Meeting Objective
The goal of this meeting is to increase communication among urologic oncology researchers and forge a strong relationship between the National Cancer Institute and the Society of Urologic Oncology, as well as the Society’s members and others interested in urologic oncology.

Needs and Objectives
Following participation in this program, attendees will be able to identify:

- New methods for neo-adjuvant therapies in prostate cancer.
- Recent advances in molecular therapeutic approaches for the treatment of cancer of the kidney.
- New methods for treatment of patients with advanced, hormone refractory prostate cancer.
- New biomarkers for screening for bladder cancer.
- Recent advances in radiation therapy of localized and locally advanced prostate cancer.
- Recent advances in minimally invasive therapies for prostate and kidney cancer.
- The molecular genetic basis of kidney, bladder and prostate cancer and how these findings lead to the development of better methods for diagnosis, prevention and treatment of genitourinary malignancies.
- Recent advances in surgical treatment of patients with localized bladder cancer.
- The role of neo-adjuvant and adjuvant therapies for patients with bladder cancer as well as chemotherapies for patients with advanced bladder cancer.

The NIH/FAES is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education through the Joint sponsorship of the Society of Urologic Oncology. The National Institutes of Health/Foundation for Advanced Education in the Sciences (NIH/FAES) is accredited by the ACCME to provide continuing medical education for physicians.

The NIH/FAES designates this educational activity for a maximum of 12.50 category 1 credits toward the AMA Physician’s Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

 Meals
A continental breakfast, lunch and mid-morning snack on both days of the meeting and an afternoon snack on the first day are included in the registration fee.

**SUO Dinner at the Hyatt Regency Bethesda**
Friday, December 3, 2004
7:00 p.m. – 10:00 p.m.
Enjoy dinner with friends and colleagues at the Hyatt Regency Bethesda. Registration for this is an additional cost of $60.00 per person ($30.00 for fellows, nurses and residents). To purchase tickets, please visit the registration desk.

*Business casual attire is appropriate.*
Please note that all General Session lectures take place in the Main Auditorium, and the Poster Session and all breaks take place in the Main Auditorium Foyer.

**Continental Breakfast: Registration**

**Introduction**

*SUO President:*
Robert C. Flanigan, MD – Loyola University Medical School

*Program Directors:*
W. Marston Linehan, MD – National Cancer Institute
Eric A. Klein, MD – Cleveland Clinic

**Prostate Cancer I: Neo Adjuvant Paradigm**

**Overview: Neo Adjuvant Paradigm for Localized Prostate Cancer**
Martin E. Gleave, MD – University of British Columbia, Vancouver

**Molecular Targets for Prostate Cancer**
Robert Reiter, MD – UCLA

**Neo Adjuvant Chemotherapy**
Rob Dreicer, MD – Cleveland Clinic

**Discussion Panel:**
Martin E. Gleave, MD – University of British Columbia, Vancouver
Robert Reiter, MD – UCLA
Rob Dreicer, MD – Cleveland Clinic
Eric A. Klein, MD – Cleveland Clinic
Laurence H. Klotz, MD – Sunnybrook Medical Science Centre

**Bladder Cancer I: Has the Time Arrived for Screening for Bladder Cancer?**

**Overview**
Edward M. Messing, MD – University of Rochester Medical Center

**Screening At-Risk Populations**
George P. Hemstreet III, MD, PhD – University of Nebraska Medical Center

**Commercially Available Diagnostic Tests**
Yves Fradet, MD, FRCSC – Laval University Cancer Research Center

**New Diagnostic Markers (MSA, Survivin, BLCA4, others)**
Mark Philip Schoenberg, MD – Johns Hopkins

**Discussion Panel:**
Edward M. Messing, MD – University of Rochester Medical Center
George P. Hemstreet III, MD, PhD – University of Nebraska Medical Center
Yves Fradet, MD, FRCSC – Laval University Cancer Research Center
Mark Philip Schoenberg, MD – Johns Hopkins

**Break**
10:45 a.m. – 11:05 a.m. State-of-the-Art Talk: The Hereditary Basis of Cancer of the Prostate
Elaine Ostrander, PhD – National Human Genome Research Institute, National Institutes of Health

11:05 a.m. – 12:05 p.m. Kidney Cancer I: Molecular Therapeutics of Renal Cell Carcinoma
Moderator: W. Marston Linehan, MD – National Cancer Institute

11:05 a.m. – 11:15 a.m. Bayer 43-9006
Walter Stadler, MD – University of Chicago

11:15 a.m. – 11:25 a.m. SU11428
Robert Motzer, MD – Memorial Sloan Kettering

11:25 a.m. – 11:35 a.m. Targeting HIF by Inhibiting Hsp90: An Oxygen- and VHL-Independent Regulatory Pathway
Len Neckers, PhD – National Cancer Institute

11:35 a.m. – 11:45 a.m. Investigation of Molecularly Targeted Agents
Michael Atkins, MD – Beth Israel Deaconess Medical Center

11:45 a.m. – 12:05 p.m. Discussion Panel:
W. Marston Linehan, MD – National Cancer Institute
Walter Stadler, MD – University of Chicago
Robert Motzer, MD – Memorial Sloan Kettering
Len Neckers, PhD – National Cancer Institute
Michael Atkins, MD – Beth Israel Deaconess Medical Center

12:05 p.m. – 1:15 p.m. Lunch

1:15 p.m. – 1:25 p.m. Huggins Medal Presentation:
Donald G. Skinner, MD – USC Norris Cancer Center
W. Marston Linehan, MD
Robert C. Flanigan, MD

1:25 p.m. – 1:45 p.m. Huggins Award Lecture:
Lessons Learned in the Management of Invasive Bladder Cancer
Donald G. Skinner, MD – USC Norris Cancer Center

1:45 p.m. – 2:45 p.m. Prostate Cancer II: Recent Advances in Radiation Therapy
Moderator: Mary K. Gospodarowicz, MD – Princess Margaret Hospital

1:45 p.m. – 1:55 p.m. New Technology: Tomotherapy, Protons, Cyberknife
Martin Fuss, MD – University of Texas Health Sciences Center

1:55 p.m. – 2:05 p.m. Gene Therapy and Radiation Therapy
Theodore L. DeWeese, MD – Johns Hopkins

2:05 p.m. – 2:15 p.m. Prostate Brachytherapy: Is it Ready for Prime Time?
W. Robert Lee, MD – Wake Forest University School of Medicine

2:15 p.m. – 2:25 p.m. Phase III High RT Dose Trial
William U. Shipley, MD – Mass General Hospital

Continues on next page
2:25 p.m. – 2:45 p.m.  Discussion Panel:
Mary K. Gospodarowicz, MD – Princess Margaret Hospital
Martin Fuss, MD – University of Texas Health Sciences Center
Theodore L. DeWeese, MD – Johns Hopkins
W. Robert Lee, MD – Wake Forest University School of Medicine
William U. Shipley, MD – Mass General Hospital

2:45 p.m. – 3:00 p.m.  Radiofrequency Ablation Kidney Cancer: Where Are We and Where Are We Going?
Martin I. Resnick, MD – Case Western Reserve University

3:00 a.m. – 3:45 p.m.  Late Breaking Developments I
Moderator: Eric A. Klein, MD – Cleveland Clinic

03:00 PM  EFFICACY OF SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS) IN A MURINE XENOGRRAFT MODEL BEARING HUMAN BLADDER CANCER
Guru Sonpavde, MD, Yu Jiang, MD, Steve Shen, MD, PhD, Barbara Richardson, PhD, Isaac Kim, MD, PhD, Smith Carolyn, PhD, Heidi Weiss, PhD and Seth Lerner, MD (Presented By: Seth Lerner, MD)

03:07 PM  DNA-REPAIR GENETIC POLYMORPHISMS AND PROSTATE CANCER
Peter Clark, MD, Marshall Hall, MD, Kristin Lockett, PhD, Joseph Phillips, MD, Jianfeng Xu, MD, DRPH, Shu-Chun Zheng, Shu-Chun Chuang and Jennifer Hu, PhD (Presented By: Peter Clark, MD)

03:14 PM  SINGLE CELL PROTEOMICS IN CELLS AND TISSUES ASSOCIATED WITH THE PREMALIGNANT FIELD PROVIDE A POWERFUL APPROACH FOR INDIVIDUAL RISK ASSESSMENT
George Hemstreet III, MD, PhD, Dali Haung, MD, Nizar Wehbi, MD and George Casale, PhD (Presented By: George Hemstreet III, MD, PhD)

03:21 PM  CASTRATION INITIATES THE EARLY TRANSITION TO ANDROGEN INDEPENDENT PROSTATE CANCER THROUGH SRC KINASE
Christopher Evans, MD, Joy Yang, PhD, Erik Busby, MD and Hsing-Jien Kung, PhD (Presented By: Christopher Evans, MD)

03:28 PM  TUMOR EXOSOMES EXPRESSING FAS LIGAND MEDIATE CD8+ T CELL APOPTOSIS
Ashraf Abusamra, MB, BS, FRCSC, Thomas Ichim, BSc, Wei-Ping Min, BSc, MD, PhD, Jonathan Izawa, BSc, MD, FRCSC and Joseph Chin, BSc, MD, FRCSC (Presented By: Ashraf Abusamra, MB, BS, FRCSC)

4:00 p.m. – 6:00 p.m.  Poster Session/Reception

Poster #1  HIGH-THROUGHPUT CLINICAL ANALYSIS OF FOS RELATED ANTIGEN 1(FRA-1) EXPRESSION IN PROSTATE TUMORS: A NEW TUMOR MARKER IN PROSTATE CANCER
Aaron Grotas, MD, John Phillips, MD, Mark Rafelled, MD, Lukas Bubendorf, MD and Eric Gerber, MD (Presented By: Aaron Grotas, MD)

Poster #2  LAPAROSCOPIC RADICAL PROSTATECTOMY: CRITICALLY EVALUATING PATHOLOGICAL SPECIMENS TO GUIDE FUTURE OUTCOME IMPROVEMENTS
Doug Soderdahl, MD, Jose Diaz, MD, Danny Rabah, MD, Adam Ball, MD, Paul Schellhammer, MD and Michael Fabrizio, MD (Presented By: Adam Ball, MD)
| Poster #3 | MANAGEMENT AND FOLLOW-UP OF PATIENTS WITH CARCINOMA IN SITU AT A POSITIVE DISTAL URETERAL MARGIN FOLLOWING RADICAL CYSTECTOMY  
Albert Ong, MD, Richard Link, MD, Sam Bhayani, MD, Ioannis Varkararkis, MD, Mohammad Allaf, MD, Mark Schoenberg, MD and Thomas Jarrett, MD (Presented By: Albert Ong, MD) |
| Poster #4 | GENE EXPRESSION PROFILING FOR GENE IDENTIFICATION AND PROGNOSIS IN RENAL CELL CARCINOMA  
Alessandro Volpe, MD, Sanoj Punnen, BSc, Monique Albert, MSc, Mona Prasad, MSc, Andrew Evans, MD, PhD, Pascale Macgregor, PhD and Michael Jewett, MD (Presented By: Alessandro Volpe, MD) |
| Poster #5 | SHEDDING OF C-MET ECTODOMAIN IN UROLOGIC MALIGNANCIES  
Alessio Giubellino, MD, Pathirage Dharmawardana, MD, Katrina Salazar, BS, Jennifer Wimberly, MD, Jonathan Coleman, MD and Donald Bottaro, PhD (Presented By: Alessio Giubellino, MD) |
| Poster #6 | PROEPITHELIN PROMOTES CELL MIGRATION AND INVASION OF BLADDER CANCER CELLS  
Monami Giada, Phar. Doctor, Eva M. Gonzalez, PhD, John Sedor, MS, Leonard G. Gomella, MD, Raffaele Baffa, MD, Renato V. Iozzo, MD and Andrea Morrione, PhD (Presented By: Andrea Morrione, PhD) |
| Poster #7 | RETROPERITONEAL LYMPH NODE DISSECTION FOR NONSEMINOMATOUS GERM CELL TESTICULAR CANCER: IMPACT OF PATIENT SELECTION FACTORS ON OUTCOME  
Andrew Stephenson, MD, George Bosl, MD, Dean Bajorin, MD, Robert Motzer, MD, Jason Stasi, BS and Joel Sheinfeld, MD (Presented By: Andrew Stephenson, MD) |
| Poster #8 | EVALUATION OF URETERO-INTESTINAL ANASTOMOSIS: WALLACE VS. BRICKER  
Apostolos Evangelidis, MD, Michael Karellas, MD, Eugene Lee, John Brosa, J. Brantley Thrasher, MD and Jeffrey Holzbeierlein, MD (Presented By: Apostolos Evangelidis, MD) |
| Poster #9 | PERSISTENT C-FLIP(L) EXPRESSION IS NECESSARY AND SUFFICIENT TO MAINTAIN RESISTANCE TO TRAIL-MEDIATED APOPTOSIS IN PROSTATE CANCER  
Xiaoping Zhang, MD, PhD, Tai-Guang Jin, PhD, Hongmei Yang, PhD, William DeWolf, MD, Roya Khosravi-Far, PhD and Aria Olumi, MD (Presented By: Aria Olumi, MD) |
| Poster #10 | ROLE OF OXIDATIVE STRESS IN TUMORIGENIC POTENTIAL OF BLADDER CANCER CELLS  
Badar Mian, MD, J. Andre Melendez, PhD and Xiao Ha (Presented By: Badar Mian, MD) |
| Poster #11 | A POPULATION-BASED SURVEY OF PSA TESTING AMONG CALIFORNIA MEN AT HIGHER RISK FOR PROSTATE CANCER  
Benjamin Spencer, MD, MPH, Susan Babey, PhD, David Etzioni, MD, MS, Ninez Ponce, MPP, PhD, E. Richard Brown, PhD, Hongjian Yu, PhD and Mark Litwin, MD, MPH (Presented By: Benjamin Spencer, MD, MPH) |
| Poster #12 | DOES RACE PREDICT PROSTATE CANCER ON REPEAT BIOPSY?  
Brent Yanke, MD, MPH, Jeffrey Donohoe, MD, Rosalia Misseri, MD, Ivan Colon, MD and Michael Kattan, PhD (Presented By: Brent Yanke, MD, MPH) |
| Poster #13 | LONG-TERM OUTCOMES FOLLOWING RADICAL PROSTATECTOMY IN MEN WITH CLINICAL T3 PROSTATE CANCER  
Brett Carver, MD, Fernando Bianco, MD, Peter Scardino, MD and James Eastham, MD (Presented By:Brett Carver, MD) |
Poster #14  GENE EXPRESSION/BIOCHEMICAL PATHWAY SIGNATURES OF PROSTATE CANCER CELLS OF PATIENTS WITH HIGH RISK AND MODERATE RISK PROGRESSION OF DISEASE
Bungo Furusato, MD, Syed Shaheduzzaman, PhD, Vasantha Srikantan, DVM, PhD, Gyorgy Petrovics, PhD, Michael Valladares, BS, Isabella A Sesterhenn, MD, Maryanne Vahey, PhD, David G McLeod, MD, Judd W Moul, MD and Shiv Srivastava, PhD (Presented By: Bungo Furusato, MD)

Poster #15  EXPRESSION OF KIT IN HEREDITARY RENAL CELL CARCINOMA
Carlos Torres-Cabala, MD, Etsu Li Ning Tapia, MD, Mauricio Palau, MD, Berton Zbar, MD, Maria Merino, MD and W. Marston Linehan, MD (Presented By: Carlos Torres-Cabala, MD)

Poster #16  FLUORESCENT MICROSATELLITE ANALYSIS (MSA) IDENTIFIES D3D2447 AS A NEW SEMINOMA SPECIFIC MARKER
Carsten-Henning Ohlmann, MD, Lutz Konrad, PhD and Axel Heidenreich, MD (Presented By: Carsten-Henning Ohlmann, MD)

Poster #17  PROSTATE SPECIFIC ANTIGEN TESTING IN MEN OVER 75
Charles Scales, MD, Regina Norris, MD, Lesley Curtis, PhD, David Albala, MD and Judd Moul, MD (Presented By: Charles Scales, MD)

Poster #18  CHARACTERIZATION OF DIFFERENTIAL FUNCTION OF HYPOXIA INDUCIBLE FACTOR 1 AND 2 ALPHA IN CLEAR CELL RENAL CORTICAL TUMORIGENESIS
Chong Kim, MD, PhD, McCllelan Walther, MD and W. Marston Linehan, MD (Presented By: Chong Kim, MD, PhD)

Poster #19  LOCAL AND SYSTEMIC CYTOSTATIC EFFECTS OF 17-(DIETHYLAMINOETHYLAMINO)-17-DEMETHOXYGELDANAMYCIN IN A XENOGRAFT
Christopher Williams, MD, Len Neckers, PhD, Ray Tabios, W. Marston Linehan, MD and Jonathan Coleman, MD (Presented By: Christopher Williams, MD)

Poster #20  CLINICAL OUTCOMES OF PATIENTS DOWNSTAGED AT RADICAL CYSTECTOMY
Craig Rogers, MD, Patrick Bastian, MD, Ganesh Palapattu, MD, Bruce Trock, PhD, Mark Schoenberg, MD and Theresa Chan, MD (Presented By: Craig Rogers, MD)

Poster #21  TRANSRECTAL ULTRASOUND VERSUS MAGNETIC RESONANCE IMAGING FOR DETECTION OF RECTAL WALL INVASION BY PROSTATE CANCER
Dan Leibovici, MD, Ashish Kamat, MD, Kim Do, PhD, Curtis Pettaway, MD, Chaan Ng, MD, Robert Evans, PA-C, Miguel Rodriguez-Bigas, MD, John Skibber, MD, Xuemei Wang, MS and Louis Pisters, MD (Presented By: Dan Leibovici, MD)

Poster #22  NEUTRAL ENDOPEPTIDASE GENE THERAPY FOR PROSTATE CANCER
David Chen, MD, Ruojian Shen, PhD, Oscar Goodman, Jr, MD, PhD, Daniel Navarro, MS, Hanjun Guan, MS, Louis Hersh, PhD and David Nanus, MD (Presented By: David Chen, MD)

Poster #23  RENAL MASS MALIGNANCY IS PREDICTED BY MASS SIZE: AN EIGHT-YEAR EXPERIENCE
Deborah Glassman, MD, Jim Johannes, BS, Stephen Strup, MD, Leonard Gomella, MD and Dolores Byrne, PhD (Presented By: Deborah Glassman, MD)

Poster #24  VARIANTS OF SEMAPHORIN 3F ARE ASSOCIATED WITH PROSTATE CANCER PROGNOSIS
Edith Canby-Hagino, MD, Xin He, Ruihua Xiang, Dawn Garcia, MS, Jacques Baillargeon, PhD, Dean Troyer, MD, Brad Pollock, PhD, Javier Hernandez, MD, Ian Thompson, MD and Susan Naylor, PhD (Presented By: Edith Canby-Hagino, MD)
Poster #25  PARTIAL ADRENALECTOMY: THE NATIONAL CANCER INSTITUTE EXPERIENCE
Eric Diner, MD, Michael Franks, MD, Ashish Behari, MD, W. Marston Linehan, MD and McClellan Walther, MD
(Presented By: Eric Diner, MD)

Poster #26  Efficacy of combining selective estrogen receptor modulators and Casodex™ in androgen-dependent prostate cancer cells
Melissa M. Walls, MD, Asim Abdel-Mageed, DVM, PhD, Rodney Davis, MD and Erik P. Castle, MD
(Presented By: Erik P. Castle, MD)

Poster #27  THE IMPACT OF PERFORMING CONCOMITANT LYMPHADENECTOMY DURING ROBOTIC RADICAL PROSTATECTOMY
Fatih Atug, MD, Scott V. Burgess, MD, Jon R. Glass, MD, Rodney Davis, MD, Raju Thomas, MD and Erik P. Castle, MD
(Presented By: Erik P. Castle, MD)

Poster #28  INFLUENCE OF AGE ON RESPONSE TO INTRAVESICAL IMMUNOTHERAPY
Fadi Joudi, MD, Badrinath Konety, MD and Michael O’Donnell, MD (Presented By: Fadi Joudi, MD)

Poster #29  THE ASSOCIATION OF PREOPERATIVE SERUM CELL-FREE DNA CONTENT AND PSA RECURRENCE FOLLOWING RADICAL PROSTATECTOMY
Ganesh Palapattu, MD, Patrick Bastian, MD, Craig Rogers, MD, Xiaohui Lin, PhD, Yegnasubramanian Srinivasan, BS, Mangold Leslie, MS, Trock Bruce, PhD, Alan Partin, MD, PhD and William Nelson, MD, PhD (Presented By: Ganesh Palapattu, MD)

Poster #30  IMPACT OF LYMPH NODE DENSITY ON BLADDER CANCER SURVIVAL OUTCOMES: A COOPERATIVE GROUP REPORT
Ganesh Raj, MD, PhD, Harry Herr, MD and Bladder Cooperative Group (Presented By: Ganesh Raj, MD, PhD)

Poster #31  THE EFFECT OF ADJUVANT HORMONAL THERAPY AFTER RADICAL PROSTATECTOMY FOR PT3B PROSTATE CANCER
Gregory Schenk, MD, Michael Blute, MD, Erik Bergstrahl, MS, Jeffrey Slezak, MS and Horst Zincke, MD, PhD (Presented By: Gregory Schenk, MD)

Poster #32  NEOADJUVANT DOCETAXEL AND ESTRAMUSTINE FOLLOWED BY RADICAL PROSTATECTOMY OR RADIATION THERAPY FOR PATIENTS WITH HIGH-RISK PROSTATE CANCER
Heather Stefaniak, MD, Eric Wallen, MD, Paul Godley, MD, Julian Rosenman, MD, Young Whang, MD and Raj Pruthi, MD (Presented By: Heather Stefaniak, MD)

Poster #33  MOUSE MODEL FOR BLADDER CANCER INDUCTION AND IMAGING
Isla Garraway, MD, PhD, Chau Tran, PhD, Katie Cai and Robert Reiter, MD (Presented By: Isla Garraway, MD, PhD)

Poster #34  INCIDENTAL FINDING OF PROSTATE CANCER AT CYSTOPROSTATECTOMY: CHANGES IN INCIDENCE IN THE PSA ERA
J Slade Hubbard, MD, Heather Stefaniak, MD, Joseph Moliterno, MD, Eric Wallen, MD and Raj Pruthi, MD (Presented By: J Slade Hubbard, MD)

Poster #35  DETECTION OF PROSTATE CANCER WITH CONTRAST ENHANCED SONOGRAPHY USING HARMONIC GRAY SCALE, COLOR DOPPLER AND POWER DOPPLER IMAGING
Ethan Halpern, MD, J. Robert Ramey, MD, Ferdinand Frauscher, MD, Peter McCue, MD and Leonard Gomella, MD (Presented By: J. Robert Ramey, MD)

Continues on next page
Poster #36  DOES PREOPERATIVE ENDORECTAL MRI IMPACT ON THE LAPAROSCOPIC RADICAL PROSTATECTOMY POSITIVE MARGIN RATE?
James Brown, MD and Douglas Dahl, MD (Presented By: James Brown, MD)

Poster #37  RECOMBINANT PROSTATE CANCER VACCINES AND COMBINATION THERAPIES
James Gulley, MD, PhD, Philip Arlen, MD, Nushin Todd, MD, PhD, William Dahut, MD, Kevin Camphausen, MD, C. Norman Coleman, MD and Jeffrey Schlom, PhD
(Presented By: James Gulley, MD, PhD)

Poster #38  P53 ARG72PRO SINGLE NUCLEOTIDE POLYMORPHISM (SNP) IS ASSOCIATED WITH INCREASED RISK FOR PROSTATE CANCER AMONG AFRICAN AMERICAN MEN
Javier Hernandez, MD, Ivana Balic, MD, Teresa Johnson-Pais, PhD and Ian Thompson, MD
(Presented By: Javier Hernandez, MD)

Poster #39  CHARACTERIZING THE EFFECTS OF SILENCING VHL IN NON-CANCEROUS CELL LINES
Jean-Baptiste Lattouf, MD, July Xanthopoulos, Bsc, Ray Tabios, W. Marston Linehan, MD and James Vasselli, MD (Presented By: Jean-Baptiste Lattouf, MD)

Poster #40  POPULATION-BASED SURVIVAL DATA OF URACHAL TUMORS
Jehonathan H Pinthus, MD, PhD, Riad Haddad, MD, John Trachtenberg, MD FRCSC, Eric Holowety, MD, Jeff Bowler, Michael Jewett, MD, FRCSC and Neil Fleschner, MD, MPH, FRCSC
(Presented By: Jehonathan H Pinthus, MD, PhD)

Poster #41  IMPACT OF NOX4 ON HIF-ALPHA EXPRESSION AND TRANSACTIVATION
Jodi Maranchie, MD (Presented By: Jodi Maranchie, MD)

Poster #42  FLAP ENDONUCLEASE 1 (FEN-1) IS OVEREXPRESSED IN PROSTATE CANCER AND ASSOCIATED WITH HIGH GLEASON SCORE
John Lam, MD, Hong Yu, MD, PhD, Ai Li, BS, David Seligson, MD, John Leppert, MD, Mervi Eevi, BS, Oleg Shvarts, MD, Allan Pantuck, MD, Steve Horvath, PhD and Arie Beldegrun, MD
(Presented By: John Lam, MD)

Poster #43  EXPRESSION OF VASCULAR ENDOTHELIAL GROWTH FACTOR A (VEGF-A), VEGF RECEPTOR 1 (VEGFR-1) AND VEGFR-2 IN CLEAR CELL AND PAPILLARY RENAL CELL CARCINOMA (RCC): IMPLICATIONS FOR THERAPY
John Leppert, MD, John Lam, MD, Hong Yu, David Seligson, MD, Jun Dong, PhD, Steve Horvath, PhD, Allan Pantuck, MD, Robert Figlin, MD and Arie Beldegrun, MD (Presented By: John Leppert, MD)

Poster #44  RADICAL PROSTATECTOMY FOR CLINICALLY ADVANCED (CT3) PROSTATE CANCER IN THE PSA ERA: 15-YEAR OUTCOMES
John Ward, MD, Michael Blute, MD, Erik Bergstralh, Jeffrey Slezak and Horst Zincke, MD, PhD
(Presented By: John Ward, MD)

Poster #45  ANDROGEN AND ANDROGEN RECEPTOR ANTAGONIST RESPONSIVE PRIMARY AFRICAN AMERICAN BENIGN PROSTATE EPITHELIAL CELL LINE
Yongpeng Gu, MD, PhD, Kee-Hong Kim, PhD, Shiv Srivastava, PhD, Judd W Moul, MD, David GMcLeod, MD and Johng S Rhim, MD (Presented By: Johng S Rhim, MD)
Poster #46 COMPARISON OF HAND-ASSISTED LAPAROSCOPIC NEPHRECTOMY AND NEPHROURETERECTOMY TO STANDARD LAPAROSCOPY
Jonathan Taylor, MD, Alex Ernest, MD, Michael Fabrizio, MD and Robert Given, MD
(Presented By: Jonathan Taylor, MD)

Poster #47 NEW INTRAVESICAL SEQUENTIAL CHEMOTHERAPY FOR PATIENTS WITH TREATMENT REFRACTORY SUPERFICIAL UROTHELIAL CARCINOMA
Jose Maymi, MD, Nicole Saltsgaver, PA and Michael O’Donnell, MD (Presented By: Jose Maymi, MD)

Poster #48 LYMPHOSCINTOGRAPHIC MAPPING OF THE LYMPHATIC DRAINAGE OF THE PROSTATE AND SEMINAL VESICLES USING 99TECHNETIUM-SULFACOLLOID
Joseph Basler, PhD, MD, Nunes Wendy, MD and Chaudhury Turin, MD
(Presented By: Joseph Basler, MD, PhD)

Poster #49 REVIEW OF 12 CORE PROSTATE BIOPSIES FOR DETECTION OF PROSTATE CANCER AT THE NATIONAL NAVAL MEDICAL CENTER
Joseph Clark, MD, Jason Capra, BS and Timothy Donahue, MD (Presented By: Joseph Clark, MD)

Poster #50 ROLE OF THE VON HIPPEL-LINDAU (VHL) GENE IN THE REGULATION OF RECEPTOR TYROSINE KINASE PATHWAYS LEADING TO TUMOR SUPPRESSION: IMPLICATIONS FOR THE DEVELOPMENT OF NOVEL TREATMENTS FOR VHL(-/-) CLEAR CELL RENAL CARCINOMA
Julie Xanthopoulos, BS, Girma Woldemichael, PhD, Ray Tabios, BS, Jean Lattouf, MD, W. Marston Linehan, MD and James Vasselli, MD (Presented By: Julie Xanthopoulos, BS)

Poster #51 PRIMARY ANDROGEN DEPRIVATION THERAPY USE IN LOCALIZED DISEASE: RESULTS FROM CAPSURE
Jun Kawakami, MD, Janet Cowan, Eric Elkin, David Latini, PhD and Peter Carroll, MD
(Presented By: Jun Kawakami, MD)

Poster #52 IMPACT OF SIX MONTH LAPAROSCOPIC RADICAL PROSTATECTOMY FELLOWSHIP ON INITIATION OF A LAPAROSCOPIC RADICAL PROSTATECTOMY PROGRAM
Kamran Sajadi, MD and James Brown, MD (Presented By: Kamran Sajadi, MD)

Poster #53 QUALITY IMPROVEMENT IN LAPAROSCOPIC RADICAL PROSTATECTOMY FOR PT2 PROSTATE CANCER: IMPACT OF VIDEO DOCUMENTATION REVIEW ON POSITIVE SURGICAL MARGIN
Karim Touijer, MD, Kentaro Kuroiwa, MD, Jeffery Saranchuk, MD, Waleed Hassen, MD, Edouard Trabulsi, MD, Victor Reuter, MD and Bertrand Guillemonneau, MD (Presented By: Karim Touijer, MD)

Poster #54 TARGETED DRUG THERAPIES AND CELLULAR RESPONSE IN HUMAN BLADDER CANCER CELL LINES
Katrina Salazar, BS, James Vasselli, MD, W. Marston Linehan, MD, Donald Bottaro, PhD, Len Neckers, PhD and Jonathan Coleman, MD (Presented By: Katrina Salazar, BS)

Poster #55 COMPUTATIONAL ANALYSIS OF UPSTREAM REGULATORY SEQUENCES OF ANDROGEN-INDUCED GENES REVEALED ADJACENT LOCATION OF GATA ELEMENTS TO ANDROGEN RESPONSIVE ELEMENTS
Katsuaki Masuda, MD, PhD, Shilpi Maheshwari, BS, Soyon Oh, BS, Thomas Werner, MD, Shiv Srivastava, PhD and Albert Dobi, PhD (Presented By: Katsuaki Masuda, MD, PhD)
Poster #56

PROSTATE BIOPSY TUMOR NUMBER AND EXTENT BUT NOT LOCATION OR CONTIGUITY PREDICTS RECURRENCE AFTER RADICAL PROSTATECTOMY
Kirsten Greene, MD, Armine Karapetian, BA, Eric Elkin, MPH, Janeen Duchane, PhD, Christopher Kane, MD and Peter Carroll, MD (Presented By: Kirsten Greene, MD)

Poster #57

THE INTERACTION OF SMOKING AND PELVIC RADIATION ON THE RISK OF SUBSEQUENT BLADDER CANCER
Kristin Chrourser, MD, Bradley Leibovich, MD, Horst Zincke, MD, PhD and Michael Blute, MD (Presented By: Kristin Chrourser, MD)

Poster #58

RELATIONSHIP BETWEEN PRIOR PERSONAL MALIGNANCY OR FAMILY HISTORY OF PROSTATE CANCER AND REPETITIVE SCREENING FOR PROSTATE CANCER
Lincoln Olsen, MD, Peter Langenstroer, MD and J. Brantley Thrasher, MD (Presented By: Lincoln Olsen, MD)

Poster #59

A LONGITUDINAL COMPARISON OF SYMPTOMS FOLLOWING THREE TYPES OF TREATMENT FOR PROSTATE CANCER
Lucille Sanzero Eller, PhD, RN, Elise Lev, EdD, RN, Ihor Sawczuk, MD, Glen Gejerman, MD, Joan Colella, MSN, RN, Patricia Lane, MSW, Susan Schroine, BS, RNBC, OCN, Michael Esposito, MD, Vincent Lanteri, MD and John Scheuch, MD (Presented By: Lucille Sanzero Eller, PhD, RN)

Poster #60

PROGNOSTIC SIGNIFICANCE OF LYMPHOVASCULAR INVASION IN BLADDER CANCER TREATED WITH RADICAL CYSTECTOMY
Marcus L. Quek, MD, John P. Stein, MD, Peter W. Nichols, MD, Jie Cai, MS, Gus Miranda, Susan Groshen, PhD, Siamak Daneshmand, MD, Elsa C. Skinner, MD and Donald G. Skinner, MD (Presented By: Marcus L. Quek, MD)

Poster #61

RELATIONSHIP BETWEEN PRIMARY GLEASON PATTERN ON NEEDLE BIOPSY AND CLINICOPATHOLOGICAL OUTCOMES AMONG MEN WITH GLEASON 7 ADENOCARCINOMA OF THE PROSTATE
Mark Gonzalgo, MD, PhD, Leslie Mangold, Jonathan Epstein, MD, Patrick Walsh, MD and Alan Partin, MD, PhD (Presented By: Mark Gonzalgo, MD, PhD)

Poster #62

QUANTITATION OF TESTOSTERONE AND DIHYDROTESTOSTERONE TISSUE LEVELS IN RECURRENT PROSTATE CANCER USING LIQUID CHROMATOGRAPHY TANDEM MASS SPECTROMETRY
Mark Titus, PhD, Fred Lih, BS, Liguo Song, PhD, Michael Schell, PhD, Kenneth Tomer, PhD and James Mohler, MD (Presented By: Mark Titus, PhD)

Poster #63

APPLICATION OF CHROMOGENIC IN SITU HYBRIDIZATION (CISH) IN THE DIFFERENTIAL DIAGNOSIS OF RENAL TUMORS
Mauricio Palau, MD, Ruben Ronchetti, MD, Elsa Li Ning, MD, Carlos Torres-Cabala, MD, Maria Merino, MD and W. Marston Linehan, MD (Presented By: Mauricio Palau, MD)

Poster #64

PROGNOSTIC NOMOGRAM FOR RENAL INSUFFICIENCY AFTER RADICAL OR PARTIAL NEPHRECTOMY
Maximiliano Sorbellini, MD, Michael Kattan, PhD, Mark Snyder, BA, Ari Hakimi, BS, Debra Berger, MD and Paul Russo, MD (Presented By: Maximiliano Sorbellini, MD)

Poster #65

PROSPECTIVE, LONGITUDINAL, COMPARATIVE STUDY OF HEALTH RELATED QUALITY OF LIFE IN PATIENTS UNDERGOING INVASIVE TREATMENTS FOR LOCALIZED PROSTATE CANCER
Doug Soderdahl, MD, Adam Ball, MD, John Davis, MD, Paul Schellhammer, MD, Robert Given, MD, Donald Lynch, MD, Mark Shaves, MD, Monnie Burke and Michael Fabrizio, MD (Presented By: Michael Fabrizio, MD)
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<td>ANALYSIS OF BRG1 AND HBRM EXPRESSION IN PROSTATE CANCER CELLS</td>
<td>Michael Karellas, MD, Xinbo Liao, PhD and Benyi Li, MD, PhD</td>
<td>Michael Karellas, MD</td>
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<td>#67</td>
<td>RISE IN PSA FOLLOWING INTRAMUSCULAR TESTOSTERONE INJECTION CORRELATES HIGHLY WITH TUMOR VOLUME AND Gleason SUM IN MEN WITH PSA 2.4 TO 4 DIAGNOSED WITH PROSTATE CANCER (CAP) FOLLOWING TRANSRECTAL ULTRASOUND-GUIDED (TRUS) PROSTATE BIOPSY</td>
<td>Michael Shulman, MD, Vitaly Margulis, MD and Elie Benaim, MD</td>
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<td>Nicol Corbin, MD, Gladys Glenn, MD, PhD, Paul Albert, PhD, James Peterson, Jodi Maranchie, MD, Donald Bottaro, PhD, Peter Choyke, MD, McClellan Walther, MD, Berton Zbar, MD and W. Marston Linehan, MD</td>
<td>Nicol Corbin, MD</td>
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<td>A PHASE II STUDY OF SEQUENTIAL VACCINATIONS WITH RFOWLPOX-PSA (L155)-TRICOM ALONE, OR IN COMBINATION WITH RVACCINIA-PSA (L155)-TRICOM, AND THE ROLE OF GM-CSF, IN PATIENTS(PTS) WITH METASTATIC ANDROGEN INSENSITIVE PROSTATE CANCER (AIPC)</td>
<td>Nushin Todd, MD, PhD, James Gulley, MD, PhD, William Dahut, MD, Jeffrey Schlom, PhD and Philip Arlen, MD</td>
<td>Nushin Todd, MD, PhD</td>
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<td>Oliver Sartor, MD, Robert Reid, MD, Celestia Higano, MD, David Bushnell, MD and Donald Quick, MD</td>
<td>Oliver Sartor, MD</td>
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<td>Padraig Warde, MB</td>
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<td>#72</td>
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<td>Pankaj Kalra, MD, Deborah Glassman, MD, Leonard Gomella, MD, Stephen Strup, MD, David McGinnis, MD, Daniel Simon, BS, Mark Chang, MD, Dolores Byrne, PhD and Ramsay Kuo, MD</td>
<td>Pankaj Kalra, MD</td>
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<td>#73</td>
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<td>Pathirage Dharmawardana, MD, Alessio Giubellino, MD, Zhen-Dan Shi, PhD, Terrence Burke, PhD and Donald Bottaro, PhD</td>
<td>Pathirage Dharmawardana, MD</td>
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<td>#74</td>
<td>PROSTATE CANCER ON THE INTERNET: INFORMATION OR MISINFORMATION?</td>
<td>Peter Black, MD and David Penson</td>
<td>Peter Black, MD</td>
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<td>#75</td>
<td>TESTOSTERONE REPLACEMENT THERAPY AFTER PRIMARY TREATMENT OF PROSTATE CANCER</td>
<td>Piyush Agarwal, MD and Michael Oefelein, MD</td>
<td>Piyush Agarwal, MD</td>
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Poster #76  DIAGNOSTIC SERUM PROTEIN PATTERN RECOGNITION AND BIOMARKER DISCOVERY FOR PROSTATE CANCER USING SELDI-TOF
Premkala Prasanna, PhD, Lionel Bañez, MD, Jaroslaw W. Tuszynski, PhD, Amina Ali, MS, Bao Ling Adam, PhD, David G. McLeod, MD, Judd W. Moul, MD and Shiv Srivastava, PhD
(Presented By: Premkala Prasanna, PhD)

Poster #77 EXTRA-PERITONEAL VS. INTRA-PERITONEAL ROBOTIC PROSTATECTOMY
Rabii Madi, MD, Stephanie Faruzzi, MS and David Wood, MD (Presented By: Rabii Madi, MD)

Poster #78 EXENTERATIVE SALVAGE SURGERY FOR HORMONE REFRACTORY (HRCP) OR RADIATION (XRT) RECURRENT PROSTATE CANCER (CAP)
Rajen Doshi, MD, Daniel Lin, MD, Higano Celestia, MD, Ellis William, MD and Lange Paul, MD
(Presented By: Rajen Doshi, MD)

Poster #79 IMAGING METASTASIS OF RENAL CLEAR CELL CARCINOMA IN MURINE MODELS USING THE LUCIFERASE SYSTEM
Ray Tabios, Girma Woldemichael, PhD, Julie Xanthopoulos, BS, W. Marston Linehan, MD and James Vasselli, MD (Presented By: Ray Tabios)

Poster #80 MODELING THE COST OF MANAGEMENT OPTIONS FOR STAGE I NONSEMINOMATOUS GERM CELL TUMORS: A DECISION TREE ANALYSIS.
Richard Link, MD, PhD, Mohamad Allaf, MD, Roberto Pili, MD and Louis Kavoussi, MD
(Presented By: Richard Link, MD, PhD)

Poster #81 BIOLOGICAL-MRI GUIDED TRANSRECTAL PROSTATE BIOPSY
Robert Grubb, MD, Robert Susil, BS, Axel Krieger, MS, Peter Guion, Karen Ullman, RRT, Kevin Camphausen, MD, W. Marston Linehan, MD, Peter Choyke, MD, Cynthia Ménard, MD and Jonathan Coleman, MD (Presented By: Robert Grubb, MD)

Poster #82 THE SAFE AND EFFECTIVE APPLICATION OF LAPAROSCOPIC PARTIAL NEPHRECTOMY (PN) FOR SMALL RENAL MASSES: DUPLICATION OF OPEN PRINCIPLES AND PRACTICES
Robert Santa-Cruz, MD, Eric Wallen, MD and Raj Pruthi, MD (Presented By: Robert Santa-Cruz, MD)

Poster #83 PRE-TREATMENT NOMOGRAM FOR DISEASE-SPECIFIC SURVIVAL OF PATIENTS WITH ANDROGEN INDEPENDENT PROSTATE CANCER
Robert Svatek, MD, Pierre Karakiewicz, MD, Michael Shulman, MD, Jose Karam, MD, Paul Perrotte, MD and Elie Benaim, MD (Presented By: Robert Svatek, MD)

Poster #84 PROSTATE CANCER SPECIFIC ACTIVITY OF THE SELENIUM METABOLITE, METHYLESELENIC ACID (MSA)
Rosalia Viterbo, MD, Robert G Uzzo, MD, Kenya Yamaguchi, MD, Eric M Horowitz, MD, Richard E Greenberg, MD, Alan Pollack, MD and Vladimir M Kolenko, PHD
(Presented By: Rosalia Viterbo, MD)

Poster #85 THROMBOCYTOSIS ASSOCIATED WITH RENAL CELL CANCER: DOES TUMOR LATERALITY MAKE A DIFFERENCE?
Sagar Shah, MD, Sandy Srinivas, MD, Taiye Oguniype and Martha Terris, MD
(Presented By: Sagar Shah, MD)

Poster #86 LOW DOSE IL-2, INTERFERON, PIROXICAM, AND CIMETIDINE IN THE TREATMENT OF METASTATIC RENAL CELL CARCINOMA
Sam Graham, MD, Chuck Wadsworth, PA and Nada Wood, PhD (Presented By: Sam Graham, MD)

Poster #87 ENVIRONMENTAL STRESSORS TO PROSTATIC CANCER CELLS IN VITRO CAUSE AN UP-REGULATION OF COX-2 EXPRESSION
Satoshi Anai, MD, Suesan Boehlein, PhD and Charles Rosser, MD (Presented By: Satoshi Anai, MD)
IMPACT OF CHANGES IN TNM CLASSIFICATION ON STAGING OF BLADDER CANCER
Sharon Sharir, MD, MPH, FRCSC, Mary Gospodarowicz, MD, FRCPC and Michael Jewett, MD, FRCSC
(Presented By: Sharon Sharir, MD, MPH, FRCSC)

HISTOLOGICAL TUMOR NECROSIS AS A PROGNOSTIC FACTOR IN RENAL CELL CARCINOMA
Shomik Sengupta, MBBS, MSurg, FRACS, Christine Lohse, BS, Bradley Leibovich, MD, Igor Frank, MD, Horst Zincke, MD, PhD, Michael Blute, MD, Eugene Kwon, MD and John Cheville, MD
(Presented By: Shomik Sengupta, MBBS, MSurg, FRACS)

PHASE I/II TRIAL OF INTERFERON A2B AND LIPOSOME-ENCAPSULATED ALL-TRANS RETINOIC ACID IN THE TREATMENT OF PATIENTS WITH ADVANCED RENAL CELL CARCINOMA
Stephen Boorjian, MD, Matthew Milowsky, MD, Deirdre Coll, MD, Marta Cobham, Jodi Kaplan, Lorraine Gudas, PhD and David Nanus, MD
(Presented By: Stephen Boorjian, MD)

GENE EXPRESSION DIFFERENCES BETWEEN PROSTATE CANCERS FROM OBESE AND NORMAL WEIGHT MEN
Stephen Freedland, MD, Jun Luo, PhD, Angelo Demarzo, MD, PhD, Dunn Thomas, BS, Helen Fedor, BS, Medha Darshan, MS, Mohan Ishwaria, MS and William Isaacs, PhD
(Presented By: Stephen Freedland, MD)

THE COMBINED TREATMENT APPROACH FOR MEN UNDERGOING HORMONAL THERAPY FOR PROSTATE CANCER (PCA)
Sylvie Aubin, PhD and Celestia Higano, MD
(Presented By: Sylvie Aubin, PhD)

PATTERNS OF RECURRENCE AFTER NEPHROURETERECTOMY FOR TRANSITIONAL CELL CARCINOMA OF THE UPPER URINARY TRACT
Theresa Koppie, MD, Anthony Corcoran, MS, Machelle Donat, MD, Harry Herr, MD, Guido Dalbagni, MD and Bernard Bochner, MD
(Presented By: Theresa Koppie, MD)

CHARACTERISTICS OF PATIENTS WITH COMPLICATIONS FOLLOWING PERCUTANEOUS RADIOFREQUENCY ABLATION OF RENAL TUMORS
Alon Weizer, MD, Ganesh Raj, MD, PhD, Costas Lallas, MD, Ari Silverstein, MD, Martin O’Connell, MD, Rendon Nelson, MD and Thomas Polascik, MD
(Presented By: Thomas Polascik, MD)

OPTIMIZATION OF VASCULAR-TARGETED PHOTOTHERAPY (VTP) WITH WST09 FOR EBRT-RECURRENT PROSTATE CANCER
John Trachtenberg, MD, Mostafa Elhilali, MD, PhD, Mark Gertner, PhD, Arjen Bogaards, BSc, Masoom Haider, MD, Andrew Evans, MD, PhD, Patrick Cohen, MD, Avigdor Scherz, PhD, Armen Aprikian, MD and Brian Wilson, PhD
(Presented By: John Trachtenberg, MD)

7:00 p.m. – 7:30 p.m.  SUO Reception – Hyatt Regency Bethesda

7:30 p.m.  SUO Dinner – Hyatt Regency Bethesda

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**7:30 a.m. – 8:30 a.m.** Continental Breakfast

**8:30 a.m. – 9:00 a.m.** Bladder Cancer II: Current Issues in Surgical Management  
Moderator: Eila C. Skinner, MD – USC Norris Cancer Center

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| 8:30 a.m. – 8:40 a.m. | T Pouch Versus Studer  
Eila C. Skinner, MD – USC Norris Cancer Center |
| 8:40 a.m. – 8:50 a.m. | Sexual Dysfunction After Female Cystectomy  
Craig D. Zippe, MD – Cleveland Clinic |
| 8:50 a.m. – 9:00 a.m. | Perioperative Chemotherapy: When and Why  
Cheryl T. Lee, MD – University of Michigan |
| 9:10 a.m. – 9:30 a.m. | Discussion Panel:  
Eila C. Skinner, MD – USC Norris Cancer Center  
Craig D. Zippe, MD – Cleveland Clinic  
Cheryl T. Lee, MD – University of Michigan |

**9:30 a.m. – 9:45 a.m.** Fellow/Resident Poster Session Awards  
Committee:  
Steven C. Campbell, MD, PhD – Loyola University Medical Center  
John Phillips, MD – Beth Israel  
Jodi K. Maranchie, MD – University of Massachusetts  
Christian Pavlovich, MD – Johns Hopkins University

**9:45 a.m. – 10:30 a.m.** Kidney Cancer II: Recent Advances in Molecular Genetics of Kidney Cancer  
Moderator: Steven C. Campbell, MD, PhD – Loyola University Medical Center

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| 9:45 a.m. – 9:55 a.m. | Familial Renal Carcinoma  
Berton Zbar, MD – National Cancer Institute |
| 9:55 a.m. – 10:05 a.m. | Detection of Circulating Cells in Clear Cell RCC  
Taro Shuin, MD – Kochi Medical School |
| 10:05 a.m. – 10:15 a.m. | Micrarray Analysis RCC  
Ben Teh, MD |
| 10:15 a.m. – 10:30 a.m. | Discussion Panel:  
Steven C. Campbell, MD, PhD – Loyola University Medical Center  
Berton Zbar, MD – National Cancer Institute  
Taro Shuin, MD – Kochi Medical School  
Ben Teh, MD |

**10:30 a.m. – 10:45 a.m.** Break

**10:45 a.m. – 11:45 a.m.** Prostate Cancer III: Adjuvant Therapy for Prostate Cancer: “When Primary Therapy Fails”  
Moderator: Alan Partin, MD – Johns Hopkins

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| 10:45 a.m. – 10:52 a.m. | Salvage Prostatectomy after Radiation Therapy  
David P. Wood, Jr., MD – University of Michigan |
| 10:52 a.m. – 10:59 a.m. | Salvage Radical Prostatectomy Versus Salvage Cryotherapy:  
Comparison of Biochemical Results  
L.L. Pisters, MD – M.D. Anderson Cancer Center |
| 10:59 a.m. – 11:06 a.m. | Post Primary and Post Radiotherapy Cryotherapy Treatment  
Daniel B. Rukstalis, MD – MCP Hahnemann University Medical Center |
### Program Schedule

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| 11:06 a.m. – 11:13 a.m. | Adjuvant Chemotherapy after Radical Prostatectomy  
Oliver Sartor, MD – LSU Stanley Scott Cancer Center |
| 11:13 a.m. – 11:45 a.m. | Case Presentation – Discussion  
Presenter: Alan Wayne Partin, MD – The Brady Urological Institute  
Discussants:  
David P. Wood, Jr., MD – University of Michigan  
L.L. Pisters, MD – M.D. Anderson Cancer Center  
Daniel B. Rukstalis, MD – MCP Hahnemann University Medical Center  
Oliver Sartor, MD – LSU Stanley Scott Cancer Center |
| 11:45 p.m. – 12:30 p.m. | Late Breaking Developments II  
Moderator: George Bartsch, MD – University of Innsbruck |
| 11:45 AM        | RISE IN PSA FOLLOWING INTRAMUSCULAR TESTOSTERONE IS AN INDEPENDENT PREDICTOR OF SUBSEQUENT DIAGNOSIS OF ADENOCARCINOMA ON TRANSRECTAL ULTRASOUND-GUIDED PROSTATE BIOPSY IN MEN WITH PSA 2.5 TO 4  
Vitaly Margulis, MD, Michael Shulman, MD and Elie Benaim, MD (Presented By: Vitaly Margulis, MD) |
| 11:52 AM        | ROBOTIC-ASSISTED INPATIENT TELEROUNDING: A PROSPECTIVE, RANDOMIZED TRIAL COMPARING SAFETY AND PATIENT SATISFACTION WITH ROBOTIC-ASSISTED VS. TRADITIONAL INPATIENT ROUNDS  
Ann Soh, MD, Adam Ball, MD, Louis Kavoussi, MD, John Davis, MD, Robert Given, MD, Guillermo Mosquera, MD, Steven Schlossberg, MD, Bethany Gambill, Sc.M and Michael Fabrizio (Presented By: Michael Fabrizio) |
| 11:59 AM        | TARGETED BIOPSY OF THE PROSTATE WITH CONTRAST-ENHANCED TRANSRECTAL SONOGRAPHY IN PATIENTS WITH PREVIOUS NEGATIVE BIOPSY  
J. Robert Ramey, MD, Leonard Gomella, MD and Ethan Halpern, MD (Presented By: J. Robert Ramey, MD) |
| 12:06 PM        | NATURAL HISTORY OF PROGRESSION TO DISTANT METASTASIS AFTER FAILURE TO ACHIEVE AN UNDETECTABLE PSA FOLLOWING RADICAL PROSTATECTOMY  
Craig Rogers, MD, Masood Khan, MD, Craig Miller, BS, Robert Veltri, PhD and Alan Partin, MD (Presented By: Craig Rogers, MD) |
| 12:13 PM        | ADOPTIVE IMMUNOTHERAPY OF PROSTATE CANCER BONE LESIONS USING REDIRECTED EFFECTOR LYMPHOCYTES  
Jehonathan Pinthus, MD, PhD, Tova Waks, MSc, Victoria Malina, MSc, Keren Kaufman-Francis, Alon Harmelin, MVD, Itzhak Aizenberg, MVD, Hannah Kanety, PhD, Jacob Ramon, MD and Zelig Eshhar, PhD (Presented By: Jehonathan Pinthus, MD PhD) |
| 12:20 PM        | A NOVEL SUPERFICIAL BLADDER CANCER MODEL IN RABBIT TO FACILITATE ENDOSCOPIC DIAGNOSIS AND TREATMENT: A PRELIMINARY REPORT  
Canan Agartan, MD, Catherine Whitbeck, BS, Tipu Nazeer, MD, Robert Levin, PhD and Badar Mian, MD (Presented By: Badar Mian, MD) |
| 12:30 p.m. – 1:30 p.m. | Lunch |
| 1:30 p.m. – 5:30 p.m. | Young Urologic Oncologist Forum |
| 5:30 p.m.       | Adjourn |
Committee

Jeffrey Maxwell Holzbeierlein, MD, Chair
University of Kansas Medical Center

Daniel Lin, MD
University of Washington

Peter Clark, MD
Wake Forest University Medical Center

John Davis, MD
Eastern Virginia Medical School

Jonathan Coleman, MD
National Institutes of Health

Douglas Scherr, MD
Cornell University/New York Hospital
01:30 PM  RADICAL PROSTATECTOMY FOR CLINICALLY ADVANCED (CT3) PROSTATE CANCER IN THE PSA ERA: 15-YEAR OUTCOMES
John Ward, MD, Michael Blute, MD, Erik Bergstralh, Jeffrey Slezak and Horst Zincke, MD, PhD
(Presented By: John Ward, MD)

01:40 PM  PROSTATE CANCER ON THE INTERNET: INFORMATION OR MISINFORMATION?
Peter Black, MD and David Penson, MD (Presented By: Peter Black, MD)

01:50 PM  QUALITY IMPROVEMENT IN LAPAROSCOPIC RADICAL PROSTATECTOMY FOR PT2 PROSTATE CANCER: IMPACT OF VIDEO DOCUMENTATION REVIEW ON POSITIVE SURGICAL MARGIN
Karim Touijer, MD, Kentaro Kuroiwa, MD, Jeffery Saranchuk, MD, Waleed Hassen, MD, Edouard Trabu, MD, Victor Reuter, MD and Bertrand Guillonneau, MD (Presented By: Karim Touijer, MD)

02:00 PM  PERSISTENT C-FLIP(L) EXPRESSION IS NECESSARY AND SUFFICIENT TO MAINTAIN RESISTANCE TO TRAIL-MEDIATED APOPTOSIS IN PROSTATE CANCER
Xiaoping Zhang, MD, PhD, Tai-Guang Jin, PhD, Hongmei Yang, PhD, William DeWolf, MD, Roya Khosravi-Far, PhD and Aria Olumi, MD (Presented By: Aria Olumi, MD)

02:10 PM  IMPACT OF NOX4 ON HIF-ALPHA EXPRESSION AND TRANSACTIVATION
Jodi Maranchie, MD (Presented By: Jodi Maranchie, MD)

02:20 PM  CYSTOPROSTATECTOMY FOR EFFECTIVE PALLIATION OF SYMPTOMATIC BLADDER INVASION BY PROSTATE CANCER
Dan Leibovici, MD, Ashish Kamat, MD, Curtis Pettaway, MD, Lance Pagliaro, MD, Charles Rosser, MD, Christopher Logothetis, MD and Louis Pisters, MD (Presented By: Dan Leibovici, MD)

02:30 PM  LONG-TERM OUTCOMES FOLLOWING RADICAL PROSTATECTOMY IN MEN WITH CLINICAL T3 PROSTATE CANCER
Brett Carver, MD, Fernando Bianco, MD, Peter Scardino, MD and James Eastham, MD
(Presented By: Brett Carver, MD)

02:40 PM  MYCOPLASMA EFFECTS ON HUMAN TUMOR INVASION
Satoshi Anai, MD, Susan Boehlein, PhD, Catherine Ketcham, PhD and Charles Rosser, MD
(Presented By: Satoshi Anai, MD)

02:50 PM  TRANSITIONAL CELL CARCINOMA OF THE BLADDER IS INFILTRATED BY HIGH PROPORTIONS OF REGULATORY T-LYMPHOCYTES
Maria Mercader-Bravo, BS, MS, PhD, Shomik Sengupta, MBBS, MSurg, FRACS, Haidong Dong, MD, PhD, Xavier Frigola, BS, Scott Webster, MD, R Houston Thompson, MD, Bradley Leibovich, MD, Horst Zincke, MD, PhD, Michael Blute, MD and Eugene Kwon, MD
(Presented By: Shomik Sengupta, MBBS, MSurg, FRACS)

03:00 PM  RECOMBINANT PROSTATE CANCER VACCINES AND COMBINATION THERAPIES
James Gulley, MD, PhD, Phillip Arlen, MD, Nushin Todd, MD, PhD, William Dahut, MD, Kevin Camphausen, MD, C. Norman Coleman, MD and Jeffrey Schlom, PhD (Presented By: James Gulley, MD, PhD)

03:10 PM  IMIQUIMOD, A TOLL-LIKE RECEPTOR AGONIST AND IMMUNE RESPONSE MODIFIER, INDUCES APOPTOSIS AND CYTOKINE PRODUCTION IN BLADDER CANCER CELL LINES
Eric Smith, MD, Hidekki Kawamoto, MD, Xuecke You, MD and Douglas Scherr, MD
(Presented By: Eric Smith, MD)
HIGH-THROUGHPUT CLINICAL ANALYSIS OF FOS RELATED ANTIGEN 1 (FRA-1) EXPRESSION IN PROSTATE TUMORS: A NEW TUMOR MARKER IN PROSTATE CANCER
Aaron Grotas, MD, John Phillips, MD, Mark Rafelled, MD, Lukas Bubendorf, MD and Eric Gerber, MD
(Presented By: Aaron Grotas, MD)

A PHASE II STUDY OF SEQUENTIAL VACCINATIONS WITH RFOWLPOX-PSA (L155)-TRICOM ALONE, OR IN COMBINATION WITH RVACCINIA-PSA (L155)-TRICOM, AND THE ROLE OF GM-CSF, IN PATIENTS (PTS) WITH METASTATIC ANDROGEN INSENSITIVE PROSTATE CANCER (AIPC)
Nushin Todd, MD, PhD, James Gulley, MD, PhD, William Dahut, MD, Jeffrey Schlom, PhD and Philip Arlen, MD
(Presented By: Nushin Todd, MD, PhD)

CLASSIFICATION AND TRENDS OF PERIOPERATIVE MORBIDITIES FOLLOWING LAPAROSCOPIC RADICAL PROSTATECTOMY
Mark Gonzalgo, MD, PhD, Christian Pavlovich, MD, Matthew Gretzer, MD, Richard Link, MD, PhD, Sam Bhayani, MD, Wendy Sullivan and Li-Ming Su, MD
(Presented By: Mark Gonzalgo, MD, PhD)

MANAGEMENT AND FOLLOW-UP OF PATIENTS WITH CARCINOMA IN SITU AT A POSITIVE DISTAL URETERAL MARGIN FOLLOWING RADICAL CYSTECTOMY
Albert Ong, MD, Richard Link, MD, Sam Bhayani, MD, Ioannis Varkarakis, MD, Mohammad Allaf, MD, Mark Schoenberg, MD and Thomas Jarrett, MD
(Presented By: Albert Ong, MD)

ANALYSIS OF 14-3-3 PROTEINS IN PROSTATE CANCER
Michael Karellas, MD, Xinbo Liao, PhD, Jeffrey Holzbeierlein, MD, J. Brantley Thrasher, MD and Benyi Li, MD, PhD
(Presented By: Michael Karellas, MD)

NEOADJUVANT CHEMOTHERAPY DOES NOT INCREASE COMPLICATION RATE AFTER RADICAL CYSTECTOMY
Rabii Madi, MD, James Montie, MD, David Smith, MD, David Wood, MD, Stephanie Faruzzi, MS, Yingxi Zhang, MS and Cheryl Lee, MD
(Presented By: Rabii Madi, MD)

MOUSE MODEL FOR BLADDER CANCER INDUCTION AND IMAGING
Isla Garraway, MD, PhD, Chau Tran, PhD, Katie Cai and Robert Reiter, MD
(Presented By: Isla Garraway, MD, PhD)

Efficacy of combining selective estrogen receptor modulators and Casodex™ in androgen-dependent prostate cancer cells
Melissa M. Walls, MD, Asim Abdel-Mageed, DVM, PhD, Rodney Davis, MD and Erik P. Castle, MD
(Presented By: Erik P. Castle, MD)

Expression of vascular endothelial growth factor A (VEGF-A), VEGF receptor 1 (VEGFR-1) and VEGFR-2 in clear cell and papillary renal cell carcinoma (RCC): Implications for therapy
John Leppert, MD, John Lam, MD, Hong Yu, David Seligson, MD, Jun Dong, PhD, Steve Horvath, PhD, Allan Pantuck, MD, Robert Figlin, MD and Arie Belldegrun, MD
(Presented By: John Leppert, MD)

Clinical outcomes of patients downstaged at radical cystectomy
Craig Rogers, MD, Patrick Bastian, MD, Ganesh Palapattu, MD, Bruce Trock, PhD, Mark Schoenberg, MD and Theresa Chan, MD
(Presented By: Craig Rogers, MD)

Adjourn
Efficacy of Selective Estrogen Receptor Modulators (SERMs) in a Murine Xenograft Model Bearing Human Bladder Cancer
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We have demonstrated through Western Blot and Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) that estrogen receptor (ER)-beta is expressed in RT-4, 5637, T-24, TSU-PR1 and TCC-SUP human bladder cancer cell lines, while ER-alpha is expressed at very low levels. Raloxifene, a SERM, induced apoptosis and decreased the viability of RT-4, T-24, and 5637 cell-lines in-vitro in a dose dependent manner. Using tissue microarray analysis ER-beta was expressed in 133 (63.3%) of 210 bladder tumors, while ER-alpha was expressed in only 2 tumors. The expression of ER-beta was associated with stage and grade.

We constructed a murine xenograft model bearing human bladder cancer to evaluate the efficacy of SERMs in an animal model. A total of 10(7) 5637 human transitional cell carcinoma cells (suspended in 0.1 ml of a 1:1 mixture of RPMI with 10% FBS and matrigel) were injected into one site at a mammary fat pad of 6-8 week old female athymic BALB/c nu/nu mice. Only mice that developed measurable subcutaneous tumor (at least 3 mm in one dimension) within 2 weeks were chosen for further study. Raloxifene 100 mg (Sigma-Aldrich) powder was suspended in 9 ml of double-distilled water. One milliliters of 90% CMC and 10% PEG400/Tween80 was added to the raloxifene solution for a final concentration of 10 mg/ml. Five cohorts of mice consisting of 6-8 mice per cohort were administered no therapy, placebo (solvent only without raloxifene), raloxifene 0.01 mg/day, raloxifene 0.1 mg/day and raloxifene 1 mg/day for 5 days a week by oral gavage for 8 weeks. All of the doses of raloxifene significantly inhibited the growth of tumor (p<0.05). In a separate experiment, 10(7) 5637 cells were subcutaneously injected into the flanks of 6-8 week old female athymic nu/nu mice. Four cohorts of mice with measurable tumors of 6-8 mice per cohort were implanted with subcutaneous 60-day time-release pellets (Innovative Research of America, Sarasota, FL) delivering placebo, tamoxifen 0.008 mg/day, tamoxifen 0.125 mg/day and tamoxifen 1.25 mg/day, respectively. Again, significant inhibition of tumor was observed with all of the doses of tamoxifen (p < 0.01).

The expression of estrogen receptors in human bladder cancers in conjunction with the anti-tumor activity of SERMs both in vitro and in a murine xenograft model bearing human bladder cancer cell-lines provides the rationale for evaluating SERMs as a targeted therapeutic for patients with bladder cancer.

DNA-Repair Genetic Polymorphisms and Prostate Cancer
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Studies suggest that deficient DNA repair and elevated DNA damage may contribute to prostate cancer (CaP) risk. Since single nucleotide polymorphisms (SNPs) may contribute to deficient DNA repair, this study was designed to test the hypothesis that CaP risk or clinical parameters are associated with DNA-repair SNPs.

Using samples from an ongoing, institutional-review-board approved, case-control study (623 cases and 646 controls), we tested whether CaP risk or aggressiveness is associated with 20 amino acid substitution variants in three major DNA repair pathways: (1) Base Excision Repair (BER): ADPRT, APE1, POLD1, and XRCC1; (2) Nucleotide Excision Repair (NER): ERCC2/XPD, ERCC4/XPF, ERCC5/XPG, hHR23B, and XPC; and (3) Mismatch Repair (MMR): MLH1, MSH3, and MSH6. Cases were CaP patients prior to treatment or no active treatment for at least 6 months. Controls had a normal serum prostate specific antigen (PSA) level and digital rectal exam or a negative prostate biopsy. Data was adjusted based on age, race, smoking, benign prostatic hyperplasia, and family history of CaP. In 320 cases data was collected on pretreatment PSA, clinical stage, and biopsy Gleason score (GS). Genotyping was performed on extracted DNA from whole blood using the MassARRAY system (SEQUENOM Inc., San Diego, CA). Statistical analysis was performed using commercially available software.

In Caucasians, CaP risk was associated with three genotypes: ADPRT 762AA (OR=2.16, 95%CI = 1.00-4.65), ERCC2 NN (OR=0.66, 95%CI = 0.44-0.99), and MSH3 940 QQ (OR=3.51, 95%CI = 1.27-9.74). Data also suggest that XRCC1 399QQ (OR = 1.34, 95%CI = 0.92-1.97) and ERCC4/XPF 415 QQ (OR = 1.37, 95%CI = 0.95-1.97) may contribute to a slightly increased CaP risk. Among cases, in Caucasians, XRCC1 R399Q was different among 3 PSA groups (≤10, 10+ to 20, and >20; p=0.055). There was a significant association between high PSA and XRCC1 399QQ (OR = 3.79, 95%CI = 1.19-12.06, RR/RQ = referent group) but not in the intermediate PSA group (OR = 1.04, 95%CI = 0.39-2.77). No significant association was observed for other SNPs or stage/grade.

This study provides evidence that SNPs in multiple repair pathways (BER, NER, and MMR) contribute to CaP susceptibility. In addition, XRCC1 R399Q is associated with high pretreatment PSA. Future studies are needed to evaluate whether genetic variants contribute to DNA-repair functional phenotype and CaP risk or can help predict clinical outcome.
SINGLE CELL PROTEOMICS IN CELLS AND TISSUES ASSOCIATED WITH THE PREMALIGNANT FIELD PROVIDE A POWERFUL APPROACH FOR INDIVIDUAL RISK ASSESSMENT

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Introduction and Objectives: Based on the concept of biochemical field disease or field effect we previously demonstrated that molecular changes in exfoliated uroepithelial cells predict the development of benzidine initiated bladder cancer 3-5 years prior to clinically manifest bladder cancer utilizing quantitative fluorescence image analysis (QFIA).\textsuperscript{3,4} There is a major need to extend this technology to assay biomarkers in tissues based systems such as core biopsies in patients with an elevated PSA and a negative biopsy. In support of this approach we demonstrated the differential expression of three biomarkers in normal tissues in a gland with prostate cancer and the cancer tissues with QFIA and conventional IHC.\textsuperscript{1,2,5} Here we report for the first time the use of QFIA to quantify proteins in prospectively collected and archival prostate tissues with the ultimate objective for individual risk assessment to identify patients with biologically active prostate cancer.

Materials and Methods: Age-matched archived issue blocks (6 cases of BPH and 6 cases of prostate cancer) from the Department of Pathology/Microbiology at the University of Nebraska Medical Center. Tissue sections were deparaffinized, re-hydrated, processed for antigen retrieval, and stoichiometrically labeled for tissue transglutaminase or beta-catenin with either biotinylated secondary antibody and streptavidin-AlexFluor488 or directly conjugated 2ndary antibody (Alexa Flour 488). Fluorescence images were captured and analyzed by a Leica automated micro-scope system and Image-Pro Plus software. Differences between group means were statistically elevated by Students t-Test.

Results: The frequency of labeled glands was higher in the BPH specimens (41%) compared to the cancer specimens (17%; \( P<0.05 \)). Within cancer-bearing glands, labeling frequency was significantly higher (\( P<0.05 \)) in the normal-appearing areas (46%) compared to cancerous areas (7%). The mean intensity of all positive BPH gland (342 from 6 cases) was greater than that of all positive glands in either the normal-appearing (625 glands) or cancerous areas (236 glands) of the 6 cancer cases (\( P<0.001 \)). There was no difference, however, between the normal-appearing and cancerous area of cancer-bearing glands. However, because of the heterogeneous expression of tissue transglutaminase in normal prostate tissue, the small areas in core biopsies in normal glands signaled a problem with this marker for small tissue samples. Subsequently, we have developed the assay for beta-catenin that is more homogenously expressed in the normal tissue and compared the results between the normal and the normal areas in the gland with prostate cancer. Using a dot plot analysis 3 of the 6 normal areas in the prostate cancer gland were well below the threshold of normal-normal tissue. These results suggest this marker may be useful in a multiplexing profile.

CASTRATION INITIATES THE EARLY TRANSITION TO ANDROGEN INDEPENDENT PROSTATE CANCER THROUGH SRC KINASE
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Introduction: Androgen deprivation (AD) is standard therapy for patients with metastatic prostate cancer (CaP). Despite initial responses in nearly all patients, progression to androgen independence (AI) is inevitable. We hypothesize, that castration induces expression of chemokines and neuropeptides that facilitate the progression to AI through Src kinase.

Methods: LNCaP cells underwent AD and expression of IL-8, neuropeptides and the neuroendocrine phenotype evaluated. Focusing on neuropeptides, we constructed an LNCaP neuropeptide expression model by stable transfection of gastrin-releasing peptide (GRP). LNCaP-GRP cells were evaluated for anchorage and androgen independent growth in soft agar and migration. LNCaP-GRP cells alone or in admixture with LNcap cells were injected orthotopically into castrated nude and SCID mice and tumor growth and metastasis evaluated. Evidence of activation of the androgen receptor (AR) and the PSA gene was performed. We investigated the activation of the non-receptor tyrosine kinases Src, Fak and Etk in IL-8 and neuropeptide induced AI LNCaP mechanisms. Recultured orthotopic tumors were treated with inhibitors against GRP, AR and Src and soft agar colony formation measured. Src activation was assessed in the cell lines and xenografts.

Results: AD of LNCaP cells resulted in expression of IL-8, neuropeptides and a neuroendocrine phenotype. LNCaP-GRP cells resulted in AI growth and migration in vitro and in vivo with metastasis in castrated SCID mice. GRP activated AR nuclear translocation and expression of PSA. Neuropeptide mediated activation of the androgen receptor is shown to be through the non-receptor tyrosine kinases Src, Fak and Etk. A novel Src inhibitor significantly inhibited GRP mediated proliferation and a decrease in Src phosphorylation is demonstrated. A monoclonal antibody against GRP or the AR inhibitor bicalutamide caused partial inhibition of colony formation (p<0.05). The Src kinase inhibitors showed greatest colony formation inhibition (p<0.05). LNCaP-GRP cells supported the growth of LNCaP cells under AD conditions in vitro and in vivo.

Conclusions: Our model of neuropeptide-mediated AI CaP is dependent on both GRP and AR and suggests that castration initiates events that promote the development of AI CaP. Importantly, we find a role for Src kinase inhibition in this model, which may have therapeutic implications.

Supported by NIH Grants KO8 DK60748-01, 2RO1 DK/AG52659-04, and Department of Defense Grants PC10520 and PC040161.

TUMOR EXOSOMES EXPRESSING FAS LIGAND MEDIATE CD8+ T CELL APOPTOSIS
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INTRODUCTION: Tumor-induced immune suppression remains an obstacle to the successful use of immunotherapy. Tumor exosomes, microvesicles expressing MHC-I and tumor antigens, have been identified in a variety of cancers. The function of tumor exosomes remains largely unknown, whether they have a role in tumor-induced immune suppression remains to be investigated. Utilizing prostate cancer as a model, we hypothesized that tumor exosomes could inhibit host CD8+ T-cell responses.

METHODS: Prostate cancer exosomes were purified from patient plasma and in vitro cultures (cell lines: PC-3, DU-145, LNCaP) by ultracentrifugation. Control exosomes were isolated from volunteer plasma. A flowcytometry assisted cell sorter was utilized to identify the differential expression of prostate-specific membrane antigen (PMSA) between exosomes derived from prostate cancer patients and those derived from male volunteers. Allogeneic CD8+ T-cells were co-cultured with exosomes, Annexin-V was utilized to assess CD8+ T-cell apoptosis. Exosome-T-cell interactions were investigated using blocking antibodies to MHC-I and Fas Ligand (FasL).

RESULTS: Active production of exosomes by tumor cells was observed. Exosomes from both patients and prostate cancer cell lines expressed FasL, whereas control exosomes did not express FasL. Cell line derived exosomes induced dose-dependent apoptosis of CD8+ T-cells. At the highest exosomal concentration tested (10ug/ml) 73%-87% of CD8+ T-cells underwent apoptosis. Control exosomes only induced 2%-7% apoptosis. Exosomes from prostate cancer patients induced CD8+ T-cell apoptosis (65%-78%), however exosomes from healthy controls resulted in negligible rates of apoptosis (9%-13%). CD4+ T cells underwent negligible levels of apoptosis (3%-7%). Addition of MHC-I or FasL-blocking antibodies to CD8+ T cell and exosome co-cultures resulted in dose-dependent inhibition of apoptosis by both cell line and patient derived exosomes.

CONCLUSION: This work represents the first report of immune evasion induced by tumor exosomes. The results demonstrate that these microvesicles can act as systemic antigen presenting death signals that play a critical role in specifically inhibiting anti-tumor immune responses. Exosome induced immune suppression may represent an important hurdle to overcome in the utilization of immune modulation for cancer therapy.
RISE IN PSA FOLLOWING INTRAMUSCULAR TESTOSTERONE IS AN INDEPENDENT PREDICTOR OF SUBSEQUENT DIAGNOSIS OF ADENOCARCINOMA ON TRANSRECTAL ULTRASOUND-GUIDED PROSTATE BIOPSY IN MEN WITH PSA 2.5 TO 4

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Introduction: The purpose of this study was to determine if PSA kinetics following the administration of intramuscular testosterone to men with PSA levels between 2.5 to 4 are predictive of the subsequent diagnosis of adenocarcinoma on transrectal ultrasound-guided (TRUS) prostate biopsy.

Methods: The Institutional Review Board at the Dallas Veterans Affairs Medical Center approved this study. Forty men with PSA levels between 2.5 to 4, normal digital rectal exams, and normal testosterone levels were prospectively enrolled. Each participant received one intramuscular injection of 400 mg of Testosterone Cypionate at the start of the study. Free PSA (fPSA), total PSA (tPSA) and early morning serum testosterone levels were measured at baseline, 48 hours, and at weeks 1, 2, and 4. All men underwent a 12-core TRUS prostate biopsy with concurrent determination of total prostate volume (TV) and transition zone volume (TZ) at week 4.

Results: 18 of 40 men (45%) were diagnosed with prostate cancer. At baseline, men with cancer and benign findings on TRUS biopsy had similar age, racial distribution, tPSA, fPSA and testosterone levels. Median TV was higher in men without cancer (46.45 cm$^3$, range 33.70 to 145.40) than in men with cancer (39.5 cm$^3$, range 24.6 to 69.3) (p=0.022, Mann-Whitney U). The median change in tPSA from baseline to 4 wks in men with cancer (0.90 ng/mL, range -0.6 to 28.0) was significantly higher than in men without cancer (0.25 ng/mL, range -0.90 to 1.20) (p=0.006, Mann-Whitney U). On univariate analysis, TV (odds ratio (OR)=0.940, p=0.030), change in tPSA from baseline to 4 weeks (OR=5.120, p=0.022), and tPSA velocity (OR=687.291, p=0.022) were significant predictors of cancer diagnosis. On multivariate analysis, both TV (OR 0.929, p=0.048) and change in tPSA at 4 weeks (OR 6.78 p=0.027) remained significant predictors of subsequent cancer diagnosis.

Conclusions: In men with tPSA range of 2.5 to 4, magnitude of PSA rise following testosterone stimulation is an independent predictor of prostate cancer diagnosis on TRUS biopsy.

ROBOTIC-ASSISTED INPATIENT TELEROUNDING: A PROSPECTIVE, RANDOMIZED TRIAL COMPARING SAFETY AND PATIENT SATISFACTION WITH ROBOTIC-ASSISTED VS. TRADITIONAL INPATIENT ROUNDS

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Introduction and Objectives: We describe our experience with using remote telepresence robotic technology (InTouch Health, Goleta, CA) to supplant rounds on our inpatient urology service.

Materials and Methods: Fifty-six patients scheduled for urologic surgery between April and August 2004 were prospectively randomized to receive either traditional attending rounds or robotic-assisted telerounds during their hospital stay. A nurse-administered questionnaire was provided at the time of patient discharge. Data was evaluated for overall patient satisfaction, as well as any morbidity/mortality events resultant to robotic-assisted rounds.

Results: Twenty-four patients (43%) were randomized to receive robotic telerounds and 32 (57%) were randomized to receive traditional attending rounds. There was no statistically significant difference in the way either group rated their physician’s concern and caring, skill, communication, awareness, personal attention, and availability. Patients who received robotic telerounds were pleased with their care, with 60% either strongly agreeing or agreeing that their care was better because of telerounds. Seventy-five percent of patients felt that telerounding should become a regular part of patient care. Satisfaction did not vary by gender, but patients under age 60 were more comfortable with robotic telerounds than patients over age 60. Two morbidity events were noted but were unrelated to the type of rounding, and no mortality events were experienced.

Conclusions: Robotic telerounding is a safe and feasible adjunct to traditional attending rounds. Satisfaction and morbidity/mortality events were equivalent between those patients who received traditional attending rounds and those who received robotic telerounds. The robotic interface was generally well-received. Future studies directed at cost-analysis and length of hospital stay would be an important determinant in the clinical utility of remote telepresence technology.
TARGETED BIOPSY OF THE PROSTATE WITH CONTRAST-ENHANCED TRANSRECTAL SONOGRAPHY IN PATIENTS WITH PREVIOUS NEGATIVE BIOPSY
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PURPOSE: Patients with rising PSA are often subjected to multiple biopsy procedures before cancer is identified. The positive biopsy rate on repeat sextant biopsy is approximately 19% after one initial negative biopsy, and drops to 8% after two negative biopsy procedures (J. Urol 151, 1571-1574, 1994). The current study was performed to determine whether a targeted biopsy approach based upon contrast-enhanced sonography can improve the detection of prostate cancer in patients with a previously negative biopsy.

METHOD AND MATERIALS: Contrast-enhanced transrectal ultrasound (TRUS) guided prostate biopsy was performed in 134 subjects with at least one prior negative biopsy. Repeat biopsy was performed for either a persistent PSA elevation (> 4ng/ml) or abnormal digital rectal examination. Sonography was performed during continuous intravenous infusion of Imagent (Imcor; San Diego, CA), a microbubble contrast agent. A modified sextant biopsy approach was used with one core directed to the area of greatest flow within each outer gland sextant location. Up to 4 additional targeted cores were obtained from the areas of greatest flow within the prostate.

RESULTS: Cancer was detected in 36 of 134 patients (27%). Cancer was detected in 22/63 (35%) of subjects with one prior biopsy, in 8/42 (19%) of subjects with two prior biopsies, 3/16 (19%) of subjects with three prior biopsies and 3/13 (23%) of subjects with greater than three prior biopsies. The 95% confidence interval for detection of cancer was 23-48% in subjects with one prior biopsy and 11-31% in subjects with more than one prior biopsy.

CONCLUSIONS: Targeted biopsy based upon contrast-enhanced sonography is superior to repeat systematic sextant biopsy for the detection of prostate cancer. Our targeted technique provides cancer detection rates similar to those reported for “saturation” biopsy strategies without the increased morbidity and pathology costs associated with more extensive systematic sampling of the prostate.

NATURAL HISTORY OF PROGRESSION TO DISTANT METASTASIS AFTER FAILURE TO ACHIEVE AN UNDETECTABLE PSA FOLLOWING RADICAL PROSTATECTOMY
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Introduction: In men who fail to achieve an undetectable PSA after radical retropubic prostatectomy (RRP), the natural history of progression to distant metastasis is not well defined. The purpose of this study was to predict the time to distant metastasis in men with a persistently detectable PSA following RRP for clinically localized prostate cancer (PCa) and to stratify these patients into risk groups using pathologic and clinical variables and PSA kinetics.

Methods: Between 1989 and 2002, 9056 consecutive men underwent RRP at a single academic institution. Both long term follow-up and PSA information was available in 2680 patients. A total of 224 of these men failed to achieve an undetectable PSA (=0.1 ng/ml) following RRP for clinically localized PCa. Men were excluded who received neoadjuvant hormonal therapy (13), immediate postoperative adjuvant radiation therapy prior to the onset of metastasis (19), and early adjuvant hormonal therapy prior to onset of metastasis (32), leaving160 patients in the final study group (mean age = 58 years, range = 38-75 years), with a mean follow-up time of 5.3 years (range = 1-17 years). The Kaplan-Meier method was used to estimate distant metastasis-free survival. Univariate and multivariate Cox proportional hazards regression was used to assess the ability of pathologic and clinical variables to predict distant metastasis-free survival.

Results: The probability of distant metastasis-free survival at 3, 7, and 10 years was 68%, 38%, and 22%, respectively (median survival 5.0 years). Seventy-five men (47%) developed distant metastases after RRP [median time to metastases = 5.0 years, range 0.5-13 years]. The combination of RRP Gleason score, SV status, and LN status resulted in three risk groups for prediction of distant metastasis-free survival (HR=1.6, p<0.01). The slope of PSA changes 3 to 12 months after RRP at a cutoff of ≥0.05 ng/ml/month was even more predictive of distant metastasis-free survival (HR=2.9, p<0.01).

Conclusions: Of patients who fail to achieve an undetectable PSA following RRP for clinically localized PCa, many remain free of metastatic disease for an extended period of time, whereas others experience rapid progression to distant metastasis. Clinical (PSA slope) and pathologic (RRP Gleason score) variables can help identify patients with a higher risk of developing distant metastasis after RRP and may help determine the need, timing and extent of adjuvant treatments.

Continues on next page
ADOPTIVE IMMUNOTHERAPY OF PROSTATE CANCER BONE LESIONS USING REDIRECTED EFFECTOR LYMPHOCYTES
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Prostate cancer is currently the most commonly diagnosed non-cutaneous malignancy in American men. Following metastasis, usually to the bone, the disease is no longer curable and is usually treated palliatively with androgen ablation. However, following the conversion to androgen independent disease, there is no currently available effective therapy. The “T-body” approach, which employs genetically re-programmed lymphocytes, derived from the patient and expressing chimeric receptor genes, combines the effector functions of T lymphocytes and natural killer cells with the ability of antibodies to recognize pre-defined surface antigens with high specificity and in a non-MHC restricted manner. We show here the therapeutic efficacy of anti-erbB2 chimeric receptor-bearing human lymphocytes on human prostate cancer bone lesions in a SCID mouse model following conditioning of the recipient to allow homing and persistent functioning of the adoptively transferred cells. Induction of SDF-1 production within the bone marrow vicinity using low dose irradiation or cyclophosphamide combined with IL-2 administration, enhance the homing of systemically delivered T-bodies resulting in decreased tumor growth and PSA secretion, prolongation of survival and even cure of the treated mice. These pre-clinical studies strongly support the therapeutic potential of the T-body approach for disseminated prostate cancer.

A NOVEL SUPERFICIAL BLADDER CANCER MODEL IN RABBIT TO FACILITATE ENDOSCOPIC DIAGNOSIS AND TREATMENT: A PRELIMINARY REPORT
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Most bladder cancers are superficial at diagnosis, and require multiple endoscopic evaluations and interventions. While animal models of advanced bladder cancer are available, there are no reliable bladder cancer models that allow us to diagnose, or treat the cancers in a manner similar to the clinical practice. Our previous studies demonstrated that acute bladder overdistention results in the overexpression of bFGF, VEGF, HIF-1 alpha, as well as c-myc and ras family of oncogenes. Similar changes are also noted in bladder cancer of various grades and stages. We hypothesized that exposure of the rabbit urothelium, while it is undergoing the above-stated cellular and molecular changes, to a carcinogen will convert the rabbit urothelium to a malignant phenotype. We also sought to determine the feasibility of multiple endoscopic manipulations of the rabbit bladder, similar to that required in humans. Eight adult male NZW rabbits were anesthetized and the bladder was distended for 30 minutes following which nitrosonomethylurea 2.5-5 mg in 25 ml of normal saline was instilled into the bladder, once/week for up to 8 weeks. A pediatric cystoscope was used prior to each instillation to inspect the urothelium and obtain biopsies from abnormal appearing areas. The control group included two rabbits without distention or instillation. We found that the rabbits did not experience any significant untoward effects from multiple cystoscopies or biopsies. The animals were sacrificed at the end of the study and full thickness bladder walls were sectioned and formalin-fixed for pathologic evaluation. The specimens were reviewed by a pathologist and a urologist, who were blinded to the origin of tissue samples. At 4 weeks, the urothelium appeared to develop lesions that cystoscopically appeared similar to human papillary TCC. In most of the animals, the biopsies revealed presence of pre-malignant and early malignant lesions such as papillary hyperplasia, intestinal metaplasia, squamous metaplasia and low-grade dysplasia. The full thickness bladder wall specimens revealed presence of mild to marked papillary hyperplasia, focal to diffuse atypia, and low-grade dysplasia in all animals. The findings of this preliminary study suggest that exposing the urothelium to a carcinogen at a time when it is undergoing specific cellular and molecular changes, can result in a malignant phenotype. This model allows us to perform serial cystoscopic examinations to assess disease progression or response to therapy, without sacrificing the animals. In order to develop a more reliable and reproducible range of tumors, further experiments with modifications in the overdistention/instillation schedules, or carcinogen doses are currently ongoing.
Poster #1

HIGH-THROUGHPUT CLINICAL ANALYSIS OF FOS RELATED ANTIGEN 1 (FRA-1) EXPRESSION IN PROSTATE TUMORS: A NEW TUMOR MARKER IN PROSTATE CANCER
Aaron Grotas, MD, John Phillips, MD, Mark Rafelled, MD, Lukas Bubendorf, MD and Eric Gerber, MD

Purpose: As part of a high-throughput cytogenetic and genomic interrogation of a prostate tumorigenesis model, we identified Fos Related Antigen 1 (fra-1) as a target of chromosomal amplification. Fra1 is a nuclear target of the MEK -> ERK pathway and, with jun-family peptides, a co-factor of AP1. We hypothesized that fra1 expression may correlate with tumor progression in clinical specimens of prostate cancer. We used tissue arrays to optimize histologic preparation for and screening of fra1 expressivity in 276 prostate specimens simultaneously.

Methods: Paraffin-embedded, formalin fixed specimens were stained after antigen retrieval, and stained with 1:1200 mouse anti-human fra-1 (Santa Cruz). We developed an ordinal visual scoring system to grade positive staining specimens and employed logistic regression for predictive modeling. Positive staining was assigned for strong or obvious nucleolar staining and negative staining was assigned for no or cytoplasmic staining.

Results: Fra-1 staining emerges, in strongly positive cases, from the nucleolus with background nucleoplasmic and cytoplasmic signal. Fra1 stained positive in 68% of hormone refractory cancer (hrpc) specimens versus 12% of control, benign prostatic hyperplasia (bph) specimens (sensitivity 99%, specificity of 38%) Positive staining correlated with an Odds Ratio (OR) of 16:1 favoring hrpc vs. bph and comparing hrpc with all other benign tissue types (ANOVA, p<.01). No significant staining pattern was seen among low stage (clinically gland confined) prostate cancers despite varying grades and no significant difference (P>.05, ANOVA) was seen between low grade prostate cancer and benign tissue.

Conclusion: Positive nucleolar fra-1 staining is highly prevalent in hormone refractory prostate cancer (hrpc) and predicts for hrpc over benign disease. Molecular targeting of fra-1 may, therefore, have clinical relevance in hrpc and provides the basis for our current xenograft model using water-soluble ERK1 inhibitors.

Poster #2

LAPAROSCOPIC RADICAL PROSTATECTOMY: CRITICALLY EVALUATING PATHOLOGICAL SPECIMENS TO GUIDE FUTURE OUTCOME IMPROVEMENTS
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Introduction and Objectives: To evaluate pathological outcomes of laparoscopic radical prostatectomy (LRP) from our institution by examining pathological staging, surgical margins and benign parenchymal exposure to determine areas for improvement in operative technique.

Materials and Methods: A retrospective review of 110 consecutive LRP’s from April 2001-April 2003 was performed. Oncological data was assessed by standard pathological examination for stage, grade and margin status. All slides were examined by a single experienced genitourinary pathologist (J.I.D.). Exposure of benign glands at the inked margin was also reported. Pathological outcomes from year one (Group I) were compared to subsequent clinical experience (Group II).

Results: Groups I and II consisted of 52 and 58 patients, respectively. The overall positive surgical margin rate was 18.2%. The rate in pT2 disease was 13.5%. Benign parenchymal exposure was identified in 16 patients (14.5%). Six of these patients had concomitant negative surgical margins. The positive margin rate for pT2 patients was 22.2% in Group I and 5.9% in Group II. The positive margin rates were 34.8%, 13.6% and 13.8% for bilateral, unilateral and non-nerve sparing procedures, respectively.

Conclusions: LRP offers comparable surgical margins to reported open radical prostatectomy series. After careful pathological review and technique modifications, these rates can improve with clinical experience. A low but significant positive margin or benign parenchymal exposure rate in pT2 disease demonstrates areas for technical improvement. Benign glands at the inked margin are not routinely reported, but do provide an additional parameter of surgical adequacy.
Poster #3

MANAGEMENT AND FOLLOW-UP OF PATIENTS WITH CARCINOMA IN SITU AT A POSITIVE DISTAL URETERAL MARGIN FOLLOWING RADICAL CYSTECTOMY

Albert M. Ong, Richard E. Link, Sam B. Bhayani, Ionnis Varkarakis, Takeshi Inagaki, Mohammed Allaf, Mark Schoenberg, Thomas W. Jarrett

Purpose: The impact of carcinoma in situ (CIS) at a positive distal ureteral margin following radical cystectomy has not previously been characterized. Although patients with CIS of the urinary bladder at the time of cystectomy have a higher upper tract recurrence rate, the literature is ambivalent regarding CIS in a positive distal ureteral margin at the time of cystectomy.

Materials and Methods: We examined our records from 1999-2004 to identify patients with CIS at a positive distal ureteral margin at the time of cystectomy. We found eleven patients who fulfilled this criteria. One the patients was excluded from analysis, as the initial pathology was not available. For the remainder, carcinoma in situ was present in the bladder in all cystectomy specimens. These patients were followed with surveillance ureteroscopy every six months, and annually with computed tomography. The mean age of the patients was 69.8 years. Three patients were female, and the remainder were male. The majority of patients in this series had received intravesical therapy prior to extirpative surgery. The mean follow-up in this group of patients was 869 days.

Results: Distal ureteral margins were positive bilaterally in 60% of cases and unilateral in the remainder. The recurrence rate was 40%, and the mean time to recurrence was 273.3 days following cystectomy. There was no correlation between initial tumor stage and recurrence of the upper tract lesion. There was only one recurrence at the site of the initial positive margin, and half of the recurrences were contralateral to the site of the positive margin. Recurrences were treated with laparoscopic nephroureterectomy on the affected side, and were organ confined in all cases. Three of the four cases were recurrent upper tract CIS. There was one death in the series unrelated to cancer.

Conclusion: Though small, our series suggests that the entire urothelium in patients with CIS at a positive margin should be examined closely and frequently, as recurrences are often clinically silent and can progress rapidly.

Poster #4

GENE EXPRESSION PROFILING FOR GENE IDENTIFICATION AND PROGNOSIS IN RENAL CELL CARCINOMA

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Introduction: The incidence of renal cell carcinoma (RCC) continues to increase. The majority of RCC’s being treated surgically present as asymptomatic, incidentally detected masses, most of which appear to grow slowly or not at all. Recent evidence suggests that global gene expression profiling correlates very well with histological subtypes of RCC and can provide useful prognostic information.

Methods: Genetic profiles of both small and large, low grade and high grade RCC’s were compared in an attempt to identify genomic changes that may be predictive of a more aggressive clinical behaviour. Tumor tissue from 20 patients with RCC who had their tumor surgically removed was collected. Tumor RNA was extracted and gene expression profiles were defined using the microarray technology.

Results: Most small and large RCC’s cluster separately on supervised analysis. Better discrimination in clustering is seen with a cut-off of 3 cm. as opposed to 4 cm. to distinguish small from large tumors. Low grade and high grade tumors have distinct gene expression profiles. Some of the specific genes more accurately differentiating between small and large, low and high grade tumor encode for proliferative markers, tumor-associated antigens of the cytoskeleton and growth factors. These genes have the potential for offering an insight into the biological and molecular differences between indolent and aggressive tumors.

Conclusions: Most small and large, low grade and high grade RCC’s have different gene expression profiles. Genomic signatures can potentially be used as a prognostic factor to distinguish between indolent and aggressive RCC’s in the clinical setting.
**Poster #5**

**SHEDDING OF C-MET ECTODOMAIN IN UROLOGIC MALIGNANCIES**

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The release of soluble, truncated forms of cell surface transmembrane receptors, called shedding, may have important roles in physiologic processes as well as in several human diseases, including cancer. Among the many receptors for which ectodomain shedding has been demonstrated is c-Met, the hepatocyte growth factor (HGF) receptor tyrosine kinase. HGF stimulates mitogenesis, motogenesis, and morphogenesis in a wide range of cellular targets during development, homeostasis and tissue regeneration. Inappropriate HGF signaling resulting in unregulated cell proliferation, motility and invasion occurs in several human malignancies, including kidney, prostate and bladder cancers. Inherited germline mutations in c-Met predispose affected individuals to human papillary renal cell carcinoma type 1.

We characterized the shedding of c-Met ecto-domain in a series of genitourinary cancer cell lines with the immediate goal correlating of c-Met shedding with cancer type and level of cell transformation. In the process, methods for the detection of c-Met ectodomain shedding were optimized for sensitivity and high throughput. Conditioned media from cultured cell lines was harvested after 24 and 48 hours of serum deprivation, concentrated and immunoprecipitated with antibodies against the c-Met ecto-domain. Samples were analyzed by SDS-PAGE and immunoblotting using a commercially available c-Met ectodomain-Fc chimera as a positive control. Conditioned media harvested from c-Met negative cell lines was a source of negative control samples. Initial results confirmed the presence of c-Met ectodomain shedding in several cell lines, and facilitated the development of a sensitive two-site ELISA to detect and quantitate soluble c-Met ectodomain in the conditioned media from several bladder cancer cell lines. Our long term goal is to extend our study to include patient samples where results can be correlated with disease type, stage, and outcome.

**Poster #6**

**PROEPITHELIN PROMOTES CELL MIGRATION AND INVASION OF BLADDER CANCER CELLS**


**Introduction:** The growth factor proepithelin (also known as progranulin or PC-derived growth factor) has emerged in recent years as an important regulator of cell growth, migration and transformation in several epithelial cells. In this study we have investigated whether proepithelin plays any role in the migration and invasion of bladder cancer cells using an *in vitro* system.

**Methods:** In these studies we performed migration and invasion assays in Boyden chambers, Western immunoblot analyses of activated proteins and wound healing assays in monolayer cultures.

**Results:** In our earlier experiments, using conditioned medium from proepithelin-overexpressing fibroblasts as source of proepithelin, we established that proepithelin promotes migration of normal and transformed bladder cells. Here we demonstrate a direct activity of human recombinant proepithelin purified to homogeneity from 293-EBNA cells. Specifically, we show that nanomolar amounts of proepithelin promote the migration and invasion through a three dimensional extracellular matrix (Matrigel™) of 5637 transitional carcinoma-derived cells. Moreover, proepithelin stimulates *in vitro* closure of a wound. These effects require the activation of the Erk1/2 kinases pathway, as determined by Western blot using phospho-specific antibodies for the activated proteins. The role Erk1/2 in proepithelin-stimulated cell signaling of 5637 cells was further confirmed using specific inhibitors of the Erk1/2 kinase pathway (UO126).

**Conclusions:** Our results provide the first evidence for a role of proepithelin in stimulating migration and invasion of bladder cancer cells, and support the hypothesis that this growth factor may play a significant role in the establishment of the transformed phenotype in bladder cancer, and perhaps in other solid tumors.
Poster #7

RETROPERITONEAL LYMPH NODE DISSECTION FOR NONSEMINOMATOUS GERM CELL TESTICULAR CANCER: IMPACT OF PATIENT SELECTION FACTORS ON OUTCOME
Andrew Stephenson, MD, George Bosl, MD, Dean Bajorin, MD, Robert Motzer, MD, Jason Stasi, BS and Joel Sheinfeld, MD

Objective: To investigate the impact of patient selection criteria on the outcome of patients with low-stage non-seminomatous germ cell testicular cancer (NSGCT) treated by RPLND. Since 1999, our criteria have excluded patients with persistent post-orchiectomy elevation of serum tumor markers (STM) or with clinical stage (CS) IIB disease from RPLND.

Methods: Between 1989 and 2002, 453 patients underwent primary RPLND at our institution for CS I-IIB NSGCT. By retrospective analysis, retroperitoneal pathology and relapse rates were compared for patients treated before (pre-1999) and after (post-1999) application of the current selection criteria.

Results: By excluding patients with elevated STM or CS IIB disease after 1999, the proportion of pathologic stage II patients with low-volume (PN1) retroperitoneal disease increased significantly (40% pre- vs 64% post-1999, P=.01) without significantly affecting the rate of retroperitoneal teratoma (21% vs 22%, P=.89) or pathologic stage I (56% vs 67%, P=.06). For patients who did not receive adjuvant chemotherapy, the 4-year progression-free probability improved significantly from 83% pre-1999 (95% confidence interval [CI], 79-88%) to 96% post-1999 (95% CI, 91-100%) (P=.005). Elevated post-orchiectomy STM (P<.0001), clinical stage (P=.0002), and pre-1999 RPLND (P=.05) were independent pretreatment predictors of progression.

Conclusions: Excluding patients with CS IIB disease or elevated post-orchiectomy STM from primary RPLND has had a favorable impact on the extent of retroperitoneal disease and has significantly reduced the risk of relapse after RPLND. These results are likely to serve as useful guidelines for the selection of patients with low-stage NSGCT for primary RPLND.

Poster #8

EVALUATION OF URETERO-INTESTINAL ANASTOMOSIS: WALLACE VS. BRICKER
Apostolos Evangelidis, MD, Michael Karellas, MD, Eugene Lee, John Brosa, J. Brantley Thrasher, MD and Jeffrey Holzbeierlein, MD

Purpose: There exist no published reports comparing the complication rates of the two most frequently used uretero-intestinal anastomoses. We compared the Bricker method versus the Wallace method, in terms of stricture rate.

Materials and Methods: A retrospective review of the cystectomy database at our institution covering the time period of 1997-2003 was conducted. Patients were reviewed in terms of type of anastomosis, stricture formation, intervention, radiation therapy, type of diversion, and operating room time.

Results: 237 patients at our institution underwent cystectomy during the time period evaluated. Thirty-three patients had incomplete data, two patients were anephric and did not require diversion, and four patients underwent LeDuc anastomosis. These patients were excluded, leaving 237, 86 patients (43%) undergoing Bricker anastomosis and 112 patients (56%) undergoing Wallace. Bricker anastomoses were considered as two anastomotic units while Wallace anastomoses were considered as a single unit. Therefore there were 162 (59%) total Bricker anastomoses to 112 (41%) Wallace anastomoses. There was no statistically significant difference between the two groups in terms of type of diversion, number of patients undergoing adjuvant radiation therapy, type of diversion, and operating room time. Days of follow-up, 639 days for Bricker versus 559 days for Wallace. There were 3 strictures (1.85%) in the Bricker group and 2 strictures (1.78%) in the Wallace group. There was no statistically significant difference between the stricture rate in these two groups (P=0.97). Stricture rates for patients undergoing adjuvant radiation were not statistically significant from the patients with no adjuvant therapy.

Conclusion: Overall the stricture rate for ureterointestinal anastomoses was low at 1.76%. There was no difference in stricture rate between types of ureteral-intestinal anastomosis. There should be no preference in terms of type of anastomosis in patients thought to be at high risk for ureteral-intestinal stricture.
Poster #9

PERSISTENT C-FLIP(L) EXPRESSION IS NECESSARY AND SUFFICIENT TO MAINTAIN RESISTANCE TO TRAIL-MEDIATED APOPTOSIS IN PROSTATE CANCER
Xiaoping Zhang, Tai-Guang Jin, Hongmei Yang, William C. DeWolf, Roya Khorasani-Far and Aria F. Olumi

Tumor-Related Apoptosis Inducing Ligand (TRAIL) has been shown to induce apoptosis in a variety of tumorigenic and transformed cell lines but not in many normal cells. Hence, TRAIL has the potential to be an ideal cancer therapeutic agent with minimal cytotoxicity. FLICE Inhibitory Protein (c-FLIP) is an important regulator of TRAIL-induced apoptosis. Here, we demonstrate that persistent expression of c-FLIP(L) is inversely correlated with the ability of TRAIL to induce apoptosis in prostate cancer cells. In contrast to TRAIL-sensitive cells, TRAIL-resistant LNCaP and PC3-TR (a TRAIL-resistant subpopulation of PC3) cells demonstrated increased c-FLIP(L) mRNA levels and maintained steady protein expression of c-FLIP(L) after treatment with TRAIL. Ectopic expression of c-FLIP(L) in TRAIL-sensitive PC3 cells changed their phenotype from TRAIL-sensitive to TRAIL-resistant. Conversely, silencing of c-FLIP(L) expression by siRNA in PC3-TR cells reversed their phenotype from TRAIL-resistant to TRAIL-sensitive. Therefore, persistent expression of c-FLIP(L) is necessary and sufficient to regulate sensitivity to TRAIL mediated apoptosis in prostate cancer cells.

Poster #10

ROLE OF OXIDATIVE STRESS IN TUMORIGENIC POTENTIAL OF BLADDER CANCER CELLS
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Reactive oxygen species (ROS) cause DNA mutations, chromosomal aberrations and tumor suppressor gene inactivation, ultimately leading to tumorigenesis and play a role in tumor invasion and metastasis. Conversely, antioxidants detoxify ROS and may reverse the damage caused by ROS. Loss of this balance leads to accumulation of oxidants, i.e. oxidative stress. The relationship between oxidative stress and bladder cancer has been poorly investigated. These studies were performed to test the hypothesis that imbalances in the oxidant scavenging potential of the bladder cancer cell lines may be related to their tumorigenic and metastatic potential. We determined the expression levels of oxidant-generating (superoxide dismutases-2, SOD-2) and anti-oxidant enzymes (Catalase) in three bladder cancer cell lines i.e. oxidative stress index (OSI). We found that the OSI in highly malignant variant, 253J-BV cells is about 2-fold higher than the parental 253J cells. In addition, the expression of MMP-9 and VEGF was increased in the more malignant 253J-BV cell as compared to 253J cells, p < 0.01. Overexpression of the H2O2 detoxifying enzyme catalase in the 253J-BV and UMUC-3 cells suppressed MMP-9 activity, while the H2O2 generating enzyme, SOD2, induced MMP-9 activity. In addition, the enhanced clonogenic activity of the highly tumorigenic cells, 253J-BV and UMUC-3, was significantly attenuated by catalase overexpression. Our results suggest that the OSI correlates with the tumorigenic potential and that effective H2O2 detoxification by catalase may provide a therapeutic target for the treatment of human bladder cancer.
A POPULATION-BASED SURVEY OF PSA TESTING AMONG CALIFORNIA MEN AT HIGHER RISK FOR PROSTATE CANCER

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Introduction: Despite the lack of clinical trial evidence demonstrating a prostate cancer-specific survival benefit from prostate specific antigen (PSA) screening, its use has become widespread, several national organizations have encouraged physicians to discuss the risks and benefits of early detection of prostate cancer with men 50 and older, and two higher risk groups (African Americans and men with a family history of prostate cancer) have been recognized. The purpose of this study is to determine whether African Americans and men with a family history of prostate cancer undergo PSA testing preferentially and to examine variations in patterns of test use by age, race, and other factors.

Methods: The 2001 California Health Interview Survey is a population-based, random-digit dial telephone survey conducted in California. Responses from 8,713 men age 50 and older without a history of prostate cancer were analyzed. The main outcome measure was PSA test use in the past year. We used multivariate logistic regression to identify predictors of PSA testing.

Results: The overall rate of PSA test use in CHIS 2001 was 36.4%. Higher age and socioeconomic status and having better health status, a usual source of healthcare, a family history of prostate cancer, and recent colorectal cancer screening were the strongest predictors of testing. Among the higher risk groups aged 45-49, African American men (OR 0.23, 95% CI 0.12, 0.44) and men with a family history of prostate cancer (OR 0.42, 95% CI 0.22, 0.78) were less likely to have been tested than men aged 50 and older.

Conclusions: Rates of PSA test use in California among higher risk groups are lower for men aged 45-49 than for older men. Until clinical trials establish whether PSA screening prolongs population survival, PSA test use should be determined by individual patient and physician preferences after informed consent. Unequal access to informed decision-making for PSA testing should be eliminated.

DOES RACE PREDICT PROSTATE CANCER ON REPEAT BIOPSY?

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Introduction and Objective: The presence of high grade intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP) increases the probability of cancer on a subsequent prostate biopsy. We investigated whether race was prognostic in detecting cancer in patients undergoing repeat prostate biopsies.

Materials and Methods: At one institution, a total of 429 men underwent two or more prostate biopsies from January 1993 to June 2003 for a total of 1026 biopsies. We retrospectively examined multiple factors including age, race, total number of biopsy cores, total number of previous negative biopsy cores, prostate specific antigen (PSA), PSA slope, digital rectal exam (DRE), and family history of prostate cancer. The presence of previous HGPIN and ASAP and Gleason score of positive biopsies were recorded from histopathology review. Clinical variables were compared between African-American (AA) and Caucasian men using the Wilcoxon rank sums test and Fisher's exact test. Cox proportional hazards model was used for the multivariate analysis.

Results: Of the 416 men, 216 (51.9%) were AA, 174 (41.8%) were Caucasian, and 26 (6.3%) were other races. The average number of biopsy sessions for AA and Caucasian men was 2.41 and 2.51 respectively. Cancer detection rates were 35.1% on the second biopsy, 34.6% on the third biopsy, and 32.0% on the fourth biopsy. Cancer was diagnosed in 43.5% of AA men compared to 25.9% of Caucasian men (p=0.0004). When clinical and pathological variables were compared between the racial groups, AA men had a significantly higher PSA (p=0.02). There was no statistically significant difference in age, total cores, number of previous negative cores, PSA slope, abnormal DRE, family history, and presence of previous HGPIN or ASAP. Multivariate analysis showed that race approached but did not achieve statistical significance as a predictor of prostate cancer on repeat biopsy (p=0.09). Previous HGPIN (p=0.0025), previous ASAP (p=0.0049), DRE (p=0.0076), and PSA slope (p=0.0005) were independent predictors of prostate cancer on repeat biopsy.

Conclusion: Previous HGPIN and ASAP, DRE, and PSA slope were independent predictors of prostate cancer on repeat biopsy. Race approached but did not reach significance after adjusting for disease features.
**Poster #13**

**LONG-TERM OUTCOMES FOLLOWING RADICAL PROSTATECTOMY IN MEN WITH CLINICAL T3 PROSTATE CANCER**

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**Introduction:** We evaluated patients at our institution who underwent radical prostatectomy for clinical stage T3 (cT3) prostate cancer to determine their long-term clinical outcomes.

**Materials and Methods:** We reviewed our radical prostatectomy database and identified 5182 men who underwent radical retropubic prostatectomy (RRP) from 1983 to 2003. Of these men, 176 were clinical stage T3 prior to RRP and constituted our study cohort. Clinical and pathologic data were reviewed and evaluated in a COX proportional hazards model to determine pre-operative predictors of biochemical recurrence. Clinical disease states were defined for patients with biochemical recurrence (BCR) and long-term follow-up was reported.

**Results:** Of the 176 patients with cT3 prostate cancer, 64 (36.4%) received neo-adjuvant hormonal therapy (NHT). The mean age of our patient population was 61.0 years and the mean pre-treatment serum prostate specific antigen (PSA) was 19.7 ng/dl. A biopsy Gleason score of <6, 7, >8 occurred in 47.2%, 38.1%, and 14.8% of patients respectively. Pathologic organ confined disease was found in 53 (30.1%) patients. Seminal vesicle invasion, extra-capsular extension and lymph node invasion was reported in 55 (33.5%), 107 (60.8%), and 33 (18.8%) patients respectively. At a mean follow-up time of 6.4 years, 92 (52.3%) of patients remained disease free with an actuarial 10-year freedom from recurrence of 44%. 84 (47.7%) patients had disease recurrence with a median time to BCR of 4.6 years. On multivariate analysis of pre-operative clinical parameters, biopsy Gleason score, pre-treatment serum PSA, and year of surgery were independent predictors for BCR.

**Conclusion:** Over half (52.3%) of our patients remained free of disease recurrence following radical prostatectomy. Neo-adjuvant hormonal therapy offered no advantage with respect to disease recurrence. Radical prostatectomy remains an integral component in the management of select patients with clinical stage T3 prostate cancer.

**Poster #14**

**GENE EXPRESSION / BIOCHEMICAL PATHWAY SIGNATURES OF PROSTATE CANCER CELLS OF PATIENTS WITH HIGH RISK AND MODERATE RISK PROGRESSION OF DISEASE**

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**Introduction:** The focus of the current study is to identify prostate cancer (CaP) associated gene expression signatures in specific cell types of the human prostate gland with a goal to carefully define the pathobiology of epithelial cell components in prostate tumorigenesis and cancer progression. Here we report the expression signature that has the potential to distinguish prostate cancer patients with moderate and high risk of progression.

**Methods:** Matched benign and malignant epithelial cells of the prostate tissues were obtained after radical prostatectomy. Using laser capture micro-dissected (LCM) epithelial cells from prostate glands of carefully selected CaP patients and Affymetrix U133A GeneChips, gene expression clusters predictive of high risk and moderate risk forms of the disease are being evaluated. We have completed the evaluations of the expression patterns in paired benign and cancer epithelial cells from two patient groups (9 patients per group), one with “high risk” CaP (PSA recurrence, Gleason score 8-9, seminal vesicle invasion, poorly differentiated tumor cells) and the other with “moderate risk” CaP (no PSA recurrence, Gleason score 6-7, no seminal vesicle invasion, well to moderately differentiated tumor cells). We have further enhanced bioinformatics analysis using Pathway Analysis software from Ingenuity, which uses a knowledge based network relation between the differentially expressed genes.

**Results:** We generated multidimensional scaling (MDS) plots using supervised analysis of nine tumor and normal pairs of samples from high risk CaP and nine pairs from moderate risk CaP. A subset of 200 genes were obtained which can serve as a classifier for our samples. Among the top ten genes were KINN, GNA13, HIPPI, SAP1, GBP1, SKIP (with a p-Value ranged from 0.00011 to 0.007579) that differ strongly between the high risk and moderate risk patients. In silico validation analysis for the predicted classifier was carried out using two independent data sets, which clearly separated samples from the patients of high risk and moderate risk of disease progression. By pathway analysis we have identified genes differentiating high risk and moderate risk groups from several different pathways. Genes associated with the apoptosis pathway like ATF3, BTG2, FOSB were significantly down regulated in HR group, whereas genes in cell proliferation pathway GRB10, NR3C1 were overexpressed in HR group.

**Conclusions:** Our study defines gene expression signatures in benign and malignant prostate tissues that have potential to distinguish CaP with moderate and high risk progression. Gene expression signatures of different biochemical pathways had their potential in: (1) delineating epithelial cell specific prognostic biomarkers and (2) identification of novel therapeutic targets for high risk CaP.
**Poster #15**

**EXPRESSION OF KIT IN HEREDITARY RENAL CELL CARCINOMA**

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**Background:** The c-kit proto-oncogene encodes a transmembrane receptor tyrosine kinase (KIT, CD117). After binding to its ligand, the stem cell factor (SCF), KIT plays an important role in cell survival, proliferation, and differentiation. Recent reports have postulated that KIT is overexpressed in specific types of Renal Cell Carcinoma (RCC). However, no studies have been performed in hereditary syndromes with predisposition to renal tumors, especially in Birt-Hogg-Dubé (BHD), where patients present with chromophobe RCC, oncocytomas, and hybrids tumors.

**Design:** 74 tumors from patients with hereditary and sporadic types of RCC were assessed for immunohistochemical expression of KIT. The hereditary conditions included: BHD, von Hippel-Lindau (VHL), Hereditary Papillary RCC (HPRCC), and Hereditary Leiomyomatosis and RCC (HLRCC). Distribution pattern and intensity were recorded.

**Results:** Chromophobe RCC (7 cases) in both, hereditary and sporadic cases, showed strong membranous overexpression of KIT. Hybrid tumors (12 cases) displayed a complex expression pattern in which the more eosiinophilic cells were strongly positive whereas the pale cells were negative or weakly positive. Sporadic oncocytomas (7 cases) were strongly positive for KIT. One sporadic type 2 PRCC was focally positive. There were 3 (33%) clear cell RCC focally positive for KIT. Morphologic re-evaluation showed chromophobe areas in all these clear cell tumors. Clear cell RCC in the setting of BHD (3 cases) were all negative. All other tumors analyzed: VHL – Clear cell RCC (6), HPRCC – Type 1 PRCC (4), HLRCC (12), sporadic Type 1 PRCC (4), sporadic Type 2 PRCC (2), sporadic Clear cell RCC (9), sporadic clear cell RCC with sarcomatoid features (6), collecting duct carcinoma (2), multicystic RCC (3), and metanephric adenoma (1), were negative.

**Conclusion:** KIT is overexpressed in chromophobe RCC and oncocytomas in both sporadic and familiar settings. Hybrid tumors, which display a characteristic chromophobe/oncocytoma mixed morphology, and are almost exclusive of the BHD syndrome, were positive for KIT. They display an intermediate immunostain pattern, which add more evidence to the postulated common pathogenesis of chromophobe RCC and oncocytomas. Clear cell RCCs, even in BHD patients, were always negative. It seems that a focal KIT expression in clear cell RCC is related to areas of chromophobe morphology and therefore may assist in recognizing chromophobe RCC. The overexpression of KIT in a subset of benign and malignant renal tumors which are present in a background of a genetic condition (BHD) could imply that KIT overexpression is not directly related to malignant phenotype in these tumors.

**Poster #16**

**FLUORESCENT MICROSATellite ANALYSIS (MSA) IDENTIFIES D3D2447 AS A NEW SEMINOMA SPECIFIC MARKER**

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**Introduction:** Molecular events triggering the malignant transformation of primordial germ cell to testicular intraepithelial neoplasia and being involved in the progression of TIN to locally invasive GCT are still unknown. Amplification of the chromosomal subregion 12p11.2-p12.1 represents a characteristic finding in >90% of all CT, but no specific genes have been identified. Purpose of our study was to identify new chromosomal regions potentially being involved in the pathogenesis of GCT.

**Materials and Methods:** Fresh specimen of tumour and normal parenchyma were collected in 44 TGCT and 10 healthy controls. DNA was extracted by phenol-chloroform method from both tissue and blood samples. For MSA, 21 polymorphic markers on 9 chromosomal arms were analysed. Following PCR amplification detection of allelic imbalance (AI), LOH, deletion, amplification (AMP) was carried out using an automated laser sequencer. With regard to 12p11.2-p12.1 the encoded genes SOX5, JAW1 and K-ras were analysed by RT-PCR and Southern Blot.

**Results:** No DNA alterations were detected in normal tissue samples of controls; at least 1 molecular event (LOH, AI, AMP) was identified in 41/44 (93.2% of TGCT. Most frequently tumour associated LOH/AI were detected for D1S1656 (41%), D2S2447 (42%), D9S1748 (53%), D11S1978 (42%), D17S799 (37%). Alterations for D3S2447 were only demonstrated in seminomas and associated TIN but not in nonseminomas; amplification of D17S799 were only detected in seminomas. SOX5, JAW1 and K-ras did not demonstrate TGCT-specific alterations.

**Conclusions:** For the first time, D3S2447 was identified as a new seminoma specific chromosomal marker. D3S2447 encodes for the DAZL-1 gene and the expression of the protein product has also only been found in seminomas. The seminoma specific amplification of D17S799 might contribute to the progression of TIN into locally invasive seminomas. JAW1, SOX5 and K-ras are not involved in the pathogenesis of TGCT. Grant of Kempkes Stiftung Marburg, Germany.
**Poster #17**

PROSTATE SPECIFIC ANTIGEN TESTING IN MEN OVER 75  

**Introduction and Objective:** Current guidelines for prostate cancer (CaP) screening recommend testing prostate specific antigen (PSA) in men between the ages of 50 and 75 who have at least a ten year life expectancy. Patient-reported PSA testing rates among elderly men exceed 30%. The objective of this study was to examine physician-reported PSA testing of elderly men.

**Methods:** National estimates of PSA tests were generated using data from the 2002 National Ambulatory Medical Care Survey (NAMCS). The NAMCS is a national probability sample of office-based visits. There were a total of 28,738 records from 3,150 participating physicians in the 2002 sample. Data from these records were weighted to produce national estimates. To identify PSA tests for prostate cancer screening, men with diagnoses of prostate cancer and men under age 40 were excluded. Visits to urologists, primary care physicians, and internal medicine specialists were considered eligible visits. National estimates of PSA tests were generated using SAS version 8.2, and PSA testing rates per eligible visit were calculated. Estimates were compared with the z test to account for standard error.

**Results:** An estimated 12,477,887 PSA tests for CaP screening were performed in 2002. Of these, 1,870,898 (15.0%) were performed on men over 75, representing a population-adjusted rate of 34.4%. Physicians performed an estimated 1,086,190 (8.7% of total) tests in men 79 or older, representing a population rate of 29.9%. Urologists accounted for 30.3% of PSA tests in men over 75. While testing rates by urologists decreased with patient age, almost one in four visits by men 79 or older resulted in a PSA test (364,556 tests, 23.6% of visits).

**Conclusions:** This study demonstrates a population PSA testing rate in excess of 30% in men over 75. The results of the present study are important, as these PSA tests are physician reported, rather than patient reported. Further investigation is required to determine what patient and physician factors drive PSA testing in elderly men.

**Poster #18**

CHARACTERIZATION OF DIFFERENTIAL FUNCTION OF HYPOXIA INDUCIBLE FACTOR 1 AND 2 ALPHA IN CLEAR CELL RENAL CORTICAL TUMORIGENESIS  
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**Purpose:** The role of hypoxia inducible factor (HIF) class of transcription factors has been implicated to be a critical step in clear cell kidney tumorigenesis. This report characterizes the possible differential function of HIF-1 alpha and HIF-2 alpha in clear cell kidney tumorigenesis.

**Experimental Design:** Nascent renal tumors of distinct histology from von Hippel Lindau syndrome patients were characterized for HIF expression using high amplification immunohistochemistry and light microscopy. In addition, indirect immunofluorescence and confocal microscopy was used for subcellular localization of HIF-1 alpha and 2 alpha in clear cell renal carcinoma cells. Biochemical profile HIF-1 alpha and HIF-2 alpha structure is characterized with respect to protein processing and stability in clear cell renal carcinoma cells.

**Results:** Clear cell RCC tumors from von Hippel Lindau patients strongly express both HIF-1 alpha (10/12 tumors) and HIF-2 alpha (12/12 tumors). Distinct subcellular localization of HIF-1 and 2 alpha is demonstrated in nascent clear cell RCC tumors. This was further confirmed in clear cell RCC cells using immunofluorescence and confocal microscopy. Differential HIF-1 and 2 alpha stability / protein processing is demonstrable using heat shock protein 90 inhibitors.

**Conclusions:** Consistent simultaneous expression of both HIF-1 alpha and HIF-2 alpha appears to be specific to VHL negative clear cell RCC. Differential function of HIF-1 alpha vs HIF-2 alpha is suggested by the distinct subcellular localization pattern and differing biochemical profiles of HIF-1 and 2 alpha in clear cell renal carcinoma cells.
Poster #19
LOCAL AND SYSTEMIC CYTOSTATIC EFFECTS OF 17-(DIMETHYLAMINOETHYLAMINO)-17-DEMETHOXYGELDANAMYCIN IN A XENOGRAFT BLADDER TUMOR MODEL
Christopher R. Williams, Len Neckers, Ray Tabios, W. Marston Linehan, and Jonathan Coleman
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Introduction: We proposed that local administration of 17DMAG, a water-soluble hsp90 inhibitor, may be as effective as systemic delivery, allowing for higher intratumoral drug concentration with less side-effects.

Methods: Two separate experiments were conducted in a murine xenograft model using two high-grade human bladder cancer cell lines (Bandit and a T24 subclone). Subcutaneously implanted tumors grew to an average size of 549 mm$^3$ in the T24 groups and 1044 mm$^3$ in the Bandit group before treatment was initiated. Pre-treatment T24 and Bandit tumor growth rates averaged 17 and 34 mm$^3$/day, respectively. Animals received intraperitoneal 17DMAG at 15 mg/kg (low-dose) and 30 mg/kg (high-dose) every four days in the T24 study. In the Bandit study, the intratumoral dose of 100 mg/kg twice a week for two weeks was decreased to 50 mg/kg, thereafter. Control animals received phosphate-buffered saline. Upon treatment cessation, tumor growth characteristics were measured to a size endpoint.

Results obtained: A dose-dependent cytostatic response was seen in both studies while control animals demonstrated no change in tumor growth rates. The average tumor sizes upon cessation of treatment were 589, 773, and 851 mm$^3$ in the high and low-dose T24 and high-dose Bandit groups, respectively. During treatment, tumor growth averaged 3, 8, and 7 mm$^3$/day in the high and low-dose T24 and high-dose Bandit groups, respectively. Stopping T24 group therapy and halving the Bandit intratumoral dose resulted in growth rates exceeding pre-treatment and control rates (94, 123, and 127 mm$^3$/day in the high and low-dose T24 and Bandit groups, respectively). In addition, diarrhea requiring supplemental hydration occurred in the majority of the systemic group only, despite apparent poorer initial health in the intratumoral group, presumed due to large tumor burden.

Conclusions: These preliminary findings suggest the effects of 17DMAG are largely dose-dependent and cytostatic in this bladder cancer model. Intratumoral administration allows for optimization of effect via higher achievable dosing, without systemic side effects. These data support current Phase I clinical testing of 17DMAG for solid malignancies and suggest interstitial administration may be as effective as systemic therapy for localized disease.

Poster #20
CLINICAL OUTCOMES OF PATIENTS DOWNSTAGED AT RADICAL CYSTECTOMY
Craig G. Rogers, Patrick J. Bastian, Ganesh S. Palapattu, Bruce J. Trock, Mark P. Schoenberg, and Theresa Chan

Objectives: We present the clinical outcomes of patients with bladder cancer (BCA) who were downstaged from muscle invasion at transurethral resection (TUR) to nonmuscle invasive disease following radical cystectomy.

Methods: We retrospectively reviewed the records of 248 consecutive patients who underwent radical cystectomy for urothelial carcinoma (TCC) at our institution between 1994 and 2002. Of these patients, 112 (45%) had documented muscle-invasive disease by TUR prior to radical cystectomy.

Results: Of the 112 patients with muscle-invasive disease by TUR, 25 (22.3%) were downstaged to nonmuscle-invasive disease (pT1 or less) at cystectomy, whereas 87 (77.7%) had persistent muscle-invasive disease (pT2 or greater) at cystectomy. Recurrence occurred in 4 (16.0%) downstaged patients compared to 29 (33.3%) non-downstaged patients ($p=0.094$). Kaplan Meier analysis demonstrated a statistically significant improvement in recurrence-free survival with downstaging (Log rank $p=0.02$) Multivariate analysis demonstrated a 3-fold reduction in recurrence risk with tumor downstaging (HR=0.33, 95% CI: 0.10-1.12) with a trend towards statistical significance ($p=0.075$).

Conclusions: After adjusting for the effect of positive lymph nodes, patients who are downstaged from muscle-invasive TCC on TUR to non-muscle invasive TCC on radical cystectomy may have a reduced risk of disease recurrence compared to patients with persistent muscle-invasive disease on cystectomy.
**Poster #21**

**TRANRECTAL ULTRASOUND VERSUS MAGNETIC RESONANCE IMAGING FOR DETECTION OF RECTAL WALL INVASION BY PROSTATE CANCER**

Dan Leibovici, MD, Ashish Kamat, MD, Kim Do, PhD, Curtis Pettaway, MD, Chuan Ng, MD, Robert Evans, PA-C, Miguel Rodriguez-Bigas, MD, John Skibber, MD, Xuemei Wang, MS and Louis Pisters, MD (Presented By: D Leibovici, MD)

**BACKGROUND:** We compared the accuracy of transrectal ultrasound (TRUS) with that of magnetic resonance imaging (MRI) in detection of rectal wall involvement (RWI) by prostate cancer in patients undergoing salvage total pelvic exenteration (TPE) or cystoprostatectomy.

**METHODS:** 16 patients underwent TPE and 24 patients underwent cystoprostatectomy for locally advanced prostate cancer as salvage palliative procedures. Patients were examined by TRUS, MRI or both within the month preceding surgery. The gold standard diagnostic criterion for RWI was histological examination of the rectum in patients undergoing TPE, and a combination of posterior prostatic surgical margins and clinical evidence of rectal wall recurrence during a median follow-up duration of 18.6 months, for patients undergoing cystoprostatectomy. The sensitivity, specificity and overall accuracy with which TRUS and MRI detected RWI were compared.

**RESULTS:** 15 (93.7%) of the patients who underwent TPE had histologically proven RWI. Rectal and perineal recurrence developed 10 months after surgery in 1 patient (4.1%) in the cystoprostatectomy group. The sensitivity, specificity, and overall accuracy of TRUS were: 92.9% (66.1-99.8); 87.0% (66.4-97.2), and 89.2% (74.6-97.0), respectively. The sensitivity, specificity, and overall accuracy of MRI were: 54.6% (23.4-83.3); 100% (76.8-100.0), and 80% (59.3-93.2), respectively.

**CONCLUSION:** TRUS is a highly sensitive diagnostic modality for RWI in patients with locally advanced prostate cancer. Although MRI is very specific, it cannot reliably rule out RWI in the presence of a positive TRUS.

**Poster #22**

**NEUTRAL ENDOPEPTIDASE GENE THERAPY FOR PROSTATE CANCER**

David Y T Chen*, Ruqian Shen, Oscar B Goodman, Jr, Daniel Navarro, New York, NY; Hanjun Guan, Louis B Hersh, Lexington, KY; David M Nanus, New York, NY

**INTRODUCTION AND OBJECTIVE:** Neuropeptides such as endothelin-1 and bombesin have been implicated in prostate cancer (PC) progression. Neutral endopeptidase (NEP) is a cell-surface protein that normally inactivates these neuropeptides. In early primary PCs, NEP expression is lost in ~50% of cases, and it is absent in the majority of androgen-independent PCs. Re-expressing NEP in NEP deficient PC cells can inhibit cell growth in vitro and tumor formation in vivo. We developed a strategy to express NEP in NEP deficient PC cells using lentiviral vectors. We report our findings confirming the feasibility of this approach and further evidence for NEP tumor suppressor activity in vivo.

**METHODS:** Third generation lentiviral vectors that express wildtype NEP (L-NEP) as well as a catalytically inactive mutant, NEPx (L-NEPx) have been generated (Marr et al J Neurosci 2003). We assessed the transduction efficiency of PC cells using L-NEP, L-NEPx, and L-GFP, a control vector that expresses green fluorescent protein (GFP). In transduced PC cell lines PC3 and DU145, protein expression was measured from cell lysates by western blotting and NEP enzyme activity, and from intact cells by fluorescence activated cell sorter (FACS) analysis. Growth of transduced PC cells was measured by proliferation assay. Transduced PC cells were used to establish xenografts in immunodeficient mice, and in vivo tumor growth was determined.

**RESULTS:** We found efficient transduction of PC cells by all lentiviral vectors. NEP or NEPx was expressed in roughly 50% or more of PC cells transduced by L-NEP or L-NEPx at a multiplicity of infection (MOI) > 10. GFP was similarly expressed at a MOI > 3. NEP, NEPx and GFP were detectable in transduced PC cells by western blot and FACS. NEP enzyme activity was measurable only in PC cells transduced by L-NEP. NEP, NEPx or GFP expression showed no effect on in vitro PC cell growth. NEP but not NEPx or GFP expression inhibited growth of DU145 PC xenografts in immunodeficient mice.

**CONCLUSIONS:** Lentivirus vectors allow introduction of genes into a wide range of tissue types and have been safely used in vivo. We demonstrate efficient transduction of PC cells by NEP or NEPx expressing lentiviral vectors, and show reduced tumor growth of NEP expressing PC cells in an in vivo xenograft model. These findings support further investigation of NEP gene therapy as a potential therapy for advanced PC.
Poster #23

RENAL MASS MALIGNANCY IS PREDICTED BY MASS SIZE: AN EIGHT-YEAR EXPERIENCE
Deborah Glassman, Jim Johannes, Dolores Byrne, Stephen Strup, Leonard Gomella.

INTRODUCTION: As an increasing proportion of renal masses are discovered incidentally, it is crucial to identify which masses are more likely to represent malignant processes requiring more aggressive treatment. The purpose of this study is to evaluate the frequency of malignant disease in renal masses based on size and to determine the predictive value of size to final histopathology.

METHODS: We performed a retrospective review of radical nephrectomy, partial nephrectomy and nephroureterectomy performed between 1998-2004. We categorized lesions by size, based on pathologic reports, using the 1997 TNM staging system. When available, radiographic sizing was used as well. Chi square test was performed to assess statistical significance with p < 0.01 as a significant value.

RESULTS: 412 patients underwent surgical treatment for 466 renal lesions. 106 cases were excluded leaving 360 evaluable renal parenchymal masses. 284 (79.5%) of the renal lesions were malignant. 97.8% (n=278) of the malignant lesions were renal cell carcinoma (RCC) with clear cell carcinoma being the most predominant subtype (60.9%). 199 lesions were < 4 cm in size, 107 were 4-7 cm and 54 > 7 cm. 72.4% of lesions < 4cm (n=144) were malignant and 27.6% were benign. Of lesions 4-7 cm, 92 (86%) were malignant. Finally, of 54 lesions > 7 cm in diameter, 48 (88.9%) were malignant.

CONCLUSIONS: The overall malignancy rate of 78.8% is consistent with previously published series (1, 2). Additionally, our data suggests that lesions < 4cm in greatest diameter have a significantly lower rate of malignancy (p=0.0031) than those greater than 4cm. Recent evidence suggests that renal tumors less than 4cm may be safely monitored with careful observation (3). Our data suggests that more than one in five patients may have benign that can be treated expectantly and thus spared surgery.


Poster #24

VARIANTS OF SEMAPHORIN 3F ARE ASSOCIATED WITH PROSTATE CANCER PROGNOSIS
Edith D. Canby-Hagino, Ivana Balic, Xin He, RuiHua Xiang, Dawn Garcia, Jacques Baillargeon, Dean A. Troyer, Brad H. Pollock, Javier Hernandez, Ian M. Thompson, Robin J. Leach, Susan L. Naylor University of Texas Health Science Center, San Antonio, Texas

Introduction: Semaphorins 3B and 3F (SEMA3B) and SEMA3F are two closely related genes on chromosome 3 that have been shown to suppress tumor formation in vivo and in vitro. We examined four single nucleotide polymorphisms in this region in a case-control study comprised of 527 prostate cancer (CaP) cases and 1558 matched controls to determine CaP risk and prognosis (as indicated by Gleason grade) associated with SEMA3B and SEMA3F.

Methods: We identified and genotyped 337 cases and 855 controls for Caucasian men of non-Hispanic origin, 138 cases and 427 controls for Caucasian men of Hispanic origin, 39 cases and 276 controls for African Americans. The loci of interest were SEMA3F 5’end, SEMA3F rs2073726, SEMA3F rs10005678, and SEMA3B C1844241. Controls were limited to individuals with a normal prostate examination and a prostate specific antigen < 2.5 ng/ml.

Results: In the total study population, the CC genotype of SEMA3F 5’end showed a tendency towards increased odds for CaP risk. The odds ratio for the total population was 1.785 (95%CI 0.917-3.473). The odds ratio for the Hispanic population was 1.759 (95%CI 0.868-3.567). The most striking association for this marker was with Gleason scores ≥ 7. For patients diagnosed with CaP, the CC genotype was associated with a 3.9-fold increased risk of Gleason score ≥ 7 (OR=3.929, 95%CI 1.141-13.527). The association of the CC genotype with high-grade cancers was especially pronounced among Hispanics with CaP (OR=4.190, 95%CI 1.186-14.809). The presence of any A allele in SEMA3F rs2073726 was also associated with Gleason score ≥ 7 in non-Hispanic Caucasians (OR=3.773,95% CI 1.716-8.298).

Conclusions: Polymorphisms in SEMA3F are associated with prostate cancers of worse prognosis (as indicated by Gleason score ≥ 7).
POSTER #25
PARTIAL ADRENALECTOMY: THE NATIONAL CANCER INSTITUTE EXPERIENCE
Eric K. Diner, Michael E. Franks, Ashish Behari, W. Marston Linehan and McCellan M. Walther. Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda MD

Purpose: Total adrenalectomy has been used largely in the treatment of patients with hereditary adrenal pheochromocytomas. Adrenal cortical sparing surgery is an alternative approach that aims to balance tumor removal with preservation of adrenocortical function. We report our experience of partial adrenalectomies and demonstrate whether adrenal function can be preserved in these patients.

Materials and Methods: From 1995 to 2004, 33 patients with hereditary pheochromocytomas or metastatic renal cell carcinoma (mRCC) presented with adrenal masses. Partial adrenalectomy (open or laparoscopic) was performed if there was evidence of normal adrenocortical tissue on preoperative imaging or by intraoperative ultrasonography. Various operative parameters as well as postoperative function of residual adrenal remnants were determined.

Results: Eight patients underwent open partial adrenalectomy and 25 patients underwent laparoscopic partial adrenalectomy over a 10-year period. Ten patients had simultaneous, bilateral partial adrenalectomy. Eight patients had operations on a solitary adrenal gland and four of these patients received post-operative steroid replacement (stopped in three patients after 1-3 months). All other patients have normal catecholamine levels and remain tumor free by imaging with a mean follow up of 36 months (3-102).

Conclusions: Partial adrenalectomy can preserve adrenal function in patients with adrenal masses. Laparoscopic approach is technically safe and associated with less morbidity without compromising tumor removal. With careful surgical planning, especially in patients with tumors in solitary glands, adrenocortical function may be preserved thereby avoiding the morbidity associated with medical adrenal replacement.

Poster #26
EFFICACY OF COMBINING SELECTIVE ESTROGEN RECEPTOR MODULATORS AND CASODEX™ IN ANDROGEN-DEPENDENT PROSTATE CANCER CELLS
Melissa M. Walls, MD, Asim Abdel-Mageed, DVM, PhD, Rodney Davis, MD, and Erik P. Castle, MD

Introduction: Casodex™ has been shown to inhibit cell growth in androgen dependent cell lines. Raloxifene (Sigma) and tamoxifen(Sigma) are selective estrogen receptor modulators (SERMs) that have been shown to affect cellular biology of prostate cancer cell lines. We compared the growth inhibitory effects of combining Casodex™ with each of these SERMs to those of Casodex™ alone in an LNCaP cell line.

Materials and Methods: LNCaP cells were cultured in a T-medium (GIBCO) supplemented with 10% fetal bovine serum (FBS), streptomycin and ampicillin and were incubated at 37°C in an incubator. Cells were diluted to 1,000 cells per well in 200μL of medium and divided into 4 groups. Group A was treated with the vehicle, DMSO, alone and served as the controls. Group B was treated with Casodex™ alone at three different concentrations (10μM, 50μM, 100μM). Group C was treated with tamoxifen (1μM, 5μM, 10μM) and Casodex™ using all nine possible concentration combinations of both drugs. Group D was treated with raloxifene (1nM, 1μM, 100μM) and Casodex™ in similar fashion. Cell proliferation and growth inhibition was measured with a Cell Counting Kit (CCK-8) employing a highly water soluble salt (WST-8). A spectrometer was then used to measure absorbance at 450 nm.

Results: Casodex™ inhibited LNCaP cellular proliferation by 33%, 33% and 60% at concentrations of 10μM, 50μM, 100μM respectively (Fig. 1). Cellular proliferation was increasingly inhibited in a dose-dependent fashion when tamoxifen was added to the Casodex™ treatment. Proliferation was inhibited up to 80% when combining the highest dose of Casodex with the higher doses of tamoxifen (Fig. 2). Enhanced growth arrest was also seen when Casodex™ treatment was combined with raloxifene. Even at the lowest dose of Casodex™, 10μM, the addition of raloxifene inhibited proliferation by 66%, 70% and 80% at 1nM, 1μM and 10μM, respectively (Fig 3). Maximal inhibition for both treatment combinations was 80% while the maximal inhibition of Casodex™ alone was 60% at the highest dose.

Conclusions: Casodex™ inhibition of LNCaP cellular proliferation is enhanced by the addition of raloxifene or tamoxifen. Raloxifene had a greater effect at lower concentrations than tamoxifen. Lower doses of Casodex™ were required to significantly inhibit LNCaP cells even at nanomolar concentrations of raloxifene. The mechanism of these findings is still unknown and should be investigated further.
**Poster #27**

**THE IMPACT OF PERFORMING CONCOMITANT LYMPHADENECTOMY DURING ROBOTIC RADICAL PROSTATECTOMY**

Fatih Atug, MD, Scott V. Burgess, MD, Jon R. Glass, MD, Rodney Davis, MD, Raju Thomas, MD, and Erik P. Castle, MD

**Introduction:** Robotic radical prostatectomies continue to be performed across the country in increasing numbers. Often lymphadenectomy (LAD) is not performed in the setting of low stage disease. Herein we compare the effects of performing concomitant obturator lymphadenectomy on several surgical variables.

**Materials and methods:** A total of 50 robotic radical prostatectomies were performed at our institution. The last 20 cases were selected for this analysis. Variables including operative time, length of hospital stay (LOS), estimated blood loss (EBL) and cost were evaluated.

**Results:**

<table>
<thead>
<tr>
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<th>OR Time (min)</th>
<th>LOS (days)</th>
<th>EBL (ml)</th>
<th>OR charges (dollars)</th>
<th>Hospital charges (dollars)</th>
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<tr>
<td><strong>LAD +</strong></td>
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<td>Mean</td>
<td>270.8 (192-442)</td>
<td>1.1 (1-3)</td>
<td>315 (150-500)</td>
<td>23,343 (18,595-33,368)</td>
<td>39,564 (28,266-42,200)</td>
</tr>
<tr>
<td>Median</td>
<td>259.5 (192-442)</td>
<td>1 (1-3)</td>
<td>275 (150-500)</td>
<td>21,952 (18,595-33,368)</td>
<td>34,557 (28,266-42,200)</td>
</tr>
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<td><strong>LAD -</strong></td>
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<tr>
<td>Mean</td>
<td>236.8 (165-361)</td>
<td>1.4 (1-6)</td>
<td>316.8 (110-750)</td>
<td>23,687 (17,367-36,856)</td>
<td>37,677 (25,821-40,837)</td>
</tr>
<tr>
<td>Median</td>
<td>223.5 (165-361)</td>
<td>1 (1-6)</td>
<td>300 (110-750)</td>
<td>22,840 (17,367-36,856)</td>
<td>34,275 (25,821-40,837)</td>
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Discussion: There were no significant differences in LOS, EBL, OR charges or hospital charges. The only significant difference seen was in operative time. Mean and median operative times were longer by 14.4% and 16.1% respectively when LAD was performed (Table 1). These last 20 cases were after we had overcome our learning curve and should be taken into consideration. There were no unique or additional complications when performing LAD.

Conclusion: Once the learning curve is overcome, there is no significant impact of concomitant lymphadenectomy on LOS, EBL, and charges when robotic radical prostatectomy is performed. As expected, operative times will be slightly longer, but is not unusual as an additional procedure is being performed.

**Poster #28**

**INFLUENCE OF AGE ON RESPONSE TO INTRAVESICAL IMMUNOTHERAPY**

Fadi N. Joudi, Badrinath R. Konety, Michael A. O'Donnell

**Objective:** Determine age related differences in response to intravesical immunotherapy in patients with superficial bladder cancer.

**Methods:** Data from the National Phase II multicenter trial of intravesical BCG + interferon-alpha (IFN) for superficial bladder cancer were analyzed. Recurrence free survival at 2 years post initiation of therapy was examined in patients by incremental decade of age. BCG naïve patients received 81mg BCG and 50 million units IFN, while patients who were previously treated with BCG received 1/3 the BCG dose with 50 million units IFN, and those who were BCG intolerant received 1/10 BCG dose with 100 million units IFN. Age groups analyzed were <50, 51-60, 61-70, 71-80, and >80 yrs. Kaplan Meier survival curves were calculated.

**Results:** Overall, patients in the 61-70 year age group had the highest response rate of 61% recurrence-free survival at 2 years follow-up. The most substantial difference in response rate was between patients 61-70 years of age (n=289) and patients >80 years of age (n=123). The difference in cancer-free survival at a median follow-up of 23 months was 22% (61% for patients 61-70 years vs. 39% for patients >80 yrs, p = 0.0002). Response rates for the other groups were: 45% (<50 yrs), 59% (51-60yrs), 49% (71-80 yrs). Patients older than 80 years had a 74% lower likelihood of response to intravesical therapy with BCG + IFN. Patients <50 years represented the smallest group (n=58) and had a lower response rate of 45%, which was still appreciably higher than that of the oldest patients. These differences persisted even after stratifying for prior BCG treatment status.

Conclusion: Very elderly patients with superficial bladder cancer have a decreased response to intravesical immunotherapy. One potential explanation for the decreased response rates to intravesical BCG+IFN therapy observed in elderly patients could be their depressed baseline immune status and consequent inability to mount an immune reaction to BCG or IFN.
**Poster #29**

THE ASSOCIATION OF PREOPERATIVE SERUM CELL-FREE DNA CONTENT AND PSA RECURRENCE FOLLOWING RADICAL PROSTATECTOMY  
Ganesh Palapattu, MD, Patrick Bastian, MD, Craig Rogers, MD, Xiaohui Lin, PhD, Yegnasubramanian Srinivasan, BS, Mangold Leslie, MS, Trock Bruce, PhD, Alan Partin, MD, PhD and William Nelson, MD, PhD

**Introduction:** We evaluated the association of preoperative serum cell-free DNA content in men with clinically localized prostate cancer who underwent radical prostatectomy with PSA recurrence.  

**Methods:** One hundred and ninety-two men with clinically localized prostate cancer, who underwent radical prostatectomy at the Johns Hopkins Hospital and had preoperative serum available for analyses constituted our study population. All serum samples were collected prior to prostate biopsy. DNA was isolated from 600μl of serum with the Qiagen Blood Mini Kit (Valencia, CA). Quantitative PCR was performed with primers flanking the promoter region of the GSTP1 gene. A 10-fold dilution series of known DNA concentrations was used to generate a standard curve (100ng to 0.001ng). The total amount of DNA from each sample was calculated using this standard curve. PSA recurrence was defined as a single postoperative PSA level of ≥0.2. The natural logarithm (ln) of the DNA concentration was used for statistical analyses.  

**Results:** Of the 192 men in our study, 56 (29%) experienced PSA recurrence within the study period (median time to PSA recurrence 2 yrs). The median follow-up time for men free of disease at last follow-up was 3 yrs. The median cell-free DNA concentration of all men in the study was 5.3 ng/ml (range 0.2-320 ng/ml). The mean serum DNA concentration for men who recurred and for those who did not was 29.5 + 34.1 ng/ml and 13.1 ± 33.6 ng/ml, respectively (t-test, p=0.007). In a univariate analysis, ln DNA concentration was significantly associated with PSA recurrence, HR 1.49 [95% CI (1.3-1.8)], p<0.001. In a multivariate model that accounted for established prognostic factors, ln DNA concentration was significantly associated with PSA recurrence, HR 1.3 [95% CI (1.1-1.6)], p=0.13.  

**Conclusion:** Our study suggests that preoperative serum cell-free DNA content may be a useful prognostic biomarker for prostate cancer in men with clinically localized disease.

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**Poster #30**

IMPACT OF LYMPH NODE DENSITY ON BLADDER CANCER SURVIVAL OUTCOMES: A COOPERATIVE GROUP REPORT  
Raj GV, Herr HW and the bladder cooperative group. Memorial Sloan-Kettering Cancer Center, New York, NY USA

**Purpose:** A randomized cooperative group trial (Southwest Oncology Group 8710, intergroup 0080) reported increased survival of patients treated with neoadjuvant chemotherapy for locally advanced bladder cancer. In another study, Lymph node density has been also been shown to influence survival. Herein, we decided to evaluate the effect of neoadjuvant chemotherapy on lymph node density and their correlation with bladder cancer outcomes.  

**Materials and Methods:** Of the 266 patients with evaluable lymph node numbers, half the patients received neoadjuvant MVAC chemotherapy. The median follow-up time was 8.4 years. Surgical and pathological variables were available for all patients. Lymph node density (LND) is calculated as the percentage of positive nodes in the total number of nodes and the cutoff of 20% proposed by Herr and Stein was used. Variables were tested in univariate and multivariate analyses for associations with post-cystectomy survival (PCS) and local recurrence.  

**Results:** Among 137 patients undergoing radical cystectomy alone, 92 (67%) had pathologically negative nodes, 18 (13%) had positive lymph nodes with LND <20%, and 27 (20%) had LND >20%. In contrast, of the 129 patients undergoing radical cystectomy after neoadjuvant MVAC, 106 (82%) had negative nodes, 15 (12%) had LND <20%, and 8 (6%) had LND >20%. The difference in the distribution of patients was statistically significant (P<0.001). Kaplan-Meier analyses for the entire cohort reveal a LND <20% confers comparable survival (62%) to patients with negative nodes (65%) but significantly improved survival over patients with LND >20% (7%) (p<0.001). Survival outcomes associated with LND >20% are not influenced by neoadjuvant chemotherapy (p>0.5). In multivariate analyses, pathological stage >P2 (Hazard ratio (HR) 2.89, p<0.001), neoadjuvant chemotherapy (HR 0.537, p<0.001), number of lymph nodes >10 (HR 0.41, p<0.001), and LND >20% (HR 1.94, p=0.011), were significantly associated with post-cystectomy survival.  

**Conclusions:** LND >20% is associated with a significantly worse post-cystectomy survival prognosis in comparison to LND <20%. Interestingly, we find that neoadjuvant chemotherapy significantly reduces the number of patients with a higher LND, pathologically downstaging these patients into a more favorable outcome category. These data further support the use of neoadjuvant chemotherapy prior to radical cystectomy for patients with locally advanced bladder cancer.
Poster #31

THE EFFECT OF ADJUVANT HORMONAL THERAPY AFTER RADICAL PROSTATECTOMY FOR PT3B PROSTATE CANCER
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Introduction and Objective: Adjuvant hormonal therapy (AHT) should be offered to those patients at highest risk for recurrence. A retrospective non-randomized cohort comparison of adjuvant hormonal therapy was evaluated in patients with pT3b disease to determine the impact on outcome after radical retropubic prostatectomy (RRP).

Methods: We evaluated patients, who underwent RRP from 1987 to 2000, had lymph node negative disease and no pre-operative treatment. Patients with immediate post-op radiation were excluded. Of 800 patients in this study, 211 (26%) received AHT within 90 days of RRP. Mean age at surgery and median follow-up were 66 and 8.4 years respectively. Biochemical failure was defined by a single PSA >= 0.4 after surgery. The Kaplan-Meier method was used to estimate event-free rates, while the Cox model was used to estimate hazard ratios and to adjust for clinical characteristics.

Results: Patients with AHT had significantly worse clinical and pathologic characteristics. AHT led to significantly better progression-free survival (60% +/- 4% vs. 23% +/- 2% at 10 years, p = .0001) and cancer specific survival (97% +/- 2% vs. 90% +/-2% at 10 years, p = .036). The effect of AHT remained significant after adjusting for Gleason score, pre-operative PSA, surgical margin status, and DNA ploidy (hazard ratio [HR]=0.24, 95% confidence interval [CI]= 0.18-0.31, p = .0001). Similar effects were seen for clinical progression (HR=0.33, CI=0.21-0.54, p < .0001), systemic progression (HR=0.38, CI=0.20-0.71, p = .002) and prostate cancer death (HR=0.36, CI=0.14-0.94, p = .036).

Conclusions: This retrospective, non-randomized study suggests that early AHT provides improved outcome after RRP in patients with seminal vesicle positive prostate cancer including improved cancer specific survival.

Poster #32

NEOADJUVANT DOCETAXEL AND ESTRAMUSTINE FOLLOWED BY RADICAL PROSTATECTOMY OR RADIATION THERAPY FOR PATIENTS WITH HIGH-RISK PROSTATE CANCER
H Stefaniak, E Wallen, M Baggstrom, P Godley, L Goyal, Y Whang, J Rosenmann, R Pruthi and the Multidisciplinary Genitourinary Oncology Study Group. UNC-Chapel Hill School of Medicine, Chapel Hill, North Carolina.

Introduction: After surgery or radiation as primary therapy, biochemical failure and clinical progression rates are high for patients with high-risk localized adenocarcinoma of the prostate. There may be a role for neoadjuvant chemotherapy in these patients. We evaluated the efficacy and safety of neoadjuvant docetaxel (D) and estramustine (E) followed by either radical prostatectomy (RP) or radiation therapy (XRT).

Methods: Patients eligible for this phase II trial possessed any of the following: Clinical stage T3, clinical stage T1 or T2 and biopsy Gleason score > 8, or biopsy Gleason score of 7 and PSA > 10 ng/mL. Three cycles of D (36 mg/m^2) days 2, 9, & 16 and E (140 mg TID) on days 1-3 q28 days were administered followed by either XRT or RP. Warfarin (2 mg) was given to all patients during chemotherapy. Patients electing XRT also received concurrent LHRH agonist therapy.

Results: To date, 25 pts have been enrolled and 19 have completed local therapy. Patients had the following characteristics prior to the start of chemotherapy: Median age 63 years, median PSA 21.8 (range 5.9 - 175), clinical stage T1 in 6 patients, T2 in 8, and T3 in 5. Gleason scores were < 7 in 7 patients and > 8 in 12 patients. In general, chemotherapy was well tolerated. The most common toxicities related to chemotherapy were grade III dyspnea (3 pts) and grade III fatigue (2 pts). One patient died during the first cycle due to unrelated cardiopulmonary disease. All patients reached castrate levels of testosterone during chemotherapy. Following chemotherapy, 7 patients underwent RP (5 retropubic and 2 laparoscopic) and 9 received XRT. Surgeon evaluation of the operative difficulty revealed that 6/7 post-chemotherapy cases were assessed to be no more difficult than routine RP. All patients who underwent RP had residual disease in the pathologic specimen. Two minor surgical complications occurred (anastomotic leak, transient adductor weakness). In the 9 patients who received XRT, one patient developed urinary retention.

Conclusions: Neoadjuvant chemotherapy is well tolerated, potentially active, and does not increase complication rates of XRT or RP. Based on these preliminary results, neoadjuvant chemotherapy for pts with high-risk CaP is worthy of further study. Supported by Aventis.
Poster #33

MOUSE MODEL FOR BLADDER CANCER INDUCTION AND IMAGING
Isla P. Garraway, Chau Tran, Katie Cai, and Robert E. Reiter

Transitional cell carcinoma (TCC) is one of the most common malignancies of the genitourinary (GU) tract. The heterogeneous nature of TCC has led to studies to elucidate the molecular events involved in tumorigenesis. The paucity of animal models, however, is a major drawback. Our lab has taken advantage of the TVA retroviral gene delivery system to develop a transgenic mouse that expresses the TVA receptor under control of the urogenital tissue-specific prostate stem cell antigen (PSCA) promoter. The PSCA promoter drives TVA receptor expression almost exclusively in GU tissues. Genetically engineered avian retroviral vectors can then be introduced specifically into cells where TCC is expressed. The advantage of the TVA system is that a single transgenic mouse can be used to study multiple genetic changes. In addition to the analysis of single oncogenes, multiple oncogenes may be introduced into a single cell via multiple rounds of infection. Oncogenes are introduced somatically, which differs from typical transgenic strategies that introduce mutations into the germline. Another advantage of the TVA system is the ability to concomitantly deliver the imaging gene, luciferase. The luciferase gene imparts luminescence to infected cells and may enable the natural history of urothelial cell transformation to malignancy to be tracked in a minimally invasive fashion. We have found that PSCA-TVA mice infected with Myc develop urothelial hyperplasia, while those infected with polyoma virus MT antigen do not demonstrate urothelial changes. Investigation is underway in elucidating the genetic background, oncogene, or combination of genes sufficient to induce transitional cell carcinoma. Combining luciferase imaging with oncogene induction will likely enable the process of tumorigenesis to be followed with CCD imaging.

Poster #34

INCIDENTAL FINDING OF PROSTATE CANCER AT CYSTOPROSTATECTOMY: CHANGES IN INCIDENCE IN THE PSA ERA
J. Slade Hubbard, Heather Stefaniak, Joseph A. Molitierno, Eric M. Wallen and Raj S Pruthi
Chapel Hill, North Carolina

Introduction: Historically, approximately one-third of men undergoing cystoprostatectomy have incidentally-detected prostate cancer (CaP). We sought to determine the incidence and pathologic features of incidental CaP at our institution, evaluating changes in incidence that may have occurred in the era of PSA screening.

Methods: 151 men who underwent cystoprostatectomy for urothelial cancer between 1990-present were retrospectively reviewed. The incidence of CaP was measured and pathologic evaluation of Gleason score was reported overall and at each of 3 time periods representing different eras with regard to PSA screening: 1990-1995, 1996-2000, and 2001–present. Patients with prior treatment for prostate cancer were excluded.

Results: The overall incidence of prostate cancer in our cohort was 30% (45/151). Of these cancers, 73% (33/45) of the tumors were low-grade tumors (Gleason < 6) and 27% were moderate/high grade (Gleason ≥ 7). The incidence has appears to have decreased since the mid-1990's, perhaps accounting for the effect of widespread PSA screening. Interestingly, however, the rate of incidental high-grade tumors has actually increased. Of note, no patient in this series is known to have died from prostate cancer.

Table 1. Incidence of Prostate Cancer During Various Time Periods

<table>
<thead>
<tr>
<th>Date Range</th>
<th>Incidental CaP (%)</th>
<th>Gleason &lt; 6 (%)</th>
<th>Gleason ≥ 7 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990-1995</td>
<td>13 (41%)</td>
<td>12 (38%)</td>
<td></td>
</tr>
<tr>
<td>1996-2000</td>
<td>10 (27%)</td>
<td>7 (19%)</td>
<td></td>
</tr>
<tr>
<td>2001-present</td>
<td>22 (27%)</td>
<td>14 (17%)</td>
<td></td>
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</tbody>
</table>

Discussion: The overall rate of incidental prostate cancer found at cystoprostatectomy in our modern cohorts is lower than that of the early PSA era, and this rate has remained stable since throughout the PSA era. Interestingly, the percentage of higher grade cancers has increased. These results suggest that PSA screening may have affected the overall rate of incidental prostate cancer in cystoprostatectomy specimens, but has not seemed to influence the number of high-grade cancers.
DETECTION OF PROSTATE CANCER WITH CONTRAST ENHANCED SONOGRAPHY USING HARMONIC GRAY SCALE, COLOR DOPPLER AND POWER DOPPLER IMAGING

E J Halpern (P); J R Ramey; F Frauscher; P McCue; L G Gomella

PURPOSE: To evaluate the discrimination of benign from malignant prostate outer gland tissue during contrast-enhanced sonography.

METHOD AND MATERIALS: 301 subjects with an elevated PSA or abnormal digital rectal examination were evaluated with transrectal sonography during infusion of a microbubble contrast agent (Imagent; Imcor). Baseline imaging was performed with conventional gray scale, color and power Doppler. Contrast-enhanced imaging was performed with harmonic gray scale, including continuous harmonic imaging (CHI) and intermittent harmonic imaging (IHI) with interscan delay times of 0.2s, 0.5s, 1.0s, 2.0s, as well as with continuous color and power Doppler. Six biopsy cores were obtained in a modified sextant distribution with one core from the most suspicious area in each sextant. A sextant with no suspicious area was sampled with a laterally directed core. Each biopsy site was prospectively rated for suspicion of cancer on a 1-5 scale with each imaging technique. In order to compensate for clustering of data within each subject, clustered ROC analysis was performed.

RESULTS: Cancer was detected in 188 sextant cores from 93 of 301 subjects (31%). Clustered ROC analysis demonstrated the following values for area under the curve, Az: pre-contrast gray scale – 0.58, pre-contrast color Doppler – 0.53, pre-contrast power Doppler – 0.58, CHI – 0.62, IHI (0.2s) – 0.64, IHI (0.5s) – 0.63, IHI (1.0s) – 0.65, IHI (2.0s) – 0.61, contrast-enhanced color Doppler – 0.60, contrast enhanced power Doppler – 0.62. A statistically significant benefit was found for IHI over baseline gray scale and Doppler imaging (p < 0.05).

CONCLUSIONS: Contrast-enhanced transrectal sonography with IHI provides a statistically significant improvement in discrimination between benign and malignant areas of the prostate outer gland. However, as evidenced by relatively low ROC areas, contrast enhanced sonography cannot definitively differentiate benign from malignant tissue without biopsy confirmation.

DOES PREOPERATIVE ENDORECTAL MRI IMPACT ON THE LAPAROSCOPIC RADICAL PROSTATECTOMY POSITIVE MARGIN RATE?

James A. Brown* and Douglas M. Dahl, Boston MA and Augusta, GA*.

INTRODUCTION: While transrectal ultrasound imaging is not a useful tool for predicting tumor extent, endorectal magnetic resonance imaging (MRI) has demonstrated promise in assessing tumor stage preoperatively in men with prostate cancer. We evaluated the efficacy of preoperative endorectal MRI in predicting pathologic tumor stage and its impact on surgical positive margins.

METHODS: We evaluated 19 men who underwent preoperative endorectal MRI prior to transperitoneal (8) or extraperitoneal (11) laparoscopic radical prostatectomy (LRP) between March 2002 and June 2003. Tumor (T) stage was estimated by MRI in 18 cases. Body mass index (BMI), clinical stage, biopsy grade, preoperative serum prostate specific antigen (PSA), operative time, and pathologic grade, stage and margin status were recorded.

RESULTS: Eleven patients’ endorectal MRIs were interpreted as stage T2 disease (no extracapsular extension [ECE]). Six and 5 patients were clinical T1c and T2, respectively. Nine had bilateral, 1 unilateral and 1 non nerve sparing LRP. Ten (91%) of the 11 had pathologic stage T2a (3) or T2b (7) tumors while only 1 (9%) had pathologic T3a disease. The latter and 4 of the former (45.4%) had positive margins. Six patients’ MRIs were interpreted as T3 (ECE) disease. Four patients had clinical T1c disease and 3 were clinical T2a. Two had bilateral, 4 unilateral and 1 no neurovascular bundle sparing. Five (83%) had pathologic T3a disease while 1 (17%) was pathologic T2a. Additionally 1 patient had an MRI suspicious for T3 disease versus biopsy change. Pathology confirmed T2b disease. All 7 MRI T3 patients had negative margins and lymph nodes.

CONCLUSIONS: Endorectal MRI is a valuable tool in preoperative staging, with a 91% and 83% sensitivity in correctly identifying pathologic T2 and T3 disease. Patients with MRIs concerning for ECE had a significantly lower positive margin rate (0% versus 45%) consistent with a less aggressive neurovascular bundle sparing and an increased effort to avoid positive margins. We believe continued evaluation of the role for preoperative endorectal MRI, aggressiveness of neurovascular bundle sparing, postoperative potency and PSA recurrence is warranted.
**Poster #37**

**RECOMBINANT PROSTATE CANCER VACCINES AND COMBINATION THERAPIES**  
James L. Gulley, Philip M. Arlen, Nushin Todd, William Dahut, Kevin Camphausen, C. Norman Coleman, and Jeffrey Schlom

**Introduction:** Prostate cancer remains the most common cancer among men in the US and the second most common cause of cancer death. Vaccine strategies directed at PSA have gained interest in this disease.

**Methods:** We completed 3 randomized phase II studies with pox viral vector vaccines in various patient populations as outlined below. The purpose of these trials was to determine if these vaccines could be given in combination with other modalities commonly used in prostate cancer (radiation therapy and chemotherapy). Results—Radiation Therapy: Recent preclinical studies in mice have demonstrated that local external beam irradiation of tumor *in situ*, at doses insufficient to reduce the rate of tumor growth, leads to phenotypic alterations of tumor cells (including upregulation of fas) that make them more susceptible to specific immune attack. Tumor radiation and vaccine when used together were shown to act synergistically in inducing anti-tumor responses. A recently completed clinical trial combining radiation with our vaccine strategy in patients with clinically localized or locally advanced prostate cancer demonstrated that this strategy can be employed safely and can lead to immune responses in the majority of patients. In addition there is indirect evidence of immune mediated tumor killing as demonstrated by the formation of *de novo* immune responses to prostate-associated antigens not found in the vaccine. Chemotherapy: Other combination strategies have emerged with one recently completed randomized phase II study in prostate cancer that evaluated concurrent chemotherapy (docetaxel) and vaccine. This trial showed that immune responses could be maintained in the face of chemotherapy and concurrent steroids and that vaccine was safe with chemotherapy. Vaccine vs. Second Line anti-androgen: Another randomized phase II study showed apparent equivalence of vaccine with nilutamide in terms of time to treatment failure, with less toxicity in patients with androgen insensitive prostate cancer but no radiographic evidence of disease. Several patients on this trial had sustained decreases in PSA > 50% due to vaccine.

**Summary:** Early clinical trial results suggest that safety of the vaccines will not be a serious concern even when combined with chemotherapy or radiation therapy. Furthermore immunologic responses have been seen with vaccine alone and in combination with either radiation or chemotherapy. Evidence of clinical benefit from these vaccines is emerging. Future trials will examine alternate strategies of augmenting the immune response.

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**Poster #38**

**P53 ARG72PRO SINGLE NUCLEOTIDE POLYMORPHISM (SNP) IS ASSOCIATED WITH INCREASED RISK FOR PROSTATE CANCER AMONG AFRICAN AMERICAN MEN**  
Javier Hernandez MD, Ivana Balic MD, Teresa L. Johnson-Pais PhD, Ian M. Thompson MD, Robin Leach PhD. The University of Texas Health Science Center at San Antonio, San Antonio, TX.

**Background and Objective:** A recent small case-control study reported an increased risk of prostate cancer among Caucasian men with the p53 codon 72 Arg/Pro and Arg/Arg genotypes. Others have associated the Pro/Pro genotype of this SNP with more favorable stage and grade of disease. In this study we sought to assess the association of the p53 Arg72Pro SNP and the risk of prostate cancer in a large multiethnic cohort.

**Materials and Methods:** We conducted a case-control study of 541 prostate cancer cases and 942 optimal controls evaluating participants of the San Antonio center for Biomarkers Of prostate cancer Risk (SABOR) study (249 African-American, 743 Caucasian, 476 Hispanic, 15 Other). Relevant demographic and case-control ascertainment data were obtained from SABOR and other official health records. Study participants underwent p53 Arg72Pro genotyping using the TaqMan assay.

**Results:** There is a significant difference in the allelic distribution across ethnic groups in our study population. Age-adjusted logistic regression analysis stratified by ethnic/racial group indicates that the Arg/Pro and Arg/Arg variants of the p53 Arg72Pro SNP are associated with a higher risk of prostate cancer among African American men (OR = 3.12, 95% CI = 1.14 – 8.51, p = 0.03 and OR = 3.93, 95% CI = 1.12 – 13.9, p = 0.03, respectively)

**Conclusions:** Our study suggests that African American men with the Arg/Pro and Arg/Arg p53 codon 72 genotypes are at an increased risk for developing prostate cancer. At this time, we are unable to confirm the same findings by others among Caucasian men.
Poster #39

CHARACTERIZING THE EFFECTS OF SILENCING VHL IN NON CANCEROUS CELL LINES
Jean-Baptiste Lattouf, Julie Xanthopoulos, Ray Tabios, W. Marston Linehan, James R. Vasselli

Introduction & Objective: The effect of re-introducing VHL in kidney tumor cells lines has been well characterized. However findings derived from such a model do not take into account the presence of other mutations that could potentially be present in these cell lines. We seek to test the effect of knocking out VHL in non cancerous lines of cells in vitro.

Material & Methods: 3 non-cancerous cell lines, 293 (embryonic immortalized renal tubular cells), PRT (proximal renal tubular cells) and fibroblast cells were used. Quantification of VHL gene expression was done using real time RT-PCR and western blotting for each line of cells. Knocking out VHL was carried out using shRNA manipulation, which has the advantage of being sustainable through multiple cell generations; this implied trans-fec- tion of all three cell lines with plasmid containing four different constructs of shVHL. Efficacy of VHL silencing will be verified afterwards in the trans-fected cells with the same techniques mentioned above. Cell invasion assay into collagen/ proteoglycan matrix as well as in vitro cell growth in various conditions will allow us to characterize the invading potential of VHL-knock-out clones.

Results: All original three cell lines express VHL. Manipulation with shRNA showed approximately a 50-70% trans-fec- tion rate 293 cells and about 5-10% trans-fec- tion rate in fibroblasts. Trans-fec- tion rate seemed independent of type of plasmid construct used for trans-fec- tion. VHL expression in knock-out cells, as well as invasion assays, are pending verification.

Discussion: If shRNA manipulation allows VHL suppression in our three cell line, down stream products of the VHL pathway implicating HIF (such as VEGF and glut-1) will be tested and the effect of knocking out VHL on these products will be evaluated. This provides a much more controlled setting than the study of these end products in actual kidney tumor cell lines where other mutations and by-products may be present.

Conclusion: Establishing a model for VHL in vitro will allow us to test different pharmacologic blockages in the VHL pathway in vitro before we transfer our finding to our animal model. Ultimately, because VHL expression will be stably “knocked down”, we will be able to observe if the cells with silenced VHL can form tumors in mice.

Poster #40

POPULATION-BASED SURVIVAL DATA OF URACHAL TUMORS
Jehonathan H Pinthus, MD, PhD, Riad Haddad, MD, John Trachtenberg, MD FRCSC, Eric Holowety, MD, Jeff Bowler, Michael Jewett, MD, FRCSC and Neil Fleshner, MD, MPH, FRCSC

Background: Urachal carcinoma accounts for less than 1% of all bladder cancers. Limited data on disease-related outcomes, originating from case reports and select referral centers exist. The objective of this study was to describe a population-based outcomes analysis with long-term follow-up of patients in the Province of Ontario.

Methods: We reviewed the data source of The Ontario Cancer Registry for patients diagnosed with urachal cancer during 1976-2001. A cohort of 40 patients with urachal adenocarcinoma was found. The primary outcome measures were overall and disease specific survival. The effect of age, sex, grade, classification, treating hospital (university versus non academic) as predictor for outcome was determined.

Results: Median age of the patients was 52 years. Median follow-up was 72.7 months. Mean overall survival was 121.6 ± 21 months. Mean disease specific survival for patients treated operatively was 165 ± 27 months with 5 and 10-year disease specific survival of 61.3% and 49.2% respectively. Disease specific mortality was not evident after 7 years from diagnosis. Well-differentiated tumors (one third of the patients) were associated with a 70% cure rate when treated by partial cystectomy. Well-differentiated tumors (p=0.005), non-involvement of adjacent organs (p= 0.003) or the peritoneum (p=0.045) correlated with better prognosis.

Conclusions: Urachal adenocarcinoma occurs in all age groups. Long term disease specific survival can be achieved with partial cystectomy. Covariates associated with better disease specific survival are well-differentiated tumor grade and absence of adjacent organ or peritoneal involvement. Survival of 7 years with no evidence of disease may be considered as cure.
**Poster #41**

**IMPACT OF NOX4 ON HIF-ALPHA EXPRESSION AND TRANSACTIVATION**  
Jodi K Maranchie, Ye Zhan, Worcester, MA

Introduction and Objective: Inactivation of the von Hippel Lindau tumor suppressor (VHL) is an early event in 60-80% of sporadic clear cell renal cell carcinoma (RCC). We previously showed that renal tumorigenesis occurs via loss of VHL E3 ubiquitin ligase function, resulting in accumulation of the alpha subunit of the hypoxia-inducible heterodimeric transcription factor (HIF-α). Subsequent activation of HIF-α via a second hypoxic switch results in transcription of an array of genes including VEGF and erythropoetin (Epo). Recent evidence suggests that HIF-α can be alternatively activated by reactive oxygen species. We examined the impact of superoxide generation by the kidney-specific NADPH oxidase, Nox4, on HIF-α expression and transactivation.

Methods: A Nox4 expression vector was generously provided by Dr. Leto of the NIDDK. Transfections were performed using Fugene (Roche) or Nucleofector electroporation. Whole cell lysates and cell membrane fractions were subjected to Western analysis for HIF1-α, HIF2-α, and Nox4. Nox4, HIF2-α and VEGF expression was evaluated by Northern blot and by real-time quantitative RT-PCR of total RNA extracts. Luciferase reporter constructs containing the minimal promoter region of VEGF or Erythropoetin were used to measure HIF-α transactivation.

Results: We designed small inhibitory RNA (siRNA) capable of decreasing endogenous Nox4 expression by 70-80% in HEK293 and 786-0 PRC. No change in HIF2-α expression was detected following knock-down or exogenous expression of Nox4. Similarly, cell lysates confirmed markedly reduced Nox4 by Western blot using an affinity purified rabbit polyclonal antibody raised against the C-terminus of Nox4, but no change was seen in HIF2-α protein levels in normoxia or hypoxia (0.5% O2 for 16 hours). However, quantitative real time PCR, demonstrated a 10-fold decrease in VEGF mRNA in VHL-deficient 786-0 PRC cells after Nox4 knock-down. Further, luciferase reporters showed markedly decreased transcription from the minimal promoters of both VEGF and Epo after Nox4 knock-down.

Conclusions: Although Nox4 levels have no impact on HIF-α expression at the mRNA or protein level, specific Nox4 knock-down results in decreased transcription of HIF-regulated genes. These studies suggest that Nox4 plays a role in HIF-α transactivation, independent of VHL-mediated protein stabilization. The existence of a secondary tissue-specific HIF-α activation pathway provides a novel molecular target for directed RCC therapy. Studies are ongoing to determine if Nox4 knock-down or inhibition will alter tumor growth in vivo.

Funding: NIDDK

**Poster #42**

**FLAP ENDONUCLEASE 1 IS OVEREXPRESSED IN PROSTATE CANCER AND ASSOCIATED WITH HIGH GLEASON SCORE**  
John S. Lam, Hung Yu, Ai Li, David B. Seligson, John T. Leppert, Mervi Eeva, Oleg Shvarts, Allan J. Pantuck, Steve Horvath, Ari S. Belldegrun. Los Angeles, CA.

Introduction and Objectives: Novel molecular markers are vital for the development of prognostic and therapeutic modalities in prostate cancer. Using oligonucleotide microarrays, we recently reported that structure-specific flap endonuclease 1 (FEN-1) gene is overexpressed in the most aggressive pure clone, CL1.1, of a newly developed hormone refractory prostate cancer cell line, CL1. In this study, we investigated the expression and potential clinical usefulness of FEN-1 in prostate cancer using tissue microarray technology.

Methods: Immunohistochemical analysis using a FEN-1 monoclonal antibody was performed on tissue microarrays constructed from paraffin embedded specimens from 246 patients who underwent radical retropubic prostatectomy. FEN-1 staining was correlated with established prognostic factors (Gleason score, PSA, and pathologic stage) and biochemical recurrence-free survival was analyzed. Data were compared using standard statistical methods.

Results: There were a total of 1083 informative tissue spots, which included 651 cancer, 264 normal, 120 benign prostatic hyperplasia (BPH), and 48 prostatic intraepithelial neoplasia (PIN). Mean expression of FEN-1 was significantly higher in cancer (36.7%) compared to normal (13.2%), BPH (4.5%), and PIN (15.4%) specimens (p < 0.0001). FEN-1 expression was strongly correlated with Gleason score ≥7 (p = 0.00075). Preoperative PSA (p = 0.0052), Gleason score ≥7 (p < 0.0001), seminal vesicle invasion (p < 0.0001), capsular invasion (p = 0.0013) was associated with recurrence-free survival, whereas FEN-1 expression was not. On multivariate analysis, only Gleason score ≥7 (p = 0.0007), seminal vesicle invasion (p = 0.004), and capsular invasion (p = 0.0084) were retained as independent prognostic indicators for PSA recurrence.

Conclusions: FEN-1 is overexpressed in prostate cancers with an aggressive phenotype and a Gleason score of 7 and higher. These results suggest that FEN-1 may be a tumor marker for the selection of patients at high risk for progression and may be a useful target for prostate cancer diagnosis and therapy.
**Poster #43**

EXPRESSION OF VASCULAR ENDOTHELIAL GROWTH FACTOR A (VEGF-A), VEGF RECEPTOR 1 (VEGFR-1) AND VEGFR-2 IN CLEAR CELL AND PAPILLARY RENAL CELL CARCINOMA (RCC): IMPLICATIONS FOR THERAPY

**John T. Leppert**, John S. Lam, Hong Yu, David B. Seligson, Jun Dong, Steve Horvath, Allan J. Pantuck, Robert A. Figlin, Arie S. Belldegrun

**Introduction:** VEGF-A, a potent angiogenic signaling peptide, acts through high affinity tyrosine kinase receptors VEGFR-1 and VEGFR-2. Therapies targeting this pathway have demonstrated objective clinical responses and improvement in time to progression in metastatic clear cell RCC. Understanding the expression of these markers in both clear cell and papillary subtypes may guide patient selection and optimize the benefit of agents targeting the VEGF-A pathway.

**Methods:** A tissue microarray was constructed from paraffin-embedded clear cell (N=340) and papillary (N=42) RCC specimens from patients treated with nephrectomy. Immunohistochemistry was performed and the percentage of tumor cells expressing the marker was scored in 3 locations and averaged. The Kruskal-Wallis test was used to compare the expression of each marker between the two tumor histologies. Pearson correlation coefficients were determined to analyze the co-expression of the protein and receptors. Tumors were then categorized by percentage of tumor cells expressing the marker. Strong staining was defined as >66% expression, where medium staining = 33-65% expression, light staining = 1-32% and no staining = 0% expression.

**Results:** Papillary RCC demonstrated a higher mean expression of VEGF-A (57.3% vs 37.0%, p=7.6x10^-5) and VEGFR-2 (49.3% vs 37.06%, p=1.7x10^-5) than clear cell RCC. No difference was seen in the expression of VEGFR-1 between papillary and clear cell type RCC (58.0% vs 54.8%, p=.53). The frequency of strong, medium, light and no staining for VEGF-A was 45%, 33%, 17%, and 5% in papillary RCC versus 19%, 34%, 36% and 11% in clear cell RCC, respectively. VEGFR-1 demonstrated a distribution of 38%, 36%, 26%, and 0% in papillary RCC versus 38%, 35%, 24%, and 3% in clear cell RCC, respectively. VEGFR-2 exhibited a distribution of 33%, 38%, 24%, and 5% in papillary RCC and 17%, 35%, 39%, and 8% in clear cell RCC, respectively.

**Conclusions:** Papillary type RCC exhibits higher VEGF-A and VEGFR-2 expression than clear cell type RCC. Patients with papillary RCC warrant inclusion in clinical trials targeting this pathway. Profiling the strength of marker expression in RCC, regardless of histology, may refine patient selection for anti-angiogenesis therapy.

**Poster #44**

RADICAL PROSTATECTOMY FOR CLINICALLY ADVANCED (CT3) PROSTATE CANCER IN THE PSA ERA: 15-YEAR OUTCOMES

**John F Ward**, Michael L Blute, Erik J Bergstralh, Jeffrey M Slezak, Horst Zincke

**Purpose:** The proper management of patients with locally advanced (ct3) prostate cancer (PCA) remains a problem. Excluding radical prostatectomy (RP) from the treatment options available to these patients is based upon antiquated misconceptions. We report our long-term experience with extirpative surgery in patients presenting with ct3 PCA.

**Materials and Methods:** A single institution retrospective study identifying 5,652 men who underwent RP for histologically proven PCA in the prostate specific antigen (PSA) era (1987-1997). In 15% (842), RP was performed despite the presence of ct3 disease. Median follow-up was 10.3 years. Cancer specific, overall, and disease free survival plots were constructed and compared with patients undergoing RP for ct2 disease during the same time period. Perioperative morbidity, continence and erectile function rates were examined. Multivariate analysis for risk factors of disease recurrence was performed.

**Results:** Cancer specific survival five, 10- and 15-years following RP for ct3 PCA were 95%, 90% and 79%. One-quarter of men were clinically over-staged (pT2). Adjuvant or salvage therapy was delivered to the majority (78%) of patients. Pathologic grade (≥7), positive surgical margins, and non-diploid chromatin were all independently associated with a significant risk for clinical disease recurrence while pre-operative PSA had little impact on outcome. Complications and continence rates following RP in ct3 patients mirrored those observed in patients with ct2 disease.

**Conclusions:** Radical prostatectomy as the primary therapy in a multimodality approach to locally advanced PCA offers cancer control and survival rates approaching those achieved in patients with ct2 disease while not experiencing significantly different complications or incontinence rates.
Poster #45

ANDROGEN AND ANDROGEN RECEPTOR ANTAGONIST RESPONSIVE PRIMARY AFRICAN AMERICAN BENIGN PROSTATE EPITHELIAL CELL LINE

Yongpeng Gu, Kee-Hong Kim, Shiv Srivastava, Judd W. Moul, David G. Mcelod, and Jhoong S. Rhim

Center for Prostate Disease Research, USUHS, Bethesda, MD; Walter Reed Army Medical Center, Washington, D.C.

Introduction and Objectives: Generation of suitable in vitro models is critical for understanding process associated with development and progression of prostate cancer in high-risk African American men. However, the generation of long-term human prostate epithelial cell lines derived from primary human prostate epithelium have been unsuccessful due to the absence of in vitro immortalization. Our goal is to generate new continuously proliferating androgen responsive HPE cell lines from benign prostate tissues by using telomerase, the gene that prevents cellular senescence.

Materials and Methods: The actively proliferating secondary African American prostate epithelial RC-165N cells derived from benign prostate tissue of a radical prostatectomy specimen were transduced through infection with a retrovirus vector expressing the human telomerase catalytic subunit (hTERT). Both infected and uninfected cells were maintained in keratinocyte serum-free growth medium (K-SFM) (Gibco) and passaged at a split ratio of 1:2 weekly for serial subcultivation. The cells were characterized phenotypically and genetically.

Results: A high level of telomerase activity was detected in RC-165N/hTERT cells but not in RC-165N cells. RC-165N/hTERT cells are currently growing well at passage 50 whereas RC-165N cells senesced within passage 3. RC-165N/hTERT cells exhibit epithelial morphology. These immortalized cells showed no cell growth in soft agar, and no tumor formation in SCID mice. The RC-165N/hTERT cells express androgen-regulated prostate-specific homeobox gene, NKX 3.1 and epithelial cell specific cytokeratin 8, androgen receptor (AR), prostate stem cell antigen and p16 but not PSA. AR protein was detected by Western blot analysis. AR gene sequencing analysis indicated that this cell line expresses wild-type AR. The cell growth is stimulated by dihydrotestosterone (1.0nM DHT) and the stimulatory effect is blocked by flutamide (50 nM). Chromosome analysis revealed that this cell line is aneuploid human male (XO), with most chromosome counts in the 80’s-90’s range. There were losses of chromosomes Y, 1q, 4q, 10q, 12p, 22 and gains of chromosome 15 and 20.

Conclusions: This is the first documented case of the establishment of androgen and androgen receptor antagonist responsive African American epithelial cell line derived from benign prostate tissue with telomerase. This unique in vitro model may be useful for the study of prostate cancer biology and molecular basis of prostate carcinogenesis, especially for high-risk African American men.

Poster #46

COMPARISON OF HAND-ASSISTED LAPAROSCOPIC NEPHRECTOMY AND NEPHROURETERECTOMY TO STANDARD LAPAROSCOPY

Jonathan H. Taylor, MD, Alex Ernest, MSIV, Michael Fabrizio, MD, Robert Given, MD

Laparoscopic nephrectomy and nephroureterectomy for suspected renal cell carcinoma (RCC) and upper tract transitional cell carcinoma (TCC) has become more commonplace recently in a urologic community that has been slow to embrace minimally invasive oncologic surgery. It has been argued that hand-assisted laparoscopic procedures have the advantage of both minimally invasive as well as open surgery. We present data on the first 23 hand assisted procedures by a novice laparoscopic surgeon comparing them to standard laparoscopic procedures by an experienced laparoscopic surgeon.

Retrospective analysis of 18 hand-assist laparoscopic nephrectomies (HALN) and 5 hand-assist laparoscopic nephroureterectomies (HALNU) by a single surgeon were compared with 16 patients undergoing standard laparoscopic nephrectomy (LN), and 5 patients undergoing standard laparoscopic nephroureterectomy (LNU) by a single fellowship trained experienced laparoscopic surgeon. Hospital and office charts were reviewed systematically, and donor nephrectomies excluded.

No significant differences were revealed in hand-assist verses standard laparoscopy for length of stay (5.3 vs. 4.2 days), analgesia requirements (203 vs. 132 morphine equivalents), operative time (275 vs. 257 minutes), specimen weight (582 vs 616 grams), body mass index, estimated blood loss, transfusion requirements, or open conversion rates.

Our data suggests that HALN/HALNU versus standard LN/LNU are comparable techniques in terms of efficacy and morbidity, while allowing direct control of the operative field. Furthermore, it has been argued that hand-assist procedures are an option for the less experienced laparoscopic surgeons and centers to perform and become more comfortable with minimally invasive procedures and we believe this data supports this concept.
Poster #47

NEW INTRAVESICAL SEQUENTIAL CHEMOTHERAPY FOR PATIENTS WITH TREATMENT REFRACTORY SUPERFICIAL UROTHELIAL CARCINOMA
Jose Maymi, MD, Nicole Saltsgaver, PA and Michael O’Donnell, MD

Purpose: The efficacy of intravesical Gemcitabine and Mitomycin chemo-ablative therapy is reported for patients with previous treatment refractory superficial urothelial carcinoma.

Materials and Methods: Ten patients diagnosed with urothelial carcinoma, nine involving the bladder and one with de novo upper tract urothelial carcinoma were selected, all with a prior history of multiple recurrences with a median of four range (2 - 14). The diagnoses included Ta low grade urothelial carcinoma (1), T2 high grade (2), CIS (2) and/or combination of these (5). Previous treatments received included Thiotepa, Valrubicin, Mitomycin, BCG, BCG plus interferon and Gemcitabine alone. The median number of previous treatments was two range (1 to 6). Treatment consisted of intravesical Gemcitabine (1 gram in 50 cc buffered saline) for 1 ½ hours dwell time with subsequent drainage followed by Mitomycin (40 mg in 20cc sterile water) for an additional 1 ½ hours retention. The protocol treatment was comprised of two cycles of eight treatments given biweekly with a month off between cycles. With good response patients have been following with monthly maintenance therapy. Treatment courses varied depending upon patient tolerability.

Results: Seven of ten patients are recurrence free after Gemcitabine and Mitomycin with routine surveillance of cystoscopies, cytologies and mucosal biopsies with a median time of nine months range (3 to 16 months). Two patients presented at three months with urothelial carcinoma recurrence. The third patient was categorized with a probable recurrence based on suspicious lesions at a subsequent nephroscopy. All three patients who presented with recurrence were unable to complete the minimum treatment cycle due to other co-morbidities. The remaining seven patients have all completed a minimum of one cycle and are recurrence free. Most of the patients tolerated the therapy well with few complaining of cystitis-like symptoms, bladder spasms, nausea, vomiting, fatigue, hematuria and/or rash, occasionally leading us to discontinue the Mitomycin but not Gemcitabine.

Conclusion: Early findings with this novel Gemcitabine and Mitomycin intravesical chemotherapy suggest it is a safe and efficacious treatment for selected patients with refractory superficial urothelial carcinoma.

Poster #48

LYMPHOSCINTOGRAPHIC MAPPING OF THE LYMPHATIC DRAINAGE OF THE PROSTATE AND SEMINAL VESICLES USING 99TECHNETIUM-SULFACOLLOID
Joseph Basler, PhD, MD, Nunes Wendy, MD and Chaudhury Turin, MD

Introduction and Objective: Modifications in the pelvic node dissection for prostate cancer staging have been made over the years in order to minimize the potentially morbid side-effects of lower extremity lymphedema. However, a significant proportion of men undergoing the standard obturator node dissection may be understaged as evidenced by a long-term biochemical failure rate of up to 20% in men with pT2b, N0 prostatectomy specimens. Recent use of lymphoscintigraphy to identify “sentinal” nodes (those representing the first landing zone near the tumor) has been helpful in treatment of breast cancer, melanoma and penile cancer among others. We report our experience with lymphoscintigraphic mapping of the drainage of various areas of the prostate.

Methods: Starting in 2002 at the Audie L. Murphy Veterans Administrative Hospital, 24 men, who were scheduled to undergo prostate biopsy underwent prebiopsy TRUS-guided injection of one microcurie 99mTc sulfacolloid into specific areas of their prostates and scanning prior to their biopsies. Injections were randomized to one of eight sites: the left or right - apex, transition zone, base, or seminal vesicle. A foley catheter was placed prior to injection. Patient characteristics: Age - 55 to 82 years; PSA - 2.04 to 38.25 ng/mL; Prostate size - 18.5cc to 59.2cc. Previous biopsy history: 16 - none, 4 - one, 1 - two, and 1 –three. Instrumentation: Siemens Variable-angle E.CAM Dual Detector with E.SOFT software, or the Siemens Multispect II, both equipped with a low energy/high resolution color meter. Three types of imaging were obtained after injection: a dynamic immediate post-injection series, during which one anterior-posterior frame was obtained every five minutes for 1 hour; next, a Spect 180-degree range was obtained at 32 frames/minute with the patient supine in a clockwise and circular orbit (step and shoot mode)- matrix size 64 x 64 and zoom of 1.23; Finally, static delayed images were obtained AP, RPO, LPO, RAO, LAO, R-lateral, L-lateral. The pattern of both initial nodes and subsequent secondary nodes were assessed as well as cross-over to contralateral nodes and liver and spleen visualization.

Results: For the 18 prostate injections, the initial nodes seen were: ipsilateral internal iliac (6), contralateral internal iliac (1), bilateral internal iliac (2), ipsilateral iliac bifurcation (3), contralateral common iliac (1), and no nodes (5). For the 6 seminal vesicle injections, no uptake in the lymph nodes was observed in 5, and the presacral lymph nodes in 1. Delayed secondary lymph nodes visualized included those at the paracaval, paraaortic, presacral, common iliac, subdiaphragmatic, and iliac bifurcation areas. Only one patient, injected in the right base of the prostate, had a left obturator lymph node identified on delayed scans.

Conclusions: Lymphoscintography after injection of various anatomic areas of the prostate and the walls of the seminal vesicles demonstrate that the ipsilateral internal iliac nodes are the most common “sentinal” or initial lymph nodes of drainage. This suggests that the current method of obturator node dissection with radical retropubic prostatectomy is inadequate and may explain a proportion of patients who fail local treatment.
Poster #49

REVIEW OF 12 CORE PROSTATE BIOPSIES FOR DETECTION OF PROSTATE CANCER AT THE NATIONAL NAVAL MEDICAL CENTER
Joseph Y. Clark, Jason Capra, and Timothy F. Donahue. National Naval Medical Center and Urologic Oncology Branch, National Cancer Institute, Bethesda, MD

Introduction: Widespread prostate specific antigen (PSA) testing has revolutionized our ability to screen and detect prostate cancer (CAP) by prompting prostate biopsy. Sextant prostate biopsy has been standard strategy for detecting CAP. It is intuitive that taking more cores at the time of biopsy would increase detection of CAP; at the National Naval Medical Center (NNMC), a 12 core prostate biopsy technique, which includes the traditional sextant biopsies plus bilateral laterally directed cores at the base, mid, and apex portions of the prostate have been the standard protocol. The objective of this study is to compare the effect on cancer detection rate by the addition of the 6 lateral biopsies (12 core biopsy) to the standard sextant biopsies.

Methods: The records of all transrectal ultrasound guided prostate biopsies at the NNMC from January 2002 to June 2004 were retrospectively reviewed. Patients who had less than 12 cores taken at the time of biopsy and those who had a prior diagnosis or treatment for CAP were excluded. Patient demographics, indications for biopsy, and biopsy results were recorded.

Results: A total of 529 prostate biopsies were performed in 476 patients over the 30 month time period. The mean age at the time of biopsy was 59 years (range 37-86). The overall cancer detection rate using the 12 core technique was 29% (156 patients). The overall cancer detection rate assuming that only sextant biopsies were performed was 21% (113 patients). With the extra 6 lateral biopsies, 43 additional patients were diagnosed with CAP. There were 88 patients who had cancer detected in both the sextant and lateral biopsies. In 33 (38%) of these 88 patients, the laterally directed biopsies either increased the overall grade of the cancer (12), caused the cancer to be diagnosed bilaterally (12), or both (9).

Conclusion: To increase CAP detection, urologists should consider the 12 core biopsy technique. In those patients diagnosed with CAP, the extra lateral biopsies can give additional prognostic information that would be important for patient counseling.

Poster #50

ROLE OF THE VON HIPPEL-LINDAU (VHL) GENE IN THE REGULATION OF RECEPTOR TYROSINE KINASE PATHWAYS LEADING TO TUMOR SUPRESSION: IMPLICATIONS FOR THE DEVELOPMENT OF NOVEL TREATMENTS FOR VHL(-/-) CLEAR CELL RENAL CARCINOMA

Introduction: When the von Hippel-Lindau (VHL) gene is re-expressed in VHL -/- clear cell renal carcinoma cell lines, a decrease in the cells' ability to form tumors in mice is observed. Additionally, VHL-positive cells demonstrate marked decreases in the branching morphogenesis, motility and invasion when compared to the corresponding VHL-negative cells. It is hypothesized that the VHL protein may in part exert its tumor suppressor function by affecting the signaling through one or more receptor tyrosine kinase pathways.

Objective: This study attempts to reveal the mechanism of interaction between the VHL protein and the receptor tyrosine kinase pathway which leads to tumor suppression.

Methods: Three VHL-/- clear cell renal carcinoma cell lines 786.O, 121 and C-2 were utilized in this study. Each cell line was retrovirally infected with the reporter gene luciferase in order to better monitor primary tumor growth rates and metastasis in mice. Additionally, the VHL protein was reintroduced in each cell line to establish corresponding VHL positive and negative lines. Selected genes in the Met, EGFR and PDGFR pathways were knocked down in each of the cell lines using small interfering RNA. Similarly, each cell line was treated with small molecule inhibitors of phosphorylation to targeted molecules in these pathways. The effects of both manipulations were monitored on a molecular level utilizing western blots and real time RT-PCR. Phenotypic observations were made in vitro with branching, invasion/motility and growth rates assays. The tumorigenicity and invasiveness of each of the modified cell lines were also observed in in vivo murine studies.

Results: Plasmid constructs were successfully engineered allowing for the insertion of the luciferase gene into each of the three cell lines as well as constructs for the retroviral delivery of short-hairpin RNA. Currently, the efficacies of several siRNA sequences are being evaluated by RT-PCR and western blotting. Several preliminary in vitro evaluations of the effects of small molecule inhibitors on cell growth rate and invasion have been performed.

Conclusion: By understanding the interaction between the VHL protein and the receptor tyrosine kinase pathway which leads to tumor suppression, it will be possible to identify specific molecular targets for the development of effective treatments for VHL- clear cell renal carcinoma.
**Poster #51**

**PRIMARY ANDROGEN DEPRIVATION THERAPY USE IN LOCALIZED DISEASE: RESULTS FROM CAPSURE**

Jun Kawakami, Janet Cowan, Eric Elkin, David Latini, and Peter Carroll

**Introduction and Objectives:** The use of androgen deprivation therapy as the primary treatment in prostate cancer has increased over time. Patients with localized disease have increasing rates of primary androgen deprivation therapy (PADT) despite having potentially curable disease. Our objective is to describe the demographic and clinical characteristics of patients undergoing this treatment with localized disease.

**Methods:** CAPSURE (Cancer of the Prostate Strategic Urologic Endeavor) information was screened to include patients diagnosed with localized disease diagnosed between 1989 and 2002 who underwent primary androgen deprivation therapy and had no other treatment for at least nine months. Descriptive data was analyzed with chi square statistical tests. Time to failure data was analyzed using Log Rank testing and the Kaplan-Meier method.

**Results:** Of 7045 patients in CAPSURE with localized disease, 993 (14.1%) received primary hormonal therapy. Compared to patients undergoing treatment with localized disease, PADT patients had higher risk disease with more comorbidities. Patients undergoing PADT are older, less educated, have lower income, more Medicare and less private insurance. In this population, the dominant forms of hormonal therapy were LHRH monotherapy (483 of 993 patients, 48.6%) and combined androgen blockade (385 of 993 patients, 38.8%).

At five years after initiation of primary androgen deprivation 67.3% were still being treated with only androgen deprivation. 103 (13.8%) patients went on to receive definitive second treatment, 27 (3.9%) underwent second line therapy, 22 (4.1%) died from prostate cancer, and 146 patients (19%) died from all causes.

**Conclusions:** Primary androgen deprivation is a commonly used modality in patients with localized disease. These patients are older, have more comorbidities and a high overall death rate of 19% over 5 years of follow up. The majority of patients (67%) started on PADT continue on it without other interventions. Physicians are employing this durable therapy in select patients. This may represent a triaging effect where those who may not tolerate the morbidity of curative therapy are treated with androgen deprivation alone.

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**Poster #52**

**IMPACT OF SIX-MONTH LAPAROSCOPIC RADICAL PROSTATECTOMY FELLOWSHIP ON INITIATION OF A LAPAROSCOPIC RADICAL PROSTATECTOMY PROGRAM**

Kamran P. Sajadi* and James A. Brown, Augusta, Georgia*

**Introduction:** Laparoscopic radical prostatectomy (LRP) is an increasingly popular alternative to open prostatectomy. The learning curve is estimated at 40 – 60 cases. A urologist (JB) at our center completed two 3-month fellowships at high-volume LRP centers. There he participated in 29 transperitoneal (TP) and 23 extraperitoneal (EP) LRPs, performing part or all of 28 cases. Our center then initiated a LRP program. We review our experience to assess the impact of this training sequence on patient outcomes.

**Methods:** We reviewed the outcomes of our first 9 patients who had at least 3-months follow-up. We recorded age, body mass index (BMI), preoperative prostate specific antigen (PSA), clinical stage, operative time, estimated blood loss (EBL), change in hemoglobin, hospital stay, complications, pathology, and postoperative continence and erectile function.

**Results:** 9 patients, ages 50 to 71 years, were scheduled for LRP between 7/03 and 4/04. Mean BMI was 27 (range 21 – 35) kg/m². In one case, preoperative equipment malfunction led to the decision to initiate open prostatectomy. Of the other 8 (4 TP and 4 EP), 6 were clinical T1c and 2 were T2a. Preoperative PSA ranged from 4.8 to 13 ng/mL. Operative time was 282 to 629 (average 410) minutes, with 3 patients undergoing simultaneous bilateral pelvic lymph node dissection. Six were bilateral and one was unilateral nerve-sparing. Mean EBL was 225mL (75 to 500mL). Mean hemoglobin decrease in the first postoperative day was 3.3 (2.2 to 5.3) mg/dL, with 1 patient receiving transfusion. Hospital stays were 2 – 6 days. Three patients had clinically evident anastomotic extravasation which resolved spontaneously. Two required prolonged catheter drainage. There were no other complications. 5 and 3 pathologic specimens were stage T2 and T3, respectively. 3, 4, and 1 were Gleason 6, 7, and 9, respectively. Four (50%) had positive margins. No patient required pad use after 3 months. 3 of 6 preoperatively potent patients had postoperative Sexual Health Inventory for Men scores > 20.

**Conclusions:** Six months of LRP fellowship training is adequate to successfully initiate a LRP program. However, this remains a challenging procedure with significant variation in operative times.
Poster #53
QUALITY IMPROVEMENT IN LAPAROSCOPIC RADICAL PROSTATECTOMY FOR PT2 PROSTATE CANCER: IMPACT OF VIDEO DOCUMENTATION REVIEW ON POSITIVE SURGICAL MARGIN
Karim Touijer, MD, Kentaro Kuroiwa, MD, Jeffery Saranchuk, MD, Waleed Hassen, MD, Edouard Trabulsi, MD, Victor Reuter, MD and Bertrand Guillonneau, MD

Purpose: To correlate intraoperative video documentation and pathology findings in order to understand the mechanisms by which positive surgical margins occur and improve the surgical technique.

Material and Methods: Between January 2003 and May 2004, 240 consecutive patients underwent laparoscopic radical prostatectomy, of these, 180 had pT2 prostate cancer and represent the population of this study. After the first 90 patients (group I), we started a quality assurance study analyzing the intraoperative video recordings and correlating them to the pathology findings of patients with positive margin. The cancer characteristics and positive margin rate were compared between the first 90 patients and the subsequent 90 patients after the study was initiated (group II).

Results: of the 12 cases of positive surgical margins studied, the video review helped identify 8 cases with a technical error. In all the 4 cases where a technical error could not be identified, the positive margin site was at the distal apex. The most frequent identifiable mechanism by which positive margins occur was a capsular tear during the neurovascular bundle dissection. Both groups were comparable in regards to preoperative cancer characteristics and total tumor volume. In patients who had a bilateral nerve sparing, the positive margin rate was 10.6% in the first group and 5.4% in the second group (p=0.18). All of the positive margins in group II involved the prostatic apex.

Conclusion: Quality assurance efforts through pathological and intraoperative documentation review can help reduce the positive margin rate particularly in organ-confined disease. However, eradicating positive margins at the distal prostatic apex remains a challenge.

Poster #54
TARGETED DRUG THERAPIES AND CELLULAR RESPONSE IN HUMAN BLADDER CANCER CELL LINES
Katrina L. Salazar, James Vasselli, W. Marston Linehan, Donald Bottaro, Len Neckers, Jonathan Coleman
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Introduction: Interest in targeted drug therapies that interfere with specific cellular pathways involved in tumor pathogenesis has led to an increase in research for therapeutic approaches that are tailored to specific malignancies. We investigated the use of 3 classes of investigational drugs (HSP-90 inhibitors, proteosome inhibitors and a demethylating agent) through in vitro studies with human bladder cancer cell lines to assess the cellular response to these agents either alone or in combination with standard chemotherapeutic drugs.

Methods: Moderate to high-grade human bladder cancer cell lines were obtained (TcSup, 5637, J82, Scaber, UMUC, T24; ATCC, Rockville, MD) or developed (T24R, T24R1, T24M3, Bandit) by our lab and grown in sterile tissue culture conditions with prescribed serum supplemented media. Samples of purified medical grade therapeutic agents included the geldanamycin derivatives 17-DMAG and 17-AAG, bortezomib (Velcade), zebularine, cisplatin, paclitaxel, and gemcitabine. Subconfluent populations of cells were exposed for 24 hours to solubilized drug in serial dilutions prior to assay and assays were performed in triplicate or greater. Standard MTT assays for cell viability were performed per manufacturers directions. Western blotting and invasion assays were also utilized to determine the effects on downstream pathways and cellular mobility and movement.

Results: A dose-dependent decrease in viability was seen with all three classes of drugs. Slightly greater efficacy was seen with DMAG over 17-AAG that was also evident when used in combinations with cisplatin, gemcitabine, or paclitaxel. Zebularine when used with either paclitaxel or gemcitabine produced similar results. Velcade when used alone at a low dose significantly reduced viability. No additive effects were noted when using Velcade in combination with another drug. Downstream pathway components including AKT, GSK3B, cMET, and ERK were shown to decrease after drug treatment. 17-DMAG was found to inhibit cellular mobility to a greater extent than C-90, a Grb2 inhibitor.

Conclusions: Molecular therapeutics for bladder cancer appear to be effective in targeting pathways associated with the pathogenesis of malignancy such as cell survival and motility. Functional assays also show significant drug effects in pre-clinical in vitro studies supporting their further clinical investigation.


**Poster #55**

**COMPUTATIONAL ANALYSIS OF UPSTREAM REGULATORY SEQUENCES OF ANDROGEN-INDUCED GENES REVEALED ADJACENT LOCATION OF GATA ELEMENTS TO ANDROGEN RESPONSIVE ELEMENTS**

Katsuki Masuda, Shilpi Maheshwari, Soyon Oh, Thomas Werner, Shiv Srivastava and Albert Dobi

One of the most frequent expression changes during the progression of prostate cancer is the elevation of the androgen receptor (AR) levels. AR is a nuclear transcription factor that regulates the expression of downstream androgen regulated genes (ARGs). In prostate cancer (CaP) pathogenesis AR and ARGs may play the central role. Current treatment options for advanced CaP are primarily focused on the inhibition of the AR function by androgen ablation. However, CaP cells may become resistant to androgen ablation therapy leading to an incurable stage of the disease.

Our objective in the present study was to assess the sequences of androgen-induced genes by computational methods. The specific goal of our transcriptional bioinformatic analysis was to evaluate the positional relation of androgen responsive elements to other transcription factors in order to recognize complex regulatory models within the upstream sequences of androgen-induced genes. This hypothesis was consistent with the notion that gene regulation by the combination of closely situated regulatory elements is essential feature in eukaryotic transcriptional regulation.

To select a gene set where androgen induction was confirmed, we used the Center for Prostate Disease Research gene chip database that included time kinetics and dose dependency parameters of gene expression profiles in response to androgen-induction (http://cgap.nci.nih.gov/SAGE). These parameters allowed us to select genes with robust expression response (KLK3 and NDRG1), and to select genes with prompt expression profile (Nix3.1 and IHPK1).

Towards the identification of complex regulatory models, we first localized androgen responsive elements within the selected data set (www.genomatix.de). AR can recognize sequence motifs shared by members of the glucocorticoid receptor family known as GREF matrix. Then we compared pair-wise other matrices with a specific distance criterion that would allow the positioning of an adjacent matrix within 2-3 DNA helical turns only. We found that GATA matrices were apparent within the promoter upstream regions of 100% of the examined androgen-induced gene. Therefore, we formulated a GREF_GATA model that described complex AREs. To test this model we analyzed the promoter of the androgen-inducible PMEPA1 gene. We found two GREF_GATA models within the analyzed DNA sequence. To validate the model predictions we assessed the presence of androgen receptors by Chromatin Immunoprecipitation (ChIP) assay within the promoter upstream sequences of the PMEPA1 gene. Indeed, ChIP assay using androgen-induced LNCaP cells revealed that androgen receptor was bound preferentially to the predicted GREF_GATA models.

We believe that the realization of GREF_GATA regulatory module will substantially accelerate the identification of functional AREs within the regulatory sequences of androgen-induced genes. The rapid identification of critical regulatory modules will reveal novel therapeutic targets for treating prostate cancer.

**Poster #56**

**PROSTATE BIOPSY TUMOR NUMBER AND EXTENT BUT NOT LOCATION OR CONTIGUITY PREDICTS RECURRENCE AFTER RP**

Kirsten L. Greene, Armine Karapetian, Eric P. Elkin, Janeen DuChane, Christopher R. Kane, and Peter R. Carroll

**Introduction:** Prostate cancer biopsy information is important for patient risk assessment. Although the number and extent of positive biopsies has been described as a predictor of recurrence, the impact of positive biopsy location and contiguity is less well understood. We therefore sought to determine whether pretreatment prostate biopsy tumor volume, location, and pattern predict recurrence after radical prostatectomy.

**Methods:** From the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), we identified 2,037 men treated with radical prostatectomy from 1992 to 2002 for whom the detailed diagnostic biopsy record and 2 or more follow up PSA values were available. We included patients receiving at least 6 biopsy cores ( sextant biopsy or more being standard practice during study period). Treatment failure was defined as two consecutive PSA values of 0.2 ng/ml or higher, or by a second treatment more than 6 months after RP. Using preoperative PSA, T stage, and Gleason grade, patients were categorized using a modified D’Amico risk stratification. Biopsy tumor volume (# positive sites and % positive sites), location of disease (anatomic site, laterality), and contiguity of positive biopsies were entered into Cox proportional hazards models to predict risk of disease recurrence while controlling for standard risk factors of Gleason grade, PSA, and T stage.

**Results:** 70% of treatment failures were defined by biochemical criteria and 30% by second treatment. Both higher number and percent of positive biopsy cores were associated with higher likelihood of prostate cancer recurrence, risk stratification category, and Gleason grade. Number of biopsy cores taken, laterality, contiguity, and positive biopsy location (apex, midgland, base) were not associated with disease recurrence.

**Conclusion:** Prostate biopsy tumor volume, both the number of positive biopsies and the percentage of biopsies positive for cancer, correlates with treatment failure after radical prostatectomy. The site, contiguity and laterality of positive biopsies was not associated with recurrence.
**Poster #57**

THE INTERACTION OF SMOKING AND PELVIC RADIATION ON THE RISK OF SUBSEQUENT BLADDER CANCER

Kristin Chrouser, MD, Bradley Leibovich, MD, Horst Zincke, MD, PhD, Michael Blute, MD

Introduction: The “two-hit hypothesis” of cancer postulates that multiple genetic events are required for malignant transformation. A recent meta-analysis reports a 3-fold increase in transitional cell carcinoma (TCC) of the bladder among smokers. Whether pelvic radiation is associated with an increased risk of TCC is controversial. This study was designed to compare the effect of smoking on bladder cancer risk in patients with prostate cancer treated with and without radiation.

Methods: The Mayo Clinic Cancer Registry was used to retrospectively identify patients who were diagnosed with prostate cancer (treated with external beam radiation or radical prostatectomy) and subsequently developed TCC of the bladder (case cohort). Then, a randomly selected control cohort without TCC was matched by age, treatment, and time since diagnosis. Smoking status and number of pack years was determined from the medical record. Odds ratios were calculated for smoking and TCC for each of the two treatment groups and then the ratios were compared.

Results: TCC developed after prostate cancer in 107 patients (case cohort). Radiation was used to treat the cancer in 32 patients (91% smokers) while 75 patients (75% smokers) had a radical prostatectomy (RRP). The control cohort included 32 patients treated with radiation (53% smokers) and 75 who underwent RRP (33% smokers). For irradiated patients, using a matched analysis, the odds ratio (CI) of smoking and TCC was 13.0 (1.7, 99). For RRP patients, using matched analysis, the odds ratio of smoking and TCC was 5.4 (2.4, 12). These were all highly significant. When we compare the two treatment groups, although the odds ratios were larger in irradiated patients, the difference between the two did not reach statistical significance (p = .43). Pack year analysis demonstrated a statistically significant increase in TCC risk with increasing pack years within each treatment group. However, when the treatment groups were compared to each other, although the risk of TCC in heavy smokers was greater in patients after radiation than after RRP, this trend did not reach statistical significance (p = 0.16).

Conclusions: The risk of TCC after prostate cancer treatment is higher in smokers, with a significant dose response. Smokers who received pelvic radiation are at an even higher risk of subsequent TCC than those who underwent RRP but this synergistic trend does not reach statistical significance.

**Poster #58**

RELATIONSHIP BETWEEN PRIOR PERSONAL MALIGNANCY OR FAMILY HISTORY OF

Lincoln Olsen, MD, Peter Langenstroer, MD, J. Brantley Thrasher, MD

Introduction: This study was being done to determine the relationship between the presence of a previous personal malignancy or the presence of a family history of prostate cancer (CaP) or breast cancer and the likelihood of having undergone previous screening for CaP.

Methods: The University of Kansas Cancer Center and Department of Urology screened 1662 men for CaP using digital rectal examination (DRE) and serum prostate specific antigen (PSA). This free screening clinic was available for all men on a walk-in or appointment basis and was performed on the first Monday of every month. The results presented here represent the men screened from 1995 to 2001. Participants were asked to fill out a survey that included information on past medical history and family medical history as well as previous prostate cancer screening visits. Statistical significance was determined by Fisher’s exact test with P < 0.0001 being considered statistically significant.

Results: Men who had a relative with a history of CaP (175/1662) or had a history of a previous personal malignancy (510/1662) were much more likely to have been screened prior to their presentation to the University of Kansas Cancer Center (123/175 and 449/1662 respectively) than those in the general screening population (600/1662) (P < 0.0001 for both). Contrarily, those that had a relative with a history of breast cancer were no more likely to have been screened previously (120/299) (P = 0.19).

Conclusions: Men who have a family member with CaP or who have had a previous personal malignancy are much more likely to present for repeated CaP screening than are those people who have no such family or personal history of malignancy. Having a relative with breast cancer does not increase the likelihood of having been screened previously for CaP.
A LONGITUDINAL COMPARISON OF SYMPTOMS FOLLOWING THREE TYPES OF TREATMENT FOR PROSTATE CANCER

Lucille Sanzero Eller, PhD, RN, Elise Lev, EdD, RN, Ihor Sawczuk, MD, Glen Gejerman, MD, Joan Colella, MSN, RN, Patricia Lane, MSW, Susan Scrofino, BS, RNBC, OCN, Michael Esposito, MD, Vincent Lanteri, MD and John Scheuch, MD

Multiple treatment options make choice of prostate cancer treatment more complex because rates of tumor control appear are similar across approaches. Knowledge of symptoms across time after treatment can inform treatment decisions. This is a prospective study of symptoms in 162 men with prostate cancer (54 in each of 3 groups) treated with either: IMRT + HDR, IMRT + seed implantation, or RP. Data were collected on 162 participants at baseline, 127 at 1-month, 110 at 3-months, 100 at 6 months, and 59 at 12 months. The study is still in progress.

The Prostate Symptom Self Report measured incidence, severity and bothersomeness of urinary, bowel and sexual symptoms on a 0-100 scale. Analyses included descriptive statistics and RM-ANOVAs for within and ANOVAs for between group differences across time. Mean age was 65 years (range 42-82 years); 86.4% white; 49% completed college; 54.3% working full or part-time. 55% had incomes at or above $50,000/year; 82% lived with a partner and/or children. Symptom scores by time and treatment are as follows:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Time</th>
<th>RP n=47</th>
<th>HDR n=48</th>
<th>PD103 n=67</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary</td>
<td>Baseline</td>
<td>14.3(18.1)</td>
<td>26.1(17.8)</td>
<td>14.7(16.1)</td>
</tr>
<tr>
<td></td>
<td>1 month</td>
<td>33.9(18.6)</td>
<td>30.9(21.1)</td>
<td>42.6(21.7)</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>21.2(19.2)</td>
<td>22.1(16.3)</td>
<td>32.7(25.4)</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>16.1(14.6)</td>
<td>23.1(23.4)</td>
<td>20.9(21.0)</td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td>14.8(13.9)</td>
<td>27.3(20.9)</td>
<td>20.7(17.7)</td>
</tr>
</tbody>
</table>

| Bowel   | Baseline | 3.3(7.3) | 10.6(13.0) | 6.9(11.9) | .00* |
|         | 1 month  | 13.6(18.8) | 17.2(17.8) | 11.7(13.4) | .32 |
|         | 3 months | 5.2(12.2)  | 9.6(12.9)  | 10.8(16.3) | .22 |
|         | 6 months | 2.5(5.8)  | 12.1(16.6) | 7.0(10.9)  | .01* |
|         | 12 months| 6.9(16.1) | 16.4(13.9) | 6.0(12.2)  | .03* |

| Sexual  | Baseline | 23.4(14.7) | 31.2(19.6) | 23.9(18.5) | .05* |
|         | 1 month  | 32.9(18.6) | 34.1(20.8) | 29.6(23.1) | .60 |
|         | 3 months | 37.5(21.4) | 35.4(20.2) | 32.4(19.5) | .56 |
|         | 6 months | 40.2(20.1) | 40.1(24.0) | 32.2(21.0) | .23 |
|         | 12 months| 36.0(21.8) | 42.9(17.8) | 31.3(19.9) | .20 |

p = between group differences across time; ** = significance <.05; ** = significance = .05

This study provides preliminary evidence of differences in symptoms by time and treatment modality up to one year post-treatment.

PROGNOSTIC SIGNIFICANCE OF LYMPHOVASCULAR INVASION IN BLADDER CANCER TREATED WITH RADICAL CYSTECTOMY

Marcus L. Quek, John P. Stein, Peter W. Nicholls, Jie Cai, Gus Miranda, Susan Groshen, Siamak Daneshmand, Ella C. Skinner, and Donald G. Skinner

Purpose: To determine the prognostic significance of lymphovascular invasion (LVI) in patients treated for invasive transitional cell carcinoma (TCC) of the bladder with radical cystectomy.

Materials and Methods: From August 1971 to June 2004, 2005 patients underwent radical cystectomy for primary bladder cancer with the intent to cure. All patients with non-TCC histology, palliative procedures, unknown lymphovascular status, <pT1 pathologic stage, or any neoadjuvant or adjuvant chemotherapy/radiation therapy were excluded, leaving 702 patients comprising the study cohort. Median age was 68.5 years (range: 30.1 to 93.0 years), and males accounted for 77% of the patients. Of the 702 patients, 249 (36%) had LVI.

Results: Median follow-up was 11.0 years (range: 8 days to 23.2 years). The overall 5- and 10-year survival for the cohort was 51% and 34%, respectively; while the 5- and 10-year recurrence-free survival was 66% and 64%, respectively. The 10-year recurrence-free survival for those without LVI was 74% compared to 42% with LVI (p < 0.0001). In the organ-confined/lymph node negative and lymph node positive pathologic subgroups, survival outcomes were significantly worse if LVI was present. Although a trend was observed, LVI status did not reach statistical significance in patients with extravesical, node-negative disease. Step-wise Cox regression analysis revealed pathologic subgrouping (organ-confined, extravesical, lymph node positive) (p < 0.0001) and LVI status (p = 0.004) to be independent prognostic variables for recurrence-free survival.

Conclusions: Lymphovascular invasion appears to be an important and independent prognostic variable in patients with invasive bladder cancer treated with radical cystectomy. The status of LVI should be determined in cystectomy specimens which may provide further risk stratification in patients following radical cystectomy.
Poster #61

RELATIONSHIP BETWEEN PRIMARY GLEASON PATTERN ON NEEDLE BIOPSY AND CLINICOPATHOLOGICAL OUTCOMES AMONG MEN WITH GLEASON 7 ADENOCARCINOMA OF THE PROSTATE

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Purpose: To determine the relationship between needle biopsy primary grade, pathological variables, and post-prostatectomy biochemical recurrence among men with Gleason 7 adenocarcinoma of the prostate.

Methods: We identified 320 men with Gleason score 7 tumors on needle biopsy treated with radical prostatectomy between 1991 and 2001 by a single surgeon. None of these patients received neoadjuvant or adjuvant hormonal or radiation therapy. The chi-square test and Kaplan-Meier method were used to evaluate the correlation between biopsy Gleason score, pathological outcomes, and biochemical recurrence.

Results: A total of 252 (78.7%) and 68 (21.3%) men had primary Gleason pattern 3 and 4 identified on needle biopsy, respectively. Among patients with Gleason 3 + 4 tumors on biopsy, 76% were primary Gleason grade \(<3\) while 24% were upgraded to primary pattern \(\geq4\) on final pathologic analysis. Among patients with Gleason 4 + 3 tumors on biopsy, 53% were primary pattern \(\geq4\) while 47% were downgraded to primary pattern \(<3\) on final pathologic analysis. Patients with a needle biopsy Gleason score of 3 + 4 were more likely to have capsular penetration if the prostatectomy Gleason score was upgraded (p = 0.004). The actuarial risk of biochemical PSA recurrence was significantly higher among patients with Gleason pattern 4 + 3 on biopsy if the prostatectomy Gleason score was \(\geq4 + 3\) compared to \(<3 + 4\) (p = 0.03).

Conclusions: Approximately 47% of men with a diagnosis of Gleason 4 + 3 on needle biopsy will be downgraded to a Gleason sum of \(<3 + 4\) on final pathologic analysis. This group of patients will have significantly better biochemical PSA recurrence-free outcomes compared to patients diagnosed with Gleason 4 + 3 on biopsy who were not downgraded on final pathologic analysis. These data support the need for identification of additional molecular markers to improve the utility of distinguishing between primary Gleason pattern on needle biopsy among patients with Gleason 7 adenocarcinoma of the prostate.

Poster #62

QUANTITATION OF TESTOSTEROONE AND DIHYDROTESTOSTERONE TISSUE LEVELS IN RECURRENT PROSTATE CANCER USING LIQUID CHROMATOGRAPHY TANDEM MASS SPECTROMETRY

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Prostate cancer (CaP) recurs during androgen deprivation therapy despite castrate levels of serum androgens. Radioimmunoassay (RIA) analysis found high levels of testicular androgens in recurrent CaP tissue (Mohler, Clin Cancer Res, 2004). We have confirmed these results in 18 recurrent CaP using liquid chromatography tandem mass spectrometry (LC/MS/MS).

Recurrent CaP tissue was obtained from 18 men who underwent transurethral resection to relieve urinary retention from local recurrence during androgen deprivation therapy. Androgen-stimulated benign prostate specimens were obtained from 18 radical prostatectomies performed for clinically localized prostate cancer. The superior vascular pedicles were left intact until all other portions of the procedure were completed. Upon removal of the operative specimen, the specimen was inked, samples obtained and frozen in liquid nitrogen.

Androgens were extracted from prostate tissue homogenates that contained 1 ng deuterated T and DHT internal standards. Samples were purified using C18 solid-phase extraction cartridges, reconstituted and separated using a capillary HPLC system and methanol/water gradient. Ionization was accomplished using turbospray ionization (ESI). LC/MS/MS was performed using triple quadrupole mass spectrometer. The molecular ion was generated for T or DHT and collision induced dissociation product ions 97.0 (T) and 255.2 (DHT) were used for quantitation.

T levels were similar in 18 specimens of recurrent CaP (3.75 pmol/gm tissue) and androgen-stimulated benign prostate (2.75 pmol/gm tissue) (Wilcoxon, 2-sided P = 0.30). DHT levels were lower in recurrent CaP (1.25 pmol/gm tissue) than benign prostate (13.7 pmol/gm tissue) (Wilcoxon, 2-sided P < 0.0001). Tissue DHT levels in recurrent CaP specimens were found to be sufficient for AR activation. These results indicate that recurrent CaP often develops the capacity to synthesize testicular androgens from adrenal androgens or cholesterol. (Supported by NCI-CA-77739)
APPLICATION OF CHROMOGENIC IN SITU HYBRIDIZATION (CISH) IN THE DIFFERENTIAL DIAGNOSIS OF RENAL TUMORS

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Background: Ninety renal cell tumors, 28 type 1 PRCC (8 sporadic, 9 hereditary and 11 unknown) and 63 cases representing the spectrum of renal tumors (18 clear cell RCC, 10 oncocytomas, 9 type 2 PRCC, 8 chromophobe, 4 medullary, 6 CDC, 2 metanephric adenomas, 4 hybrid tumors, and 2 unclassified) were studied. All cases were classified following the WHO classification. CISH was performed utilizing commercial probes for chromosomes 7 and 17. Cases were categorized as diploid (two copies) or aneuploid if they had three or more copies in more than 10% of tumor cells.

Design: Ninety renal cell tumors, 28 type 1 PRCC (8 sporadic, 9 hereditary and 11 unknown) and 63 cases representing the spectrum of renal tumors (18 clear cell RCC, 10 oncocytomas, 9 type 2 PRCC, 8 chromophobe, 4 medullary, 6 CDC, 2 metanephric adenomas, 4 hybrid tumors, and 2 unclassified) were studied. All cases were classified following the WHO classification. CISH was performed utilizing commercial probes for chromosomes 7 and 17. Cases were categorized as diploid (two copies) or aneuploid if they had three or more copies in more than 10% of tumor cells.

Results: Fifteen type 1 PRCC tumors showed aneuploidy for chromosome 7 (9 hereditary, 3 sporadic and 3 unknown) and 13 cases were diploid. Seven cases were aneuploid for chromosome 17 (5 hereditary and 2 unknown). Three type 2 PRCC were aneuploid for chromosome 7 and 2 for chromosome 17. Aneuploidy for chromosome 7 was also found in 3 clear cell RCC, one CDC, one chromophobe, and 1 unclassified tumor. Aneuploidy for chromosome 17 was detected in 2 chromophobes and one unclassified.

Conclusion: These results indicate that CISH is a useful tool for pathologists to identify chromosomal abnormalities and to improve the diagnosis of renal tumors. There is a clear correlation between aneuploidy for chromosome 7 identified by CISH and hereditary PRCC type 1. Absence of aneuploidy for chromosome 17 can help to identify sporadic PRCC type 1. Identification of aneuploid RCC clear cells with sarcomatoid features for chromosome 7 suggests high grade and new hits in tumor progression.

RESULTS

<table>
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<th>Ch 7 Diploidy</th>
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PROGNOSTIC NOMOGRAM FOR RENAL INSUFFICIENCY AFTER RADICAL OR PARTIAL NEPHRECTOMY

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Purpose: No published studies to date have simultaneously analyzed multiple prognostic factors to predict renal insufficiency after nephrectomy, either partial or radical. We developed and performed internal validations of a postoperative nomogram for this purpose. We utilized a prospectively updated database of over 1500 patients treated at a single institution.

Materials and Methods: From July 1989 to October 2003, 1185 radical nephrectomies and 438 partial nephrectomies for renal cell carcinoma performed at Memorial Sloan-Kettering Cancer Center (MSKCC) were reviewed from the MSKCC kidney database. Computer tomography studies were reviewed by a single radiologist. Kidney volume was calculated using the ellipsoid formula (V = L1 x L2 x L3 x Pi / 6). Renal failure was defined by two serum creatinine values of >2.0 mg/dL, at least one month post-operatively. Patients not having both pre- and post-operative CT-scans, or having pre-operative CT-scans older than 6 months or post-operative CT-scans obtained < 4 months or >24 months post-operatively were excluded from the study. All renal cortical neoplasms were included in the study regardless of histology but not cases with bilateral synchronous disease. We modeled clinical data for 161 patients having undergone partial nephrectomies and 857 patients having undergone radical nephrectomies. Prognostic variables for the nomogram included pre-operative serum creatinine values, ASA (American Society of Anesthesiologists) score, % change in kidney volume after surgery, age and gender of patients.

Results: Renal failure was noted in 105 (12.3%) patients having undergone radical nephrectomy and 6 (3.7%) patients having undergone partial nephrectomy of the 1018 patients in the study. 328 (27.7%) patients having had radical nephrectomies and 277 (36.2%) patients having had partial nephrectomies were excluded from the study. Patients had a median and maximum follow-up of 21.2 and 157.9 months, respectively. The nomogram was designed based on the Cox proportional hazards regression model. The 7-year probability of freedom from renal failure for the patient cohort was 79.1% (95% confidence interval 74.6 to 83.6). Following internal statistical validation, predictions by the nomogram appeared accurate and discriminating. The concordance index was found to be 0.835 for freedom from renal failure.

Conclusions: A nomogram has been developed that can be used to predict the 7-year probability of renal failure for patients undergoing either radical or partial nephrectomy.
**Poster #65**

PROSPECTIVE, LONGITUDINAL, COMPARATIVE STUDY OF HEALTH RELATED QUALITY OF LIFE IN PATIENTS UNDERGOING INVASIVE TREATMENTS FOR LOCALIZED PROSTATE CANCER

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Introduction and Objectives: Health related quality of life (QOL) concerns are important for patients selecting treatment options for clinically localized prostate cancer and are critical in evaluating outcomes following intervention. We report pre- and post-treatment general and disease specific QOL for the following invasive interventions: open radical prostatectomy (ORP), laparoscopic radical prostatectomy (LRP), and $^{103}$Pd brachytherapy ($^{106}$Pd).

Materials and Methods: We performed a prospective, longitudinal survey of 452 newly diagnosed patients treated at a single medical center between 2001 and 2003. An IRB approved questionnaire comprised of validated QOL instruments was sent to patients scheduled to undergo ORP, LRP or $^{103}$Pd. The same questionnaire was sent out at 1, 3, 6, 9 and 12 months after therapy. Comparisons were made between the different groups to determine if the choice of therapy resulted in differences in QOL.

Results: The survey was sent to 116, 186 and 150 men who underwent LRP, ORP and $^{103}$Pd respectively. General QOL scores were minimally affected by the choices; however, the disease specific domains of bowel, urinary, and sexual function were adversely affected by all modalities. The ORP and LRP groups were similar among disease specific domains, and received lower post-treatment urinary and sexual scores than $^{103}$Pd. At 12 months, 38% of ORP and 46 % of LRP patients returned to baseline urinary function compared to 75% of $^{103}$Pd patients. At 12 months, 63% of $^{103}$Pd patients returned to baseline sexual function, compared to 19% and 19% of the LRP and ORP groups, respectively.

Conclusions: Invasive treatments for localized prostate cancer have little impact on general QOL but significantly affect disease specific domains. ORP and LRP have a greater initial negative impact on urinary and sexual function than $^{103}$Pd. The differences among the treatments in regards to QOL provide information to patients in the medical decision process.

**Poster #66**

ANALYSIS OF BRG1 AND HBRM EXPRESSION IN PROSTATE CANCER CELLS

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Introduction: Prostate cancer remains the second most lethal cancer for American men. The androgen receptor (AR) plays a key role in the development and progression of prostate cancer. BRG1 and hBRM are two core ATPases that are essential for activation of the AR. We investigated the expression levels of BRG1 and hBRM in human prostate specimens.

Methods: Random samples of human prostate tissue were obtained from 46 patients who had undergone radical prostatectomy between 2001 and 2003. Non-cancerous and cancerous portions of the prostate were analyzed by Western Blot to detect expression levels of core ATPases BRG1 and hBRM. Pathologic data consisting of Gleason score, percent of prostate involved by tumor, lymph node status, surgical margin status, Ki-67, p53, p21, and tumor ploidy were recorded. These data were then tabulated, and analyzed using univariate analysis was performed using an unpaired student's t-test. P-values less than 0.05 were considered statistically significant.

Results: Mean patient age was 61.4 years of age, mean Gleason sum was 6.8 with a mean percent of prostate involved by tumor was 20%. Vascular invasion by the tumor was present in 6 patients (13%) while perineural invasion was present in 26 patients (56%). These data were then tabulated, and analyzed using univariate analysis was performed using an unpaired student's t-test. P-values less than 0.05 were considered statistically significant.

Conclusions: There was increased expression of BRG1 in prostate cancer tissue, although it was not statistically significant. We failed to demonstrate increased levels of hBRM in our prostate cancer tissue specimens. However, correlations were also found with expression of Ki-67 and p21. Further studies are needed to delineate to role that BRG1 and hBRM will play in the diagnosis of prostate cancer.
Poster #67

RISE IN PSA FOLLOWING INTRAMUSCULAR TESTOSTERONE INJECTION CORRELATES HIGHLY WITH TUMOR VOLUME AND GLEASON SUM IN MEN WITH PSA 2.4 TO 4 DIAGNOSED WITH PROSTATE CANCER (CaP) FOLLOWING TRANSRECTAL ULTRASOUND-GUIDED (TRUS) PROSTATE BIOPSY
Michael J. Shulman, Vitaly Margulis, and Elie A. Benaim. University of Texas Southwestern Medical Center, Dallas Veterans Affairs Medical Center, Dallas, Texas

Introduction: The purpose of this study was to determine if a rise in PSA following the administration of intramuscular testosterone (T) to men with PSA levels between 2.4 to 4 would correlate with Gleason sum and tumor volume in men diagnosed with CaP following TRUS prostate biopsy.

Methods: 40 men with PSA levels between 2.4 to 4, normal digital rectal exams, and normal T levels were prospectively enrolled. All men with a prior history of CaP were excluded. Each participant received one intramuscular injection of 400 mg Testosterone Cypionate at the start of the study. PSA and early morning T levels were measured at baseline, 48 hours, and at weeks 1, 2, and 4. All men underwent a TRUS prostate biopsy at week 4. The Institutional Review Board at the Dallas Veterans Affairs Medical Center approved this study.

Results: 18 of 40 men (45%) were diagnosed with CaP. Baseline demographics included: median age 58 years (range 47-68), 17 white (94.4%), 5 with family history of CaP (27.8%), median PSA 2.9 ng/ml (range 2.5-3.9), and median T 3.9 mg/ml (range 1.6-7.2). PSA increased significantly from baseline to 4.0 mg/ml four weeks following T injection (p=0.001, Wilcoxon Ranks Test). Histological evaluation demonstrated 14 (77.8%) and 4 (22.2%) men with Gleason 6 and 7 CaP, respectively. The median number of percent positive cores was 16.7 (range 8.3-41.7) and median percent tissue with cancer was 15 (range 5-50). The change in PSA from baseline to 4 weeks significantly correlated with percent positive cores (correlation coefficient (cc) 0.469, p=0.002, Spearman), percent tissue with cancer (cc=0.484, p=0.002, Spearman), and Gleason sum (cc=0.469, p=0.002, Spearman). The median change in PSA from baseline to 4 weeks for patients with Gleason 6 cancer (0.75 ng/ml, range –0.60 to1.50) was significantly lower than for men with Gleason 7 cancer (2.25 ng/ml, range 0.30 to 28.00) (p=0.036, Independent Sample T-test).

Conclusions: The rise in PSA stimulated by T significantly and positively correlated with both tumor volume and aggressiveness in men with PSA levels between 2.4 to 4 and prostate cancer detected following TRUS biopsy for PSA levels between 2.4 to 4.

Poster #68

GENOTYPE-PHENOTYPE CORRELATIONS FOR GERMLINE MUTATIONS IN THE VHL TUMOR-SUPPRESSOR GENE
Nicol S. Corbin, Gladys Glenn, Paul S. Albert, James Peterson, Kathy Hurley, Jodi K. Maranchie, Anna Cheh, Donald P. Bottaro, Peter L. Choyke, McClellan M. Walther, Berton Zbar, and W. Marston Linehan

Alterations in the VHL tumor-suppressor gene are associated with the development of von Hippel Lindau (VHL) disease, an autosomal-dominant familial cancer syndrome. Patients with this disorder are at risk to develop a variety of tumors, including cystic and solid tumors of the kidney, pheochromocytomas, central nervous system hemangioblastomas, retinal angiomas, pancreatic cystic and solid tumors, endolymphatic sac tumors, and cystadenomas of the epididymis and broad ligament. Inter- and intrafamilial variability of tumor involvement is considerable and has been shown to vary with the underlying germline mutation(s) in the VHL gene. We compared the clinical phenotypes of 291 families (602 patients) with germline VHL gene mutations. Clinical evaluation of phenotype included history and physical, serum and urine laboratory investigation, imaging studies, and surgical intervention when necessary. Genotype evaluation consisted of analysis of peripheral blood lymphocytes for mutations or deletions of the VHL gene in individuals suspected of or at risk for VHL. Mutations were detected in 291/291 (100%) of families tested. Statistical analyses were performed comparing types of VHL mutations, types of tumors, affected domains, and affected exons. The overall prevalence of each of the different tumor types averaged by family involvement includes central nervous system hemangioblastomas 84%, kidney cysts 73%, pancreas cysts 67%, retinal angiomas 58%, solid kidney tumors 58%, pheochromocytoma 20%, solid pancreas tumors 19%, and endolymphatic sac tumors 7% (standard errors <= 0.01). We confirm notable differences in phenotype between missense and truncation mutations and identify strong pair-wise dependence between central nervous system hemangioblastomas, kidney solid tumors, kidney cysts, and pancreas cysts. Pheochromocytomas are negatively associated with these tumors. We found an attenuated phenotype for patients with complete VHL deletions versus other mutation types. In summary, we report the genotype/phenotype correlations for the largest collection of VHL families to date in order to enhance understanding of the molecular pathogenesis of VHL disease and to aid in clinical management and provide the basis for molecular therapeutic approaches for VHL-associated cancers.
**Poster #69**

**SAFETY PROFILE OF REPEATED DOSE SAMARIUM 153 LEXIDRONAM IN PROSTATE CANCER PATIENTS**

Oliver Sartor, MD, Robert Reid, MD, Celestia Higano, MD, David Bushnell, MD and Donald Quick, MD. LSU Medical School, New Orleans, LA; London Health Sciences Center, London, Ontario; University of Washington Medical Center, Seattle, WA; Iowa City VA Medical Center, Iowa City, IA; Joe Arrington Cancer Center, Lubbock, TX

**Introduction:** Bone metastases represent a major source of morbidity for patients with prostate cancer. Two prospective randomized placebo controlled multi-center studies have demonstrated safety and efficacy of single 1.0 mCi/kg doses of samarium-153 lexidronam (153Sm-EDTMP) in relieving pain and reducing opioid analgesic use in hormone-refractory patients with symptomatic bone metastases. Clinically significant toxicity was restricted to transient and reversible suppression of white blood cells (WBC) and platelets. Less data exist on the safety of repeated doses of radiopharmaceuticals.

**Methods:** We prospectively investigated the safety of multiple dose 153Sm-EDTMP in two separate clinical settings for patients with bone metastases: a) symptomatic patients (primarily hormone-refractory prostate cancer) received multiple administrations of 1.0 mCi/kg (the FDA approved dose) based on recurrence of symptoms and normal baseline WBC and platelet counts, and b) hormonally sensitive stage D2 prostate cancer patients received multiple higher dose administrations at fixed intervals.

**Results:** Repeat administrations (range 2-11 doses/patient) at 1 mCi/kg were given to 54 patients. The mean WBC nadir (and % baseline) was 3.6 ± 1.1 (49%), 3.6 ± 1.1 (54%), and 3.5 ± 0.9 (57%) for patients administered 1, 2, or ≥3 doses (respectively). The mean platelet nadir (and % baseline) was 129 ± 37 (50%), 105 ± 49 (48%), and 93 ± 38 (50%) after similar doses. No grade 4 platelet or WBC toxicities were observed. At the higher fixed interval dose of 2.0 mCi/kg/dose q 12 weeks for four planned cycles, 2/6 hormonally sensitive chemotherapy naïve D2 prostate cancer patients were unable to receive the fourth cycle due to persistently low platelets. An additional group of 6 patients with hormonally sensitive chemotherapy naïve D2 prostate cancer were planned to receive 3 doses at 2.0 mCi/kg/dose at intervals of 16 weeks. Three planned doses were completed in 5/6 patients. At this dose and schedule, the mean WBC nadir (and % baseline) was 2.5 ± 0.5 (46%), 2.4 ± 0.5 (52%), and 2.5 ± 0.7 (57%) for patients administered 1, 2, or ≥3 doses (respectively). The mean platelet nadir (and % baseline) was 113 ± 69 (47%), 110 ± 45 (60%), and 102 ± 21 (52%). Time to nadir was 5-6 weeks for both WBC and platelets. No grade 3-4 platelet toxicities were observed but 5/6 patients had grade 3 WBC decreases. There were no grade 4 WBC decreases.

**Conclusions:** These data clearly indicate that multiply doses of 1 mCi/kg of Samarium-153 lexidronam can be safely administered to patients with painful bone metastases provided normal WBC and platelets are present at the time of dosing. For fixed interval dosing, we conclude that 2.0 mCi/Kg/dose q 16 weeks X 3 is readily feasible from a safety perspective in patients with D2 prostate cancer without prior chemotherapy.
Poster #71

SURVEILLANCE IS THE APPROPRIATE MANAGEMENT STRATEGY IN PATIENTS WITH STAGE I SEMINOMA

Purpose: Standard management for patients with stage I seminoma is adjuvant radiotherapy (RT) to the para-aortic + ipsilateral pelvic lymph nodes. Despite the documented increased risk of second malignancies with adjuvant RT, surveillance, reserving treatment for patients who relapse, has not become widely accepted. We reviewed all patients with stage I disease over an 18 year period to document the outcome in patients managed with these two management strategies.

Materials and Methods: Between January 1981 to December 1999 627 patients with stage I seminoma were seen at our institution. Of those, 345 were managed with surveillance and 282 received adjuvant RT. Patient preference determined management approach. The median age for both surveillance and adjuvant RT was 34 years. The median follow-up was 8.8 years (surveillance 9.4 years, adjuvant RT 8.3 years).

Results: Of 345 patients on surveillance, 55 relapsed (para-aortic nodes in 49, pelvic nodes - 2, other- 4) giving a 5 year relapse rate of 15%. Forty were managed by RT, 13 with chemotherapy, and 2 with surgery. Of 40 patients managed with RT for first relapse, 5 developed a second relapse and were salvaged with chemotherapy. The actuarial risk of requiring chemotherapy for treatment of first or second relapse on surveillance was 5.1%. Of 282 patients who received adjuvant RT, 14 patients have relapsed giving a 5 year relapse rate of 5%. Of those, 10 (3.6 %) were managed with chemotherapy, 3 with RT (inguinal recurrences), and 1 with surgery. The actuarial rate of requiring chemotherapy for treatment of relapse with adjuvant RT was 3.5%.

Conclusions: Surveillance policy for stage I seminoma allows 85% of patients to avoid unnecessary RT. No increase in the number of patients who require chemotherapy has been observed. Surveillance should be offered as standard management to all patients with stage I seminoma.

Poster #72

OUTCOMES OF HAND ASSISTED LAPAROSCOPIC NEPHRECTOMY (HALN) IN TECHNICALLY CHALLENGING CASES
Pankaj Kaira, Mark Chang, Deborah Glassman, Leonard Gomella, Stephen Strup, David McGinnis, Daniel Simon, Dolores Byrne, Ramsay L. Kuo.

Introduction and Objectives: HALN combines the advantage of manual dissection with the decreased morbidity of pure laparoscopy. Although HALN opponents feel this approach precludes the development of advanced laparoscopic skills, pure laparoscopy may be difficult in circumstances involving large renal lesions, renal vein thrombus, and prior extensive abdominal surgery. These situations may be better suited for HALN.

Methods: We retrospectively reviewed 322 consecutive HALNs from 1998 to 2004 performed at a single institution. Patients with prior extensive abdominal surgery or procedures on the affected kidney, perirenal inflammation, lesions > 10 cm, or pathological stage T3b tumors were included. Pathologic stage T3a lesions not meeting the above criteria were not considered.

Results: 42 patients were included. 16 (38%) patients had > 10 cm lesions, with 10 (24%) cases involving renal vein thrombus. 4 (10%) patients underwent concurrent perihilar lymphadenectomy with positive pathology. 1 renal tumor with muscle invasion was successfully managed without conversion. 10 (24%) patients had prior major abdominal surgery with anticipation of significant intra-abdominal adhesions. 6 patients (14%) had prior renal procedures or chronic inflammatory processes involving the affected kidney. Overall mean operative time and blood loss was 235 minutes and 439 ml, respectively, with a mean hospital stay of 4 days. 4 cases (10%) required open conversion (1 renal hilar injury, 2 difficult dissection, 1 persistent ooze from renal fossa). Post-operative complications included ileus (4), onset of atrial fibrillation (1), and chronic obstructive pulmonary disease exacerbation (1). One patient had an incarcerated port site hernia requiring reoperation.

Conclusions: Although laparoscopic nephrectomy is advocated as the minimally invasive approach of choice, certain technically challenging cases may favor HALN to avoid undue morbidity or possibly a higher conversion rate.
**Poster #73**

**MECHANISM OF INHIBITION OF CELL MOTILITY AND INVASION BY GRB2 SH2 DOMAIN ANTAGONISTS**

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Growth factor receptor bound protein 2 (Grb2) is an essential intracellular adaptor protein involved in several growth factor signal transduction pathways, including those of hepatocyte growth factor, epidermal growth factor, and vascular endothelial cell growth factor. Ligand binding and/or oncogenic mutations induce receptor tyrosine kinase (RTK) activation and autophosphorylation of specific tyrosine residues within RTK intracellular domains. Grb2 then interacts through its SH2 domain either directly with activated RTKs, or indirectly through receptor phosphorylated proteins. Through protein interactions mediated by its two SH3 domains, Grb2 then links RTKs with several key intracellular regulatory networks, including the Ras/Erk pathway and the Arp2/3/WASp/actin filament system, resulting in increased cell proliferation and motility. Potent synthetic low molecular weight antagonists of Grb2 SH2 domain binding have been developed that block RTK-Grb2 interaction, growth factor stimulated motility and matrix invasion by several normal and tumor cell lines, including kidney epithelial cells and vascular endothelial cells. These SH2 domain binding antagonists may have therapeutic value as anti-metastasis drugs in genitourinary malignancies as well as other human cancers. The molecular mechanism(s) of action of these compounds have been investigated by biotin tagging and streptavidin mediated recovery of drug-bound protein targets, followed by SDS-PAGE and immunoblot analysis. Our results suggest that multiple downstream effectors of growth factor stimulated Grb2 signaling exist, such as Gab1, Arp2/3, Shc and Sos 1.

**Poster #74**

**PROSTATE CANCER ON THE INTERNET: INFORMATION OR MISINFORMATION?**

Peter Black, David Penson

*Introduction:* As the use of the internet increases and the information available on the World Wide Web expands, patients are turning to it more and more as an important source of information on which to base medical decisions. We aimed to assess the quality of information available on prostate cancer on the internet by a web survey.

*Methods and Materials:* The search engine Webcrawler® was used with the search term “prostate cancer” to generate a list of 75 websites which were reviewed within a 2 week period. Each website was evaluated for currency (date of last update), disclosure (organization, authorship, sponsorship), attribution (references, disclaimer), links and interactivity. A rating tool was designed including 50 elements considered essential for a comprehensive review of prostate cancer, and each website was judged for degree of coverage (ratings: 1 = minimally addressed, 2 = more than minimally addressed, 3 = mostly addressed) and accuracy of information (1 = mostly incorrect, 2 = mostly correct, 3 = completely correct) for each element found on the website.

*Results:* The search generated 390,770 sites. The top 75 included 59 original sites and 16 that were dead links. Only 39 of the 59 sites had information about prostate cancer. 24 sites indicated no date of last update, 9 sites were updated within 6 months, and 6 more than 6 months previously. The organization was indicated on 38 sites, authorship on 22 and sponsorship on 33. References were rarely given (n=5) and a disclaimer was provided on less than half of sites (n=18). The sites covered a mean of 24 elements (6-43) with a mean coverage rating of 1.0 to 2.6 (1.8 overall). Six sites covered more than 35 elements. The mean accuracy rating for the sites ranged from 2.6 to 3.0 (2.9 overall). Of 943 elements covered in 39 sites, 94% were completely correct, 5% were mostly correct and 1% was mostly incorrect.

*Conclusion:* Commonly used search engines are not user-friendly for researching prostate cancer as just more than one half of sites provide information on the disease. Most sites do not indicate how current the information is or where it was obtained. Although sponsorship is usually outlined adequately, authorship is not, and most do not offer a disclaimer. While some sites provide excellent coverage of a many facets of the disease, others are very limited in scope and unbalanced. 99% of information was mostly or completely accurate. The Urologist needs to be aware of these shortcomings when counseling patients.
TESTOSTERONE REPLACEMENT THERAPY AFTER PRIMARY TREATMENT OF PROSTATE CANCER
Piyush K. Agarwal and Michael G. Oefelein

Introduction: A history of prostate cancer has been an absolute contraindication for testosterone supplementation. We studied a cohort of hypogonadal patients treated with radical retropubic prostatectomy (RRP) for organ-confined prostate cancer to determine if testosterone replacement therapy (TRT) could be efficacious and administered safely without causing recurrent prostate tumor.

Methods: 10 hypogonadal patients previously treated with RRP for organ-confined prostate cancer were identified. They presented with low serum total testosterone (TT) and symptoms of hypogonadism after RRP. Patients had baseline serum determinations of prostate specific antigen (PSA) and TT and were started on testosterone supplementation. They were assessed periodically for changes in PSA and TT and for symptomatic improvement using the hormone domain of the Extended Prostate Inventory Composite (EPIC) Health Related Quality of Life questionnaire.

Results: After a median follow-up of 19 months, no patient has developed a detectable (>0.1 ng/ml) PSA. TT increased significantly after starting TRT from a mean value of 197 ± 67 ng/dL to 587 ± 180 ng/dL (p=0.0002). The Hormone Domain of the EPIC Health Related Quality of Life questionnaire increased significantly from 38 ± 5 to 49 ± 3 (p=0.00005) primarily due to a decrease in hot flashes and an increase in energy level.

Conclusions: After a median of 19 months of TRT, hypogonadal patients with a history of prostate cancer had no PSA recurrence and had statistically significant improvements in both their TT and hypogonadal symptoms. In highly selected patients after RRP, TRT can be administered carefully and with benefit to hypogonadal prostate cancer patients.

DIAGNOSTIC SERUM PROTEIN PATTERN RECOGNITION AND BIOMARKER DISCOVERY FOR PROSTATE CANCER USING SELDI-TOF

Introduction: Although the serum prostate-specific antigen (PSA) test has made a great impact on diagnosis, as well as monitoring of progression of prostate cancer (CaP), the need for more accurate tests for early detection of clinically-significant CaP remains a critical part of the solution to this ever-growing health dilemma. Clinical utility of serum surface enhanced laser desorption/ionization time-of-flight (SELDI-TOF) proteomics is currently being investigated in our laboratory as well as in others. Reproducibility and data analysis issues are being addressed through robotic automation and use of multiple bioinformatic approaches. As a follow-up of our initial study on the diagnostic potential of serum proteomic profiling using a dual-chip SELDI-TOF assay we further evaluate the performance of this assay on a larger cohort of patients.

Methods: Sera from 207 CaP patients who underwent radical prostatectomy and 197 healthy male volunteers with PSA < 4ng/ml and with no evidence of prostate cancer were included in the study. Serum samples were processed in duplicate using a Biomek 2000 robotic workstation. SELDI-TOF profiles were generated using IMAC3-Cu and WCX2 arrays by Ciphergen Protein Biological System II ProteinChip Reader. Data analysis was performed using Classification and Regression Trees (CART), Support Vector Machines (SVM) and Artificial Neural Networks (ANN). A training set consisting of 103 CaP patients and 97 controls were used for decision tree building. A blinded test set consisting of 100 controls and 104 CaP patients was used to challenge the algorithms.

Results Obtained: Predictive algorithms generated using the three methods of bioinformatics analysis gave the following average measures of accuracy: for CART - 75% sensitivity and 80% specificity; for SVM – 80% sensitivity and 75% specificity; and for ANN – 82% sensitivity and 70% specificity. A protein peak from the WCX2 array was shown to be a consistent marker in the different methods of bioinformatics analysis and in a previously processed dataset. This candidate biomarker is currently being identified in our laboratory.

Conclusions: Using a larger cohort of CaP patients and streamlined robotic processing of specimens, serum proteomic profiling using SELDI-TOF in a follow-up study continues to show promising potential for CaP detection with high sensitivity and specificity. Consistent serum markers elucidated by SELDI-TOF-MS that can distinguish between CaP and control with high sensitivity and specificity must be identified and further validated.
**Poster #77**

**EXTRA-PERITONEAL VS. INTRA-PERITONEAL ROBOTIC PROSTATECTOMY**  
Rabii Madi, MD, Stephanie Faruzzi, MS, and David Wood, MD

**Introduction:**  
Davinci robotic prostatectomy can be performed either via an extra- or intra peritoneal approach. The extra-peritoneal approach has the advantages similar to an extra-peritoneal open radical prostatectomy, but the potential disadvantages of prolonged operative time and a small working space. We report our experience using both approaches.

**Methods:** From July 2003 to June 2004 52 patients underwent a robotic prostatectomy 31 were performed during the first 6 months and using an intra-peritoneal approach (group 1), and 21 were performed using an extra-peritoneal approach (group 2) during the next 5 months. Clinico-pathologic parameters and peri-operative complications were compared in both groups. All patients were categorized as intent-to-treat analysis.

**Results:** Median surgery time was significantly shorter in the extra- compared to the intra-peritoneal approach (3 hours and 34 minutes versus 4 hours and 1 minute, respectively) (p = 0.017). This was due to the shorter time interval between the skin incision and incision of the endopelvic fascia in the extra- vs. the intra-peritoneal approach (55 minutes versus 74 minutes, respectively) (p < 0.001). There was no significant difference in terms of patient age, clinical and pathologic stage, length of hospital stay, and peri-operative complications between the extra- and the intra-peritoneal approach.

**Conclusion:** Extra-peritoneal robotic prostatectomy offers a similar clinical outcome as the intra-peritoneal approach. However, the extra-peritoneal approach avoids potential bowel injury or complications related to an intra-peritoneal urine leak.

**Poster #78**

**EXENTERATIVE SALVAGE SURGERY FOR HORMONE REFRACTORY (HRCP) OR RADIATION (XRT) RECURRENT PROSTATE CANCER (CAP)**  
Rajen H. Doshi, Daniel W. Lin, Celestia Higano, William J. Ellis, and Paul H. Lange

**Background:** CaP patients(pts) with extensive, locally recurrent HRPC or XRT failure present difficult clinical problems. Over the last 12 yrs, we performed cystoprostatectomy (C/P), cystectomy (C) or abdominoperineal resections (A/P) for select pts with of HRPC and XRT failure under the assumption that HRPC pts could receive significant palliation and better survival, and for XRT failures, that C/P may be a better cancer control surgery with less morbidity (especially incontinence) than salvage radical prostatectomy (SRP).

**Methods:** These surgeries were performed in 33pts: 17 pts with HRPC (group I) and 16 pts with XRT failure (group II). Clinical charts were reviewed retrospectively.  

**Results:** In group I (17), primary therapy was XRT (8), hormonal ablation (6), and RP (3). Mean time to treatment failure was 40 months; mean time from treatment failure to HRPC was 12 months. Median PSA at surgery was 15.8 ng/ml (range 0.6 – 296). Local symptoms and signs will be presented. 9 pts had A/P with 8 ileal conduits and 1 had a continent reservoir (CUR); 5 pts had C/P and 3 had C of which 7 had CUR’s and 1 had a conduit. 82% had pT4 disease, 65% had N+. There were 3 complications (SBO, MI, and pelvic abscess). Survival post surgery was 29 mos (mean), 12 mos (median); range 1-129; in 88% significant palliation was achieved (details will be presented). In group II (16), median time from XRT to biochemical failure was 57 mos. Median PSA at C/P was 5.6 ng/ml (range 1-19). 14 pts had CUR’s, 2 had conduits. 38% had pT4 disease, 25% had positive nodes; 2 had positive margins but in 43% with negative margins, they would have been positive with SRP. There were 4 complications (2 UTI’s, dehydration and pleural effusion.) There was no incontinence. Mean follow up is 46 months with a median follow up of 41.3 months. 9 patients have no detectable disease, 5 have progressive ds and 2 are deceased.

**Conclusions:** This is one of the largest reported series of exenterative pelvic surgery for locally advanced CaP. In select XRT failures (significant local disease and/or possible radiation damage to the external sphincter), C/P is better for continence and possibly cancer control. In HRPC, exenterative procedures are difficult but seem to enhance quality of life and possibly improve survival with acceptable complication rates.
IMAGING METASTASIS OF RENAL CLEAR CELL CARCINOMA IN MURINE MODELS USING THE LUCIFERASE SYSTEM


Introduction: We have developed murine models in which human renal cancer cell lines (RCC) are injected into SCID/Beige either intra-renal or sub-cutaneous routes. Tumors develop over two to three weeks and lung metastasis develop in approximately 5 to 6 weeks. We also have a model in which the cells are injected via tail vein and lung tumors develop in approximately three weeks. In order to evaluate tumors that develop in areas other than the sub-cutaneous region, the mice have been sacrificed or undergone a time consuming and difficult to implement procedure such as CT or MRI scan. Even these traditional methods can miss the smallest tumors (<10mm). Transfecting our cell lines with the luciferase gene has allowed us to follow tumor growth and spread without having to sacrifice the mouse. We have also been able to identify tumors less than 5mm in size in deep tissues such as the kidney.

Methods: We transfected the luciferase gene into 786-0, C-2, and the 121 RCC cell lines. Once each of these cell lines is stably transected with the luciferase gene, they will be injected into mice via the tail vein, intra-renal, or subcutaneous route. At present, only the 786-0 cells have been injected into the mice; injections consisted of 1 or 5 million cells. Mice were imaged the one hour after injection, and then every seven days thereafter using Xenogen imaging system (Cranbury, New Jersey).

Results: We were able to successfully image tumors that developed in the mice for each of the injection routes described above. We sacrificed one mouse at 27 days post tumor injection into the kidney; imaging had clearly identified a growing tumor in the kidney. The tumor in this mouse had grown to approximately 5mm in size.

Conclusion: Transfecting RCC lines with the luciferase gene will allow us to follow tumor growth and spread in the deep tissues of mice over time without having to sacrifice the mouse. Furthermore this method will allow us to identify tumors at a very early stage when they may even be missed by gross visual examination. One of our ultimate goals is to use this system to evaluate the effect of various drug treatments on the growth and spread of RCC in the murine models.

MODELING THE COST OF MANAGEMENT OPTIONS FOR STAGE I NONSEMINOMATOUS GERM CELL TUMORS: A DECISION TREE ANALYSIS

Richard E Link, MD, PhD1, Mohamad E. Allaf, MD1, Roberto Pili, MD2, and Louis R Kavoussi, MD1.  Brady Urological Institute1, and Department of Oncology2, Johns Hopkins Medical Institutions, Baltimore, MD

Introduction: Patients with clinical stage I nonseminomatous germ cell tumors (NSGCT) have been managed with surveillance, chemotherapy or retroperitoneal lymphadenectomy (RPLND). All options have similar survival outcomes. Cost factors that may influence the choice of therapy were evaluated using computer-based decision tree analysis.

Methods: A detailed model was developed that integrates the projected costs of more than sixty possible treatment outcomes following the original choice of primary surveillance, chemotherapy or RPLND. It incorporates primary, adjuvant and salvage chemotherapy, primary and post-chemotherapy RPLND and both laparoscopic and open surgical approaches. Starting values for model variables and probabilities were derived from a comprehensive meta-analysis of the last 25 years of testes cancer literature. Hypothesis testing was performed using both one and two-dimensional sensitivity analysis.

Results: The model predicts a cost premium for both primary chemotherapy (22%) and RPLND (57%) as compared to surveillance, which was the least costly option. If laparoscopic RPLND was practiced, the cost premium for primary surgery (30%) approached that of chemotherapy. Open RPLND was 1.25x as costly as laparoscopic RPLND in this model, primarily due to the longer period of inpatient hospitalization. Equivalence in purely perioperative costs, however, could be achieved with a five-day hospital stay after open surgery. For a surveillance program based on treatment of retroperitoneal failures with open RPLND, primary chemotherapy became cost advantageous when the probability of failing surveillance was > 50% (as can be seen in stage I NSGCT with high-risk characteristics).

Conclusions: This model allows a variety of treatment cost hypotheses to be tested. Primary RPLND is never cost advantageous over surveillance or primary chemotherapy. Surgical costs can significantly increase the overall cost of a surveillance program. In stage I patients with high-risk tumor characteristics primary chemotherapy may have a cost advantage over surveillance.
Poster #81

BIOLOGICAL-MRI GUIDED TRANSRECTAL PROSTATE BIOPSY

Introduction and Objectives: Prostate cancer diagnosis is hampered by lack of specificity of PSA and standard imaging techniques. Dynamic contrast-enhanced (DCE)-MRI has been shown to improve the specificity of standard T2-weighted MRI imaging. Histopathologic analysis of imaging abnormalities is necessary to confirm the specificity of new imaging modalities. MRI-guided biopsy provides excellent co-localization of MRI images and prostate tissue. Herein we describe our technique of MRI-guided transrectal prostate biopsy.

Materials and Methods: An endorectal coil was modified for interventional procedures to deliver a needle to specific areas in the prostate. Procedures performed with the MRI system include fiducial marker placement prior to external beam radiation therapy and prostate biopsy. Patients were prepared with oral antibiotics, Fleet enema, oral lorazepam and periprostatic local anesthetic prior to entering the scanner. Procedures were performed with patients prone and an endorectal coil in place. T2-weighted fast spin echo and DCE sequences were performed. Fiducial markers were placed at the base, apex, and right and left midgland margins of the prostate gland. For biopsy procedures, suspicious lesions on T2-weighted or DCE-MRI images were specifically targeted. Using specially developed tracking software, the endorectal device was guided to the proper position to deliver the needle to the target site. After MRI confirmation of needle position, core biopsies were taken or fiducial markers were placed.

Results: 24 MRI procedures were performed (13 fiducial marker placements / 11 prostate biopsies). Mean procedure time was 97 minutes for fiducial marker placement and 95 minutes for biopsies. Mean needle tip placement accuracy was 1.9 millimeters. In 11 biopsy procedures, we detected 3 cancers and 2 cases of high grade PIN. No unexpected or severe adverse events occurred. One procedure was aborted due to a vasovagal reaction and was treated with intravenous fluids. A second patient had an infection after fiducial marker placement that resolved with antibiotics.

Conclusions: MRI-guided transrectal biopsy can be performed safely in a standard closed-bore MRI, using local anesthesia. We were able to accurately target contrast enhancing lesions. Future applications include image-guided evaluation of patients with persistently elevated PSA and previously negative biopsies. This platform allows for histologic and molecular confirmation of biological MRI-imaging modalities that can serve as the basis for future transrectal MRI-based prostate therapeutic interventions.

Poster #82

THE SAFE AND EFFECTIVE APPLICATION OF LAPAROSCOPIC PARTIAL NEPHRECTOMY (PN) FOR SMALL RENAL MASSES: DUPLICATION OF OPEN PRINCIPLES AND PRACTICES
Robert Santa-Cruz, Joseph Molitierno, Eric Derksen, Eric Wallen, Raj S. Pruthi, Chapel Hill, NC

Objectives: To demonstrate the feasibility and efficacy of performing LPN for small renal masses utilizing principles and techniques of open partial nephrectomy.

Methods: 41 consecutive patients underwent planned laparoscopic PN for enhancing renal masses via a transperitoneal approach and with the use of a hand-assist device. Blunt and sharp dissection utilizing laparoscopic scissors was primarily used for tumor excision similar to techniques described for open PN. Tumor base was biopsied, and monopolar cautery/argon beam coagulation initially was used. Fibrin tissue sealants were applied to the transected PN bed to ensure hemostasis to help prevent collecting system leak. Temporary hilar vascular occlusion was used during excision for larger, more central tumors in 8 cases. A drain was placed in all patients.

Results: Mean patient age was 59 (31-82) and mean tumor size was 2.7 cm (1.0 – 5.0 cm). Of the 41 patients, 2 were converted to laparoscopic radical nephrectomy due to positive biopsy at resection site (n = 1) and due centrally located tumor (intraoperative decision; n = 1). Three other patients underwent conversion to open PN due to persistent bleeding. Conversion to laparoscopic radical nephrectomy and to open PN were 5% and 7%, respectively. The results of the 36 patients (88%) who underwent successful laparoscopic PN are shown in the table. There was no evidence of delayed hemorrhage or urinary leak in any patient. Immediate complication was seen in 1 patient (enterotomy), and delayed complications in 4 patients (cardiac, SBO, ileus(2)). Short-term outpatient follow-up (16-160 weeks) revealed no additional problems. Pathology was renal carcinoma (33), AML (3), oncocyota (3), complex cyst (2).

Conclusion: Laparoscopic PN is a feasible and appropriate technique for the treatment of small renal tumors. Hemostatic, ablative techniques are not necessary prior to excision, and principles and techniques of open PN (e.g. sharp/blunt dissection, clean/adequate margins, biopsy of resection bed) can be maintained laparoscopically to ensure that a sound oncologic procedure is performed while maintaining benefits of a minimally invasive approach.

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**Poster #83**

**PRE-TREATMENT NOMOGRAM FOR DISEASE-SPECIFIC SURVIVAL OF PATIENTS WITH ANDROGEN INDEPENDENT PROSTATE CANCER**  
Robert Svatek, Pierre I. Karakiewicz, Michael Shulman, Jose Karam, Paul Perrotte, and Elie Benaim  
University of Texas Southwestern Medical Center, Dallas Veterans Affairs Medical Center, Dallas, Texas

**Purpose:** We developed a pre-treatment nomogram that allows prediction of prostate cancer-specific survival in patients with androgen independent prostate cancer (AIPC) based on PSA-related variables.

**Methods:** Data from 129 patients diagnosed with AIPC at a single institution between 1989 and 2002 were retrieved. No patient had received cytotoxic chemotherapy. Univariate and multivariate Cox regression models were constructed to identify factors which predicted death from prostate cancer. These variables were then used in multivariate Cox regression models to develop a nomogram predicting disease-specific survival at 12, 24, 36, 48, and 60 months after AIPC diagnosis.

**Results:** Death from prostate cancer was noted in 74 of 129 patients (57.4%). Mean actuarial overall survival for all men with AIPC was 46.1 months. Mean actuarial cancer-specific survival was 71.2 months. The mean time from AIPC to last follow-up was 39.4 months. Nomogram variables included nadir PSA while on androgen deprivation therapy (ADT), PSA at time of ADT, and PSA doubling time. All variables were significant predictors of cancer-specific mortality in Cox models. The predictive accuracy of the nomogram was 80.2%.

**Conclusion:** A nomogram has been developed to predict the disease-specific survival in patients diagnosed with AIPC. It utilizes readily available clinical parameters and can aide clinicians in treatment selection and stratification of patients during the design of non-hormonal chemotherapy trials.

**Poster #84**

**PROSTATE CANCER SPECIFIC ACTIVITY OF THE SELENIUM METABOLITE, METHYLSELENIC ACID (MSA)**  

**Introduction and Objective:** Recent findings suggest that selenium may be a physiologically important deterrent to prostate cancer. This enthusiasm is reflected in the initiation of the SELECT trial. A better understanding of the molecular mechanisms of selenium mediated prostate cancer prevention is mandatory for the development of efficient chemopreventative strategies. We studied the effects of MSA in normal, transformed and malignant prostate cancer cell lines.

**Methods:** Selenomethionine (Se-Met), the selenium compound used in SELECT, is not suitable for cell culture studies since epithelial cells have a low capacity to generate a monomethylated metabolite from Se-Met, as occurs in vivo. To obviate this problem, a monomethylated selenium metabolite, methylselenic acid (MSA), was developed from in vitro studies. The viability of normal (RWPE-1 and PZ-HPV-7), Ki-ras transformed (RWPE-2), and malignant androgen-dependent (LNCaP) and independent (DU-145) prostate cells in response to MSA was examined by propidium iodide (PI) staining. Proliferation rates were assessed by CellTiter-Blue assay. NF-kB activity was assessed by the luciferase assay.

**Results:** MSA did not affect the viability of normal prostate cells. In contrast, treatment with 5mM MSA induced extensive cell death in LNCaP (> 35%) and DU-145 (> 40%) cells in a dose and time dependent manner. We also observed a dose-dependent effect of MSA on cell death rates of Ki-ras transformed RWPE-2 but not on the non-transformed parental RWPE-1 line. Although no decrease in viability of RWPE-2 cells in response to MSA treatment was observed at 48 hours, a noticeable reduction in proliferation was documented for RWPE-2 cells for that time point. NF-kB activation is not only necessary but also sufficient to confer tumor promoter-induced neoplastic transformation. We demonstrate that MSA inhibits NF-kB activity in DU-145 cells suggesting a potential mechanism of its observed chemopreventative properties.

**Conclusions:** These data demonstrate the selective ability of selenium metabolites to preferentially affect signaling and viability in transformed cell and establish the tumor specific activity of MSA, which may be mediated via inhibition of the NF-kB pathway. These studies offer insight into novel therapeutic strategies and may provide additional opportunities for chemoprevention efforts.
Poster #85

THROMBOCYTOSIS ASSOCIATED WITH RENAL CELL CANCER: DOES TUMOR LATERALITY MAKE A DIFFERENCE?
Sagar R Shah, Augusta, GA; Sandy Srinivas, Stanford, CA; Taiye Ogundiype, Martha Terris, Augusta, GA

Introduction: Thrombocytosis has been shown to have strong prognostic value in patients with renal cell carcinoma (RCC). Our objective was to determine if thrombocytosis in renal cell carcinoma patients could be related to splenic compression versus humoral factors, we evaluated the rate of thrombocytosis in left-sided tumors compared to those on the right.

Methods: The clinical data of 196 patients undergoing radical nephrectomy for renal cell carcinoma at the VA Hospitals in Augusta, Georgia (n=88) and Palo Alto California (n=108) from May 1992 through May 2004 were reviewed for preoperative platelet counts, side of nephrectomy, pathology, age, date of surgery, and stage. Inadequate documentation of preoperative platelet count or side of tumor resulted in the exclusion of 38 patients leaving a final study group of 158. A platelet count greater than 400,000/ mm³ was considered thrombocytosis.

Results: There was no significant difference in the platelet counts, incidence of thrombocytosis, or the relative proportion of left-sided and right-sided tumors at either of the two facilities. As shown by other authors, patients with thrombocytosis had a significantly higher cancer stage than those without (p=0.023). There were also significantly higher platelet counts in patients with left-sided tumors compared to the right (p=0.026). Of the 76 right-sided tumors, 3 (3.9%), demonstrated thrombocytosis. In contrast, 6 (7.3%) of the 82 left-sided tumors were associated with thrombocytosis. This difference did not, however, achieve statistical significance (p=0.198).

Conclusions: Humoral factors have been implicated as the etiology of thrombocytosis in patients with aggressive renal cell carcinoma. We theorize that extrinsic splenic compression may also play a role in thrombocytosis by displacing platelets and limiting storage capacity. We observed higher platelet counts and trend toward a higher incidence of thrombocytosis in patients with left sided renal malignancies. These findings should be verified in larger populations and correlated with cancer survival in order to clarify their clinical implications.

Poster #86

LOW DOSE IL-2, INTERFERON, PIROXICAM, AND CIMETIDINE IN THE TREATMENT OF METASTATIC RENAL CELL CARCINOMA
Graham, SD, Wadsworth, C, Wood N (Virginia Urology Center and the Medical College of Virginia)
(Supported by an unrestricted grant from Chiron)

Introduction: Current immunotherapy regimens are predominantly designed to provide nonspecific stimulation of the host immune response, yet this nonspecific stimulation may also activate suppressor cells. Toxicity from high dose IL-2 limits its usefulness in metastatic renal cell carcinoma, while low dose trials have shown only slightly improved survival compared to the natural history of metastatic renal cell carcinoma. Cimetidine has been shown to block CD8+ suppressor activity in both tissue culture and in human patients and NSAIDS have been shown to block NK suppression. Prior work with cimetidine combined with inductive immunotherapy (autolymphocyte therapy) had shown a benefit to the addition of suppressor blockade. This study was designed to examine the effect of the suppressor blockade with outpatient cytokine therapy.

Study Design: A daily outpatient regimen of low dose (9mu) IL-2, cimetidine (2400 mg), and piroxicam (10mg) were given to 25 patients with metastatic renal cell carcinoma. Patients demonstrating progression were also given Interferon >2a (1mu/day). Outcomes measured were survival, response to therapy, and toxicity. Metastatic sites included pulmonary, bone, lymph nodes.

Results: Follow on patients was 7-72 months (Median=22). Median survival has not been reached with 9 patients dead of disease. Currently there are 3 PR, 11 with stable disease, and 2 alive with progressive disease. Grade III toxicity was seen in 4 patients requiring dose reduction.

Conclusion: The combination of IL-2 with anti-suppressor therapy has shown significantly increased survival compared to historical controls of other outpatient low dose IL-2 trials. Toxicity is acceptable and the regimen is generally well tolerated.
Poster #87

ENVIRONMENTAL STRESSORS TO PROSTATIC CANCER CELLS IN VITRO CAUSE AN UP-REGULATION OF COX-2 EXPRESSION
Satoshi Anai, Susan Boehlein, Charles J. Rosser

Cyclooxygenases (COX) are key enzymes that mediate the production of prostaglandins from arachidonic acid. Two COX isoforms have been identified, COX-1 and COX-2. COX-1 is expressed constitutively, whereas COX-2 is induced by growth factors, tumor promoters, and cytokines. In addition COX-2 may function as a survival factor by protecting cells from apoptosis. In this study we analyzed COX-2 expression in PC-3 (low-expression) and LNCaP (moderate-expression) cells subjected to various stressors; acidic environment (pH 6.9), hypoxia (1% O2), and exposure to radiation (2 Gy). All stressors up-regulated COX-2 expression as determined by immunohistochemical staining (IHC). In addition cells that over-expressed COX-2 demonstrated remarkable resistance to apoptosis. Treatment of cells with COX-2 inhibitor, celecoxib, during exposure to the stress inhibited COX-2 over-expression and enhanced apoptosis in stressed cells. These findings suggest that COX-2 promotes cell survival by up-regulation during exposure to stressor. Further studies are underway to demonstrate this phenomenon in vivo.

Poster #88

IMPACT OF CHANGES IN TNM CLASSIFICATION ON STAGING OF BLADDER CANCER
Sharon Sharir, Mary K. Gospodarowicz, and Michael A.S. Jewett. Division of Urology and Dept. of Radiation Oncology, University of Toronto

Introduction: The purpose of the TNM cancer classification system is to clearly communicate disease extent, thereby providing prognostic information and assisting treatment planning and evaluation. Since the first publication of the TNM classification for bladder cancer in 1968, modifications to the classification have been introduced as a result of evolving knowledge about this disease. Our objective was to determine whether the changes in TNM classification over time could detract from the accurate conveyance of bladder cancer staging information.

Methods: A systematic review was conducted of all TNM bladder cancer classifications from its inception to the present. A comparison of criteria for assignment of staging categories, staging rules, and nomenclature was made. Potential pitfalls in the accurate communication of bladder cancer staging were identified.

Results: Since 1968, there have been 9 UICC (Union Internationale Contre le Cancer/International Union Against Cancer) TNM classifications (6 editions, 3 with revised editions) and 6 AJCC (American Joint Committee on Cancer) classifications. Changes that occurred between these editions give rise to a number of problems including: (1) Use of different criteria for designating stage categories, resulting in altered stage category assignment; (2) Tumor extent being defined differently in different editions, resulting in the same nomenclature having different meanings over time (3) Revised versions of a given edition having different nomenclature compared to the original edition; (4) Differences between the AJCC and UICC editions of the TNM classification at some times, uniformity with lack of parity of editions at some times, and complete parity between editions at other times; (6) Changes in the hierarchy of stage category over time, potentially resulting in different stage category assignment when multiple tumors are present.

Conclusions: Modification of the TNM classification is necessary as knowledge about bladder cancer changes with time, but these alterations can create impediments to the accurate conveyance of bladder cancer staging. To circumvent these problems, alternate strategies should be adopted when modifying the TNM classification, such as avoiding revised editions that change the classification, altering nomenclature when there is a change in definitions, and specifying the classification system version to provide clarity about the edition being used.
**Poster #89**

**HISTOLOGICAL TUMOR NECROSIS: AN IMPORTANT PROGNOSTIC FEATURE OF RENAL CELL CANCER**


**Introduction:** Prognostic models for renal cell carcinoma (RCC) are useful for tailoring surveillance appropriately and selecting patients for adjuvant therapy. Widely accepted prognostic variables (e.g. patient symptoms and tumor stage) are usually incorporated into such models, but others, such as histological tumor necrosis are not. This study aims to characterize histological tumor necrosis as a prognostic feature of RCC.

**Methods:** We identified 3099 patients, treated for RCC between 1970 and 2002, from the Mayo Clinic nephrectomy registry. Clinical, laboratory and pathological features were compared between necrotic and non-necrotic tumors. Fresh frozen tissue from 196 clear cell RCCs were also immuno-histochemically assessed for lymphocytic infiltration and B7-h1 expression.

**Results:** Histological tumor necrosis was present in 690 (28.2%) of 2445 clear cell, 196 (46.6%) of 421 papillary and 28 (19.6%) of 143 chromophobe RCCs. The risk ratio for death from RCC in necrotic compared to non-necrotic tumors was 5.27 (95% CI: 4.56-6.09, p<0.001) for clear cell, 1.49 (0.81-2.74, p>0.05) for papillary and 4.20 (1.65-10.68, p<0.005) for chromophobe subtypes. The difference in survival for clear cell RCC persisted after adjusting for tumor size, stage, grade and sarcomatoid component (RR 1.90, p<0.001). Patients with necrotic clear cell RCC were significantly more likely to have tumors =10 cm (42% vs 14%), perinephric fat invasion (45% vs 12%), caval tumor thrombus (15% vs 4%), grade 3-4 tumors (93% vs 27%), sarcomatoid component (17% vs 1%), regional lymph node involvement (14% vs 2%), distant metastases (29% vs 8%), dense lymphocytic infiltration (49% vs 31%) and higher B7-h1 expression (49% vs 23%), compared with patients whose tumors were not necrotic (p<0.001).

**Conclusions:** Histological tumor necrosis is a strong predictor of outcomes for clear cell and chromophobe RCCs, and should be routinely reported and used in clinical assessment. Associations with systemic findings and tumor immunological alterations suggest that histological tumor necrosis may be a marker of immune dysfunction in RCC.

**Poster #90**

**PHASE I/II TRIAL OF INTERFERON α2B AND LIPOSOME-ENCAPSULATED ALL-TRANS RETINOIC ACID IN THE TREATMENT OF PATIENTS WITH ADVANCED RENAL CELL CARCINOMA**

Stephen Boorjian, Matthew I. Milowsky, Deirdre M. Coll, Marta Cobham, Jodi Kaplan, Lorraine J. Gudas, and David M. Nanus. New York Presbyterian Hospital-Weill Medical College of Cornell University, New York, New York

**Introduction:** Retinoic acid (RA) has been shown to augment the growth-inhibitory effects of interferon (IFN)-based therapy in patients (pts) with metastatic renal cell carcinoma (RC); however, a major limitation of retinoid therapy to date has been the increased clearance of oral retinoids during treatment. Liposome-encapsulated all-trans RA (ATRA-IV) has improved pharmacokinetics, with increased and prolonged serum retinoid levels. We conducted a phase I/II study to identify the dose limiting toxicity (DLT), maximum tolerated dose (MTD), and efficacy of weekly ATRA-IV in combination with IFN α2b in pts with advanced RC.

**Methods:** Eligible pts had histologically confirmed advanced RC, with bidimensionally measurable disease and a Karnofsky performance status of > 60%. In the phase I study, cohorts of 3-6 pts were treated with weekly ATRA-IV (dose levels: 60, 75, and 90 mg/m²) and IFN α2b (3 million units (MU), escalated weekly to 5 and 7 MU, 5 days a week), with ATRA-IV dose escalation occurring after 3 pts completed 4 weeks of therapy without a DLT. Ten patients have been treated with IFN α2b plus weekly ATRA-IV as part of the phase II trial. Pts completing 8 weeks of therapy were considered evaluable for response. Serum RA concentrations ([RA]) were determined before and after ATRA infusion using high-performance liquid chromatography (HPLC) on weeks 1 and 8 of treatment.

**Results:** In the phase I trial, 3 pts were treated at the 60 mg/m² ATRA-IV dose level without a DLT, while 1 of 3 patients treated at the 75 mg/m² dose level experienced Grade 3 leukopenia, requiring cessation of treatment. A second pt at 75 mg/m² experienced Grade 3 neurological toxicity after 6 months of treatment, which was felt to be IFN related and therefore not considered an ATRA-IV DLT. An additional 3 pts were subsequently treated at 75 mg/m² without any further DLTs. Three pts were treated at the 90 mg/m² dose level without a DLT, thereby establishing ATRA-IV at 90 mg/m² as the MTD. To date, no pt from the phase II arm of the study has experienced any Grade 3 or 4 toxicity. In 20 pts who are evaluable for response, 5 (25%) have demonstrated a response, consisting of 1 complete response in a patient with lung-only metastases, and 4 partial responses. Five additional pts (25%) have experienced stable disease, lasting 16+, 12, 10, 9+, and 2+ months. HPLC analysis demonstrated no significant difference in serum [RA] following ATRA infusion between weeks 1 and 8 of treatment.

**Conclusions:** We demonstrated acceptable tolerability and preliminary efficacy of IFN α2b and weekly ATRA-IV in pts with advanced RC. The sustained increased serum [RA] supports use of the liposomal delivery system. We are currently evaluating whether in vivo expression of retinoic-acid inducible genes, including the retinoic acid receptor RARβ, correlates with clinical response.
Poster #91

GENE EXPRESSION DIFFERENCES BETWEEN PROSTATE CANCERS FROM OBESE AND NORMAL WEIGHT MEN

Stephen J. Freedland, MD, Jun Luo, PhD, Angelo M. DeMarzo, MD PhD, Thomas Dunn, BS, Helen Fedor, BS, Medha Darshan, MS, Ishwari Mohan, BS, and William B. Isaacs, PhD

Purpose: Obesity is associated with higher failure rates following radical prostatectomy and higher prostate cancer mortality rates. We sought to identify gene expression differences between the prostate cancers of obese men and normal weight men.

Methods: Tumor specimens from snap frozen radical prostatectomy tissue from 8 morbidly obese men (body mass index (BMI) > 35 kg/m²) and 8 control normal weight men (BMI 20-25 kg/m²), matched for Gleason score, pathological stage, pre-operative serum PSA level, and age were identified. All patients had Gleason 6 tumors. RNA was extracted, amplified, and gene expression was examined using 20K glass cDNA microarrays.

Results: Using the discriminative weight (w) for each gene based upon the Euclidean distance between the samples, we determined that the actual expression differences between cancers from obese men and cancers from normal weight men were far greater than expected. Using a cut-off of p<0.001 and w > 1.7, we identified 132 differentially expressed genes.

Conclusions: Prostate cancers from obese men are biologically distinct from cancers from normal weight men. Further analysis is needed to study which of the identified differentially expressed genes, if any, contributes to the increased aggressiveness of prostate cancer among obese men.

Poster #92

THE COMBINED TREATMENT APPROACH FOR MEN UNDERGOING HORMONAL THERAPY FOR PROSTATE CANCER (PCA)

Aubin S., Higano C.

INTRODUCTION: Twenty to forty percent of men with PCa will develop biochemical relapse post primary treatment. Many will choose to be treated with androgen deprivation therapy (ADT). In addition to physical side effects, ADT has a significant impact on quality of life domains of sexual and intimate relationships. Recent study results comparing sildenafil to sildenafil plus sexual therapy (the combined treatment approach) suggest that the combined approach may be useful in men with biochemical relapse who choose to be treated with ADT. Selected study results are thus presented to support the use of this approach with ADT.

METHOD: The sample consisted of 44 couples with both medical and non-medical causes for erectile dysfunction (ED). Couples were randomly assigned to either a 12-week administration of Viagra-only (VO) (n=20) or to a Viagra plus sex therapy program (VST) (n=24) combining 12-weeks of sildenafil with eight sessions of couple sex therapy. Treatment effectiveness was evaluated using self-report questionnaires administered at pre and post-treatment.

RESULTS: Results showed significant pre to post-treatment gains for both partners in the majority of sexual function areas and intimacy (see Table 1).

CONCLUSION: Comparable treatment gains for couples of the VO and VST were partly explained by high pretreatment levels of couple intimacy and adaptation. Study implications point to baseline status as an important treatment decision factor. For example, we may recommend adding sex therapy to sildenafil for couples with troubled relationships. Men treated with ADT may thus benefit from combined treatment to address their sexual and intimate relationships needs. More generally, using the combined treatment with ADT stresses the clinical indication of using an integrative, comprehensive approach during and after treatment for PCs.

<table>
<thead>
<tr>
<th></th>
<th>VO (n=20)</th>
<th>VST (n=24)</th>
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</thead>
<tbody>
<tr>
<td>Erectile function*</td>
<td>14(7)</td>
<td>21.6(8)</td>
</tr>
<tr>
<td>Orgasmic Function*</td>
<td>6(3)</td>
<td>7.2(2.8)</td>
</tr>
<tr>
<td>Sexual Desire*</td>
<td>7(2)</td>
<td>8.4(1.5)</td>
</tr>
<tr>
<td>Sexual Intimacy–Men**</td>
<td>67.6(21.4)</td>
<td>73.3(20)</td>
</tr>
<tr>
<td>Sexual Intimacy–Women**</td>
<td>66.2(18.7)</td>
<td>77.3(15.5)</td>
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*IIEF, **PAIR

≤0.05, <0.01: pretreatment to post-treatment comparisons
INTRODUCTION: We examined patterns of recurrence after nephroureterectomy (NU) of transitional cell carcinoma (TCC) of the upper urinary tract (UT). METHODS: From July 1989 to March 2004, we identified 251 patients who underwent NU for TCC of the UT. Clinical, pathologic, and radiologic data were acquired retrospectively from computerized medical records. Detailed metastatic, nodal, local and urothelial recurrence (UR) data were collected. RESULTS: Among the 251 patients, 165 (66%) were male, and 86 (34%) were female. Left NU was performed for 133 patients (53%) and right NU was performed for 118 (47%). TCC was primarily within the renal pelvis (RP) in 181 of 245 cases (74%), and within the ureter in 64 (26%). Details regarding management of the distal ureter were available for 259 patients, of whom 218 (89%) had a NU which included ureteral resection to the bladder and 21 (9%) for whom the ureteral resection was not carried to the bladder. Pathologic stage was pTa/pTis in 85 cases (35%), T1 in 46 (19%), T2 in 37 (15%), T3 in 63 (26%), and T4 in 8 (3%). Tumors were low grade (LG) in 64 of 238 cases (27%), intermediate grade (IG) in 38 (16%), and high grade (HG) in 136 (57%). ASA score was 1 in 7 of 204 cases (3%), 2 in 120 cases (59%), and 3 in 77 cases (38%). Overall, 63 patients (30%) had disease progression at a median of 11 months (interquartile range 5-27 months). Of these, 54 had distant metastases (26%) and 31 (15%) had local or nodal recurrence. UR occurred after NU in 107 (51%) cases (9 lower urinary tract, 11 upper urinary tract) at a median time of 9 months (interquartile range 4-20 months). Stage of UR was known for 101 patients (Ta = 67, CI = 15, T1 = 13, T2 = 1, T3 = 3, T4 = 2). Grade of UR was recorded for 89 patients (LG = 30, IG = 18, and HG = 41). Thirty-six percent of patients with URs had <4 recurrences. CONCLUSIONS: UR is common after NU for UT TCC, occurring in about half of patients. Such recurrences can occur rapidly after NU, and are generally of lower stage and higher grade requiring frequent resections. Disease progression in the form of local or distant disease is in this high risk population is 30%, and generally occurs within the first 1-2 years of NU.

CHARACTERISTICS OF PATIENTS WITH COMPLICATIONS FOLLOWING PERCUTANEOUS RADIOFREQUENCY ABLATION OF RENAL TUMORS
Alon Weizer, Ganesh Raj, Costas Lallas, Ari Silverstein, Martin O’Connell, Rendon Nelson, and Thomas J. Polascik, Durham, NC.

INTRODUCTION: Radiofrequency ablation (RFA) is a minimally invasive technique for managing small renal tumors. One critical aspect is selecting appropriate patients for percutaneous RFA. We evaluated our percutaneous RFA experience to determine common characteristics of patients with complications following RFA in order to elucidate possible contraindications to therapy.

METHODS: Medical records of all patients undergoing RFA were reviewed for demographic data, medical/surgical history, RFA treatment information, and treatment complications and their management. The complication group was analyzed for common characteristics.

RESULTS: From 06/03-03, 24 patients (4 with multiple lesions) having 32 tumors were treated. Average age was 60.9 years (37-86) with a male:female ratio of 5:1. Indication for percutaneous RFA included prior renal surgery and/or chronic renal insufficiency (n=10), significant medical disease (n=6), patient choice (n=4), von Hippel-Lindau disease (n=3), and treatment of metastases (n=1). Average pre-operative tumor size on computed tomography (CT) or magnetic resonance imaging scan was 3 cm (1.2-8.6) with most tumors located on the left. RFA was performed as an outpatient under general anesthesia. One to 4 treatments per tumor were given using either the triple probe from Radionics or the RITA Starburst XL device placed percutaneously under ultrasound or CT guidance. 5 patients experienced complications from percutaneous RFA. One patient had a colonic perforation requiring colostomy, two patients experienced perinephric hematomas (one requiring intercostal artery embolization), one patient had persistent urinoma and proximal ureteral stricture requiring nephrectomy and the last patient had a colonic fistula managed by diverting colostomy. Three patients had undergone previous partial nephrectomies of the treated kidney representing 38% of the prior nephrectomy patients in the cohort. Fifty percent of patients treated for multiple tumors experienced complications and 57% (4/7) of patients with anteriorly placed tumors experienced complications.

CONCLUSIONS: Early experience with percutaneous RFA for renal tumor appears promising but indications and contraindications have not been elucidated. Our limited experience suggests caution should be entertained prior to percutaneous RFA in patients with prior renal surgery, multiple tumors treated in the same setting, and anteriorly located tumors. Further clinical research will help establish when to employ this powerful technique in the management of small renal tumors.

OPTIMIZATION OF VASCULAR-TARGETED PHOTOTHERAPY (VTP) WITH WST09 FOR EBRT-RECURRENT PROSTATE CANCER

Introduction and Objective: WST09 is a new generation intravascular photosensitizer. When activated by 763 nm laser light it eradicates tumours by destroying their blood supply. It then clears rapidly from the circulatory system. We previously reported the first application of WST09-VTP in humans in a phase I/II trial designed to cover the entire gland with the therapeutic intention of total prostate cancer ablation. We report preliminary results.

Methods: Patients receive a 2-mg/kg drug dose and increasing light doses on 5 or 6 fibres spaced around the peripheral zone. Light monitoring fibres ensure that light levels in the urethra and rectum are safe. Intravenous drug infusion lasts 20 min and lasers operate for 30 min. Treatment response is assessed at 1-wk MRI by the percentage of treatment information, and treatment complications and their management.  The complication group was analyzed for common characteristics.

Results: WST09-VTP is easily performed and well tolerated. MRI response ranged from 7% of the prostate to almost the entire gland at 84%. An average PSA decrease of 76% (range 66% - 95%) was measured in 5 patients reaching 3 mths, with 2 further patients achieving undetectable PSA. PSA decreases correlated with MRI response. Biopsy revealed sharply demarcated areas of stromal fibrosis with eradication of foci of cancer in areas of MRI effect. In spite of extensive defects at MRI and histology, no significant adverse events occurred.

Conclusions: WST09-VTP in the radiation-recurrent prostate is safe and straightforward to perform. The varied MRI response between patients is under investigation. Increased biochemical response is consistent with an expected increased coverage of the prostate in the multi-fibre setting and increased destruction of prostatic epithelium. The lack of significant side effects coupled with early beneficial cancer ablation results suggests that WST09-VTP may be useful in this class of patients. Further follow-up will be necessary to confirm this hypothesis.
RADICAL PROSTATECTOMY FOR CLINICALLY ADVANCED (CT3) PROSTATE CANCER IN THE PSA ERA: 15-YEAR OUTCOMES
John F Ward¹, Michael L Blute², Erik J Bergstralh², Jeffrey M Slezak², Horst Zincke²

Purpose: The proper management of patients with locally advanced (cT3) prostate cancer (PCA) remains a problem. Excluding radical prostatectomy (RP) from the treatment options available to these patients is based upon antiquated misconceptions. We report our long-term experience with extirpative surgery in patients presenting with cT3 PCA.

Materials and methods: A single institution retrospective study identifying 5,652 men who underwent RP for histologically proven PCA in the prostate specific antigen (PSA) era (1987-1997). In 15% (842), RP was performed despite the presence of cT3 disease. Median follow-up was 10.3 years. Cancer specific, overall, and disease free survival plots were constructed and compared with patients undergoing RP for cT2 disease during the same time period. Perioperative morbidity, continence and erectile function rates were examined. Multivariate analysis for risk factors of disease recurrence was performed.

Results: Cancer specific survival five, 10- and 15-years following RP for cT3 PCA were 95%, 90% and 79%. One-quarter of men were clinically over-staged (pT2). Adjuvant or salvage therapy was delivered to the majority (78%) of patients. Pathologic grade (≥7), positive surgical margins, and non-diploid chromatin were all independently associated with a significant risk for clinical disease recurrence while pre-operative PSA had little impact on outcome. Complications and continence rates following RP in cT3 patients mirrored those observed in patients with cT2 disease.

Conclusions: Radical prostatectomy as the primary therapy in a multimodality approach to locally advanced PCA offers cancer control and survival rates approaching those achieved in patients with cT2 disease while not experiencing significantly different complications or incontinence rates.

Figure 1: Cancer specific survival for patients with prostate cancer (segregated by clinical stage) treated with radical prostatectomy.
PROSTATE CANCER ON THE INTERNET: INFORMATION OR MISINFORMATION?
Peter Black, David Penson

Introduction: As the use of the internet increases and the information available on the World Wide Web expands, patients are turning to it more and more as an important source of information on which to base medical decisions. We aimed to assess the quality of information available on prostate cancer on the internet by a web survey.

Methods and Materials: The search engine Webcrawler® was used with the search term “prostate cancer” to generate a list of 75 websites which were reviewed within a 2 week period. Each website was evaluated for currency (date of last update), disclosure (organization, authorship, sponsorship), attribution (references, disclaimer), links and interactivity. A rating tool was designed including 50 elements considered essential for a comprehensive review of prostate cancer, and each website was judged for degree of coverage (ratings: 1 = minimally addressed, 2 = more than minimally addressed, 3 = mostly addressed) and accuracy of information (1 = mostly incorrect, 2 = mostly correct, 3 = completely correct) for each element found on the website.

Results: The search generated 390,770 sites. The top 75 included 59 original sites and 16 that were dead links. Only 39 of the 59 sites had information about prostate cancer. 24 sites indicated no date of last update, 9 sites were updated within 6 months, and 6 more than 6 months previously. The organization was indicated on 38 sites, authorship on 22 and sponsorship on 33. References were rarely given (n=5) and a disclaimer was provided on less than half of sites (n=18). The sites covered a mean of 24 elements (6-43) with a mean coverage rating of 1.0 to 2.6 (1.8 overall). Six sites covered more than 35 elements. The mean accuracy rating for the sites ranged from 2.6 to 3.0 (2.9 overall). Of 943 elements covered in 39 sites, 94% were completely correct, 5% were mostly correct and 1% was mostly incorrect.

Conclusion: Commonly used search engines are not user-friendly for researching prostate cancer as just more than one half of sites provide information on the disease. Most sites do not indicate how current the information is or where it was obtained. Although sponsorship is usually outlined adequately, authorship is not, and most do not offer a disclaimer. While some sites provide excellent coverage of a many facets of the disease, others are very limited in scope and unbalanced. 99% of information was mostly or completely accurate. The Urologist needs to be aware of these shortcomings when counseling patients.

QUALITY IMPROVEMENT IN LAPAROSCOPIC RADICAL PROSTATECTOMY FOR PT2 PROSTATE CANCER: IMPACT OF VIDEO DOCUMENTATION REVIEW ON POSITIVE SURGICAL MARGIN
Karim Touijer, MD, Kentaro Kuroiwa, MD, Jeffery Saranchuk, MD, Waleed Hassen, MD, Edouard Trabulsi, MD, Victor Reuter, MD and Bertrand Guillonneau, MD

Purpose: To correlate intraoperative video documentation and pathology findings in order to understand the mechanisms by which positive surgical margins occur and improve the surgical technique.

Material and Methods: Between January 2003 and May 2004, 240 consecutive patients underwent laparoscopic radical prostatectomy, of these, 180 had pT2 prostate cancer and represent the population of this study. After the first 90 patients (group I), we started a quality assurance study analyzing the intraoperative video recordings and correlating them to the pathology findings of patients with positive margin. The cancer characteristics and positive margin rate were compared between the first 90 patients and the subsequent 90 patients after the study was initiated (group II).

Results: of the 12 cases of positive surgical margins studied, the video review helped identify 8cases with a technical error. In all the 4 cases where a technical error could not be identified, the positive margin site was at the distal apex. The most frequent identifiable mechanism by which positive margins occur was a capsular tear during the neurovascular bundle dissection. Both groups were comparable in regards to preoperative cancer characteristics and total tumor volume. In patients who had a bilateral nerve sparing, the positive margin rate was 10.6% in the first group and 5.4% in the second group (p=0.18). All of the positive margins in group II involved the prostatic apex.

Conclusion: Quality assurance efforts through pathological and intraoperative documentation review can help reduce the positive margin rate particularly in organ confined disease. However, eradicating positive margins at the distal prostatic apex remains a challenge.
2:00 p.m.

**PERSISTENT C-FLIP(L) EXPRESSION IS NECESSARY AND SUFFICIENT TO MAINTAIN RESISTANCE TO TRAIL-MEDIATED APOPTOSIS IN PROSTATE CANCER**  
Xiaoping Zhang, Tai-Guang Jin, Hongmei Yang, William C. DeWolf, Roya Khosravi-Far and Aria F. Olumi

TNF-related Apoptosis Inducing Ligand (TRAIL) has been shown to induce apoptosis in a variety of tumorigenic and transformed cell lines but not in many normal cells. Hence, TRAIL has the potential to be an ideal cancer therapeutic agent with minimal cytotoxicity. FLICE Inhibitory Protein (c-FLIP) is an important regulator of TRAIL-induced apoptosis. Here, we demonstrate that persistent expression of c-FLIP(L) is inversely correlated with the ability of TRAIL to induce apoptosis in prostate cancer cells. In contrast to TRAIL-sensitive cells, TRAIL-resistant LNCaP and PC3-TR (a TRAIL resistant subpopulation of PC3) cells demonstrated increased c-FLIP(L) mRNA levels and maintained steady protein expression of c-FLIP(L) after treatment with TRAIL. Ectopic expression of c-FLIP(L) in TRAIL-sensitive PC3 cells changed their phenotype from TRAIL-sensitive to TRAIL-resistance. Conversely, silencing of c-FLIP(L) expression by siRNA in PC3-TR cells reversed their phenotype from TRAIL-resistant to TRAIL-sensitive. Therefore, persistent expression of c-FLIP(L) is necessary and sufficient to regulate sensitivity to TRAIL mediated apoptosis in prostate cancer cells.

2:10 p.m.

**IMPACT OF NOX4 ON HIF-ALPHA EXPRESSION AND TRANSACTIVATION**  
Jodi K Maranchie, Ye Zhan, Worcester, MA

Introduction and Objective: Inactivation of the von Hippel Lindau tumor suppressor (VHL) is an early event in 60-80% of sporadic clear cell renal cell carcinoma (RCC). We previously showed that renal tumorigenesis occurs via loss of VHL E3 ubiquitin ligase function, resulting in accumulation of the alpha subunit of the hypoxia-inducible heterodimeric transcription factor (HIF-α). Subsequent activation of HIF-α via a second hypoxic switch results in transcription of an array of genes including VEGF and erythropoietin (Epo). Recent evidence suggests that HIF-α can be alternatively activated by reactive oxygen species. We examined the impact of superoxide generation by the kidney-specific NADPH oxidase, Nox4, on HIF-α expression and transactivation.

Methods: A Nox4 expression vector was generously provided by Dr. Leto of the NIDDK. Transfections were performed using Fugene (Roche) or Nucleofector electroporation. Whole cell lysates and cell membrane fractions were subjected to Western analysis for HIF1-α, HIF2-α and Nox4. Nox4, HIF2-α and VEGF expression was evaluated by Northern blot and by real-time quantitative RT-PCR of total RNA extracts. Luciferase reporter constructs containing the minimal promotor region of VEGF or Erythropoetin were used to measure HIF-α transactivation.

Results: We designed small inhibitory RNA (siRNA) capable of decreasing endogenous Nox4 expression by 70-80% in HEK293 and 786-0 PRC. No change in HIF2-α expression was detected following knock-down or exogenous expression of Nox4. Similarly, cell lysates confirmed markedly reduced Nox4 by Western blot using an affinity purified rabbit polyclonal antibody raised against the C-terminus of Nox4, but no change was seen in HIF2-α protein levels in normoxia or hypoxia (0.5% O2 for 16 hours). However, quantitative real time PCR, demonstrated a 10-fold decrease in VEGF mRNA in VHL-deficient 786-0 PRC cells after Nox4 knock-down. Further, luciferase reporters showed markedly decreased transcription from the minimal promoters of both VEGF and Epo after Nox4 knock-down.

Conclusions: Although Nox4 levels have no impact on HIF-α expression at the mRNA or protein level, specific Nox4 knock-down results in decreased transcription of HIF-regulated genes. These studies suggest that Nox4 plays a role in HIF-α transactivation, independent of VHL-mediated protein stabilization. The existence of a secondary tissue-specific HIF-α activation pathway provides a novel molecular target for directed RCC therapy. Studies are ongoing to determine if Nox4 knock-down or inhibition will alter tumor growth in vivo.

Funding: NIDDK
We evaluated the palliative effect of cystoprostatectomy (CP) in palliating pelvic symptoms in patients with bladder invasion by prostate cancer. Methods. 38 patients with clinical T4 prostate cancer (17 primary tumors and 21 recurrent following radiation therapy) underwent palliative CP. The presence of local symptoms, the need for surgical procedures to relieve obstruction, and the use of chronic tube drainage for urinary obstruction before surgery and 3 months after surgery were compared. Time to local and systemic symptom recurrence, biochemical progression, and metastasis were measured, and disease-specific survival (DSS) was determined. Results obtained. Local symptoms were reported by 34 patients (89%) before surgery and by 8 patients (21%) after surgery (p=0.000). Preoperatively, a total of 22 tubes were inserted in 13 patients to overcome urinary obstruction. The average indwelling tube duration was 6.9 months. A total of 24 transurethral prostatic tumor resections were performed in 11 patients. Following CP, local symptoms were relieved permanently in 30 patients, and the average interval between surgery and clinical systemic disease was 26 months. No patient required tube drainage for longer than 3 weeks, and 1 patient required additional surgery consisting of revision of a continent diversion. Median durations to biochemical progression, metastasis, and systemic symptoms were 8, 18, and 26 months, respectively. Median DSS was 31 months (range 1.7-81.2 months). No perioperative death occurred. Rectal injuries occurred in 5 cases (13%) during surgery. Conclusion. Radical CP provides effective and durable palliation in patients with locally advanced prostate cancer. This procedure can be performed with acceptable morbidity in a select group of patients.

Introduction: We evaluated patients at our institution who underwent radical prostatectomy for clinical stage T3 (cT3) prostate cancer to determine their long-term clinical outcomes. Materials and Methods: We reviewed our radical prostatectomy database and identified 5182 men who underwent radical retropubic prostatectomy (RRP) from 1983 to 2003. Of these men, 176 were clinical stage T3 prior to RRP and constituted our study cohort. Clinical and pathologic data were reviewed and evaluated in a COX proportional hazards model to determine pre-operative predictors of biochemical recurrence. Clinical disease states were defined for patients with biochemical recurrence (BCR) and long-term follow-up was reported. Results: Of the 176 patients with cT3 prostate cancer, 64 (36.4%) received neo-adjuvant hormonal therapy (NHT). The mean age of our patient population was 61.0 years and the mean pre-treatment serum prostate specific antigen (PSA) was 19.7 ng/dl. A biopsy Gleason score of \( \leq 6, 7, > 8 \) occurred in 47.2%, 38.1%, and 14.8% of patients respectively. Pathologic organ confined disease was found in 53 (30.1%) patients. Seminal vesicle invasion, extra-capsular extension and lymph node invasion was reported in 55 (33.5%), 107 (60.8%), and 33 (18.8%) patients respectively. At a mean follow-up time of 6.4 years, 92 (52.3%) of patients remained disease free with an actuarial 10-year freedom from recurrence of 44%. 84 (47.7%) patients had disease recurrence with a median time to BCR of 4.6 years. On multivariate analysis of pre-operative clinical parameters, biopsy Gleason score, pre-treatment serum PSA, and year of surgery were independent predictors for BCR. Whether patients received NHT or not was not a predictor of BCR. Hormonal therapy was initiated in 65 (77.3%) patients at a median time of 1.4 years after BCR. 26 patients progressed to a PSA castrate state at a median time of 7.8 years after initiation of hormonal therapy. Overall, 19 (10.8%) of patients were deceased secondary to disease. On a univariate Cox regression model predictors of death from disease following BCR were PSA doubling time, and PSA nadir following initiation of hormonal therapy. Conclusion: Over half (52.3%) of our patients remained free of disease recurrence following radical prostatectomy. Neo-adjuvant hormonal therapy offered no advantage with respect to disease recurrence. Radical prostatectomy remains an integral component in the management of select patients with clinical stage T3 prostate cancer.
Mycoplasma Effects on Human Tumor Invasion
Satoshi Anai, Susan Boehlein, Catherine Ketcham, Shijie Sheng, Charles J. Rosser

Introduction: Studies in leukemia patients in the mid-1960’s first raised the possibility of an association between mycoplasma infection and cancer development. Mycoplasma hyorhinis has already been correlated with gastric cancer tumor grade and metastatic activity. Recently, Mycoplasma hyorhinis was shown to be a ligand for the human CD99 receptor. Preliminary evidence indicates that tumor cell invasiveness may be greatly influenced by a protein produced by M. hyorhinis, p37. We proposed to study the effects of p37 on prostate cancer cells to determine if it may increase the invasive nature of cells.

Methods: M. hyorhinis p37 was cloned and overexpressed in E.coli. The protein was purified and endotoxin was removed. PC-3 prostate cancer cells were grown under standard conditions in an invasion chamber with 10μM polycarbonated membranes coated with containing 2mg/ml Matrigel. Recombinant p37 was added to various wells at the following concentrations 0, 5.6, 14, and 28μg /μl and incubated for 16 hours. Alternatively p37 (25μg/ml) was pre-incubated with several monoclonal antibodies (1G6, 5D2, 4B10, 5G11 and 1D8) raised against p37 prior to its addition to the invasion assay. The invasion assays were processed and analyzed in standard fashion.

Results: In all cell lines, p37 stimulated invasion through the Matrigel in a dose-dependent manner (Figure a). Results were confirmed in A375 and C8161 melanoma cells.

Treatment of cultured cells with anti-p37 antibody neutralized the stimulatory effect of p37 (Figure b).

Conclusions: In a dose dependent manner, a Mycoplasma hyorhinis protein, p37 stimulated the invasive nature of prostate cancer cells in vitro. Addition of an antibody to p37 blocked this stimulatory effect. Future experiments with Mycoplasma and p37 are anticipated to further elucidate their reactions with human cells and to better define their role in cancer progression.
TRANSITIONAL CELL CARCINOMA OF THE BLADDER IS INFILTRATED BY HIGH PROPORTIONS OF REGULATORY T-LYMPHOCYTES

Maria Mercader, Shomik Sengupta, Haidong Dong, Xavier Frigola, W Scott Webster, R Houston Thompson, Bradley Leibovich, Horst Zincke, Michael Blute, Eugene D Kwon. Mayo Clinic, Rochester, MN

Introduction: Transitional cell carcinomas (TCC) are known to be infiltrated by T-lymphocytes, many specifically activated. However, TCCs often progress despite this apparent anti-tumor immune response. This study aims to examine whether tumor infiltrating lymphocytes in TCCs contain a high proportion of regulatory T-cells, which may act to suppress the anti-tumor immune response.

Methods: With institutional review board approval, fresh tumor and canister blood was obtained from 14 patients undergoing cystectomy for invasive TCC. Normal donor blood discarded from the blood bank was obtained as controls (n=10). Tumors were morcellated and digested. Lymphoprep™ gradient columns were used to purify the blood and the cell suspension obtained from tissue digestion. The lymphocytes thus isolated were doubly stained using fluorescein-labelled anti-CD4 and anti-CD25 antibodies, then counted using fluorescence activated cell sorting (FACS). T-regulatory cells were identified as being CD4$^+$CD25$^{high}$, and expressed as a percentage of CD4$^+$ cells. Data are expressed as mean ± SEM, and compared between groups using t-tests.

Figure 1: %CD4$^+$CD25$^{high}$ cells

2.9% of CD4$^+$ cells to be CD25$^{high}$ (Figure 1), which was higher than proportions seen in patients with tumors also had higher numbers of circulating CD4$^+$CD25$^{high}$ lymphocytes (p<0.05).

The bladder harbors a high proportion of CD4$^+$CD25$^{high}$ T-lymphocytes, thought to function in limiting auto-immune reactions, the presence of T-regulatory cells within the tumor may be responsible for suppressing the anti-tumor immune response, thus allowing tumors to progress. Strategies to block regulatory T-lymphocyte function may lead to the development of effective immunotherapy against TCC of the bladder.
RECOMBINANT PROSTATE CANCER VACCINES AND COMBINATION THERAPIES
James L. Gulley, Philip M. Arlen, Nushin Todd, William Dahut, Kevin Camphausen, C. Norman Coleman, and Jeffrey Schlom

Introduction: Prostate cancer remains the most common cancer among men in the US and the second most common cause of cancer death. Vaccine strategies directed at PSA have gained interest in this disease.

Methods: We completed 3 randomized phase II studies with pox viral vector vaccines in various patient populations as outlined below. The purpose of these trials was to determine if these vaccines could be given in combination with other modalities commonly used in prostate cancer (radiation therapy and chemotherapy). Results—Radiation Therapy: Recent preclinical studies in mice have demonstrated that local external beam irradiation of tumor in situ, at doses insufficient to reduce the rate of tumor growth, leads to phenotypic alterations of tumor cells (including upregulation of fas) that make them more susceptible to specific immune attack. Tumor radiation and vaccine when used together were shown to act synergistically in inducing anti-tumor responses. A recently completed clinical trial combining radiation with our vaccine strategy in patients with clinically localized or locally advanced prostate cancer demonstrated that this strategy can be employed safely and can lead to immune responses in the majority of patients. In addition there is indirect evidence of immune mediated tumor killing as demonstrated by the formation of de novo immune responses to prostate-associated antigens not found in the vaccine. Chemotherapy: Other combination strategies have emerged with one recently completed randomized phase II study in prostate cancer that evaluated concurrent chemotherapy (docetaxel) and vaccine. This trial showed that immune responses could be maintained in the face of chemotherapy and concurrent steroids and that vaccine was safe with chemotherapy. Vaccine vs. Second Line anti-androgen: Another randomized phase II study showed apparent equivalence of vaccine with nilutamide in terms of time to treatment failure, with less toxicity in patients with androgen insensitive prostate cancer but no radiographic evidence of disease. Several patients on this trial had sustained decreases in PSA >50% due to vaccine.

Summary: Early clinical trial results suggest that safety of the vaccines will not be a serious concern even when combined with chemotherapy or radiation therapy. Furthermore immunologic responses have been seen with vaccine alone and in combination with either radiation or chemotherapy. Evidence of clinical benefit from these vaccines is emerging. Future trials will examine alternate strategies of augmenting the immune response.

IMIQUIMOD, A TOLL-LIKE RECEPTOR AGONIST AND IMMUNE RESPONSE MODIFIER, INDUCES APOPTOSIS AND CYTOKINE PRODUCTION IN BLADDER CANCER CELL LINES
Eric Smith, Hidekki Kawamoto, Xuecke You, and Douglas Scherr. Department of Urology, New York Presbyterian Hospital-Weill Medical College of Cornell University

INTRODUCTION: Imiquimod, a Toll-like (TLR)-7 receptor agonist, is a potent immunomodulator currently used as a first line topical therapy for genital warts. In addition, imiquimod has been successfully applied for the treatment of several benign and malignant skin lesions including melanoma and basal cell carcinoma. Its mechanism, primarily through the stimulation of a Th1 immune response, is strikingly similar to bacillus Calmette-Guerin (BCG). Therefore, we hypothesize that imiquimod may have therapeutic potential against bladder cancer. The purpose of this study is to determine if imiquimod has direct in vitro activity against bladder cancer cell lines.

METHODS: To determine if imiquimod has biologic activity against bladder cancer cells, three bladder tumor cell lines (J82, T24, and TCC-SUP) were cultured for 24 hrs in normal culture medium or medium supplemented with imiquimod. The effects on cell viability and proliferation were then determined using the Methylthiazoltetrazolium (MTT) assay. Apoptosis was detected using an Apotag (Chemicon) kit, which selectively identifies double stranded DNA breaks in apoptotic cells. Finally, the induction of TNF-alpha and IL-6 was determined using an ELISA assay.

RESULTS OBTAINED: A dose-dependent decrease in cell viability was observed in all tumor cell lines treated with imiquimod at concentrations up to 200 ug/ml. Decreases in viability ranged from 23-91%. Apoptosis was detected in 17.1% of cells treated with imiquimod (100 ug/ml), compared to 0.8% in the untreated control group. IL-6 and TNF-alpha significantly increased 2 to 3-fold in the supernatant of cells treated with imiquimod (100 ug/ml).

CONCLUSIONS: These results demonstrate that imiquimod has direct biologic activity against J82, T24, and TCC-SUP bladder cancer cell lines by decreasing cell viability and inducing both apoptosis and cytokine production. Further in vitro and in vivo studies are ongoing.
3:20 p.m.

HIGH-THROUGHPUT CLINICAL ANALYSIS OF FOS RELATED ANTIGEN 1 (FRA-1) EXPRESSION IN PROSTATE TUMORS: A NEW TUMOR MARKER IN PROSTATE CANCER
Aaron Grotas, MD, John Phillips, MD, Mark Rafelled, MD, Lukas Bubendorf, MD and Eric Gerber, MD

Purpose: As part of a high-throughput cytogenetic and genomic interrogation of a prostate tumorigenesis model, we identified Fos Related Antigen 1 (fra-1) as a target of chromosomal amplification. Fra1 is a nuclear target of the MEK->ERK pathway and, with jun-family peptides, a co-factor of AP1. We hypothesized that fra1 expression may correlate with tumor progression in clinical specimens of prostate cancer. We used tissue arrays to optimize histologic preparation for and screening of fra1 expressivity in 276 prostate specimens simultaneously.

Methods: Paraffin-embedded, formalin fixed specimens were stained after antigen retrieval, and stained with 1:1200 mouse anti-human fra-1 (Santa Cruz). We developed an ordinal visual scoring system to grade positive staining specimens and employed logistic regression for predictive modeling. Positive staining was assigned for strong or obvious nucleolar staining and negative staining was assigned for no or cytoplasmic staining.

Results: Fra-1 staining emerges, in strongly positive cases, from the nucleolus with background nucleoplasmic and cytoplasmic signal. Fra1 stained positive in 68% of hormone refractory cancer (hrpc) specimens versus 12% of control, benign prostatic hyperplasia (bph) specimens (sensitivity 99%, specificity of 38%). Positive staining correlated with an Odds Ratio (OR) of 16:1 favoring hrpc vs. bph and comparing hrpc with all other benign tissue types (ANOVA, p<.01). No significant staining pattern was seen among low stage (clinically gland confined) prostate cancers despite varying grades and no significant difference (P>.05, ANOVA) was seen between low grade prostate cancer and benign tissue.

Conclusion: Positive nucleolar fra-1 staining is highly prevalent in hormone refractory prostate cancer (hrpc) and predicts for hrpc over benign disease. Molecular targeting of fra-1 may, therefore, have clinical relevance in hrpc and provides the basis for our current xenograft model using water-soluble ERK1 inhibitors.

3:30 p.m.

A PHASE II STUDY OF SEQUENTIAL VACCINATIONS WITH RFOWLPOX-PSA (L155)-TRICOM ALONE, OR IN COMBINATION WITH RVACCINIA-PSA (L155)-TRICOM, AND THE ROLE OF GM-CSF, IN PATIENTS (PTS) WITH METASTATIC ANDROGEN INSENSITIVE PROSTATE CANCER (AIPC)
Nushin Todd, James Gulley, William Dahut, Jeffrey Schlom, Philip Arlen.

Vaccine strategies represent a novel therapeutic approach for the treatment of metastatic AIPC. One potential target for a prostate cancer vaccine is PSA due to its restricted expression on prostate cancer and normal prostatic epithelial cells. Since PSA is a “self” antigen, vaccine strategies utilizing this as a target must be developed to enhance its immunogenicity. Preclinical and clinical studies have demonstrated that the induction of T-cell responses directed against a self-antigen can lead to anti-tumor activity in the absence of toxicity. Two novel PSA-based vaccines have been developed: (a) a recombinant (r) vaccinia virus containing the entire PSA transgene with a modified agonist epitope and three costimulatory molecule transgenes, rV-PSA-TRICOM (rV) and (b) a similar recombinant fowlpox virus, rF-PSA–TRICOM (rF). We have completed a phase I study demonstrating the clinical safety of a prime/boost vaccine strategy: priming with rV with subsequent monthly boosts using rF. We are also evaluating the combination of these agents with recombinant GM-CSF (r-GM-CSF), as well as two doses of fowlpox-GM-CSF (rF-GM-CSF). This phase II study randomizes 32 pts with metastatic AIPC without prior chemotherapy and progressive disease into one of the following 4 cohorts utilizing the same vaccine used in the phase I study. Pts randomized to cohort 1 receive vaccine alone, pts in cohort 2 receive vaccine with rGM-CSF protein, and pts in cohorts 3 and 4 receive vaccine with 2 different doses of rF-GM-CSF, respectively. Pts will receive restaging scans every 3 months while on study and may continue to receive vaccine until disease progression. To date, 23 pts have enrolled on study and 15 have undergone restaging evaluation at 3 months. Five of these patients have demonstrated PSA declines during this period, 4 pts with PSA declines of > 30% and 1 pt with a decline of > 50%. Twelve of 23 pts continue on treatment with 5 pts continuing on study beyond the initial 3 month period. One patient at 8 months has experienced a PR by RECIST criteria with > 50% decline in his hilar adenopathy. A second pt on study for 9 months continues to have stable disease. Immunologic studies are planned to monitor pts immune responses measuring changes in PSA specific T cells. A comparison of the immunologic effects of the above vaccine strategy alone, with r-GM-CSF, or with either of 2 doses of rF-GM-CSF will be presented at the completion of the trial.
CLASSIFICATION AND TRENDS OF PERIOPERATIVE MORBIDITIES FOLLOWING LAPAROSCOPIC RADICAL PROSTATECTOMY
The James Buchanan Brady Urological Institute, Baltimore, Maryland

Purpose: To classify and assess trends in the incidence, severity, and management of perioperative morbidities following laparoscopic radical prostatectomy (LRP).

Methods: We retrospectively reviewed the records of 250 patients with clinically localized prostate cancer who underwent transperitoneal LRP by two surgeons (C.P. and L.S.) between April 2001 and March 2004. The Clavien classification system was used to grade complications for those cases completed laparoscopically. The Mantel-Haenszel test was used to determine the significance of complications associated with the learning curve.

Results: Median hospital stay was 2 days (range 2 to 8 days). The median length of bladder catheterization was 10 days (range 3 to 36 days). Eleven complications occurred in the first 50 cases, 12 in cases 51 - 100, 6 in cases 101 - 150, 8 in cases 151 - 200, and 1 in cases 201 - 250. Of the 246 cases completed laparoscopically, there were 20 grade II complications, 12 grade III complications, and 2 grade IV complications encountered during a mean follow-up period of 13.7 months. Postoperative ileus that prolonged hospital stay by 1 to 5 days was the most frequent complication and occurred in 8 patients (3.3%). Seven patients required blood transfusion (2.8%). One patient presented on postoperative day 14 with a pulmonary embolus (0.4%). Bladder neck contractures were observed in 3 patients (1.2%). There was a significant decrease in the number of complications (p = 0.019) and conversion to open surgery (p = 0.013) as our experience with LRP increased.

Conclusions: Perioperative complications following LRP are mostly self-limited and grades II and III (94.1%). The incidence of complications and need for conversion to open radical prostatectomy declined with experience. Uniform reporting and grading of surgical complications via standardized classification systems may permit more meaningful comparisons among different centers and surgical techniques.

MANAGEMENT AND FOLLOW-UP OF PATIENTS WITH CARCINOMA IN SITU AT A POSITIVE DISTAL URETERAL MARGIN FOLLOWING RADICAL CYSTECTOMY
Albert M. Ong, Richard E. Link, Sam B. Bhayani, Ionnis Varkarakis, Takeshi Inagaki, Mohammed Allaf, Mark Schoenberg, Thomas W. Jarrett

Purpose: The impact of carcinoma in situ (CIS) at a positive distal ureteral margin following radical cystectomy has not previously been characterized. Although patients with CIS of the urinary bladder at the time of cystectomy have a higher upper tract recurrence rate, the literature is ambivalent regarding CIS in a positive distal ureteral margin at the time of cystectomy.

Materials and Methods: We examined our records from 1999-2004 to identify patients with CIS at a positive distal ureteral margin at the time of cystectomy. We found eleven patients who fulfilled this criteria. One the patients was excluded from analysis, as the initial pathology was not available. For the remainder, carcinoma in situ was present in the bladder in all cystectomy specimens. These patients were followed with surveillance ureteroscopy every six months, and annually with computed tomography. The mean age of the patients was 69.8 years. Three patients were female, and the remainder were male. The majority of patients in this series had received intravesical therapy prior to extirpative surgery. The mean follow-up in this group of patients was 869 days.

Results: Distal ureteral margins were positive bilaterally in 60% of cases and unilateral in the remainder. The recurrence rate was 40%, and the mean time to recurrence was 273.3 days following cystectomy. There was no correlation between initial tumor stage and recurrence of the upper tract lesion. There was only one recurrence at the site of the initial positive margin, and half of the recurrences were contralateral to the site of the positive margin. Recurrences were treated with laparoscopic nephroureterectomy on the affected side, and were organ confined in all cases. Three of the four cases were recurrent upper tract CIS. There was one death in the series unrelated to cancer.

Conclusion: Though small, our series suggests that the entire urothelium in patients with CIS at a positive margin should be examined closely and frequently, as recurrences are often clinically silent and can progress rapidly.
Introduction: In order to understand the mechanisms involved in the progression of androgen-independent prostate cancer, it is important to determine the regulatory molecules involved. 14-3-3 proteins are implicated in the regulation of cell survival and could become targets for therapeutic intervention. As part of our effort to dissect the molecular basis responsible for hormone refractory (HRF) progression, we evaluated the expression of three 14-3-3 isoforms at either the mRNA or protein levels in human prostate cancer specimens and cell lines.

Materials and Methods: Tissue was obtained from 53 frozen prostate specimens. Twenty-three patients had primary cancers, 17 had previous hormonal therapy, 9 had metastatic prostate cancer (3 were HRF cancers) while 5 specimens were normal prostate. Messenger RNAs were extracted and the gene expression profile was evaluated by means of cDNA microarray using Affymetrix U95A chip. The protein levels of three 14-3-3 isoforms were evaluated by western blot. Nine human cancer cell lines were used including 2 androgen-sensitive (LNCaP and LAPC-4), 3 androgen-insensitive (C4-2, LNCaP-RF and 22Rv1), 2 androgen receptor null (PC-3 and DU-145) and 2 breast cancer cells (T47D and MCF-7).

Results: At the mRNA level, expression of 14-3-3η was found to be higher than 14-3-3ε in all the human prostate specimens. However, there was no significant difference among normal prostate samples, primary tumors or advanced tumors. Moreover, there was a significantly higher expression of 14-3-3ζ in metastatic and HRF tumor samples suggesting tumor progression. Likewise, the protein level of 14-3-3ζ was found to be higher in androgen-insensitive prostate cancer cell lines compared to androgen-sensitive ones.

Conclusions: Increased mRNA and protein expression of 14-3-3ζ suggests a correlation with prostate cancer progression. Our findings do not suggest a correlation between 14-3-3ε/η expression and disease progression. The potential role of 14-3-3ζ in prostate cancer progression needs more extensive investigation but could provide a possible target for therapeutic intervention.
Introduction: Neoadjuvant chemotherapy is increasingly considered a strategy that can improve survival of bladder cancer after radical cystectomy, however one concern of a broader application is the risk of perioperative complication. Prospective randomized studies have compared post-cystectomy complications of patients treated with and without neoadjuvant chemotherapy. No difference has been observed in the complication rates of these populations. However, documented complications in some of these studies appear limited as 1) several common complications of cystectomy have not been identified; 2) complications are only recorded in the immediate postoperative period; and 3) intraoperative complications such as prolonged surgery time or blood loss have not been considered. We hypothesize that neoadjuvant chemotherapy may be associated with a higher incidence of complication after cystectomy, when a wider spectrum of complication is considered over time.

Methods: A contemporary cohort of 49 patients with transitional cell carcinoma (TCCa) of the bladder underwent neoadjuvant chemotherapy and radical cystectomy (Group 1). The predominant chemotherapy regimen used was paclitaxel, carboplatin, and gemcitabine. Clinicopathologic parameters were maintained in an institutional database. A retrospective review of age, gender, American Society of Anesthesiologists (ASA) classification, estimated blood loss (EBL), 30-day units transfused, operative time, pathologic stage, length of hospital stay and complication number, type and severity was undertaken. For contrast, these parameters were compared to those of a population of 394 patients who underwent primary cystectomy for TCCa of the bladder without neoadjuvant therapy (Group 2) during the same time period. The Mantel-Haenszel Chi-square and Fisher’s Exact Tests evaluated the relationship of clinical parameters between groups.

Results: Patients in Group 1 were younger (mean age, 62 years) than those in Group 2 (mean age, 66; p = .03). Mean EBL was 1200cc in Group 1 and 925cc in Group 2 (p = .056). Within 30 days of surgery, patients in Group 1 were more likely to receive a blood transfusion than those in Group 2 (p = .04). There was no observed difference in gender, ASA score, operative time, pathologic stage, or hospital or ICU length of stay between Groups 1 and 2. Complications were recorded throughout the median follow-up of 26 months for Group 1 and 32 months for Group 2. Twenty-four (49%) and 159 (40%) patients in Groups 1 and 2, experienced a complication, respectively (p = .28). The severity (p = .17) and multiplicity (p = .32) of these complications were also similar between groups. The most common complications in Group 1 were ileus, cardiovascular event, wound disturbance, and urinary tract infection; those in Group 2 were ileus, wound disturbance, and ureteral anastomotic stricture or leak.

Conclusions: Patients who receive neoadjuvant chemotherapy may expect a higher rate of blood loss during cystectomy and consequently are more likely to require blood transfusion in the perioperative period. This does not significantly increase hospital or ICU length of stay, possibly because of the younger age of this group. After a careful evaluation of complications in the extended postoperative period, post-cystectomy complications after neoadjuvant chemotherapy are otherwise similar to those after primary cystectomy in the general population treated for transitional carcinoma.

MOUSE MODEL FOR BLADDER CANCER INDUCTION AND IMAGING

Isla P. Garraway, Chau Tran, Katie Cai, and Robert E. Reiter

Transitional cell carcinoma (TCC) is one of the most common malignancies of the genitourinary (GU) tract. The heterogeneous nature of TCC has led to studies to elucidate the molecular events involved in tumorigenesis. The paucity of animal models, however is a major drawback. Our lab has taken advantage of the TVA retroviral gene delivery system to develop a transgenic mouse that expresses the TVA receptor under control of the urogenital tissue-specific prostate stem cell antigen (PSCA) promoter. The PSCA promoter drives TVA receptor expression almost exclusively in GU tissues. Genetically engineered avian retroviral vectors can then be introduced specifically into cells where TVA is expressed. The advantage of the TVA system is that a single transgenic mouse can be used to study multiple genetic changes. In addition to the analysis of single oncogenes, multiple oncogenes may be introduced into a single cell via multiple rounds of infection. Oncogenes are introduced somatically, which differs from typical transgenic strategies that introduce mutations into the germline. Another advantage of the TVA system is the ability to concomitantly deliver the imaging gene, luciferase. The luciferase gene imparts luminescence to infected cells and may enable the natural history of urothelial cell transformation to be tracked in a minimally-invasive fashion. We have found that PSCA-TVA mice infected with Myc develop urothelial hyperplasia, while those infected with polonya virus MT antigen do not demonstrate urothelial changes. Investigation is underway in elucidating the genetic background, oncogene, or combination of genes sufficient to induce transitional cell carcinoma. Combining luciferase imaging with oncogene induction will likely enable the process of tumorigenesis to be followed with CCD imaging.
EFFICACY OF COMBINING SELECTIVE ESTROGEN RECEPTOR MODULATORS AND CASODEX™ IN ANDROGEN-DEPENDENT PROSTATE CANCER CELLS
Melissa M. Walls, MD, Asim Abdel-Mageed, DVM, PhD, Rodney Davis, MD, and Erik P. Castle, MD

Introduction: Casodex™ has been shown to inhibit cell growth in androgen dependent cell lines. Raloxifene (Sigma) and tamoxifen (Sigma) are selective estrogen receptor modulators (SERMs) that have been shown to affect cellular biology of prostate cancer cell lines. We compared the growth inhibitory effects of combining Casodex™ with each of these SERMs to those of Casodex™ alone in an LNCaP cell line.

Materials and Methods: LNCaP cells were cultured in a T-medium (GIBCO) supplemented with 10% fetal bovine serum (FBS), streptomycin and ampicillin and were incubated at 37° C in an incubator. Cells were diluted to 1,000 cells per well in 200μL of medium and divided into 4 groups. Group A was treated with the vehicle, DMSO, alone and served as the controls. Group B was treated with Casodex™ alone at three different concentrations (10μM, 50μM, 100μM). Group C was treated with tamoxifen (1μM, 5μM, 10μM) and Casodex™ using all nine possible concentration combinations of both drugs. Group D was treated with raloxifene (1nM, 1μM, 100μM) and Casodex™ in similar fashion. Cell proliferation and growth inhibition was measured with a Cell Counting Kit (CCK-8) employing a highly water soluble salt (WST-8). A spectrometer was then used to measure absorbance at 450 nm.

Results: Casodex™ inhibited LNCaP cellular proliferation by 33%, 33% and 60% at concentrations of 10μM, 50μM and 100μM respectively (Fig. 1). Cellular proliferation was increasingly inhibited in a dose-dependent fashion when tamoxifen was added to the Casodex™ treatment. Proliferation was inhibited up to 80% when combining the highest dose of Casodex with the higher doses of tamoxifen (Fig. 2). Enhanced growth arrest was also seen when Casodex™ treatment was combined with raloxifene. Even at the lowest dose of Casodex™, 10μM, the addition of raloxifene inhibited proliferation by 66%, 70% and 80% at 1nM, 1μM and 10μM, respectively (Fig 3). Maximal inhibition for both treatment combinations was 80% while the maximal inhibition of Casodex™ alone was 60% at the highest dose.

Conclusions: Casodex™ inhibition of LNCaP cellular proliferation is enhanced by the addition of raloxifene or tamoxifen. Raloxifene had a greater effect at lower concentrations than tamoxifen. Lower doses of Casodex™ were required to significantly inhibit LNCaP cells even at nanomolar concentrations of raloxifene. The mechanism of these findings is still unknown and should be investigated further.
4:40 p.m.

**EXPRESSION OF VASCULAR ENDOTHELIAL GROWTH FACTOR A (VEGF-A), VEGF RECEPTOR 1 (VEGFR-1) AND VEGFR-2 IN CLEAR CELL AND PAPILLARY RENAL CELL CARCINOMA (RCC): IMPLICATIONS FOR THERAPY**

*John T. Leppert, John S. Lam, Hong Yu, David B. Seligson, Jun Dong, Steve Horvath, Allan J. Pantuck, Robert A. Figlin, Arie S. Belldegrun*

**Introduction:** VEGF-A, a potent angiogenic signaling peptide, acts through high affinity tyrosine kinase receptors VEGFR-1 and VEGFR-2. Therapies targeting this pathway have demonstrated objective clinical responses and improvement in time to progression in metastatic clear cell RCC. Understanding the expression of these markers in both clear cell and papillary subtypes may guide patient selection and optimize the benefit of agents targeting the VEGF-A pathway.

**Methods:** A tissue microarray was constructed from paraffin-embedded clear cell (N=340) and papillary (N=42) RCC specimens from patients treated with nephrectomy. Immunohistochemistry was performed and the percentage of tumor cells expressing the marker was scored in 3 locations and averaged. The Kruskal-Wallis test was used to compare the expression of each marker between the two tumor histologies. Pearson correlation coefficients were determined to analyze the co-expression of the protein and receptors. Tumors were then categorized by percentage of tumor cells expressing the marker. Strong staining was defined as >66% expression, where medium staining = 33-65% expression, light staining = 1-32% and no staining = 0% expression.

**Results:** Papillary RCC demonstrated a higher mean expression of VEGF-A (57.3% vs 37.0%, p=7.6x10^{-5}) and VEGFR-2 (49.3% vs 37.06%, p=1.7x10^{-5}) than clear cell RCC. No difference was seen in the expression of VEGFR-1 between papillary and clear cell type RCC (58.0% vs 54.8%, p=.53). The frequency of strong, medium, light and no staining for VEGF-A was 45%, 33%, 17%, and 5% in papillary RCC versus 19%, 34%, 36%, and 11% in clear cell RCC, respectively. VEGFR-1 demonstrated a distribution of 38%, 36%, 26%, and 0% in papillary RCC versus 38%, 35%, 24%, and 3% in clear cell RCC, respectively. VEGFR-2 exhibited a distribution of 33%, 38%, 24%, and 5% in papillary RCC and 17%, 35%, 39%, and 8% in clear cell RCC, respectively.

**Conclusions:** Papillary type RCC exhibits higher VEGF-A and VEGFR-2 expression than clear cell type RCC. Patients with papillary RCC warrant inclusion in clinical trials targeting this pathway. Profiling the strength of marker expression in RCC, regardless of histology, may refine patient selection for anti-angiogenesis therapy.

4:50 p.m.

**CLINICAL OUTCOMES OF PATIENTS DOWNSTAGED AT RADICAL CYSTECTOMY**

*Craig G. Rogers, Patrick J. Bastian, Ganesh S. Palapattu, Bruce J. Trock, Mark P. Schoenberg, and Theresa Chan*

**Objectives:** We present the clinical outcomes of patients with bladder cancer (BCA) who were downstaged from muscle invasion at transurethral resection (TUR) to nonmuscle invasive disease following radical cystectomy.

**Methods:** We retrospectively reviewed the records of 248 consecutive patients who underwent radical cystectomy for urothelial carcinoma (TCC) at our institution between 1994 and 2002. Of these patients, 112 (45%) had documented muscle-invasive disease by TUR prior to radical cystectomy.

**Results:** Of the 112 patients with muscle-invasive disease by TUR, 25 (22.3%) were downstaged to nonmuscle-invasive disease (pT1 or less) at cystectomy, whereas 87 (77.7%) had persistent muscle-invasive disease (pT2 or greater) at cystectomy. Recurrence occurred in 4 (16.0%) downstaged patients compared to 29 (33.3%) non-downstaged patients (p=0.094). Kaplan Meier analysis demonstrated a statistically significant improvement in recurrence-free survival with downstaging (Log rank p=0.02) Multivariate analysis demonstrated a 3-fold reduction in recurrence risk with tumor downstaging (HR=0.33, 95% CI: 0.10-1.12) with a trend towards statistical significance (p=0.075).

**Conclusions:** After adjusting for the effect of positive lymph nodes, patients who are downstaged from muscle-invasive TCC on TUR to non-muscle invasive TCC on radical cystectomy may have a reduced risk of disease recurrence compared to patients with persistent muscle-invasive disease on cystectomy.