. Fluorine-18-fluorodeoxyglucose positron emission tomography is useless for the detection of local recurrence after radical prostatectomy. Eur Urol. 1999;36:31-35.
6. Liu IJ, Zafar MB, Lai YH, et al. Fluorodeoxyglucose positron emission tomography studies in diagnosis and staging of clinically organ-confined prostate cancer. Urology. 2001;57:108-111. Abstract
7. Shreve PD, Grossman HB, Gross MD, Wahl RL. Metastatic prostate cancer: initial findings of PET with FDG. Radiology. 1996;199:751-756. Abstract
8. Yeh SD, Imbriaco M, Larson SM, et al. Detection of bony metastases of androgen-independent prostate cancer by PET-FDG. Nucl Med Biol. 1996;23:693-697. Abstract
9. Oyama N, Akino H, Suzuki Y, et al. FDG PET for evaluating the change of glucose metabolism in prostate cancer after androgen ablation. Nucl Med Commun. 2001;22:963-969. Abstract
10. Jadvar H, Pinski JK, Conti PS. FDG PET in suspected recurrent and metastatic prostate cancer. Oncol Rep. 2003;10:1485-1488. Abstract
11. Morris NJ, Akhurst T, Osman I, et al. Fluorinated deoxyglucose positron emission tomography imaging in progressive metastatic prostate cancer. Urology. 2002;59:913-918. Abstract
12. Jadvar H, Shahinian A, Li X, et al. [F-18]-fluorodeoxyglucose in metastatic prostate cancer: microPET and PET studies. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 17-19, 2005; Orlando, Florida. Abstract 156.
13. Shreve PD, Iannone P, Weinhold P. Cellular metabolism of [1-C14]-acetate in prostate cancer cells in vitro. J Nucl Med. 2002;43:272P.
14. Seltzer MA, Jahan S, Dahlbom M, et al. C-11 acetate PET imaging of primary and locally recurrent prostate cancer: comparison to normal controls. J Nucl Med. 2002;43:117P.
15. Kotzerke J, Volkmer BG, Neumaier B, et al. Carbon-11 acetate positron emission tomography can detect local recurrence of prostate cancer. Eur J Nucl Med Mol Imaging. 2002;29:1380-1384. Abstract
16. Oyama N, Akino H, Kanamaru H, et al. 11C-acetate PET imaging of prostate cancer. J Nucl Med. 2002;43:181-186. Abstract
17. Dimitrakopoulou-Strauss A, Strauss LG. PET imaging of prostate cancer with 11C-acetate. J Nucl Med. 2003;44:556-558. Abstract
18. Jadvar H, Li X, Shahinian A, et al. Biodistribution of radiolabeled acetate in castrated and noncastrated nude mouse xenografts of human prostate cancer. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 337.
19. de Jong IJ, Pruim J, Elsinga PH, et al. Visualization of prostate cancer with 11C-choline positron emission tomography. Eur Urol. 2002;42:18-23. Abstract
20. de Jong IJ, Pruim J, Elsinga PH, et al. Preoperative staging of pelvic lymph nodes in prostate cancer by 11Ccholine PET. J Nucl Med. 2003;44:331-335. Abstract
21. Picchio M, Messa C, Landoni C, et al. Value of [11C]choline-positron emission tomography for re-staging prostate cancer: a comparison with [18F]fluorodeoxyglucose-positron emission tomography. J Urol. 2003;169:1337-1340. Abstract
22. Kotzerke J, Volkmer BG, Glatting G, et al. Intra-individual comparison of [11C]acetate and [11C]choline PET for detection of metastases of prostate cancer. Nuklearmedizin. 2003;42:25-30. Abstract
23. Fricke E, Machtens S, Hofmann M, et al. Positron emission tomography with (11)C-acetate and (18)F-FDG in prostate cancer patients. Eur J Nucl Med Mol Imaging. 2003;30:607-611. Abstract
24. Larson SM, Morris M, Gunther I, et al. Tumor localization of 16beta-18F-fluoro-5alpha-dihdrotestosterone versus 18F-FDG in patients with progressive, metastatic prostate cancer. J Nucl Med. 2004;45:366-373. Abstract
25. Morris MJ, Schoder H, Smith-Jones P, et al. Pilot trial of [18F]fluoro-dihydro-testosterone (FDHT) and FDG PET imaging in patients with castrate metastatic prostate cancer. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 144
26. Tombal B. Alternatives to imaging. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. p. 85.

27. Strum SB, Scholz MC. Optimized imaging in prostate cancer (PC) is absent 95% of the time at diagnosis or PSA recurrence. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 68.
28. Fuller CD, Scarbrough T, Wong A, et al. Method comparison analysis of ultrasound- and fiducial marker-based prostate localization. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 81.
29. de Jong IJ, Breeuwsma AJ, Pruim J, et al. 18-F sodium fluoride PET for the detection of bone metastases in prostate cancer. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 146.
30. Thurairaja R, MacFarlane J, Gren wood R. Detecting early bone metastases in prostate cancer: axial skeletal magnetic resonance imaging (MRI) versus bone scintigraphy. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 158.
31. Gignac GA, Morris MJ, Schwartz H, et al. Magnetic resonance imaging of bone marrow (MRBM) as an outcome measure for patients with metastatic prostate cancer. Program and abstracts of the 2nd Annual Multidisciplinary Prostate Cancer Symposium; February 24-26, 2006; San Francisco, California. Abstract 172.

Authors and Disclosures

Author

Hossein Jadvar, MD, PhD

Assistant Professor of Radiology and Biomedical Engineering, Keck School of Medicine, University of Southern California, Los Angeles

Disclosure: Hossein Jadvar, MD, PhD, MPH, has disclosed no relevant financial relationships.

Editor

Margie Miller

Program Director, Hematology-Oncology

Disclosure: Margie Miller has disclosed no relevant financial relationships.

Registration for CME credit, the post test and the evaluation must be completed online.
To access the activity Post Test and Evaluation link, please go to:
http://www.medscape.com/viewprogram/5331_index