

Prostate and Urologic Cancers

Treatment of Locally Advanced Prostate Cancer

Joseph M. Colasanto, MD

While there have been significant advances in the delivery of radiotherapy for prostate cancer over the last two decades, residual disease at the primary site or the presence of microscopic disease outside the radiotherapy fields will lead to recurrent prostate cancer. In patients with high risk disease, based on PSA, Gleason score, and clinical stage, 65-75% of the prostate cancer patients will have a biochemical relapse within 5 years. The use of early and prolonged androgen ablation therapy with radiotherapy delays disease progression and improves overall survival, however most patients still relapse, develop androgen resistant disease, and eventually die from their cancer. To improve on these outcomes in these high risk patients, therapy needs to eradicate the local and distant disease that is composed of androgen sensitive and insensitive clones of cells (Figure 1). Until recently, effective therapy for the androgen insensitive or hormone refractory disease has not been available; however, newer combinations of taxane based regimens have shown to improve survival of patients in the advanced disease setting. With these encouraging results and following the paradigm from other malignancies, moving the taxane based therapies forward in patients with localized high risk prostate cancer may improve the long term outcomes.

To date there has been no adequately powered randomized trials that have shown a clinical benefit of adding chemotherapy before or after radiotherapy in this high risk population. However, there are several small trials with variable inclusion criteria that have evaluated the use of early chemotherapy using taxane based chemotherapy with or

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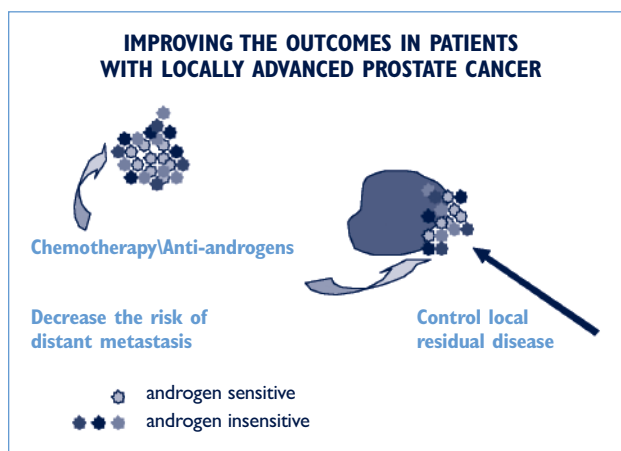


Figure 1

Novel Virus Linked to Prostate Cancer in Genetically Susceptible Men

Eric A. Klein, MD and Robert Silverman, PhD, The Cleveland Clinic

While the etiology of prostate cancer is unknown, it is clear that both genetics and environment play a role in its origin and evolution. Recent scientific and clinical evidence suggests a convergence between genetic susceptibility and predisposition to infection as potentially important in the development of prostate cancer. Of the known susceptibility genes, HPC1 is the best characterized. HPC1 encodes for the enzyme RNaseL, an antiviral gene that plays a key role in the innate immune response to viral infections. Activation of RNaseL by viral infection and endogenous interferon inhibits viral

spread by degrading single-stranded RNA and by causing the infected host cell to undergo apoptosis. Preclinical studies have shown that mice deficient in RNaseL are more susceptible to viral infection.

In humans, there is evidence that allelic variants of the RNaseL gene may increase the risk of developing prostate cancer. We have previously shown that men who are heterozygous (RQ genotype) for a single amino acid change from arginine to glutamine at position 462 of the RNaseL protein had about a 50% greater risk of prostate cancer, and men homozygous at this locus (QQ genotype)

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Editor's Letter

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The contents of this issue are presented with a great deal of enthusiasm. This excitement comes from the fact that Dr. Colberg writes about the evidence for Robotic Assisted Laparoscopic Prostatectomy, a program just initiated at Yale-New Haven Hospital with the arrival of the da Vinci system in September 2006. I think there is mounting evidence to show that this operation, when done by properly trained surgeons, can result in good oncological outcomes with low complication rates and good preservation of potency and continence. Undoubtedly, this is an evolving field and technique that will be further elucidated with well performed studies.

Secondly, we have an invited guest author who is one of the world's pre-eminent researchers and clinicians in the treatment of prostate cancer. Dr. Eric Klein, and his colleague Dr. Robert Silverman, from The Cleveland Clinic give us a synopsis of their novel and provocative work showing that virus DNA may have a pivotal role in the pathogenesis of prostate cancer. This work was recently presented at several large national meetings and has generated much interest and discussion.

Finally, we all encounter patients who have high risk prostate cancer (cT3, PSA > 10, Gleason score > 7) and often have a difficult time deciding what is in their best interest. Dr. Colasanto, a radiation oncologist and Dr. Kevin Kelly, a medical oncologist, have teamed up to treat and investigate the efficacy of combined chemotherapy and radiation therapy for this high risk group. This is a natural combination to explore with the recent data showing docetaxel-based regimens increase survival rates in men with hormone-refractory metastatic prostate cancer and the recent data showing that higher doses of radiation can safely be given with intensity modulated radiation therapy (IMRT). The basis for a chemotherapy/radiation trial is presented with a review of the literature on treatment of locally advanced prostate cancer.

This is the second issue of *Advances on Prostate Cancer* and I am encouraged by the feedback that I have received thus far. Please contact me by email or phone with your suggestions and comments.

Sincerely,

Dinesh Singh, MD

>> NOVEL VIRUS continued from page 1

carried double the risk compared to normals (RR genotype) (1). The observation that variants in an antiviral gene predispose men to prostate cancer led to our investigation into a viral etiology.

In order to test this hypothesis, we used a powerful tool known as the ViroChip (2). The ViroChip contains highly conserved sequences from all known viruses (almost 1,000 in total) in the plant, animal, and human kingdoms. Hybridizing RNA from biological samples (such as respiratory secretions or tissue) to the chip allows determination of what expressed viral genes are present in the sample, identification of which family of viruses they belong to, and cloning and identification of the exact sequence of the viruses. We hybridized RNA from the peripheral zone of radical prostatectomy specimens from men with prostate cancer who were genotyped for allelic variants of the RNaseL gene. In the initial 19 men, we identified 8 with a novel retrovirus (3). Remarkably, 7 of the 8 men with the new virus, dubbed XMRV, were found to have the QQ genotype of the RNaseL gene.

We have since screened more than 150 men. Data analysis is not complete, but preliminary findings show that about half of the men with the QQ mutation test positive for XMRV, compared to only one among those who do not have this variant. Complete sequencing of XMRV reveals that it most closely resembles Murine Leukemia Virus (MuLV), a virus that causes leukemia in mice. There are, however, important differences between XMRV and MuLV, including the fact that XMRV does not infect mice and has a deletion in the glyco-GAG leader sequence that helps determine its virulence.

Tissue localization studies have demonstrated that XMRV does not reside in the epithelium but in fibroblasts adjacent to the cancer. There is a substantial body of scientific evidence describing biological "cross-talk" between cancer-associated fibroblasts and epithelial tumors, and the hypothesis is that XMRV is exerting an effect on the tumor by means of paracrine signaling or through an indirect effect by providing an appropriate microenvironment to recruit macrophages and white blood cells that result in oxidative stress. Both of these hypotheses are currently under study. While a direct link between XMRV as a cause of prostate cancer remains to be proven, this work represents an exciting new finding in the possible pathogenesis of prostate cancer.

1. Casey G, Neville PJ, Plummer SJ, et al. RNASEL Arg462Gln variant is implicated in up to 13% of prostate cancer cases. *Nat Genet.* 2004;32:581-583.
2. Wang D, Urisman A, Liu YT, et al: Viral discovery and sequence recovery using DNA microarrays. *PLoS Biol.* 2003 Nov; 1(2):E2.
3. Urisman A, Molinaro RJ, Eischer N, et al. Identification of a novel gammaretrovirus in prostate tumors of patients homozygous for R62Q RNASEL variant. *PLoS Pathog.* 2006; Mar. 2(3):e25. Epub 2006 Mar 31.

CLINICAL TRIALS Prostate and Urologic Cancers

PROSTATE CANCER:

HIC 0508000439	A Randomized, Double-Blind, Placebo-Controlled Phase III Trial Comparing Docetaxel and Prednisone with and without Bevacizumab in Men with Hormone Refractory Prostate Cancer (CALGB 90401)	Wm. Kevin Kelly, DO	(203) 737-2572
HIC 0510000719	A Randomized, Double-Blind, Placebo-Controlled Phase III Study of Early vs. Standard Zoledronic Acid to Prevent Skeletal Related Events in Men with Prostate Cancer Metastatic to Bone (CALGB 90202)	Wm. Kevin Kelly, DO	(203) 737-2572
HIC 0612002131 (pending)	A Phase II Trial of Oral Enzastaurin in Prostate Cancer Patients who have Rising PSA During Hormonal Manipulation and After First Line Cytotoxic Therapy	Wm. Kevin Kelly, DO	(203) 737-2572
HIC (pending)	A Phase III Protocol of Androgen Suppression and 3DCRT/IMRT and 3DCRT/IMRT Followed by Chemotherapy with Docetaxel and Prednisone for Localized, High Risk Prostate Cancer	Joe Colasanto, MD	(203) 785-2359
HIC (pending)	A Randomized, Phase III Study of Neo-Adjuvant Docetaxel and Androgen Deprivation Prior to Radical Prostatectomy versus Immediate Radical Prostatectomy in Patients with High-Risk, Clinically Localized Prostate Cancer	John Colberg, MD	(203) 785-2815
BLADDER CANCER: HIC 0609001823 (pending)	A Dose Escalation, Phase II Trial of Gemcitabine, Carboplatin and Sorafenib in Chemotherapy-naïve Patients with Advances/ Metastatic Bladder Carcinoma	Wm. Kevin Kelly, DO	(203) 737-2572
RENAL CELL CANCER: HIC 05100000723	A Phase I Trial of the Combination of Sunitinib and Sunitinib (Sutent) in Patients with Advanced Solid Tumors that are Non-cur-able with Standard Therapy	Mario Sznol, MD	(203) 785-6221

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without androgen ablation. The primary outcomes for these trials were feasibility and safety. Khil, et al. were the first to report the safety of treating patients with locally advanced prostate cancer with concomitant chemotherapy and radiotherapy. They eval-

With these encouraging results and following the paradigm from other malignancies, moving the taxane based therapies forward in patients with localized high risk prostate cancer may improve the long term outcomes.

uated 65 men with a clinical stage T2-4, Gleason score 4-10, with locally advanced prostate cancer and administered estramustine phosphate and vinblastine for 7 weeks concomitantly with external beam radiotherapy (65-70Gy). Therapy was well tolerated, undetectable PSA at 6 weeks was observed in 86% of the patients, and 5 year biochemical free survival for T2 were 49%, for T3 were 38%, and T4 were 17%. Zelefsky and colleagues evaluated 23 patients with locally advanced prostate cancer defined as

Gleason scores of 7-10 with the PSA 10-20; clinical T3 disease with a PSA > 20; or T4 N0 or TXN1M0 disease. Estramustine phosphate and vinblastine was given prior and concurrently with high dose conformal radiotherapy (75.6 Gy). There was an increased incidence of late grade two gastrointestinal and genitourinary toxicities observed with this combination. The five year biochemical free survival was 25%; moreover, 48% of the patients had asymptomatic rise in the PSA without evidence of metastatic disease at 5 years that required no additional therapy. These results were encouraging and stimulated other larger trials investigating the use of more contemporary chemotherapy with high dose radiotherapy (Table I).

In summary, there is superior outcome with neoadjuvant hormonal therapy followed by concurrent hormonal therapy and radiotherapy for the treatment of locally advanced prostate cancer. There are no negative randomized trials. However, there is still a subset of patients that are at high risk of treatment failure. Current phase III trials are underway to study the benefit of adjuvant chemotherapy. Exploring the role of early chemotherapy with radiotherapy, these trials will help us to define the future treatments for these high risk patients.

1. Khil MS, Kim JH, Bricker LJ, Cerny JC. Tumor control of locally advanced prostate cancer following combined estramustine, vinblastine, and radiation therapy. *Cancer J Sci Am.* 1997 Sep-Oct;3(5):289-96.
2. Ryan CJ, Zelefsky MJ, Heller G, Regan K, Leibel SA, Scher HI, Kelly WK. Five-year outcomes after neoadjuvant chemotherapy and conformal radiotherapy in patients with high-risk localized prostate cancer. *Urology.* 2004 Jul;64(1):90-4.

TABLE I

Protocol	Sponsor	Treatment	N	Primary Trial Endpoint
A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT vs AS and 3DCRT/IMRT followed by chemotherapy with docetaxel and prednisone for localized, high-risk prostate cancer	NCI/RTOG	AS x 24 months + radiotherapy vs AS x 24 months + radiotherapy followed by Docetaxel + prednisone x 6 cycles	600	Overall Survival
Docetaxel plus 6 months of androgen suppression (AS) and radiation therapy vs. 6 months AS and radiation therapy for patients with high risk localized or locally advanced prostate cancer: A randomized, controlled trial	Aventis-Sanofi	Docetaxel + AS x 6 months + Radiotherapy vs. AS x 6 months + radiotherapy	350	Overall Survival

The New Era of Prostate Cancer Surgery: Robotic-assisted laparoscopic prostatectomy

John W. Colberg, MD

Robotic-assisted laparoscopic prostatectomy represents the latest development in surgical treatment of localized prostate cancer. This technique relies upon a minimally invasive surgical approach to laparoscopic prostatectomy augmented by robotic technology. The da Vinci surgical system (Intuitive Surgical; Mountainview, California) incorporates four multijoint robotic arms with one arm controlling the binocular endoscope camera and the others controlling small-wristed instruments (EndoWrist technology). The “robot” is controlled by the surgeon who is seated at a remote operative console. Two finger-controlled handles housed in the console control the three robotic arms and camera. The stereoscopic view of the operative field provides excellent 3-dimensional visualization with 10-fold magnification.

The robotic system offers the potential of more precise surgical technique and thus better preservation of sexual function and urinary control, although this has not yet been clearly demonstrated. Robotic surgery also has the potential benefits of less blood loss, smaller incisions, shorter hospitalizations, and quicker recovery when compared to open surgery.

Presently, there are over 400 robotic systems in the United States. Approximately 32,000 robotic-assisted laparoscopic prostatectomies were projected to be performed in 2006 (40% of all prostatectomies). Other surgical specialties involved with

the use of this system include cardiothoracic, gastrointestinal/general surgery, and obstetrics/gynecology.

The cost of the robotic system (\$1.6 million) and per case expenses (\$1600) continues to favor open surgery. However, with the rapid increase in interest and application of robotic-assisted laparoscopic prostatectomy, there is little question as to its growing acceptance and the increasing demand by patients for its application.

The robotic system offers the potential of more precise surgical technique and thus better preservation of sexual function and urinary control.

Yale - New Haven Hospital entered the robotic surgery era this year, performing its 1st robotic-assisted laparoscopic prostatectomy on August 22nd. Currently, urological procedures are performed by Dr. John W. Colberg and Dr. Dinesh Singh, from the Section of Urology, Yale School of Medicine.



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Yale - New Haven Hospital entered the robotic surgery era this year with robotic-assisted laparoscopic prostatectomy, a treatment of localized prostate cancer.

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