

18th Annual

PERSPECTIVES IN UROLOGY POINT COUNTERPOINT 2009

November 5–7, 2009 • The Scottsdale Plaza • Scottsdale, Arizona

Course Director: E. David Crawford, MD

Faculty: David C. Beyer, MD, FACR, FACRO, FASTRO Robert E. Donohue, MD

Brian J. Flynn, MD • Donald L. Lamm, MD

M. Scott Lucia, MD • Paul D. Maroni, MD

Mark A. Moyad, MD, MPH • Jacob Rajfer, MD

Matthew Rettig, MD

Sponsored by

GRANT/DOWNING
E D U C A T I O N

The views expressed in this activity are those of the faculty. It should not be inferred or assumed that they are expressing the views of the commercial supporters, any other manufacturer of pharmaceuticals, or Grant/Downing, LLC.

The drug selection and dosage information presented in this activity are believed to be accurate. However, participants are urged to consult the full prescribing information on any presented in this activity for recommended dosage, indications, contraindications, warnings, precautions and adverse effects before prescribing any medication. This is particularly important when a drug is new or infrequently used.

© 2009

All rights reserved including translation into other languages. No part of this activity may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval systems, without permission in writing from Grant/Downing, LLC.

Table of Contents

Program Information 4
Course Director and Faculty Biographies 6
Disclosures 13
Agenda..... 14



Introduction

This program has been designed to address key questions on potentially practice changing developments in the field of urology and to provide urologists, trainees, and other health care professionals involved in the diagnosis and management of urology diseases with the framework to integrate these developments into their daily practice. These educational offerings are designed to enhance patient assessment and outcomes, and will include didactic lectures, debates, case presentations, and question and answer sessions.

Objectives

After completing this activity, participants will demonstrate:

1. Improved management of patients with 'castration-resistant prostate cancer,' based on a strong knowledge base that includes current studies on role of PSA doubling time, testosterone level, and outcomes with newer vs older pharmacologic agents
2. Differentiation of fact from fiction regarding frequency of use and outcomes of robotic vs open radical prostatectomy across multiple parameters: continence, potency, cancer recurrence, PSA levels, positive margin rates, cost and experience of the surgeon
3. Evidence-based clinical decision-making regarding evaluation and treatment of androgen deficiency syndromes, based on updated data regarding diagnostic assays of testosterone, contraindications to testosterone replacement therapy (TRT), evidence of multisystem TRT benefits, and distinctive properties of diverse formulations
4. Informed resolution of concerns that impact use of TRT in aging men with symptomatic hypogonadism, with consequent benefit to untreated patients who are appropriate candidates for TRT
5. Evaluation and management of men aged >50 with these clinically documented data in mind: underdiagnosis and undertreatment of enlarged prostate and attendant lower urinary tract symptoms; predictive value of PSA for risk of enlarged prostate (EP) progression; goal of treatment to include prevention of acute urinary retention (AUR) and EP-associated surgery; documented efficacy of single and combined therapies
6. Clinical decision-making consistent with the 2009 AUA Updated Guideline for Clinical Stage 1 Renal Mass with particular focus on the significance of current histologic subtyping, consideration of tumor volume and evolving molecular markers, the diversity of treatment modalities both standard and novel, and definition of the patient population for whom active surveillance is a reasonable option
7. Treatment selection for bladder cancer based on thorough understanding of risk stratification and appropriate use of BCG to prevent treatment failures, as well as awareness of clinical data on therapeutic options post-BCG failure
8. Informed judgments on the role of radiation therapy in select populations with bladder cancer
9. Improvement in outcomes for surgical stress incontinence procedures, based on comprehensive knowledge of optional approaches and caveats for specific procedures, e.g., effective materials for transvaginal tape in pubovaginal sling procedure, predictors of voiding dysfunction post-pubovaginal sling, techniques for minimally invasive prolapse surgery, management of apical vaginal defect
10. Inclusion of complementary alternative strategies where appropriate, including chemoprevention and early treatment of prostate cancer as well as BPH, mindful of updated data analyses, e.g., cardioprotective and prostate-protective parallels; conflict regarding finasteride; role of antioxidants and vitamin D; problems with excessive supplementation

**Continuing
Education
Credit**

**GRANT/DOWNING
E D U C A T I O N**



Grant/Downing Education is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Grant/Downing Education designates this educational activity for a maximum of *15.25 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in this activity.

Acknowledgement

"Perspectives in Urology: Point Counterpoint" is supported in part by unrestricted educational grants and exhibit fees from **Abbott Laboratories , AstraZeneca, Audio-Digest Foundation, Cook Urological, Dendreon Corporation, Endo Pharmaceuticals, Ferring Pharmaceuticals, Genentech, Novartis, Olympus, Onco Diagnostics, Solvay Pharmaceuticals, and Watson Pharma, Inc.**

Course Director

E. David Crawford, MD

*Professor of Surgery/Urology/Radiation Oncology
Head, Urologic Oncology
E. David Crawford Endowed Chair in Urologic Oncology
University of Colorado, Denver*

E. David Crawford is the E. David Crawford distinguished professor of surgery, urology, and radiation oncology, and head of the Section of Urologic Oncology at the University of Colorado Health Sciences Center (UCHSC) in Denver. He serves as the senior associate director of the University of Colorado Comprehensive Cancer Center, also in Denver.

Dr Crawford received his medical degree from the University of Cincinnati. His postgraduate training included an internship and residency in urology at the Good Samaritan Hospital in Cincinnati. He subsequently completed a genitourinary cancer fellowship with Dr Donald G. Skinner at the University of California Medical Center in Los Angeles.

Dr Crawford is a nationally recognized expert in benign prostate hypertrophy, urologic cancers, and in particular prostate cancer. The recipient of more than 69 research grants, he has conducted research in the treatment of advanced bladder cancer, metastatic adenocarcinoma of the prostate, hormone refractory prostate cancer, and other areas of urological infections and malignancies. He has authored or coauthored over 450 articles that have been published in such journals as *Urology*, *The New England Journal of Medicine*, *the Journal of Urology*, and the *Journal of the National Cancer Institute*. He has published five textbooks and authored over 50 book chapters, and is an editorial reviewer or consultant for a large number of publications, including *Urology*, *Journal of Urology*, *The New England Journal of Medicine*, *Cancer*, and the *Journal of Clinical Oncology*.

Dr Crawford is an active member of many national and international organizations, including the American Society of Clinical Oncology, American Urological Association (AUA), and the American Association for the Advancement of Science. Within the AUA, he was a member of the Committee to Study Urologic Research Funding and the Prostate Cancer Clinical Trials Subcommittee. He currently serves on the board of governors, the GU committee, and the scientific advisory board of the Southwest Oncology Groups, and chairs the National Prostate Cancer Education Council. His involvement in the national prostate cancer arena has been widely recognized. Dr Crawford has received many honors and awards, including the CaP Cure Annual Award for Scientific Presentation in 1999. In 1997, he was presented with a "Freddie Award" at the AMA International Health and Medical Film Competition for the program *ITV: The Cutting Edge Medical Report (Prostate Cancer: Understanding, Diagnosing, and Defeating)*, which Dr Crawford hosted with special guest retired General Norman Schwarzkopf. He again won a prestigious "Freddie Award" in 2005. He has been recognized as one of the Best Doctors of America for the past decade, and one of the Best Cancer Doctors. In 2007 he was awarded the honor of being selected as the Best Healthcare Provider in the Denver Metro area by the Denver Business Journal, Blue Cross, and Anthem Healthcare. In 2007, he was recognized as one of the top 20 Urologists in the country for men by Men's Health Magazine.

Faculty

David C. Beyer, MD, FACR, FACRO, FASTRO

*Arizona Oncology Services
Scottsdale, Arizona*

David C. Beyer, MD, FACR, FACRO, FASTRO is Vice President of Arizona Oncology Services, Inc. He serves as Vice Chair of the Health Policy Council on the Board for the American Society of Therapeutic Radiology & Oncology (ASTRO), is on the Board of Chancellors with the American College of Radiation Oncology (ACRO), and is an Editorial Board Member of the *Journal of Brachytherapy*.

Dr Beyer earned his medical degree from the University of Arizona, College of Medicine after completing a degree in electrical engineering from Massachusetts Institute of Technology. He joined Arizona Oncology Services in 1985, after serving consecutive residencies in both internal medicine and radiation oncology at the University of Arizona Health Sciences Center and University of California, Los Angeles. He is a member of Alpha Omega Alpha Honorary Society. Dr Beyer is a Fellow of the American College of Radiation Oncology (ACRO), the American College of Radiology (ACR), and the American Society for Therapeutic Radiology and Oncology.

Dr Beyer's primary clinical interests focus on prostate cancer and prostate Brachytherapy, including seed implants, and high dose rate (HDR) Brachytherapy. He has comprehensive experience in intensity modulated radiation therapy (IMRT) and image guidance radiation therapy (IGRT). He is a frequent lecturer at implant training courses and medical meetings, and has published extensively the Arizona Oncology Services results in prostate treatment.

Dr Beyer is board certified with the American Board of Radiology, the American Board of Internal Medicine, and Therapeutic Radiology.

Robert E. Donohue, MD

*Professor of Surgery/Urology
University of Colorado Health Sciences Center
Chief of Urology
Veterans Administration Medical Center*

Robert E. "Bob" Donohue graduated from New York University School of Medicine in 1964. After medical school, Dr Donohue completed a general surgery internship at Bellevue Hospital in New York. Dr Donohue completed his urology residency at New York University Medical Center in 1970. After completing his residency training, Dr Donohue continued his surgical training as a Valentine Fellow at the New York Academy of Medicine at Memorial Hospital for Cancer and Allied Diseases (1970-1971) and as a Senior Registrar in Urology at Christchurch Hospital affiliated with the University of Otago Medical School in New Zealand.

Dr Donohue received his certification from the American Board of Urology in 1974. He joined the faculty of the University of Colorado School of Medicine as Assistant Professor of Surgery/Urology in 1972. Dr Donohue was promoted to the rank of Associate Professor at the CU School of Medicine in 1978, and was promoted to the rank of Professor in 1992. In 1977, Dr Donohue was appointed Chief of Urology at the Denver Veterans Administration Medical Center and continues to hold that appointment. Dr Donohue served as the Acting Chief of Surgical Services at the Denver VAMC from 1982 to 1984. From 1989 to the present, Dr Donohue has served as the Chairman of the Cancer Committee and the Director of the Tumor Board at the Denver VA Medical Center. *(continued...)*

Faculty

Robert E. Donohue, MD (continued)

Dr Donohue has published and presented on wide variety of topics, and from 1989 to 1994, he was the Associate Editor of the *Journal of Urology*. Dr Donohue's research interests include Hox gene expression in the prostate, polymorphism of vitamin D receptor genes, screening for prostate, lung, colo-rectal, and ovarian cancers, and treatment for benign prostatic hyperplasia. Dr Donohue's practice encompasses most areas of general urology with special interest in benign testicular masses, impalpable testicular lesions, paratesticular masses (benign and malignant), acute scrotum, and lymphoma of the testis.

Brian J. Flynn, MD

Director of Urogynecology, Reconstructive Urology and Urodynamics

Associate Professor of Surgery/Urology

University of Colorado Denver

Brian J. Flynn, MD is the Director of Urogynecology, Reconstructive Urology and Urodynamics and associate professor at the University of Colorado. Dr Flynn received his BS in Electrical Engineering from the University of Rochester, Doctorate of Medicine from Temple University. He completed a residency in Urology at Geisinger Medical Center and his fellowship in Urogynecology and Reconstructive Urology at Duke University.

His primary areas of interest are Pelvic Reconstructive Surgery and Urogynecology. He is a national leader in the use of minimally invasive surgical techniques for the treatment of urinary incontinence in men and women and reinforced pelvic floor repairs in women. He has written updates for the AUA and has provided postgraduate instruction on the surgical management of post-prostatectomy incontinence, Management of complications of prolapse and incontinence surgery. He has authored numerous clinical papers, surgical videos, textbook chapters and has presented internationally on various topics including male and female urinary incontinence, pelvic organ prolapse, urinary diversion and urethral stricture disease.

Donald L. Lamm, MD

Director, Bladder Cancer-Genitourinary Oncology

Phoenix, Arizona

After 28 years in academic practice Donald Lamm, MD, FACS, launched his private practice in Fall 2004. Dr Lamm graduated AOA from UCLA and did a rotating internship at the University of Oregon HSC in Portland. He practiced family medicine for two years as Director of the Colville Indian Health Service Clinic before returning to UCLA for a year of General Surgery and to UCSD for urology residency.

During his urology residency he developed an animal model for bladder cancer and found that Bacillus Calmette Guerin (the TB vaccine, BCG) inhibited tumor growth. After residency he and his family moved to San Antonio where Dr Lamm began his academic career as Assistant Professor of Surgery at the University of Texas Health Sciences Center. During his nine years in Texas he rose in rank to Professor and Acting Chairman of the Division of Urology. His VA and NIH research resulted in clinical studies that led to the FDA approval of BCG for bladder cancer.

(continued...)

Faculty

Donald L. Lamm, MD, (continued)

Subsequent work by Dr Lamm, then Chairman of the Department of Urology at West Virginia University, demonstrated that BCG immunotherapy is superior to Adriamycin and Mitomycin C chemotherapy for superficial bladder cancer, significantly reducing the risk of bladder cancer progression to muscle invasion and metastasis. Dr Lamm's work is in part responsible for bladder cancer being one of only five cancers in the United States that has seen a reduced mortality despite an increased incidence. This reduction in mortality coincides with a reduction in the number of patients who lose their bladder as a result of radical cystoprostatectomy for muscle invasive or aggressive superficial disease.

Dr Lamm has authored over 270 peer-reviewed medical and scientific articles, and in addition to new treatments of bladder cancer, he has developed new approaches to the treatment of renal and prostate cancer as well. His primary interest, however, continues to be BCG therapy of bladder cancer.

M. Scott Lucia, MD

Associate Professor of Pathology

Director, Prostate Diagnostic Laboratory

Department of Pathology

University of Colorado Denver School of Medicine

M. Scott Lucia, MD is Associate Professor and Chief of Genitourinary and Renal Pathology at the University of Colorado Denver and Health Sciences Center where he also serves as the Director of the Prostate Diagnostic Laboratory and Co-Director of the Prostate Cancer Research Laboratories. Dr Lucia served as the primary pathologist for the Prostate Cancer Prevention Trial (PCPT), sponsored by the Southwest Oncology Group, and the Medical Therapy of Prostate Symptoms (MTOPS) trial, sponsored by the NIDDK. He currently is the primary pathologist for the Vitamin E and Selenium Chemoprevention Trial (SELECT) also sponsored by the Southwest Oncology Group. Dr Lucia directs the operation of several tissue and serum biorepositories for prostate and prostatic diseases including those for the PCPT, MTOPS, SELECT, and the University of Colorado Cancer Center Prostate Biorepository. He has authored over 70 peer-reviewed articles, reviews and book chapters. His primary areas of interest include pathology of prostate cancer and hyperplasia, early detection and prevention of prostate cancer, and mechanisms of carcinogenesis.

Paul D. Maroni, MD

Assistant Professor of Surgery (Urology)

University of Colorado Denver

Dr Paul Maroni is fellowship-trained in Urologic Oncology. He has developed a busy practice in Urology and Urologic Oncology. Dr Maroni is extremely qualified in a broad scope of urologic surgery and in the areas of prostate, bladder, and kidney cancer and performs laparoscopic ("minimally invasive") as well as open procedures. He trained at the University of Illinois at Chicago College of Medicine, completed his residency at the University of Colorado Denver School of Medicine and completed his fellowship at Indiana University. He is a member/investigator of the Southwest Oncology Group.

Special areas of interest are minimally-invasive procedures for low-risk prostate cancer and surgery for advanced (high-risk) prostate cancer. He is an investigator in national trials for high-intensity focused
(continued...)

Faculty

Paul D. Maroni, MD (continued)

ultrasound (HIFU) treatments for prostate cancer and injection medications for the management of urinary symptoms related to benign prostate enlargement. He crafts treatment alternatives for patients based on individual values. In order to advance medical knowledge and improve patient outcomes, he will be actively recruiting patients to clinical trials for prostate cancer including active surveillance/watchful waiting (START trial), targeted therapies, and surgery for high-risk patients (PUNCH trial). He regularly participates in the genitourinary multidisciplinary second opinion conference.

Additionally, he has experience in specialized surgeries for the removal of metastatic masses in patients with advanced testicular cancer. He is happy to discuss complicated aspects of the management of testicular cancer and works closely with genitourinary medical oncologists to help treat this disease.

Mark A. Moyad, MD, MPH

Jenkins/Pokempner Director of Preventive and Alternative Medicine

Department of Urology

University of Michigan Medical Center

Dr Moyad is the co-director of the men's health program at the University of Michigan. He received his master's degree in public health from the University of South Florida, where he was one of the lead investigators of the L-tryptophan dietary supplement study that helped to remove this dangerous supplement from the market. He published his first medical article in college on the relationship between a compound found in cottonseed oil and male infertility. Dr Moyad received his M.D. from Wayne State University School of Medicine. He is currently working part-time on his Ph.D. in pathology and N.D. (naturopathic doctor) degree. Dr Moyad is the author or co-author of four books and has three additional books coming out in the next 12 months, including a guide for men's and women's health and a breast cancer prevention book. He is the primary author of over 60 medical articles. Dr Moyad is the editor of the complementary/ preventive medicine medical book series from Humana Press. He has also been the guest editor of five different medical journals and reviews or edits articles for a number of medical journals, including: *Urology, Journal of Urology, Cancer, Nutrition and Cancer, British Journal of Urology*. Dr Moyad is the director of the complementary/preventive medicine course for the Annual American Urologic Association Meeting and the Annual Urologic Nurses Meeting. He has an endowed chair/directorship at the University of Michigan Medical Center in complementary and preventive medicine. Dr Moyad has had a consulting practice for almost 10 years, and he runs clinical trials and basic science studies in regards to complementary/preventive at the university and has lectured in all 50 states to health professionals and patients. He speaks internationally and gives courses in Europe and Asia on a regular basis. His latest research includes identifying the relationship between lipid changes and cancer risk and treatment.

Sidebar header

Jacob Rajfer, MD

Professor of Urology

Chief of Urology, Harbor-UCLA Medical Center

David Geffen School of Medicine at UCLA

Jacob Rajfer, MD is professor of urology at the University of California at Los Angeles (UCLA) and chief of urology at the Harbor-UCLA Medical Center in Torrance. Dr Rajfer received his medical degree from Northwestern University Medical School in Chicago, Illinois. He completed an internship in medicine at Los Angeles County - University of Southern California Medical Center and residencies in surgery at St. Joseph's Hospital, Denver, Colorado, and in urology at The Johns Hopkins Hospital, Baltimore, Maryland.

Dr Rajfer has focused his research on various aspects of erectile dysfunction (ED) and is currently investigating the effects of aging on the penile vascular system and how it relates to the rest of the vascular system, in general. In the early 1990s, he and his colleagues at UCLA discovered that nitric oxide (NO) was the actual chemical mediator of penile erection and that inhibition of phosphodiesterase (PDE) activity actually enhanced the erectogenic aspects of NO. In addition, his group showed that testosterone, and specifically dihydrotestosterone, was the active androgen necessary for the production of NO in the penis.

A frequent contributor to the medical literature, Dr Rajfer has published more than 200 journal articles and book chapters. His work has appeared in the *New England Journal of Medicine*, *JAMA*, *Cardiovascular Research*, *American Journal of Physiology*, *Neuroendocrinology*, *Urology*, and other journals.

Dr Rajfer is a member of numerous medical organizations, including the American Urological Association, American Society of Andrology, and the Sexual Medicine Society of North America. He is a fellow of the American College of Surgeons, an honorary fellow of the American Academy of Pediatrics, and a past president of the Los Angeles Urological Society.

Matthew Rettig, MD

Associate Professor of Hematology-Oncology

Co-Director, Prostate Cancer Program

Institute for Urologic Oncology

David Geffen School of Medicine at UCLA

Matthew Rettig, MD is an Associate Professor in the Department of Medicine, Division of Hematology-Oncology, and the Department of Urology, and is the Medical Director of the Prostate Cancer Program of the Institute of Urologic Oncology at the David Geffen School of Medicine at UCLA. After receiving his medical degree from Duke University, Dr Rettig completed internal medicine residency at the University of Washington before going to hematology-oncology fellowship at UCLA.

As a medical oncologist, he focuses on the management of genitourinary malignancies with a focused clinical emphasis on advanced prostate cancer. Dr Rettig has both a clinical and bench research program. He conducts multiple prostate cancer clinical trials that span the spectrum of the states of the disease: from neoadjuvant therapies to post-chemotherapy, castration-resistant disease. Dr Rettig's bench research program, which is funded by the NIH, Department of Defense and the Department of Veterans Affairs, is focused on identifying biochemical targets for therapeutic translation in castration-resistant prostate cancer and clear cell renal cell carcinoma.

Faculty & Planner Disclosures

In accordance with the Accreditation Council for Continuing Medical Education (ACCME), Grant/Downing Education is required to disclose to the participants any relevant financial relationships the staff, authors, faculty, or planning committee members have with commercial interests whose products or health care services will be discussed in their presentations. It is Grant/Downing Education's policy to ensure that all continuing medical education activities are planned independent from commercial companies and are free from commercial bias. The following disclosures of financial relationships represent all people who were involved with the development or delivery of the content of this educational activity.

David C. Beyer, MD, FACR, FACRO, FASTRO, Faculty

David C. Beyer, MD, FACR, FACRO, FASTRO has reported that he has no relevant financial relationships.

Leslie Cohan, Planner

Leslie Cohan has reported that she has no relevant financial relationships.

E. David Crawford, MD, Course Director/Faculty

Grant Research Support: Endocare, Oncura/Galil/Eigen, Bostwick, Gen-Probe, Aeterna Zentaris, EDAP - HIFU, Ferring Pharmaceuticals, NIH/NCI, Cancer Center

Advisory/Speakers' Bureau: sanofi-aventis, Poniard, AstraZeneca, Glaxo Smith Kline, Ferring Pharmaceuticals, Endo Pharmaceuticals, Soar BioDynamics

Robert E. Donohue, MD, Faculty

Robert E. Donohue, MD has reported that he has no relevant financial relationships.

Brian J. Flynn, MD, Faculty

Advisory/Review/Board Membership: Ethicon, AMS

Donald L. Lamm, MD, Faculty

Speakers' Bureau: Sanofi-Pasteur

Advisory/Review/Board Membership: Sanofi-Pasteur

M. Scott Lucia, MD, Faculty

Advisory/Review/Board Membership: Glaxo Smith Kline, Gen-Probe, Veridex

Paul D. Maroni, MD, Faculty

Advisory/Review/Board Membership: sanofi-aventis, EDAP Technomed

James McKiernan, MD, Reviewer

Speakers' Bureau: sanofi-aventis

Mark A. Moyad, MD, MPH, Faculty

Speakers' Bureau: Abbott Laboratories

Advisory/Review/Board Membership: Guthy Renker, NBT4, Farr Labs, Abbott Laboratories, Embria

Jacob Rajfer, MD, Faculty

Speakers' Bureau: sanofi-aventis

Matthew Rettig, MD, Faculty

Speakers' Bureau: sanofi-aventis

Agenda

Wednesday, November 4

6:00 – 8:00 pm Registration

Thursday, November 5

Page

7:00 – 7:55 am Registration and Continental Breakfast in Exhibit Hall

7:55 – 8:00 am Welcome and Introduction
~ *E. David Crawford, MD*

Robotic Surgery

8:00 – 8:30 am The Role of Robotics in Urologic Surgery 1.3
~ *Paul D. Maroni, MD*

8:30 – 9:00 am Point-Counterpoint: Prostate Cancer 2.1

Robotic Surgery is Hype ~ *E. David Crawford, MD* 2.1

Robotic Surgery is the Mainstream ~ *Paul D. Maroni, MD* 2.16

9:00 – 9:10 am Questions & Answers

Renal Cell Carcinoma

9:10 – 9:30 am Histologic Subtypes of Renal Cell Carcinoma 3.1
~ *M. Scott Lucia, MD*

9:30 – 9:55 am Point-Counterpoint: Small Renal Masses 4.1

Best to Remove ~ *Paul D. Maroni, MD* 4.1

Best to Watch ~ *Donald L. Lamm, MD* 4.2

9:55 – 10:00 am Questions & Answers

10:00 – 10:15 am Break in Exhibit Hall

Female Urology, Part I

10:15 – 11:15 am Female Urology “Potpourri” 5.1
~ *Brian J. Flynn, MD*

11:15 – 11:25 am Questions & Answers

Clinical Challenges

11:25 – Noon Case Presentations and Discussion

Noon Adjourn for the day

Agenda

Friday, November 6

Page

7:00 – 8:00 am Breakfast and Industry-Supported Satellite Symposium
 The Evolving Role of Hormonal Therapy in the Management
 of Prostate Cancer

Bladder Cancer

8:00 – 8:45 am A Case-based Approach to the Management of Bladder Cancer 6.1
 ~ Moderator: Robert Donohue, MD

Panel: David C. Beyer, MD • E. David Crawford, MD
 Donald L. Lamm, MD • Paul D. Maroni, MD

8:45 – 9:00 am Questions & Answers

9:00 – 9:30 am Non-muscle Invasive Bladder Cancer, including Chemoprevention ~ 7.1
 Review of Existing Guidelines & International Recommendations
 ~ Donald L. Lamm, MD

9:30 – 9:55 am Point-Counterpoint: Radiation & Bladder Cancer 8.1

Radiation Has No Role in the Treatment of Any Stage of Bladder Cancer
 ~ Robert E. Donohue, MD 8.1

Radiation Plays a Major Role in Certain Stages of Bladder Cancer
 ~ David C. Beyer, MD 8.16

9:55 – 10:00 am Questions & Answers

10:00 – 10:15 am Break in Exhibit Hall

10:15 – 10:35 am What the Community Urologist Needs to Know About BCG 9.1
 ~ Donald L. Lamm, MD

10:35 – 10:45 am Questions & Answers

Female Urology, Part II

10:45 – 11:15 am The Spectrum of Stress Incontinence Surgery, 2009 10.1
 ~ Brian J. Flynn, MD

11:15 – 11:25 am Questions & Answers

Clinical Challenges

11:25 – Noon Case Presentations and Discussion

Noon – 1:00 pm Lunch in Exhibit Hall

Agenda **Friday, November 6** (continued)**Prostate Cancer**

1:00 – 1:20 pm	Challenges in Prostate Cancer: Why We Are 15 Years Behind Breast Cancer ~ <i>David C. Beyer, MD</i>	11.1
1:20 – 1:50 pm	Clinical and Pathologic Characteristics of Prostate Cancer (including new markers such as PCA3) ~ <i>M. Scott Lucia, MD</i>	12.1
1:50 – 2:10 pm	Chemoprevention Strategies ~ <i>M. Scott Lucia, MD</i>	13.1
2:10 – 2:40 pm	Point-Counterpoint: Early Detection of Prostate Cancer Is Not Valuable In a Lot of Men ~ <i>E. David Crawford, MD</i> We Can't Go Backwards – Of Course Screening Has Saved Lives ~ <i>Robert E. Donohue, MD</i>	14.1 14.1 14.9
2:40 – 2:50 pm	Questions & Answers	
2:50 – 3:00 pm	Break in Exhibit Hall	
3:00 – 3:20 pm	What's New in Advanced Disease (CRPC)? ~ <i>Matthew Rettig, MD</i>	15.1
3:20 – 3:50 pm	An Update on Radiation Therapy for Prostate Cancer ~ <i>David C. Beyer, MD</i>	16.1
3:50 – 4:00 pm	Questions & Answers	
4:00 pm	Adjourn for the day	

Agenda	Saturday, November 7	Page
	7:15 – 8:00 am Continental Breakfast in Exhibit Hall	
	8:00 – 8:20 am Chemotherapy for Urological Cancers ~ Matthew Rettig, MD	17.1
	8:20 – 8:25 am Questions & Answers	
Prostate Conditions		
	8:25 – 8:55 am Increasing Awareness, Diagnosis, and Treatment of BPH, LUTS, and EP ~ E. David Crawford, MD	18.1
	8:55 – 9:25 am Point-Counterpoint Are We Ignoring Level One Evidence by Not Prescribing Appropriate Medical Therapy? ~ E. David Crawford, MD Alternative Medicine Should Be the Choice ~ Mark A. Moyad, MD, MPH	19.1
	9:25 – 9:35 am Questions & Answers	
Hypogonadism		
	9:35 – 10:05 am Increasing Awareness, Diagnosis, and Treatment of Hypogonadism ~ Jacob Rajfer, MD	20.1
	10:05 – 10:35 am Point-Counterpoint: Late Onset Hypogonadism (LOH) We are Under-diagnosing and Treating Men with LOH ~ Jacob Rajfer, MD LOH is a Non-existent Disease ~ Robert E. Donohue, MD	21.1 21.1 21.8
	10:35 – 10:45 am Questions & Answers	
	10:45 – 10:55 am Break in Exhibit Hall	
Complementary Alternative Medicine		
	10:55 – 11:55 am Fad Diets and Dietary Supplements for Urology Patients: What Works and What's Worthless ~ Mark A. Moyad, MD, MPH	22.1
	11:55 – 12:10 pm Pills and Tests: What Should I (the urologist) Be Taking and Getting? ~ Mark A. Moyad, MD, MPH	23.1
	12:10 – 12:30 pm Point-Counterpoint: Why Every Man Should Be Offered Chemoprevention for Prostate Cancer ~ E. David Crawford, MD Chemoprevention Is Not for Every Man ~ Mark A. Moyad, MD, MPH	24.1 24.1 24.12
	12:30 – 12:45 pm Questions & Answers	
	12:45 pm Meeting Adjourns	

18th Annual

PERSPECTIVES IN UROLOGY
POINT COUNTERPOINT 2009

Thursday, November 5, 2009

Ballroom E-F

The Scottsdale Plaza

Scottsdale, Arizona



Agenda

Wednesday, November 4

6:00 – 8:00 pm Registration

Thursday, November 5

Page

7:00 – 7:55 am Registration and Continental Breakfast in Exhibit Hall

7:55 – 8:00 am Welcome and Introduction
~ *E. David Crawford, MD*

Robotic Surgery

8:00 – 8:30 am The Role of Robotics in Urologic Surgery 1.3
~ *Paul D. Maroni, MD*

8:30 – 9:00 am Point-Counterpoint: Prostate Cancer 2.1

Robotic Surgery is Hype ~ *E. David Crawford, MD* 2.1

Robotic Surgery is the Mainstream ~ *Paul D. Maroni, MD* 2.16

9:00 – 9:10 am Questions & Answers

Renal Cell Carcinoma

9:10 – 9:30 am Histologic Subtypes of Renal Cell Carcinoma 3.1
~ *M. Scott Lucia, MD*

9:30 – 9:55 am Point-Counterpoint: Small Renal Masses 4.1

Best to Remove ~ *Paul D. Maroni, MD* 4.1

Best to Watch ~ *Donald L. Lamm, MD* 4.2

9:55 – 10:00 am Questions & Answers

10:00 – 10:15 am Break in Exhibit Hall

Female Urology, Part I

10:15 – 11:15 am Female Urology “Potpourri” 5.1
~ *Brian J. Flynn, MD*

11:15 – 11:25 am Questions & Answers

Clinical Challenges

11:25 – Noon Case Presentations and Discussion

Noon Adjourn for the day

Hospital Stay

- No difference

Functional Outcomes

- No difference

Urinary Control

- AUA Abstract # 1605-Vanderbilt
- Robot-320 90% 1 year
- RRP- 195 88% 1 year
- No difference and this is what other series report, though not all at the same institution.
- Patients are led to believe better

Table 1: Surgical outcomes of radical prostatectomy performed in series

Center	Approach	No Pts	Mean op time	Mean EBL	Transfusion %	Mean LOS	Complications	Positive Surgical Margin
Rassweiler et al ¹	TLRP	219	288	1100	30.1	12	19.6	21
	ELRP	219	218	800	9.6	11	10.5	23.7
Goeman et al ²⁰	TLRP	165	240	678	1.2	6.7	9.1	23
Elden et al ²¹	TLRP	100	238.9	310.5	2	3.8	8	16
Guillonneau et al ³	TLRP	550	200	380	5.3	5.8	10	15
Cathelineau et al ²²	ELRP	600	173	380	1.2	6.3	11.5	17.7
Tuerk et al ²³	ELRP	174	169	176	0	1.67	9.9	14.5
Goeman et al ²⁰	ELRP	550	188	390	4.7	4.6	10.9	pT2 17.9 pT3 44.8 pT4 71.4
Elden et al ²¹	ELRP	100	190.6	201.5	0	2.6	4	16
Stolzberger et al ²⁴	ELRP	700	151	220	0.9	-	2.4	19.8
Menon et al ²⁵	RAR P	1142	154	142	0	1.14	2.3	13
Patel et al ²⁶	RAR P	200	141	75	0	1.1	2	10.5
Joseph et al ²⁷	RAR P	325	130	196	0.09	-	9.8	13
Rassweiler et al ¹	ORP	219	196	1550	55.7	16	35.6	38.7
Zincke et al ²⁸	ORP	3170	-	600-1030	5-31	-	-	24
Lepor et al ²⁹	ORP	1000	-	819	9.7	2.3	7	19.9

Table 2: Oncologic and Functional Data in series

Center	Technique	No. pts	PSA Non-Recurrence	Urinary Continence	Potency
Rajawwiler et al ¹⁸	TLRP	438	94% (3 mos)	90.3% (12 mos), 95.8% (18 mos)	Not reported
Guillonneau et al ¹⁹	ELRP	550	p12a 92.3% (36 mos) p12c 86.9% (31 mos)	82.3% No pad (12 mos)	BNS 85% (spontaneous erections), 66% (intracavernosal)
Geeman et al ²⁰	ELRP	550	p12 89.7% (5 yr) p13 58.6% (5 yr)	91% (24 mos)	BNS 64%, 78, 66, and 90.9% (12 & 24 mos) if pre-60 years old
Stohrberg et al ²¹	ELRP	700	Not reported	92% complete (12 mos) 98% 1 pad or less	BNS 47.1% (6 mos)
Memon et al ²²	RARP	1142	Overall: 97.7% (36 mos) Gleason 6 - 98.5% Gleason 7 - 95.4% Gleason 8 & 9 - 60.1%	95.2% 1 pad or less (12 mos) 94% no urine leak	Bilateral vein technique 93% (48 mos) BNS 70% (intracorporeal at 5 yrs)
Mikhail et al ²³	RARP	100	Not reported	84% return to baseline function (12 mos) 89% subjective continence (12 mos)	89% return to baseline sexual function (12 mos)
Dink et al ²⁴	RARP	700	95% (5.7 mos)	88% (12 mos)	Not reported
Chou, Albert et al ²⁵	RARP	325	97% (6 mos)	90% (6 mos)	Not reported
Camblon et al ²⁶	ORP	1325	97% (6 mos)	93%	BNS 68% IENS 47%
Geary et al ²⁷	ORP	458		80.1% No pads 8.1% 1 - 2 pads 6.6% 3 - 5 pads 2.2% totally incontinent	71% w/ mNSS
Leandri et al ²⁸	ORP	670		85% complete control	

Complication Rates Associated With Radical Prostatectomy, According to Prospective Studies

Complications	Open RRP	LRP (%)	
	Lepor & Kaci N = 500	Guillonneau et al N = 567	Ruiz et al N = 330
Rectal injury	0	1.4	1.8
Ileocolonic injury	0	0.9	0
Rectal fistula	0	NR	NR
Ureteral injury	0.2	0.7	NR
Bladder injury	0	NR	NR
Nerve injury	0	0.5	NR
Vascular injury	0	0.5	0
Wound complication	0.2	0.7	1.5

Guillonneau et al J. Urol 2002;167: 51
Ruiz et al. Eur Urol 2004; 46: 50
Lepor et al. Urology 2004; 63:499

Complication Rates Associated With Radical Prostatectomy, According to Prospective Studies

Complications	Open RRP	LRP (%)	
	Lepor & Kaci N = 500	Guillonneau et al N = 567	Ruiz et al N = 330
Urinoma	0	NR	NR
Myocardial infarction	0.4	NR	NR
Pulmonary embolus	0	NR	NR
DVT	0.4	0.3	NR
CVA	0	NR	NR
Prolonged ileus	0.4	1	1.5
Lymphocele	0	0	0.3

Guillonneau et al J. Urol 2002;167: 51
Ruiz et al. Eur Urol 2004; 46: 50
Lepor et al. Urology 2004; 63:499

Positive Surgical Margins After Radical Prostatectomy

Author(s)	Institution	Patients, N	Positive Margins (%)		Study Period
			pT ₁ Disease	pT ₂ Disease	
Open radical prostatectomy					
Lepor ²⁹	New York University	1000	2.9	31.2	2000-2005
Baumgartner et al	Emory Hospital	77	2.3		1999-2001
Chen et al	Cleveland Clinic	152	7.4	28.6	1994-1996
Laparoscopic radical prostatectomy					
Rajawwiler et al	University of Heidelberg	438	9.7	33.1	1999-2002
Guillonneau et al	Montebios Institute	1000	15.5	31.1	1998-2002
Memon et al	Honey Ford	100	0	40	2001-2002
Ruiz et al	Harriet Mauder	330	16.3	44.3	2000-2002
Baumgartner et al	Emory Hospital	85	7.8		1999-2001

²⁹Unpublished data.
Concurrent studies at same institution.

Continence Rates After Radical Prostatectomy, According to Disease-Specific Self-Administered Quality-of-Life Instruments

Author(s)	Institution	Continence Assessment	
		Patients, N	Continent* (%)
Open radical prostatectomy			
Lepor et al	New York University	500	98.5
Wei et al	University of Michigan	482	97.7
Young et al	Duke University	92	97.8
Laparoscopic radical prostatectomy			
Olsson et al	Henri Mondor	36	100
Link et al	Johns Hopkins	122	93

*Minimum of 12 months follow-up.



OK so what are alternatives to Robot?

Lap RRP

RPP

Modify how you do your standard RRP

LAP RRP

- Most European and many US Centers use Lap alone and have excellent results
 - Learning curve for suturing
 - Visualization

Demographics

Variable	Number	Mean (sd)	Median
Age	406	57.2 (7.1)	57.0
WM Gleason sum	373	6.5 (1.05)	7.0
Preoperative PSA (ng/dl)	406	6.9 (7.8)	5.6
Estimated Blood loss (ml)	341	406.2 (240.6)	350.0

Pathological stage

Pathological Stage	Frequency	Cumulative %
T1a	16	1.57
T1c	64	16.71
T2a	77	20.10
T2b	122	31.85
T2c	47	12.27
T3a	16	4.18
T3b	48	12.53
T3c	2	0.52

Advantages of LRP

Claims by LRP Surgeons	Rebuttal by open Surgeons
<ul style="list-style-type: none"> Magnification improves visualization 	<ul style="list-style-type: none"> Magnification achievable with surgical loops
<ul style="list-style-type: none"> Less blood loss 	<ul style="list-style-type: none"> Not clinically relevant, based on similar transfusion rates
<ul style="list-style-type: none"> Improved visualization allows for more precise dissection of the prostatic apex and NVB 	<ul style="list-style-type: none"> Quality of life outcomes fail to show advantages for continence or potency

Advantages of LRP

Claims by LRP Surgeons	Rebuttal by open Surgeons
<ul style="list-style-type: none"> Avoidance of lower abdominal incision decreases postoperative pain and facilitates return to activities 	<ul style="list-style-type: none"> Postoperative pain is comparable, and men can return to activities just as quickly despite an incision
<ul style="list-style-type: none"> Watertight urethrovesical anastomosis allows for earlier catheter removal 	<ul style="list-style-type: none"> No difference in achieving watertight Vesicourethral anastomosis at postoperative day 3; urinary catheters typically removed at 1 week after both approaches

Mistakes were made

- 2003 FTC allows purchase of Computer Motion, Inc by Intuitive Surgical, Inc for ~\$65M
- Price of daVinci surgical robot 2009
 - \$1.75M
- Estimated price with competition
 - Less than \$500,000
 - Source: Richard Satava MD FACS, lecture at Univ of Colorado General Surgery Grand Rounds, 2009

More mistakes

- Systematic problems force hospitals to compete
- Underserved areas think this will be an attraction
- Cancer reimbursed more favorably than other diseases
- Procedures reimbursed more favorably than most other options

- Isn't there enough other urologic disease?

Has the robot been oversold?

- Google.com search "robotic prostatectomy"
 - 127,000 hits
 - 11 paid sites on first page
- Intuitive Surgical, Inc.
 - Provides marketing advice/toolkits
- Strong incentives for medical centers' ROI
- Lost focus on patients during "dynamic growth curve" aka Gold Rush

Were there false expectations?

- Schroeck et al Eur Urol 2008
 - 400 patients surveyed from RRP and RARP 2000-2007
 - Equivalent functional outcomes and bother (EPIC) between RRP and RARP
 - More regret in RARP (24.1% v. 14.9%)

Patients who underwent RALP were more likely to be regretful and dissatisfied possibly because of high expectations of a new procedure. We suggest that urologists carefully portray the risks and benefits of new technologies during preoperative counseling to minimize regret and maximize satisfaction.

Is one approach better?

available at www.sciencedirect.com
journal homepage: www.europeanurology.com



Review – Prostate Cancer

Retropubic, Laparoscopic, and Robot-Assisted Radical Prostatectomy: A Systematic Review and Cumulative Analysis of Comparative Studies

Vincenzo Ficarra^{a,*}, Giacomo Novara^a, Walter Artibani^a, Andrea Cestari^b, Antonio Galiano^c, Markus Graefen^d, Giorgio Guazzoni^e, Bertrand Guillonneau^d, Mani Menon^f, Francesco Montorsi^g, Vipul Patel^h, Jens Rassweiler^b, Hendrik Van Poppelⁱ

- Published 2009 - 103 references

Is one approach better?

- LRP/RARP – less blood loss and transfusions
- Few or poor quality comparative studies

“...the data from this systematic review did not allow us to prove the superiority of any surgical approach...we do believe that it will never be shown that an LRP performed by a qualitatively poor surgeon would be better than an RRP done by a skilled surgeon (and vice versa).”

Is one approach better? Salvage treatment

- Hu et al J Clin Oncol 2008 – need for salvage treatments – Medicare database
 - MIRP 27.8% v. Open RP 9.1%
- Chino et al BJU Intl 2009 – 904 RP (536 open)
 - No difference in indication or referral for RT
- Hu et al JAMA 2009 (adapted)

Can Tx/100y	MIRP	RRP	P
Overall	8.2	6.9	.35
Radiation	5.1	4.9	.67
Hormone	5.3	3.7	.21

Is one approach better? Continence and Potency

Incontinence*	MIRP	RRP	P
Diagnosis	15.9	12.2	.02
Procedures	7.8	8.9	.24
Erec Dysfunc*			
Diagnosis	26.8	19.2	.009
Procedures	2.3	2.2	.78

- Medicare dbase study – MIRP > SES
- No questionnaires used, early in learning curve

* - per 100 person years, adapted from Hu et al JAMA 2009



Histologic Subtypes of Renal Cell Carcinoma

~ M. Scott Lucia, MD

Histologic Subtypes of Renal Cell Carcinoma



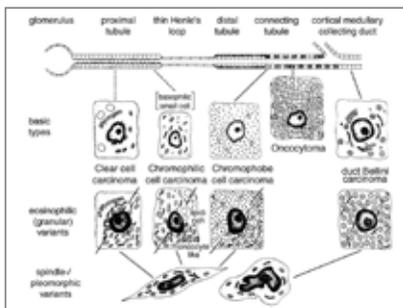
M. Scott Lucia, MD
 Associate Professor
 Chief of Genitourinary and Renal Pathology
 Director, Prostate Diagnostic Laboratory
 Dept. of Pathology
 University of Colorado Denver SOM

History of Classification of Renal Cell Neoplasms

- First case in literature reported by G. Miriel in 1810
- First classification in 1826, proposed by König, on basis of gross morphologic appearance into four types: Fungoid, Medullary, Scirrhus, Steatomatous
- Many subsequent classifications – many based upon descriptive histologic features of tumors (architectural and cytologic)
- Mainz classification proposed by Thoenes 1986
 - based upon cytologic features of tumors
 - first to correlate the subtypes of tumors with cell of origin in nephron

Delahunt B, Eble JN. History of the development of the classification of renal cell neoplasia. Clinics in Laboratory Medicine. 2005;25:231-46.

The Mainz Classification 1986



From: Delahunt B, Eble JN. Clinics in Laboratory Medicine. 2005;25:231-46. © 2005 Elsevier Inc.

Female Urology "Potpourri"

~ Brian J. Flynn, MD

Female Urology/Urogynecology Potpourri

Brian J. Flynn, MD
Director of Urogynecology, Reconstructive
Urology and Urodynamics

Associate Professor of Urology/Surgery
University of Colorado Denver
Denver, CO



Perspectives in Urology 2009

Urinary Tract Infections (UTIs) in Women

Perspectives in Urology 2009

UTI Introduction

- 8 million visits to health care providers annually *
- lead to more than 1 million admissions
- more than \$1.6 billion annually in health care dollars
- wide spectrum of disease from mild cystitis to life-threatening urosepsis

* Gupta K, et al: *Ann Intern Med* 2001

Perspectives in Urology 2009

Catheter Associated UTI (CAUTI)

Saint, S. et. al. Ann Intern Med 2009;150:877-884

Table 2. Hospital-Acquired Conditions Not Eligible for Additional Payment*

- Effective 1 October 2008**
- Catheter-associated urinary tract infection
 - Decubitus ulcer (pressure ulcers)
 - Vascular catheter-associated infection
 - Severe gastrointestinal "reperme events"
 - Foreign object retained after surgery
 - Air embolism
 - Blood incompatibility
 - Falls and trauma
 - Manifestations of acute glycemic control
 - Exacerbated brachycephalus
 - Neuroleptic malignant syndrome
 - Hyperglycemia, severe
 - Secondary diabetes with ketoacidosis or hyperosmolality
 - Deep venous thromboses or pulmonary embolism after certain orthopedic surgeries
 - Surgical site infections after certain surgical procedures
 - Mediastinitis after coronary artery bypass surgery
 - Certain orthopedic surgical site infections
 - Certain bariatric surgical site infections
- Considered for future implementation:**
- Ventilator-associated pneumonia
 - Staphylococcus aureus septicemia
 - Clostridium difficile-associated disease
 - Intraventricular hemorrhage
 - Legionnaire disease
 - Deltacoron

* Adapted from references 4 and 29–31.

Hospital-Acquired Conditions Not Eligible for Additional Payment

Catheter Associated UTI (CAUTI)

- UTI is the most common hospital acquired infection
- 1 in 5 patients in the hospital receive a Foley catheter
- 1 day of catheter use = 5% increase in bacteriuria
- CAUTI costs at least \$600 and each episode of urinary tract-related bacteremia costs at least \$2800
- Short-term catheterization was defined as up to and including 14 days

Perspectives in Urology 2009

CAUTI Microbiology

- 40% - E coli
- 30% - Pseudomonas aeruginosa,
- 30% -gram positives, staph/strep and Candida
- the investigators did not include fungal urinary tract infections as part of their study

Wagenlehner FM et al.: Int J Antimicrob Agents 2008

Perspectives in Urology 2009

CAUTI

Recommendations for Hospitals to Address the Centers for Medicare Medicaid Services Rule Changes Regarding Catheter-Associated Urinary Tract Infection

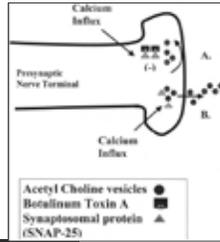
- Use only when medically indicated
 - retention or high risk of retention
 - monitoring of urinary output
 - incontinence associated with risk of skin breakdown
 - specific surgical procedures (RRP, cryo, reconstruction)
- Proper insertion techniques
 - training standards for insertion and managing catheters
 - hand hygiene, aseptic catheter insertion, and proper maintenance by using a closed urinary drainage system
 - daily review of necessity "reminders and stop orders"
 - Develop systems for removal of catheters without physician order

Saint, S. et. al. Ann Intern Med 2009

Perspectives in Urology 2009

Management of Refractory OAB Intravesical Botulinum Toxin (botox)

- Botox is derived from the organism *C. botulinum*
- Inhibits the vesicular neuronal blockade up to 9 mos
- Increasing data on the benefits of botox in patients with
 - Non-neurogenic DO
 - Neurogenic DO
 - DSD
 - Interstitial cystitis?



Schurch B, et al.: J Urol 2000
Smith CP and Chancellor MB: J Urol 2004

Management of Refractory OAB Intravesical Botulinum Toxin Type-A (botox)

- Urethra
 - 100 units in 2-3 ml of NS
 - Collagen needle used to inject 3, 6, 9 and 12 o'clock positions in striated sphincter
- Bladder
 - 200-300 units in 30 ml of
 - Inject 30-40 sites within the detrusor, targeting the trigone, base of the bladder and lateral wall.

Technique



Schurch B, et al.: J Urol 2000
Smith CP and Chancellor MB: J Urol 2004

Management of Refractory OAB Intravesical Botulinum Toxin (botox)

Open label pilot-study of 7 patients with refractory OAB that underwent detrusor injection with 150 units of botox

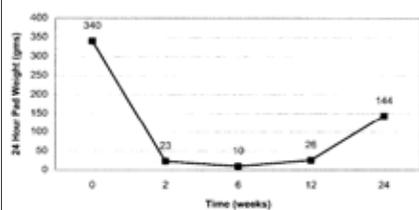


FIG. 4. Median 24-hour pad weights

Flynn, MK, Webster, GD and Amundsen, CL: J Urol 2005

Who is a candidate for intravesical Botox injection?

Typical Candidate

- MS, SCI, spina bifida patients
- Neurogenic OAB refractory to meds
- DSD

Other Potential Candidate

- Non-neurogenic OAB
- IC
- Parkinson's

As a Test

- Is the incontinence due to the bladder or a deficient outlet?
- Will they respond to bladder augmentation
 - Will they be able and willing to cath the urethra?
 - Will they be dry, or do they need a procedure on the outlet

Perspectives in Urology 2009

Who do I Implant

Characteristics

- Women respond better than men
- Younger patients (< 65) respond better than elderly
- Non-neurogenic do better than neurogenics
- Urge, frequency and urge incont. responds better than retention

Ideal Candidate

- Young female with urge, frequency, urge incontinence (without IC/PPP or neurologic condition) refractory to anti-muscarinics

Perspectives in Urology 2009

Management of Pelvic Organ Prolapse

Perspectives in Urology 2009

Anatomy of Vaginal Support POP Location ¹

- Anterior only 40%
- Anterior and apex 20%
- Posterior only 7%
- Posterior and apex 10%

- Anterior compartment involved 78%
- Highest failure in anterior compartment 30-70% ²⁻⁶

¹ Olsen et al. *Obstet Gynecol* 1997;89:501-506
² Shull et al. *Am J Obstet Gynecol* 1992;166:1764-1768
³ Holley et al. *South Med J* 1995;88:547-549
⁴ Samuelsson et al. *Am J Obstet Gynecol* 1999;180:299-305
⁵ Shull et al. *Am J Obstet Gynecol* 2000;183:1365-1373
⁶ Weber et al. *Int Urogynecol J Pelvic Fir Dysfunct* 2001;12:178-186

How are we doing with our current surgical procedures?

- 11.1% lifetime risk of surgery
- 29-40% patients require reoperation within 3 years^{1,2}
- 60% of the recurrences are at the same site³
- 32.5% of the recurrences are at a different site³

¹ Olson et al. *Obstet and Gynecol* 1997;89:501-506
² Marchionni et al. *J Reproduct Med* 1999;44:679-684
³ Clark et al. *Am J Obstet and Gynecol* 2003;189:1261-1267

Perspectives in Urology 2009

PROLIFT System: Early Outcome Data¹

Author	# Pts.	Mean Age	Site	Complications	Exposure	Length of Follow Up	"Success" (≤ Stage II)
Cosson M et al. (France)	90	65.3	A-1 T-89	Rectal perf.-1 Hemorrhage-2 VVF-1	9 (10%) S=5 (56%)	12 mo.	74 (81.6%)
Fallon BF et al. (France)	110	63.2	A-22 P-29 T-59	Cystotomy-1 Hematoma-2 Vd. Dysfcn.-6	5 (4.7%) S=2 (40%)	3 mo.	105 (95.3%)
Murphey M et al. (USA)	89	65	A-48 P-11 T-30	Cystotomy-2	0 (0%)	5 mo.	84 (94.4%)
Hinoul P et al. (France)	29	62	A-29	Cystotomy-1	2 (6.9%) S=N/A	6 mo.	28 (96.5%)
Withagen MJ et al. (Netherlands)	43	66	A-11 P-16 T-5	Cystotomy-2 Rectal perf.-1 Vd Dysfcn-1	2 (4.7%) S=N/A	6 mo.	35 (81.4%)

¹IUGA – Fallon - 2006 Abstracts all published in: Int Urogynecol J 2006;

PROLIFT System: Early Outcome Data^{1,2}

Author	# Pts	Mean Age	Site	Complications	Exposure	Length of Follow Up	"Success" (≤ Stage II)
Groenen MJC et al. (Netherlands) ¹	26	61	A-6 P-10 T-10	Vd.dysfcn-5	1 (3.8%) S=N/A	2 mo.	26 (100%)
Perscheier M et al. (Austria) ¹	80	N/A	N/A	Cystotomy-2 Hematomas-2	8 (10%) S=5 (50%)	N/A	N/A
Rivera JM et al. (USA) ²	82	63	P-19 T-63	Hematoma-1 Hemorrhage-1	7 (11.7%) S=N/A	3 mo.	Not well defined
Compiled Data	549	64	A-109 P-85 T-256	Cystotomy- 1.7% Rectal perf. 0.4% Hemorrhagic- 1.3% Void dysfcn- 6.7%	34 (6.2%) S=12 (2.6%)	6 mo.	81.4-100%

¹IUGA – Fallon - 2006 Abstracts all published in: Int Urogynecol J 2006;17(S.2):S212
²AUGS 2006 Abstract published in: Int Urogyn J 2006;17(S.3):S460

NICE Review



Systematic review of the efficacy and safety of using mesh or grafts in surgery for anterior and/or posterior vaginal wall prolapse

Xueli Jia, Cathryn Glazener, Graham Mowatt, Graeme MacLennan, Cynthia Fraser, Jennifer Burr

October 2007

Perspectives in Urology 2009

¹Jia x et al: BJOG 2008

NICE Review

- National Institute for Health and Clinical Excellence (NICE) report
- Provides national clinical guidelines in the UK
- Examined surgical repair of vaginal prolapse using mesh
- 199 page document
- Evaluated 446 reports - 49 studies selected
- 4589 patients in total

¹Jia x et al: BJOG 2008

Perspectives in Urology 2009

**Incidence of vaginal erosion following anterior prolapse repair with polypropylene mesh
Single vs. double layer vaginal wall closure**

Terlecki RT and Flynn BJ et al. AUGS 2009

75 cases of mesh reinforced anterior repair (anterior Prolift™) for cystocele performed by a BJF (2005-2008) were analyzed

Closure	Mean age (y)	Prior Repair (%)	Prior Hystx (%)	Mean LOS (d)	Mean DOC (d)	Mean F/U (mos)
SL	65	42	64	1.0	1.8	25
DL	63	59	67	1.2	2.8	10

Comparison of mesh extrusion rate following a single layer vaginal wall closure (n = 39) v. double layer closure (n = 36)

Perspectives in Urology 2009

Full-Thickness Vaginal Incision

- Identify the true vesicovaginal and rectovaginal spaces
- Consensus of experience- full thickness leads to lower extrusion rates
- 3-5 cm length with effort to keep incisions small
- Avoid the apex
- transverse incision

Perspectives in Urology 2009

**Incidence of vaginal erosion following anterior prolapse repair with polypropylene mesh
Single vs. double layer vaginal wall closure**

Terlecki RT and Flynn BJ et al. AUGS 2009

Outcome

Closure	POP Cure (%)	Erosion (#, %)
SL	97	6/39 (15%)
DL	97	0*

All vaginal wall extrusions were on the anterior incision

- 2 healed after office excision
- 4 required multiple OR excision, reclosure of vaginal incision

Perspectives in Urology 2009

**What to do with the opposite compartment?
Concomitant Repairs**

Anterior/Posterior Compartment

- Treat if
 - Prolapsed
 - Significant apical prolapse, large enterocele
- No prolapse in opposite compartment –No consensus
 - Treat with standard repair
 - Reinforced repair in lesser compartment
 - Leave untreated if asymptomatic

Perineal body

- Not advisable to treat asymptomatic perineal relaxation
- If symptomatic and there is laxity
 - repair separately "distal" to the mesh

Perspectives in Urology 2009

**What to do with the urethra?
Concomitant TVT**

SUI Surgery

- **Sling if**
 - History of SUI
 - UDS evidence of SUI with prolapse reduced
 - Stage III or IV cystocele and no prior sling
- **Stage patient if**
 - No history or UDS evidence of SUI
 - Prior successful sling in patient with large cystocele
 - No SUI in patient with posterior or apical prolapse only
 - Bladder incomplete emptying/retention in patient ± prior sling

Perspectives in Urology 2009

**Management of Complications of
SUI and Prolapse Surgery**

Perspectives in Urology 2009

**Complications
What could happen?**



Intraoperative

- Hemorrhage
- Bowel injuries
- Bladder and Urethral injuries
- Ureteral Injuries

Postoperative

- | | |
|---|--|
| <ul style="list-style-type: none"> • Erosion/extrusion • Fistula • Urinary retention • Pain | <ul style="list-style-type: none"> • Osteitis Pubis • Infection • Voiding dysfunction • Failures |
|---|--|

Perspectives in Urology 2009

**Vaginal Wall Extrusion and Urinary Tract Erosion
Incidence**

Midurethral tape composed of polypropylene mesh has become the new gold standard for treatment of female SUI^{*}

- Vaginal wall mesh extrusion occurs in 0.5 - 3% of patients and is usually amenable to tranvaginal partial mesh excision^{†‡}
- Urinary tract erosion is a more severe complication (< 1%) and may be treated with endoscopic or open partial excision

^{*} Bemelmans BLH and Chapple, CR: Cur Opin Urol Urol 2003
[†] Meschia M, et al: IntUrogynecol J Pelvic Floor Dysfunct 2001
[‡] Giri SK, et al: Urol 2007

Perspectives in Urology 2009

Urinary Tract Sling Erosion
Urethrolysis: Contemporary Outcomes

Study	No.	Type	Management	Outcome
Kobashi et al 1999	7/34	ProteGen	Sling removal Martius (4) Delayed PVS (6)	25/34 (74%) SUI
Clemens et al 2000	6/14	ProteGen	Sling removal Urethral repair or prolonged drainage Immediate PVS (1) Delayed PVS (1)	5/6 (83%) SUI
Golomb et al 2001	1/1	Autograft	Bilateral partial excision	1/1 Dry
Amundsen et al 2003	6/6	Nonsynthetic 3/3 Synthetic	Sling incision Sling removal Martius (2) Delayed PVS (1)	6/6 Dry 2/3 (67%) SUI

Polypropylene Bladder Erosion
Prevention/Diagnosis

Prevention

- Avoid tunneling the trocar if the retropubic space is scarred
- Meticulous intra-op cystoscopy (70° lens), inspect anterior wall at 2 and 11 o'clock
- Postop Foley for 3 days if bladder is perforated

Diagnosis

- ↓
- High index of suspicion in patients with
 - Hematuria, bladder pain, urgency, recurrent incontinence, adherent calculus to the bladder wall

Terlecki RT and Flynn BJ: AUA update series 2010

Polypropylene Bladder Erosion
Case Reports: Endoscopic Approach

Endoscopic Laser Excision *

- 3 patients had bladder erosion due to polypropylene mesh
- Eroded tape successfully excised, 355 µm holmium laser in 20 mins

* Giri, SK, et al: J Urol 2005

Suprapubic Assisted Endoscopic Excision †

- 1 patient underwent successful endoscopic excision
- 5 mm suprapubic trocar, 24 Fr transurethral nephroscope
- Forceps inserted through the trocar used to stretch the tape
- Endoscopic scissors inserted through the nephroscope used to excise the tape

† Jorion, JL: J Urol 2002

Perspectives in Urology 2009

Management of Urinary Tract Erosions
Synthetic Erosion

Combined Abdominal and Vaginal Explantation *

- 5 patients with polypropylene mesh erosion
 - 3 with urinary tract erosion underwent explantation
 - ALL required subsequent anti-incontinence surgery

* Sweat SD, McGuire EJ and Lightner DJ: J Urol 2002

Mesh Explantation and Concomitant Sling †

- 19 patients with polypropylene mesh erosion underwent explantation
 - 53% had recurrent SUI
 - 5 underwent simultaneous autologous or porcine dermis sling

† Starkman, JS, et al: J Urol 2006

Perspectives in Urology 2009



Salvage Protocol

Near Total Mesh Explant, Washout, Re-implant with Biological

- Step 1: EUA, cysto, DRE, procto, CT scan in complex cases
- Step 2: Remove eroded mesh with 1 cm ring of vaginal epithelium
- Step 3: Complex cases continue explanting remaining body of the vaginal mesh
- Step 4: Repair defects in the viscera, consider flap if a fistula is present
- Step 5: Cysto to asses repair, r/o ureteral injury or residual FB
- Step 6: Irrigate with four solutions
 - bacitracin 50,000 units
 - gentamicin 80 mg in 1 l of 0.9% NS
 - 1/2 strength povidine-iodine, (500 ml)
 - 1/2 strength H2O2 (500 ml)
 - vancomycin 1 gm and gentamicin 80 mg, in 1 liter of 0.9% NS
- Step 7: Change gowns and gloves
- Step 8: Implant biological material
- Step 9: Close wound in 2 layers
- Step 10: Premarin vaginal pack
- Step 11: Treat with oral abx (based on culture results) for 1 month

Terlecki RT and Flynn BJ: AUA update series 2010

Management of Mesh Complications: Vaginal Wall Extrusions and Urinary Tract Erosions Results

Convalescence

- mean f/u, 14 mos.
- mean age, 55.5 yrs
- mean length of stay
 - simple <23 hrs
 - complex 2.4 days

Graft Complication Resolution

- Simple group, n = 17
 - trimming, n = 4
 - 1 of 4 (25%) successful
 - OR excision/reclosure, n = 13
 - 12 of 13 (92%) successful
- Complex group, n = 22
 - 21 of 22 (95%) successful

* Flynn BJ et al: SUFU 2010

Perspectives in Urology 2009

Management of Mesh Complications: Vaginal Wall Extrusions and Urinary Tract Erosions Continence Outcome

Post-operative

- 30 patients with data regarding pad usage
- 25 of 30 (83%) dry, 0 ppd
- 3 required sling lysis for prolonged retention
- 1 required prolapse repair
- 1 required urethroplasty
- 1 required Interstim for UUI



* Flynn BJ et al: SUFU 2010

Perspectives in Urology 2009

Management of Vesicovaginal Fistula (VVF)

Perspectives in Urology 2009

Transvaginal Repair of Primary and Recurrent Vesicovaginal Fistula (VVF)
Introduction

Terlecki RT and Flynn BJ et al: AUGS 2009

- Transabdominal management often with the use of flaps, has been advocated for recurrent fistulae
- It is our practice to approach all nonirradiated primary or recurrent, VVFs via a transvaginal approach on an outpatient basis and to avoid the morbidity of a Martius flap
- We aim to evaluate and compare the outcomes of transvaginal management of primary versus recurrent VVFs

Perspectives in Urology 2009

Transvaginal Repair of Primary and Recurrent Vesicovaginal Fistula (VVF)

Terlecki RT and Flynn BJ et al: AUGS 2009

31 cases (16 primary, 15 recurrent) of transvaginal VVF repair with cuff excision performed by a BJF (2002-2008) was analyzed

Etiology

- open abdominal hysterectomy (23)
- laparoscopic hysterectomy (2)
- robotic hysterectomy (2)
- transvaginal hysterectomy (2)
- mesh explant (1)
- obstetric trauma (1)
- 18 prior repairs in 15 recurrent cases all at outside centers
- 12 by a transvaginal approach and 6 transabdominally

Perspectives in Urology 2009

Transvaginal Repair of Primary and Recurrent Vesicovaginal Fistula (VVF)
Results

Parameter	Primary Repair	Secondary Repair
Patients (n)	16	15
Mean age (years)	42	42
Mean time to repair (days)	173	237
Mean fistula size (mm)	4.7	3.6
Mean BMI (kg/m ²)	30.8	28.8
Mean operative time (min)	157	143
Mean EBL (cc)	108	140
Mean LOS (days)	0.5*	0.1**
Mean catheterization (days)	22	21
Recurrence	0/16	0/15
Mean follow up (months)	25	30

Terlecki RT and Flynn BJ et al: AUGS 2009

Perspectives in Urology 2009



Transvaginal Repair of Primary and Recurrent Vesicovaginal Fistula (VVF)
Results

Outcome

- No significant differences between the treatment groups in any of the measured parameters
- No operative complications occurred in either group
- Dyspareunia limited to 3 patients from the primary group
- At a f/u of 25 (primary) and 30 (recurrent) months, no patient has had a fistula recurrence

Convalescence

- 5 patients observed less than 24 hours (3 social, 2 pain)
- 1 patient observed less than 24 hours (social)

Perspectives in Urology 2009

18th Annual

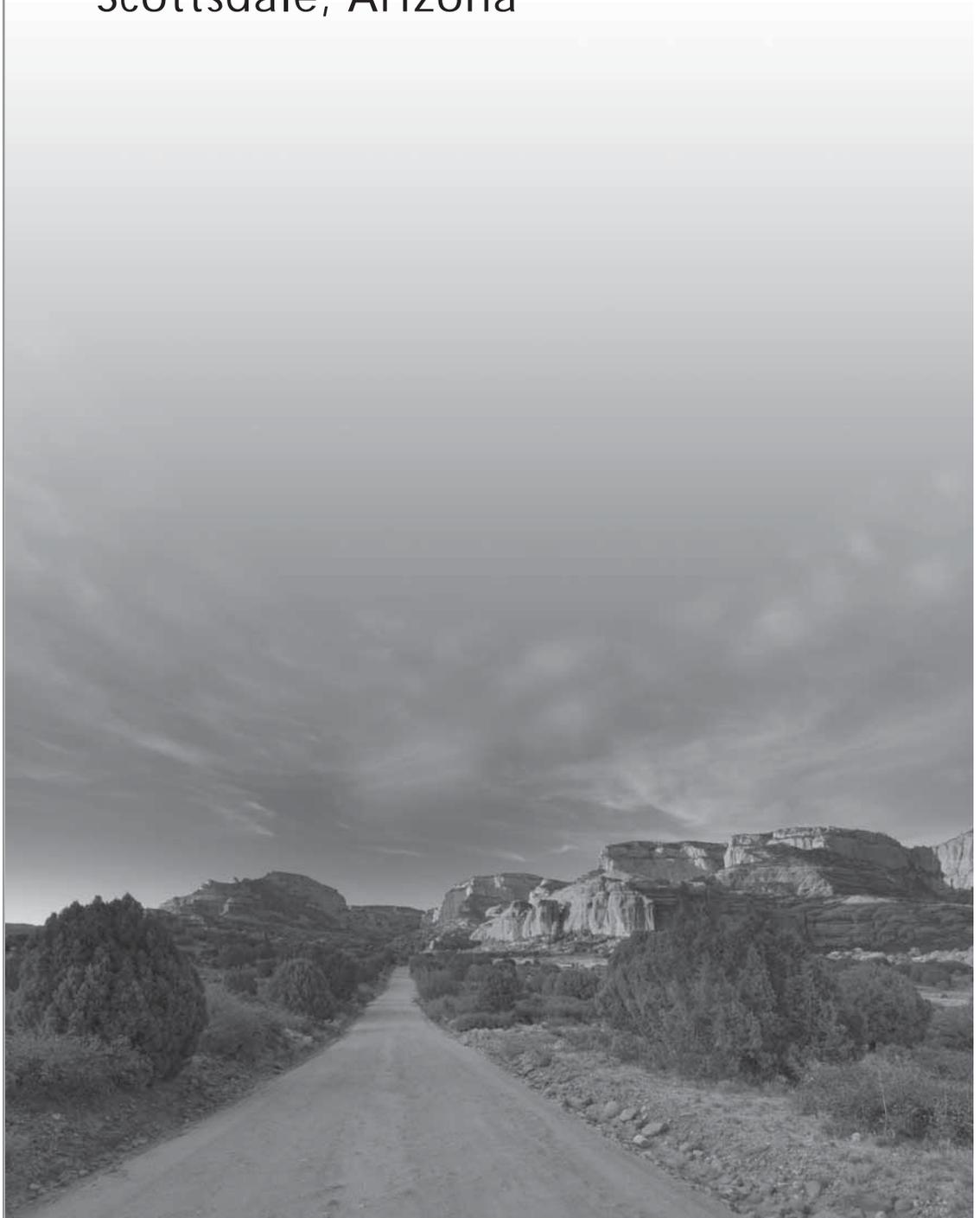
PERSPECTIVES IN UROLOGY
POINT COUNTERPOINT 2009

Friday, November 6, 2009

Ballroom E-F

The Scottsdale Plaza

Scottsdale, Arizona



Agenda

Friday, November 6

Page

7:00 – 8:00 am Breakfast and Industry-Supported Satellite Symposium
 The Evolving Role of Hormonal Therapy in the Management
 of Prostate Cancer

Bladder Cancer

8:00 – 8:45 am A Case-based Approach to the Management of Bladder Cancer 6.1
 ~ Moderator: Robert Donohue, MD

Panel: David C. Beyer, MD • E. David Crawford, MD
 Donald L. Lamm, MD • Paul D. Maroni, MD

8:45 – 9:00 am Questions & Answers

9:00 – 9:30 am Non-muscle Invasive Bladder Cancer, including Chemoprevention ~ 7.1
 Review of Existing Guidelines & International Recommendations
 ~ Donald L. Lamm, MD

9:30 – 9:55 am Point-Counterpoint: Radiation & Bladder Cancer 8.1

Radiation Has No Role in the Treatment of Any Stage of Bladder Cancer
 ~ Robert E. Donohue, MD 8.1

Radiation Plays a Major Role in Certain Stages of Bladder Cancer
 ~ David C. Beyer, MD 8.16

9:55 – 10:00 am Questions & Answers

10:00 – 10:15 am Break in Exhibit Hall

10:15 – 10:35 am What the Community Urologist Needs to Know About BCG 9.1
 ~ Donald L. Lamm, MD

10:35 – 10:45 am Questions & Answers

Female Urology, Part II

10:45 – 11:15 am The Spectrum of Stress Incontinence Surgery, 2009 10.1
 ~ Brian J. Flynn, MD

11:15 – 11:25 am Questions & Answers

Clinical Challenges

11:25 – Noon Case Presentations and Discussion

Noon – 1:00 pm Lunch in Exhibit Hall

Agenda **Friday, November 6** (continued)**Prostate Cancer**

1:00 – 1:20 pm	Challenges in Prostate Cancer: Why We Are 15 Years Behind Breast Cancer ~ <i>David C. Beyer, MD</i>	11.1
1:20 – 1:50 pm	Clinical and Pathologic Characteristics of Prostate Cancer (including new markers such as PCA3) ~ <i>M. Scott Lucia, MD</i>	12.1
1:50 – 2:10 pm	Chemoprevention Strategies ~ <i>M. Scott Lucia, MD</i>	13.1
2:10 – 2:40 pm	Point-Counterpoint: Early Detection of Prostate Cancer Is Not Valuable In a Lot of Men ~ <i>E. David Crawford, MD</i> We Can't Go Backwards – Of Course Screening Has Saved Lives ~ <i>Robert E. Donohue, MD</i>	14.1 14.1 14.9
2:40 – 2:50 pm	Questions & Answers	
2:50 – 3:00 pm	Break in Exhibit Hall	
3:00 – 3:20 pm	What's New in Advanced Disease (CRPC)? ~ <i>Matthew Rettig, MD</i>	15.1
3:20 – 3:50 pm	An Update on Radiation Therapy for Prostate Cancer ~ <i>David C. Beyer, MD</i>	16.1
3:50 – 4:00 pm	Questions & Answers	
4:00 pm	Adjourn for the day	

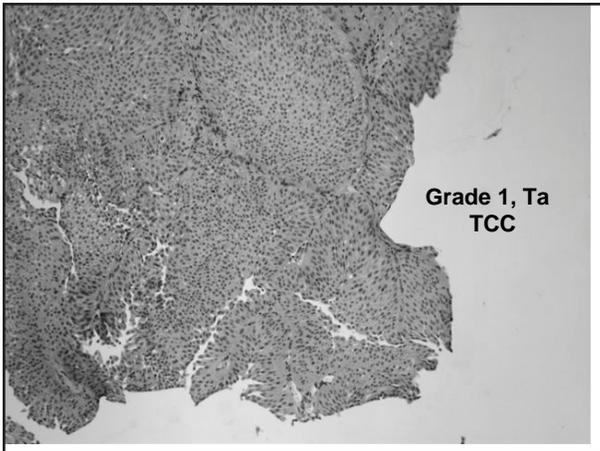


Bladder case #1

increase time interval of cystos,
reduce or eliminate ambulatory
TURBT procedures,
do office fulgurations,
< five tumors; < 0.5 cms, size
Herr

Bladder cases #2

77 – gross hematuria for two
months, 2007
2007 – 1 / Ta, M. propria negative
2009 – 1 / Ta
2009 – 2 / T1, M. propria, negative



Bladder cases #2

TURBT 3 recurrent tumors
immediate ChRx instillation
When to start BCG induction
dose, frequency, duration,
second course, 3 or 6 weeks ?
maintenance ?
1 year, 3 years, 7 years

Bladder cases #2

TURBT 3 recurrent tumors
3 instillations of BCG with induction; week 4 - UA nitrite +, Leuk esterase +, 50 WBCs/ hpf
UTI ? c/s sent; negative, serial urinalyses; Leuk esterase +, w5 >50 WBCs, >20 WBCs, > 20 WBCs
3 week hiatus ? What to do?

Bladder cases #3

64 – microscopic hematuria recurrent tumor, 2 / Ta maintenance chemotherapy 7 year plan
3 week therapy every six months; cystoscopy and cytology q 3 mths instillation Tuesday;
104* fever Friday, Sat, Sun

Bladder cases #3

64 – microscopic hematuria instillation Tuesday; NB c-i-c, warned about fever above 100*
104* fever Friday, Sat, Sun, Monday, E.R. R3 sees patient; only test I wanted was urine c/s BCG, Gram neg or Enterococcus only test not done but ordered

Bladder cases #3

64 – microscopic hematuria 3 or 6 months of anti-tuberculous therapy ?
restart BCG, normal dose ?
1/100 dose ?
switch to alpha-Interferon ?
switch to BCG + alpha-Interferon ?
Mitomycin C ?
Gemcitabine ?

Bladder cases #4

78 - 2008

recurrent tumor, 2 / T1

instillational ChRx, ?

restart BCG, ?

induction, maintenance

Oncovite ?

Bladder cases #5

68 - gross hematuria

cystoscopy

bladder negative

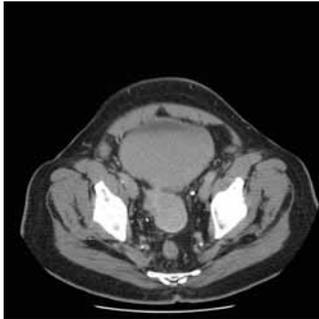
diverticulum, tumor

co-morbidities

Hpt, DM II, overweight, diverticulitis

TURBT; diverticular tumor, 2/T1

bladder mapping, negative





Bladder cases #8
Grade 3 / T2
55, needs time for business
role of neo-adjuvant ChRx,
What Chemotherapy ?
MVAC ?
MVC ?
GC ?
PC ?

Bladder cases #8
lymph node dissection extent ?
obturator, hypogastric, external
iliac and 2 cm common iliac nodes
pre-sacral nodes
inter aortic bifurcation nodes
nodes pre and para aorta and
vena cava to level of Inferior
Mesenteric Artery
separate node samples Yes, No

Bladder cases #8
Grade 3 / T2
cystectomy pTo in bladder
ileal conduit
stage, prostate invasion, No,
ChRx ? follow-up
Remember upper tracts!
Cytology? When ? Technique ?

Bladder cases #9
59, bartender –
former mayor of the town,
heavy smoker,
saloon owner,
acute urinary retention from
clots,



Non-muscle Invasive Bladder Cancer, including Chemoprevention ~ Review of Existing Guidelines & International Recommendations

~ Donald L. Lamm, MD

Non-muscle Invasive Bladder Cancer: Review of Prevention, Treatment, and Guidelines

Don Lamm, M.D.
Clinical Professor of Urology,
University of Arizona, and
Director, BCG Oncology,
Phoenix, AZ

Guidelines

- European Association of Urology (EAU) Guidelines on TaT1 (non-muscle invasive) Bladder Cancer (Babjuk M, et al., 2008)
- First International Consultation on Bladder Tumors (FICBT) (Soloway MS [Ed]., 2005)
- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Bladder Cancer, including Upper Tract Tumours and Urothelial Carcinoma of the Prostate (NCCN, 2007)
- American Urological Association (AUA) Guidelines for the Management of Non-muscle Invasive Bladder Cancer (Stages Ta,T1, and Tis): 2007 Update (AUA, 2007; Hall MC, et al., 2007)
- Synthesis: International Bladder Cancer Group

Current Approaches to the Management of NMIBC: Comparison of International Guidelines as Recommended by International Bladder Cancer Group. Persad, R. Eur Urol. 2009.

- **Level of Evidence**
 - 1a Evidence from meta-analysis of randomized trials
 - 1b Evidence from at least one randomized trial
 - 2a Evidence from a good controlled study without randomization
 - 2b Evidence from a well-designed quasi-experimental study
 - 3 Evidence from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
 - 4 Evidence from expert committee reports or opinions or clinical experience of respected authorities
- **Grade: Nature of Recommendations**
 - A Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial
 - B Based on well-conducted clinical studies, but without randomized clinical trials
 - C Made despite the absence of directly applicable clinical studies of good quality

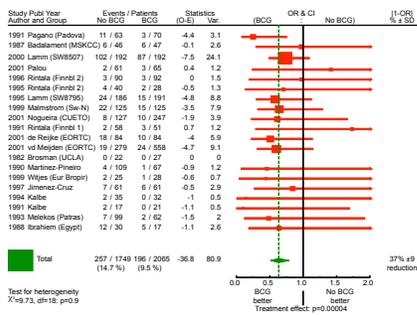
Progression: Maintenance BCG

Patients OR	No BCG	BCG
No Maint 1.28	1049 10.3%	10.8%
Maintenance 0.63	3814 14.7%	9.5%

Test for heterogeneity: P = 0.008

BCG was only effective in trials with maintenance, where it reduced the risk of progression by 37%, p = 0.00004.

Progression All Studies With Maintenance



Follow UP

- Follow-up: AUA recommends cystoscopy at 3 month intervals for 2 years, 6 month for 2 years, then annually, but for low grade, low risk patients this is excessive.
- EAU for low grade: cystoscopy at 3 months, and if negative at 9 months and then yearly for 5 years. But, risk for recurrence is lifelong and some would be missed after 5 years.



**Non-muscle Invasive Bladder Cancer, including Chemoprevention ~
 Review of Existing Guidelines & International Recommendations**

~ Donald L. Lamm, MD

Current Approaches to the Management of NMIBC: Comparison of International Guidelines as Recommended by International Bladder Cancer Group. Raj Persad,^a Donald Lamm,^b Maurizio Brausi,^c Mark Soloway,^d Joan Palou,^e Andreas Böhle,^f Marc Colombel,^g Hideyuki Akaza,^h Roger Buckley,ⁱ J Alfred Witjes^j

^aDepartment of Urology/Surgery, Bristol Royal Infirmary & Bristol Urological Institute, Bristol, United Kingdom

^bDepartment of Surgery, University of Arizona; BCG Oncology, Phoenix, Arizona, USA

^cDepartment of Urology, AUSL Modena Estense and B Ramazzini Hospitals, Modena, Italy

^dDepartment of Urology, University of Miami School of Medicine, Miami, Florida, USA

^eDepartment of Urology, Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain

^fDepartment of Urology, HELIOS Agnes Karll Hospital, Bad Schwartau, Germany

^gDepartment of Urology, Claude Bernard University, Hôpital Edouard Herriot, Lyon, France

^hDepartment of Urology, University of Tsukuba, Tsukuba, Japan

ⁱDepartment of Urology, North York General Hospital, Toronto, Ontario, Canada

^jDepartment of Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Level	Type of Evidence
1a	Evidence obtained from meta-analysis of randomized trials
1b	Evidence obtained from at least one randomized trial
2a	Evidence obtained from one well-designed controlled study without randomization
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities
Grade	Nature of Recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial
B	Based on well-conducted clinical studies, but without randomized clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

Guideline panels have used level of evidence standards similar to those above.

	Definitions		
	Low-Risk	Intermediate-Risk	High-Risk
EAU	G1-2Ta Low risk of tumour recurrence and progression (EORTC recurrence score = 0; progression score = 0)	Multifocal G2Ta, G1T1, solitary G2T1 Intermediate- or high-risk of recurrence and intermediate risk of progression (EORTC recurrence scores ranging from 1–9; progression scores ranging from 1–6)	Multifocal G2T1, G3Ta-T1, CIS High-risk of progression (EORTC progression scores ranging from 7–23)
FICBT	Low-grade Ta	Low-grade Ta with high-risk factors for recurrence or recurrent low-grade Ta tumors	High-grade Ta, all T1, CIS
NCCN	G1-2Ta	G3Ta, solitary G1-2T1	Multifocal T1, G3T1 (CIS listed separately)
AUA	Small volume, low-grade Ta	Multifocal and/or large volume low -grade Ta High risk of recurrence, low risk of progression	High-grade Ta, all T1, CIS

Panels recognize the importance of risk stratification. The most simple system, similar to that of the AUA, is to place all high grade tumors, all T1 tumors and all cases with CIS into the high risk group. Solitary/small volume low grade Ta tumors are low risk, and everything in between is intermediate risk.

Tumors are to be widely resected, with deep and wide margins that include muscle. CIS is resected/fulgurated completely and perforation avoided.

For **Low Risk Disease**: Immediate postoperative intravesical chemotherapy is recommended by all panels. Several randomized clinical trials have confirmed the benefit and Sylvester’s meta-analysis shows a 39% risk reduction (Sylvester, 2004). **BCG is NEVER given immediately postoperatively.** Maintenance therapy, including BCG, has not been demonstrated to improve recurrence prevention. Panels agree that no chemotherapy has proven to be superior to other chemotherapies.

For **Intermediate Risk Disease**: Panels vary on recommendations for intermediate disease. All agree that adjuvant therapy is indicated. BCG or chemotherapy may be used, and there is no standard recommendation for dose or duration of treatment. All panels made recommendations before the results of the EORTC comparison of maintenance BCG using the SWOG 3 week

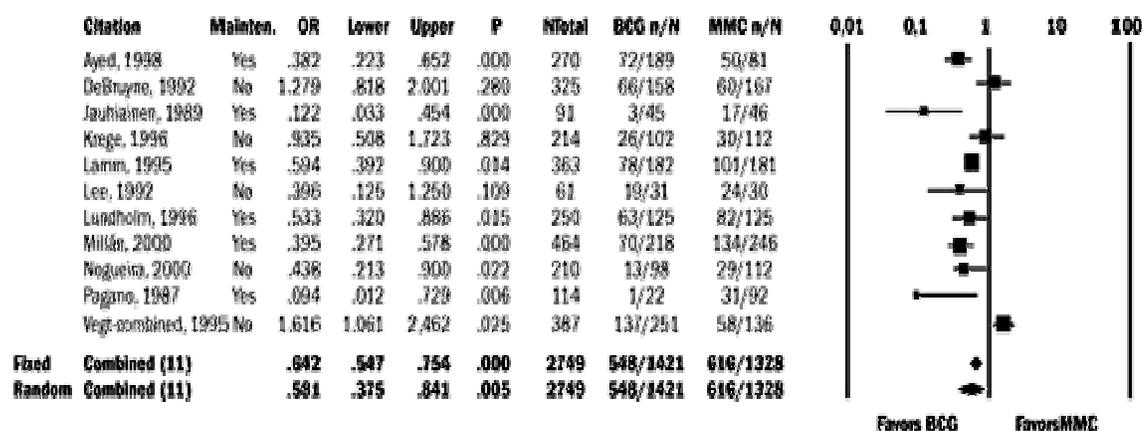
maintenance schedule versus induction Epirubicin. In that study of 957 intermediate risk patients followed for 9.2 years time to first recurrence (p<0.0001), time to distant metastases (p=0.03), and overall (p=0.02) and disease-specific survival (p=0.03) were all significantly prolonged with BCG compared to epirubicin (Sylvester RJ, et al., 2008). Considering the new level 1 evidence, the IBCG recommends 3 week maintenance BCG as the treatment of choice for intermediate risk bladder cancer. Chemotherapy remains an option for this group, and there is increasing use of maintenance schedules, though randomized trials are limited.

Guideline	Definition of Intermediate Risk	Recommendations
EAU	Multifocal G2Ta, G1T1, solitary G2T1 Intermediate- or high-risk of recurrence and intermediate risk of progression (EORTC recurrence scores ranging from 1–9; progression scores ranging from 2–6)	<ul style="list-style-type: none"> • TURBT • Single, immediate post-operative instillation of chemotherapy followed by: <ul style="list-style-type: none"> - Induction BCG plus maintenance (at least 1 year) (grade A), or - Maintenance intravesical chemotherapy (grade A) of 6-12 months (grade B)
FICBT	Multiple low-grade Ta	<ul style="list-style-type: none"> • TURBT • Single immediate post-operative instillation of chemotherapy • Further adjuvant intravesical therapy: <ul style="list-style-type: none"> - First-line: intravesical chemotherapy < 6 months (grade B) - Second-line: BCG (grade A)
	Recurrent low-grade Ta	<ul style="list-style-type: none"> • Office fulguration only in select patients with < 5 small (< 0.5 cm) low-grade recurrent tumours and negative cytology (grade C) • Formal TURBT if clinical doubt that tumour is low-grade, cytology positive, or change in tumour appearance has occurred (grade C) • Adjuvant intravesical therapy (see above)
NCCN	G3Ta, solitary G1-2T1	<ul style="list-style-type: none"> • TURBT > Observe or • Intravesical therapy <ul style="list-style-type: none"> - BCG (preferred) (category 1) or - Mitomycin (category 2A)
AUA	Multifocal and/or large volume low-grade Ta or recurrent low-grade Ta High risk of recurrence, low risk of progression	<ul style="list-style-type: none"> • TURBT • Intravesical BCG or mitomycin C (recommendation) • Maintenance BCG or mitomycin (option)

EORTC: European Organization for the Research and Treatment of Cancer; TURBT: transurethral resection of the bladder tumour; EAU: European Association of Urology; FICBT: First International Consultation on Bladder Tumors; NCCN: National Comprehensive Cancer Network; AUA: American Urological Association

High Risk disease: A single-arm meta-analysis of randomized controlled trials in high-risk patients conducted by the AUA confirms the superiority of maintenance BCG to mitomycin C with or without maintenance: the estimated five-year recurrence rate was 34% in patients receiving TURBT and BCG maintenance and 62% with mitomycin C maintenance. The meta-analysis of all risk groups found that, compared with TURBT and mitomycin C maintenance, TURBT and BCG maintenance therapy reduced recurrence by 17%. The AUA meta-analysis also found a trend to improvement in overall progression with BCG maintenance therapy compared to mitomycin C plus maintenance. (AUA, 2007; Hall MC, et al., 2007). Meta-analysis of 24 trials involving 4,863 patients showed that BCG maintenance therapy was associated with a 37% reduction in the risk of tumour progression compared to TURBT alone, TURBT plus intravesical chemotherapy, or TURBT plus another immunotherapy (Sylvester RJ, et al., 2002) Another meta-analysis of 11 clinical trials comparing BCG and mitomycin C showed that BCG was superior to mitomycin C in reducing tumour recurrence (odds ratio [OR] 0.56, 95% confidence interval [CI], 0.38 to 0.84, p=0.005; see Figure 2a). In the subgroup treated with BCG maintenance, all 6 individual studies showed a significant superiority of BCG over mitomycin C (OR, 0.43, 95% CI, 0.35 to 0.53, p<0.001; see Figure). (Böhle A, et al., 2003)

Tumour recurrence (all studies) with odds ratio (OR) as effect size. (Böhle A, et al., 2003)



MMC: mitomycin C; BCG: bacillus Calmette-Guérin; mainten: maintenance BCG therapy

Given these results, the EAU, FICBT, NCCN and AUA regard BCG as the standard adjuvant treatment for high-risk patients. There is no consensus on the optimal BCG maintenance schedule and differences exist among the four guidelines with regards to other options in high-risk patients. The EAU recommends repeat resection in 2-6 weeks and maintenance BCG for at least a year. The AUA recommends repeat resection if no muscle is present in the specimen, followed by maintenance BCG (preferred, category 1, or Mitomycin C). The other panel recommendations are listed below. Failure to achieve complete response in CIS, or recurrence of high grade, T1 disease after BCG is considered to be an indication for cystectomy.

Guidelines	Definition	Recommendations
EAU	Multiple G2T1, G3Ta-T1 High-risk of progression (EORTC progression scores ranging from 7–23)	<ul style="list-style-type: none"> • Repeat TURBT 2-6 weeks after initial resection (grade B) • Intravesical BCG induction plus maintenance for at least 1 year (grade A) • Immediate radical cystectomy for highest risk patients (grade A) <ul style="list-style-type: none"> — Multiple recurrent high-grade tumours — High-grade T1 tumours — High-grade tumours with concomitant CIS
	CIS	<ul style="list-style-type: none"> • Intravesical BCG plus maintenance for at least 1 year (grade A) <ul style="list-style-type: none"> — Assess response at 3 months: <ul style="list-style-type: none"> ▪ If no response: <ul style="list-style-type: none"> • Continue with three weekly boosters (grade B), or • Additional 6-week course of BCG (grade B), or • Cystectomy (grade B) — No complete response at 6 months: radical cystectomy (grade B)
FICBT	High-grade Ta	<ul style="list-style-type: none"> • Second-look TURBT and bladder mapping biopsies 2-4 weeks after initial resection (grade B) • If residual tumour is found: <ul style="list-style-type: none"> – Re-resection and one immediate instillation of chemotherapy – Followed 2-3 weeks later by 6-week BCG induction and 1-3 years of BCG maintenance (grade A)
	T1	<ul style="list-style-type: none"> • Repeat TURBT (grade B) • Initial intravesical BCG for patients with completely resected primary and recurrent T1 tumours (based on a negative repeat resection) (grade C)
	CIS	<ul style="list-style-type: none"> • Intravesical BCG for 6 weeks (grade A) • Maintenance BCG for ≥ 1 year (grade A)
NCCN	T1, G3	<p><i>Complete Resection:</i></p> <ul style="list-style-type: none"> • BCG preferred (category 1) or mitomycin (category 2A) • Consider cystectomy <p><i>Uncertain Resection:</i></p> <ul style="list-style-type: none"> • Repeat resection or cystectomy <ul style="list-style-type: none"> – If positive: BCG (category 1) or cystectomy (category 2A) – If negative: BCG (category 1) or mitomycin (category 2A)
	Any CIS/Tis	<ul style="list-style-type: none"> • Complete resection followed by intravesical BCG
AUA	High-grade Ta, T1 and/or CIS	<ul style="list-style-type: none"> • Repeat resection if lamina propria invasion without muscularis propria in specimen prior to intravesical therapy (standard) • Induction BCG followed by maintenance (recommendation) • Cystectomy (option)

Follow up regimens vary according to the risk group. The AUA recommends cystoscopy at 3 month intervals for 2 years, 6 months for 2 years and yearly thereafter, but for low risk patients this appears to be excessive. The EAU recommends cystoscopy at 3 months, and if negative at 9 months and then yearly for 5 years. The risk for recurrence does not continue beyond 5 years, so recurrence would be missed if follow up is stopped. Controlled trials do not exist, so firm recommendations cannot be made.

TURBT modern

office cystoscopy, cytology,
CT Scan before TURBT, [ugly]
TURBT – biopsy only, slides
TURBT – single, complete, slides
TURBT -- staged, multiple, slides
TURBT* – second look, slides
*[all tumor gone or recent referral]

Transitional Cell Carcinoma

persistence –inadequate TURBT
size, multi-focality, patient co-
morbidities, location[s] of tumor
skill of M.D.
recurrence is a new tumor !
But
T1 is superficially invasive
c-i-s, untreated, invasive in 5 years

Transitional Cell Carcinoma

recurrence and progression

Grade	multi-focality	5X
1 50% [3 yrs]	size	35X
2 58%		
3 72%	c-i-s	worsens all the others
Stage		
Ta 48%	30% progress	
T1 84%	Heney UCNA 1992	

TURBT modern

1999 Herr – second look
2000 Solsona – post-op ChRx
2004 Silvester – post-op ChRx
2000 Lamm – maintenance BCG
1999 Hurle – upper tract studies
2002 O'Donnell – BCG +/- alpha IFN
2004 Herr – office fulguration
2007 Herr – low grade, papillary TCC

TURBT

peri-operative

immediate OR or PACU [RR] drug,
Mitomycin C
40 mg in 20 ccs saline
concentration
alkalinization of urine
dehydrated patient
30' – 60' bladder time

TURBT

peri-operative

Mitomycin C
more effective with single tumors
single 35.8% recurrence
multiple 65.2% recurrence
5% American Urologists use this Rx
Sylvester
JU 171; 2186, 2004

TURBT

induction and maintenance rules
NPO after midnight,
negative urinalysis,
atraumatic catheterization,
gravity flow, minimum volume,
retain agent for two hours,
rotate patient, [keep him awake]

Induction BCG

one or two courses
BCG q week x 6 weeks
cystoscopy / cytology 6 weeks later
negative; proceed to maintenance
positive; q week x 3 weeks [20%]
cystoscopy / cytology 9 weeks later
negative; maintenance
positive; cystectomy or other RX

TURBT

fever post BCG

always get a urine culture,
c-i-c infection vs BCG infection
treat with NSAIDs, must respond within
24 – 48 hours or start anti-TB Rx
culture negative for M. bovis, treat bug
culture positive for M. bovis, treat TB
wait 6 months; restart BCG at 1/100 Rx

TURBT

induction, maintenance questions

What strain of BCG is best ?
Connaught or Tice or Pasteur ?

What dose of BCG do we give ?
full dose, 1/3 dose , 1/10 dose, 1/100 dose

What frequency ? q 1, 3, 5, 7, 14 days ?

TURBT

What dwell time ? 1 hour, 2 hours

What duration ? 6 OR 3 weeks=course

What timing between courses, off Rx
6 weeks induction, 9 weeks maintenance

What duration 7 years ? longer, shorter,

Urine Markers

NMP 22

Urovysion

BTA stat

Telomerase

Surviven

Microsatellite analysis

others

High Risk T1 Bladder Cancer

- Grade 3
- Tumor >5 cm
- Multifocal
- Multiple recurrences
- Treat with maximum TURBT
 - RT alone (28 patients)
 - Platinum based chemo + 55.8 Gy RT (113 patients)
 - 48 months median F/U

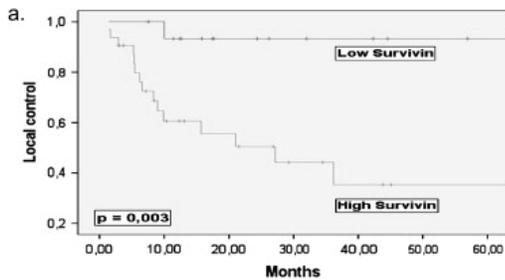
Weiss, C. et al. J Clin Oncol 24:2318-2324, 2009

Survivin in Bladder Cancer

- Protein regulates cell division and inhibition of apoptosis
- Overexpressed in human tumors
- Possible marker for early detection of bladder cancer

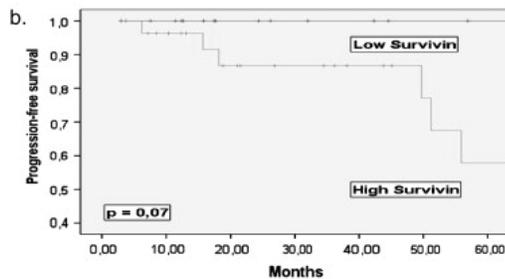
Weiss, C. et al. IJROBP V74(5): 1455-1460, 2009

Survivin Over-Expression Predicts XRT Bladder Tumor Control

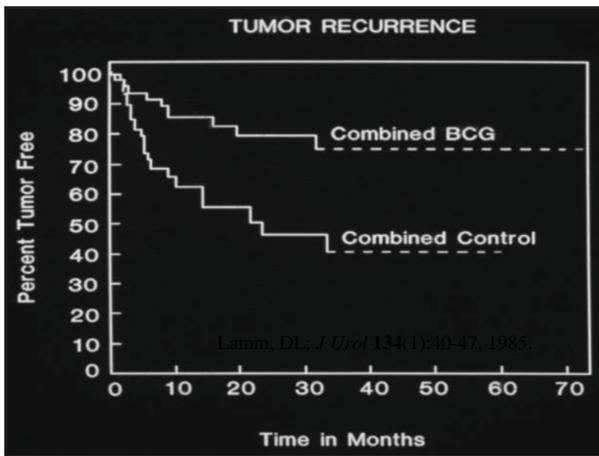


Weiss, C. et al. IJROBP V74(5): 1455-1460, 2009

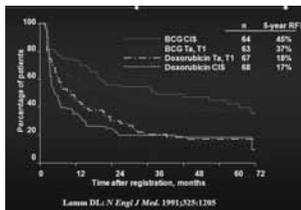
Progression-free Survival



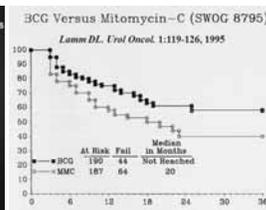
Weiss, C. et al. IJROBP V74(5): 1455-1460, 2009



BCG vs Chemotherapy



BCG reduces 5 yr recurrence by 19-28% vs Adriamycin



BCG reduces recurrence by 11% vs Mitomycin C

BCG Present

- BCG efficacy established as superior to chemotherapy
- Risk versus benefit and optimal schedule- questions remain
- Benefit in reducing progression and mortality questioned

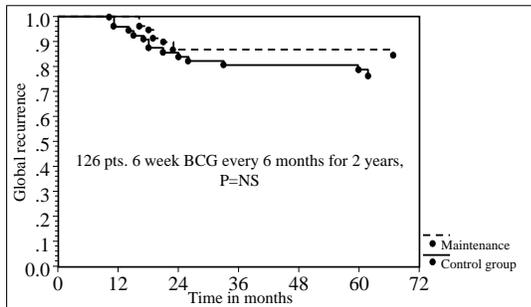
What is the best BCG regimen?

- Weekly x 6?
- Repeat weekly x 6 for recurrence?
- Maintenance BCG?
- Dose?

Repeated 6 week Maintenance BCG
 Palou J: J Urol. 165:1488,2001

- 126 pts randomized to 6 wk induction v. 6 wk maintenance every 6 months for 2 years
- Mean follow-up 79 months
- 16/61 (26%) recurrence in induction v. 10/65 (15%) with repeated 6 wk BCG
- 11/65 (34%) completed maintenance
- No significant advantage observed

Palou '01
6 weekly 6 Month Maintenance

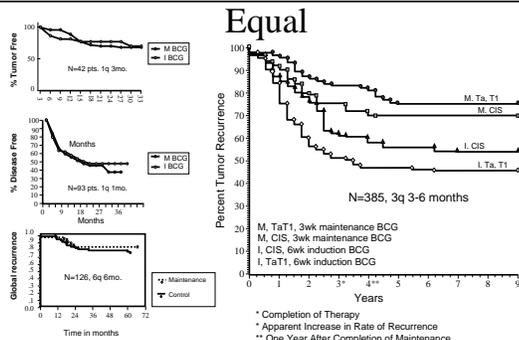


Second Induction Course of BCG

Author	N	R	R%	TTR
Bretton	28	18	64%	21 mo
Hurle	13	6	46%	27 mo
Kohjimoto	16	6	38%	35 mo
Yamada	31	20	64%	36 mo
Bui	11	6	54%	84 mo
O'Donnell	40	19	47%	26 mo*
Nadler	66	39	59%	45 mo
Total:	205	114	56%	21-84 mo

*BCG plus interferon: 53% recurrence free 26 m.

BCG Maintenance: Not Created



Progression:
Disease Type

	Patients	No BCG	BCG	Total	OR
Pap	2880	8.1%	5.1%	6.4%	0.68
CIS	403	16.2%	11.8%	13.9%	0.65

Although their prognosis is different, the size of the treatment effect was similar in papillary tumors and CIS

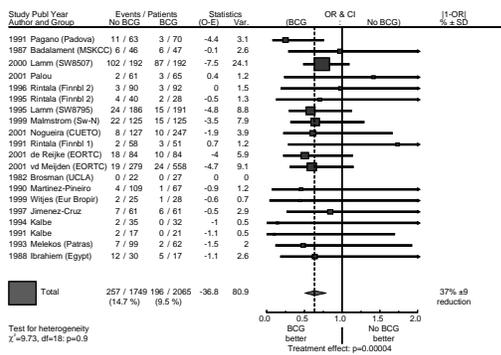
Progression:
Maintenance BCG

	Patients	No BCG	BCG	OR
No Maint	1049	10.3%	10.8%	1.28
Maintenance	3814	14.7%	9.5%	0.63

Test for heterogeneity: P = 0.008

BCG was only effective in trials with maintenance, where it reduced the risk of progression by 37%, p = 0.00004.

Progression
All Studies With Maintenance



Long-Term Efficacy of Epirubicin, BCG and BCG plus Isoniazid in Intermediate and High Risk Ta,T1 Bladder Cancer

- 957 pts randomized to 6 wk Epirubicin vs 3 wk Maintenance BCG.
- CIS excluded. 9.2 yr follow up.
- Time to recurrence (.0001), time to distant metastasis (.03), overall (.02) and disease specific survival (.03) **all** significantly favor BCG
- Advantage consistently **greater in intermediate** than high risk patients

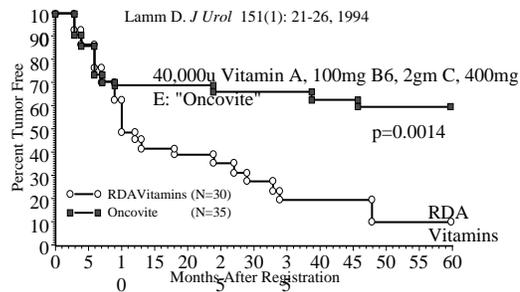
Sylvester RJ: EAU Abstract 907, 2008

BCG Future

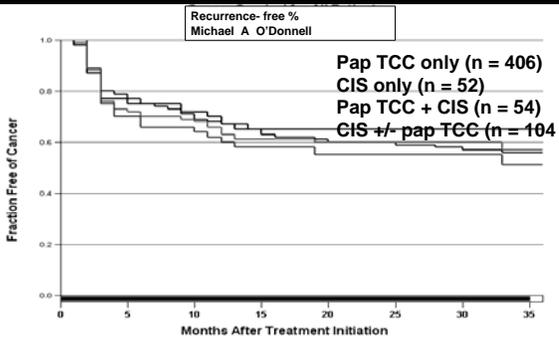
- How can the efficacy of 3 wk maintenance BCG be improved?
- Toxicity reduced?
- New preparations?

Kaplan Meier Estimate of 5 Year Tumor Free Rate

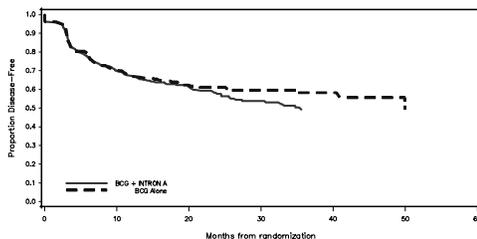
In Patients Receiving Vitamin Supplement and BCG Therapy For Bladder Carcinoma



BCG Intron A in BCG Naive



Efficacy Results – Disease Free Interval BCG + Intron A vs BCG alone



Conclusions

- BCG has had a controversial past, but is currently the treatment of choice for aggressive superficial bladder cancer
- Controlled trials clearly demonstrate superiority over current intravesical chemotherapy

Conclusions

- 6 week induction BCG is suboptimal; more BCG is better.
- Maintenance with single instillations monthly or quarterly is suboptimal.
- Repeated 6 week instillations is suboptimal and potentially immunosuppressive.
- Too much BCG reduces response and increases toxicity.

Conclusions

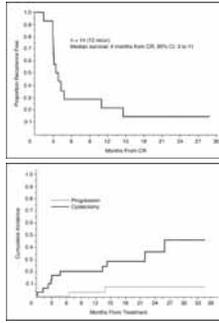
- The risk of progression in patients with CIS, high grade, and T1 TCC is long term- longer than the protection afforded by induction BCG.
- Meta-analysis of 24 controlled studies including 4,863 patients confirms that BCG significantly reduces progression, but *only* if maintenance is used.
- Maintenance BCG reduces progression by 37%, p = 0.00004.

Conclusions

- High dose vitamins A, B6, C and E appear to further reduce recurrence in BCG treated patients
- Combination BCG plus interferon alfa may be superior to BCG alone, and rescues 60% of BCG failures
- Recombinant BCG may be superior
- BCG should be evaluated in other malignancies

Gemcitabine

- N = 30
- BCG Refractory or Intolerant
- 2 courses 2 g/100 mL twice weekly for 3 weeks separated by 1 week of rest



Dalbagni G, et al. *J Clin Oncol*. 2006;24:2729-2734.

Other Drugs

- Docetaxel (Taxotere)
 - N= 18
 - 56% short-term DFS
 - 75 mg/100 mL well-tolerated (2 hours)
 - No systemic absorption
 - McKiernan JM, et al. *J Clin Oncol*. 2006;24:3080-3075.
- Apaziquone (Eoquin)
 - N =46, marker lesion study
 - CR in 30 (65%)
 - 4 mg/40 mL (1 hour)
 - Van der Heijden AG, et al. *J Urol*. 2006;176:1349-1353.

Multi-Agent Intravesical Chemotherapy

- Multidrug regimens: nearly always better in advanced TCC
- Combine to increase cell kill without increased toxicity
- Most frequent DLT for intravesical chemotherapy is cystitis
- Combine drugs with differing mechanisms of action, one or more without vesicant (irritative) side effects

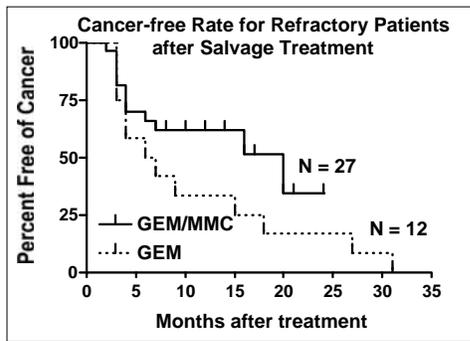
Mike O'Donnell, 2006

Vesicant Profile of Chemotherapeutic Agents

Vesicants	Non-Vesicants
Platinums ✓	Gemcitabine*
Alkylating agents	5-FU*
Mitomycin ✓	Cytarabine *
Anthracyclines	Methotrexate*
Adriamycin ✓	Pemetrexed (Alimta)
Epirubicin ✓	Bleomycin*
Valrubicin ✓	Thiotepa * ✓
Vinca Alkaloids	
Taxanes	
Paclitaxel (vesicant)	
Docetaxel (irritant) *→	

✓ moderate-severe cystitis reported * mild cystitis reported

UIHC Experience w/ BCG + IFN Failures
'06 AUA 840 (Maymi)



Other Active Combinations

Variations of Adriamycin, Mitomycin, Gemcitabine, and Docetaxel chemotherapy

- Sequential Adriamycin-Gemcitabine X 6
- Sequential Gemcitabine-Docetaxel X 6
- Sequential Docetaxel-Mitomycin X 6
- Sequential Adriamycin-Docetaxel X 6
- Double sequential Adriamycin-Gemcitabine X3 followed by Docetaxel-Mitomycin X3

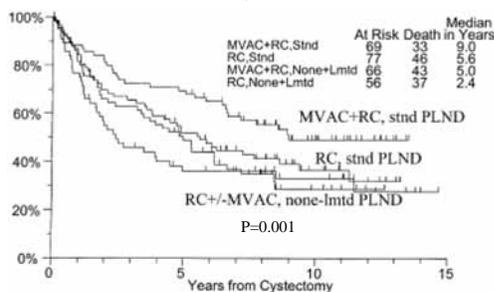
Mike O'Donnell, 2006, MD Anderson Bladder Cancer Meeting

Conclusions

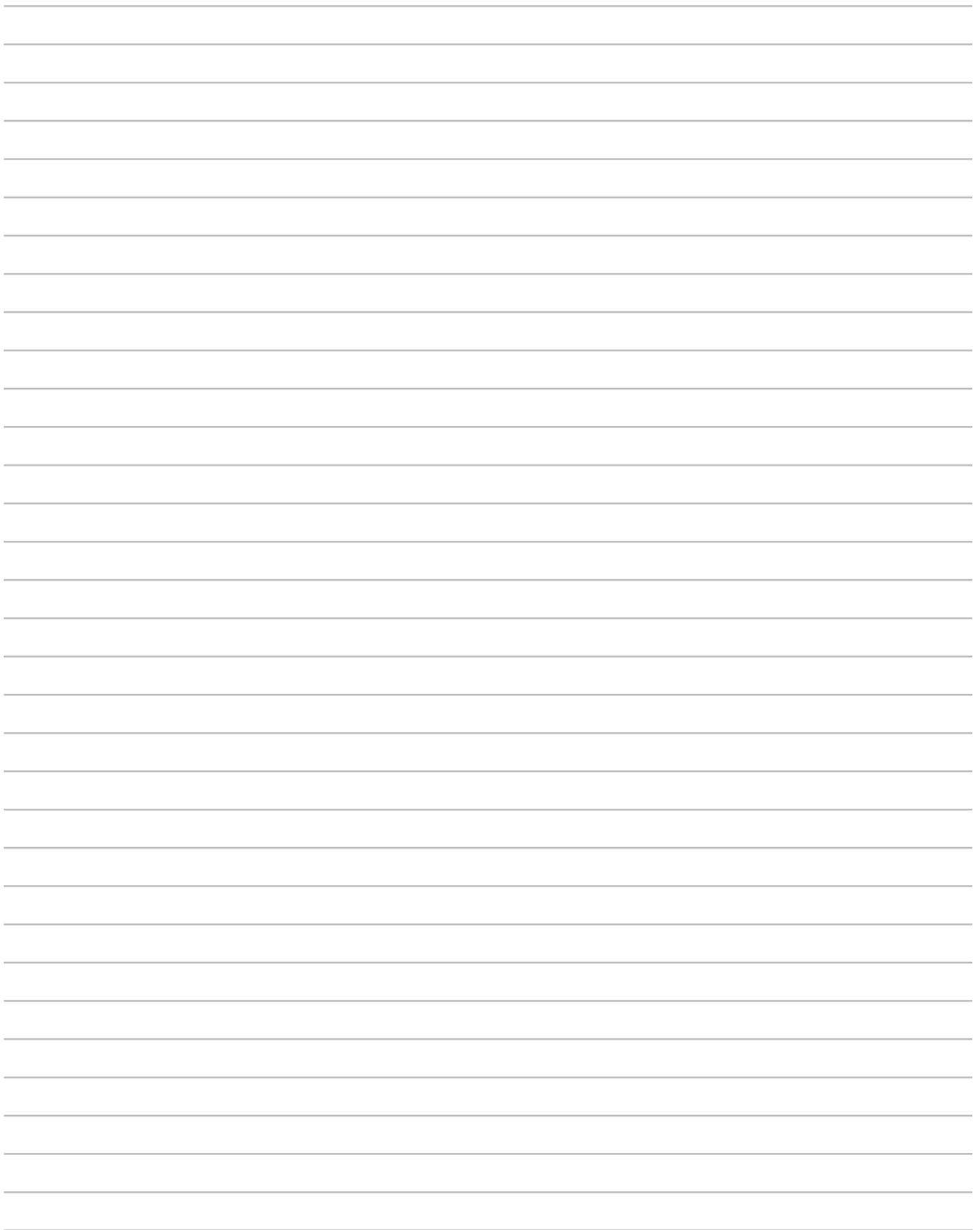
- Surgery Counts! Extend resection, send margin, then roller-balling base and edges (?); or re-resect
- Immediate postoperative chemotherapy: standard
- Concentrated chemo for low risk, BCG for high
- 3 week maintenance BCG, not repeated 6 weeks
- High grade: carefully follow upper tracts and prostate. Low threshold for TURP.
- New treatments are greatly needed. Let Andy know and support research.
- **BCGOncology.com** for slides, handout, questions.

PLND and MVAC Improve Survival

Herr HW: JCO, 2004 172:1286



5 yr survival with MVAC plus PLND 52% vs 34% with inadequate or no PLND



FDA Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence



>1,000 complications reported in past 3 years from 9 manufacturers

- obtain specialized training, be aware of risks
- be vigilant for potential adverse events (erosion, infection)
- watch for perforations from tools
- inform patients that mesh implantation is permanent
- some complications may require additional surgery that may or may not correct the complication
- inform patients about potential for serious complications effecting QOL (dyspareunia, scarring)
- provide patients with a written copy of the patient labeling

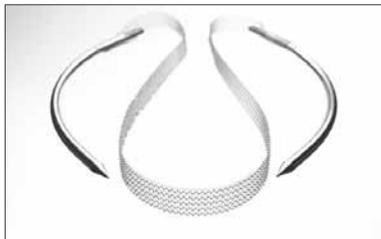
"Serious Complications with Mesh Use in PFR and SUI Repair"¹

<http://www.fda.gov/cdrh/safety/102008-surgicalmesh.html>

**Retropubic Tapes
First Generation TVT**

Perspectives in Urology 2009

**Tension-Free Vaginal Tape (TVT™)*
Original Device**



Perspectives in Urology 2009

**Tension-Free Vaginal Tape (TVT™)*
Ulmsten's Initial Data, 1996 †**



* Gynecare Inc., Summerville, NJ
75 women with urodynamically proven SUI had a ribbon-like strip of mesh tape (polypropylene) placed through a small vaginal incision under the mid-urethra

† Ulmsten, U, et al: Int Urogynecol 1996

- Single center, one experienced urogynecologist
- Mean operative time was 22 minutes (16-42 min)
- All patients discharged < 24 hours, mean convalescence 10 days
- Cured 84%, 2-year follow-up

"Main aims of the TVT operation are to reinforce functional pubourethral ligaments and suburethral vaginal hammock"

**Tension-Free Vaginal Tape
Multicenter Scandinavian Trial***

"In order to find out how easy, effective and safe the procedure could be in ordinary gynecologic units."
131 patients with GSUI prospectively underwent primary TVT in six Scandinavian community hospitals

- OR time was 28 mins, convalescence 2 weeks
- Cured 91%, improved 7%, min. f/u 12 months
- Complications (6)
 - complicated bladder perforation (1)
 - wound infection (1)
 - urinary retention lasting 3-12 days (3)
 - hematoma (2)
 - tape rejection (0)

* Ulmsten, U, Falconer, C, Johnson, P, et al: *Int Urogynecol* 1998
Perspectives in Urology 2009

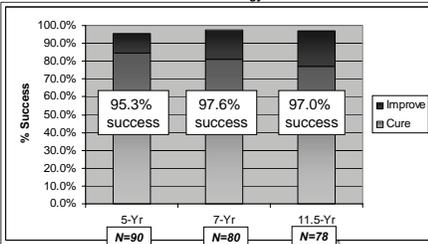
**Tension-Free Vaginal Tape
Overview of "Level I Evidence"**

Retropubic Devices	GYNECARE TVT™ Retropubic	SPARC™	Advantage®	Advantage Fit®
Total RCTs	32	7	0	0
Longest Follow-Up in Any Published Study	11.5 years ⁵	3 years ⁹	N/A	N/A

Retropubic Devices	Align®	Uretex®	Aris®	Lynx®
Total RCTs	0	0	0	0
Longest Follow-Up in Any Published Study	N/A	3 years ¹⁰	N/A	1 year ¹¹

**Tension-Free Vaginal Tape
11-year Data**

90 patients with GSUI prospectively underwent TVT in three centers
Nilsson CG et al.: *Int Urogynecol J*. 2008



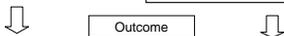
Long-term cure rates similar to traditional pubovaginal sling and Burch copulosuspension

**Tension-Free Vaginal Tape
"SUI and ISD"**

49 women with SUI and ISD underwent TVT*

161 with SUI underwent TVT†

- Recurrent SUI 28%
- Mixed UI 37%
- ISD 11%



- Few intra- or postoperative complications occurred
- Cured 74%, improved 12%
- Mean f/u 4 years
- Primary 88%
- Mixed 81%
- Recurrent 84%, low UCP 78%
- Mean f/u 16 mos

* Rezapour, M et al: *Int Urogynecol J Pelvic Floor Dysfunct* 2001 † Nilsson, CG and Kuuva, N: *BJ OBGYN* 2001

Majority of the failures were >70 years of age and had urethral resting pressure of <10 cmH2O and immobile urethra

Spectrum of SUI Surgery Other Retropubic Devices

- GYNECARE TVT (ETHICON, INC.) – 11-year data - published
- AMS SPARC™ (AMS) – 3 year data - published
- Uretex® Self-Anchoring Urethral Support (Bard) – no data
- Advantage® Sling System (Boston Scientific) – no data
- Sabre™ Bioabsorbable Sling (Mentor) – 6 mo fu data
 - multiple reports of extrusion/infection
- IVS Tunneler™ (Tyco) – withdrawn from market
- 9 other brands - no data

Perspectives in Urology 2009

*Trademark

TVT Complication

Polypropylene Bladder Erosion: Retropubic Approach

Bladder perforation is the most common complication of retropubic placement of suburethral tension free vaginal tape for the treatment of SUI

- Incidence is 2 – 24% reported in published literature*
- Incidence is as high as 19% in women with prior incontinence surgery†



* Minaglia S, Klutke C, Klutke, J: Urol 2004
† Azam J, et al: J Urol 2001

Perspectives in Urology 2009

Tension Free Tape-Learning Curve 23 residents with a single senior surgeon

- mean # of TVT's was 12.1
- bladder perforations
 - 1st 5 TVT's-40.9%
 - 2nd 5 TVT's-30.7%
 - 3rd 5 TVT's-25.9%
- more perforations with non-dominant hand
- less common with older age and increasing weight
- 37% were missed on cystoscopy by resident



McLennan and Melick Obstet Gynecol 2005

Perspectives in Urology 2009

Question

Are you aware of any severe bladder, urethral, bowel or vascular injuries in your community

- A. Yes, I have had one personally
- B. Yes, one of my partners
- C. Yes, the other group
- D. Yes, the other specialty
- E. No

Perspectives in Urology 2009

Tension-Free Vaginal Tape
How does it work?

"Urethra is resuspended to correct hypermobility vs. backboard of support during increases in intra-abdominal pressure"

- 20 patients underwent TVT had preop/postop Q-tip angle assessed *
- Cured 17/20 (85%), improved 2/20 (10%), failed 1/20 (5%)
- Mean preoperative Q-tip angle was 42° and postoperative was 32°
- 11 of the 12 patients with postop Q-tip angle > 30° were cured
- The 1 patient that failed had a preop/postop Q-tip angle of 10°

*Klutke, JJ, et al: Urol 2000

- Application of the tape does not elevate the position of the bladder neck at rest, but limits its mobility during valsalva †

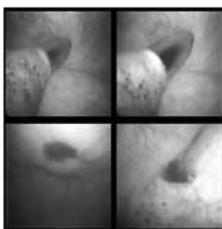
† Atherton, MJ and Stanton, SL: NeuroUrol Urodyn 1999

Perspectives in Urology 2009

Transobturator Tape
Proposed Advantages

Avoidance of retropubic space

- Eliminate risk of bladder, bowel, ureteral injury
- Avoids scar tissue from prior operations
- Less bleeding
- Lower risk of retention and de novo urgency



Perspectives in Urology 2009

PVS Using the Transvaginal Tape Obturator System (TVT-O) For all Types of SUI
1-Year Minimum Follow-up

Flynn BJ: SC AUA 2008

121 patients with SUI that underwent transobturator inside-out insertion of polypropylene mesh were retrospectively reviewed *

- 64 (53%) patients had prior surgery
- Mean follow-up 29.4, 12-46 months
- OR time, 26 minutes (range 14-38)
- Cured 111 (92%), failed 10 (8%)
- Complication (6)
 - Bladder perforation (0)
 - Mean EBL 33 ml
 - De novo urgency (1)
 - Urinary retention (3)
 - Vaginal erosion (2)
 - Urethral injury (1)



Perspectives in Urology 2009

TVT-Obturator
'Inside-Out'

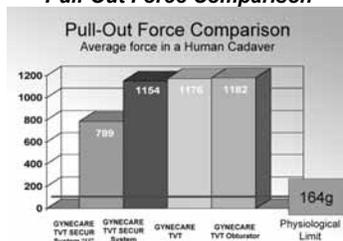
107 patients with SUI that underwent transobturator inside-out insertion of polypropylene mesh were retrospectively reviewed *

- 17 patients had prior surgery
- 1-year minimum follow-up
- Mean OR time, 14 minutes (range 7-20)
- Cured 91%, improved 9%
- Complication (6)
 - Bladder perforation (0)
 - Hematoma (0)
 - De novo urgency (2)
 - Urinary retention (3)
 - Vaginal erosion (1)
 - Urethral erosion (0)

* De Leval, J: Eur Urol 2004

Perspectives in Urology 2009

**Tension-Free Vaginal Tape Secur (TVT-S™)
Pull-Out Force Comparison**



Pull-Out force evaluated in the GU diaphragm and obturator membrane of a human cadaver

Perspectives in Urology 2009

AUA 2008 Abstract 1566: UNFAVORABLE IMMEDIATE OUTCOME OF THE TVT SECUR SLING IN TWENTY CONSECUTIVE WOMEN WITH SUI

Fabio Baracat*, et al Sao Paulo, Brazil

20 patients underwent TVT-secur in the 'hammock' configuration into the obturator internus muscle, in the same tension free process as the classic TVT

- mean preoperative VLPP, 76.3 cm H2O
 - did not differ between the groups (cured, improved and failed)
 - 40% (8 cases) dry, 20% (4 cases) improved, 40% (8 cases) failed
- cure rate was 40% at 3 months
- blood loss was minimal and no bladder perforation occurred
- only three patients (15%) needed analgesics

TVT SECUR in the hammock configuration tensioned as classic TVT leads to poor outcome

Perspectives in Urology 2009

2009 AUGS Abstract: Efficacy and complications of TVT-Secur in the management of stress urinary incontinence

Terlecki RP and Flynn BJ et al, Denver, CO

55 women with all types of SUI underwent the TVT-secur in the 'U' configuration tensioned with the mesh abutting the urethra

- concomitant pelvic procedure (n = 21)
- exclusion criteria
 - neurovesical dysfunction (n =2)
- prior incontinence surgery, 15 (27%), 9 PVS, 6 suspensions
- prior hysterectomy, 34 (62%)
- pre-op pad usage
 - mean daily pad use, 2 (1-4)
 - mean 24-hour pad weight, 65 (3-110) gms
- severe ISD (VLPP < 60 cm H2O), 14 (26%) patients
- BMI was 29.6 kg/m²

Flynn BJ et al: AUGS 2009

Perspectives in Urology 2009



2009 AUGS Abstract: Efficacy and complications of TVT-Secur in the management of stress urinary incontinence

Terlecki RP and Flynn BJ et al, Denver, CO

Anesthesia

- all cases performed IV sedation/local anesthetic
 - Propofol 175 µg
 - Midazolam 0.51 mg
 - Fentanyl 57 µg
 - 50/50 mix of 1% lidocaine/0.25% bupivacaine (40 ml)

Surgical Approach

- TVT-s inserted in the 'U' configuration
- intra-operative cough test used to adjust sling tension
- cystoscopy performed in all cases to r/o urinary tract injury



Flynn BJ et al: AUGS 2009

Perspectives in Urology 2009

**Tension-Free Vaginal Tape Secur (TVT-S™)
IUGA 2007**

Author(s)	# Pts	Mean f/u	Subjective Cure	Failed/Worse	Objective Cure	Complications
Marsh et al, UK	40 (H-U n/a)	6 wk	74% dry 12% imp	14% no Δ		1 "buttonhole" 2 vd Dysfcn 1 exp't pain
Shaare-Zedek, Israel	150	n/a	97%	3% no Δ		5 unintended device removal
Saltz et al, USA	77 (27-U/50-H)	6 wk	68.8% dry 13% imp	3% worse		2.6% vd Dysfcn 1 pain
Karram et al, USA	60 (28-U/31-H)	6 wk	86.7% >50% imp on VAS	3% worse	-cst 75% +cst 25%	1 bladder perf 3 de novo OAB 1 exp
Debodinance et al, France	40 (all H)	8 wk	76.9% dry 15.4 imp	7.7% no Δ		5 vd Dysfcn 1 exp Denovo OAB/UUI-20%
Totals (not a meta analysis)	410	6.6 wk	85.4%	8.5% no Δ 6% worse	-cst 77%	

Int Urogynecol J. :18 (Suppl): 2007

**Single-Incision (Mini) Sling
Summary**

Advantages

- small vaginal incision, no exit point
- quick, safe, minimal dissection
- done under local anesthesia

Early observations

- tensioned differently than traditional TVT
 - mesh is in direct contact with urethra
- use with caution in concomitant POP cases
- technically demanding procedure
 - patient selection
 - CST vital for success

Perspectives in Urology 2009

**Flynn Spectrum of SUI Surgery
Technical Pearls for Sling Placement**

Mini-Sling

- minimize dissection
- do not perforate endopelvic fascia or obturator membrane when dissecting
- mini-sling tensioning is tighter than retropubic or TOT procedures
- mesh should lie flat against the urethra
 - minimal-no space between the urethra and sling
- over tensioning is possible if particular attention is not paid while inserting the second tip

- cough-test is vital for success

Perspectives in Urology 2009

Head to Head RCTs

Perspectives in Urology 2009

**Midurethral Tape Debate
TOT vs. TVT in Patients with Low MUPP**

An outcome analysis was performed in 145 women that underwent sling for SUI with a MUCP < 42 cm H2O (Monarc = 85; TVT = 60)

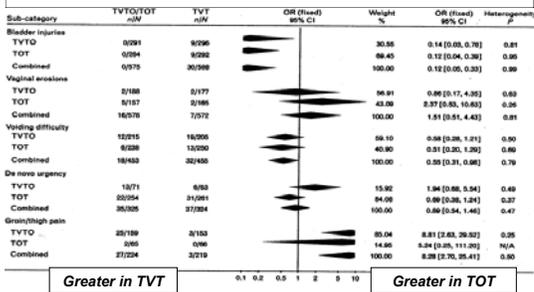
- Baseline characteristics were similar
- Relative risk of postoperative SUI 3 months after surgery was 2.85 in all patients when Monarc was compared to TVT
- RR was 0.56 if MUCP > 42 cm H2O
- RR was 5.89 if MUCP < 42 Cm H2O

The cure rate after TOT is inferior to TVT in women with ISD

* Miller JJ, Sand PK et al, Obstet Gynecol 2006

Perspectives in Urology 2009

**Spectrum of SUI Surgery
Risk of Complications with TVT vs TOT**

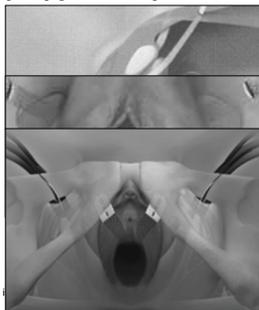


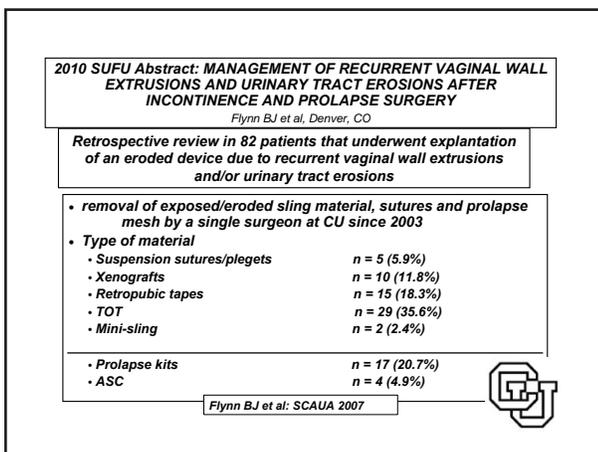
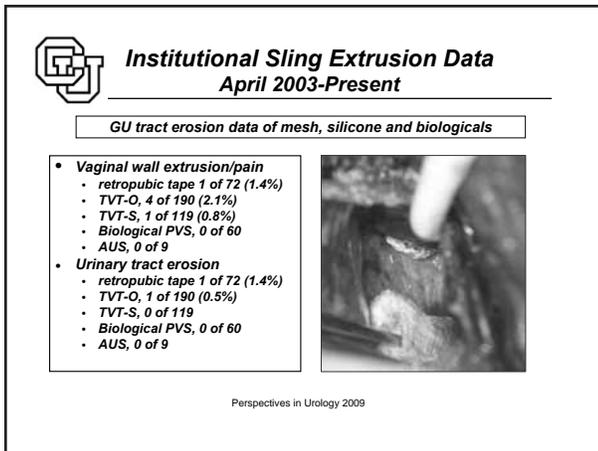
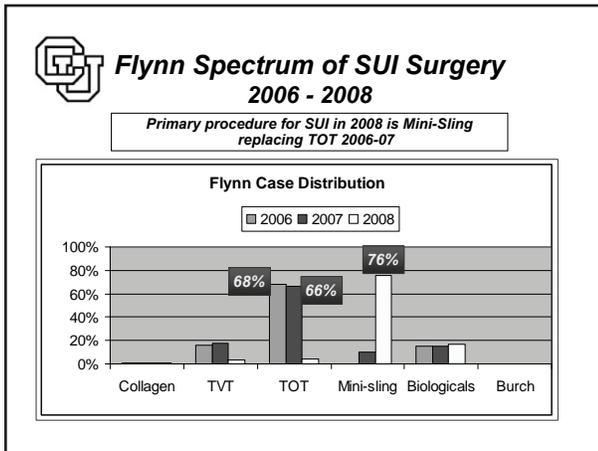
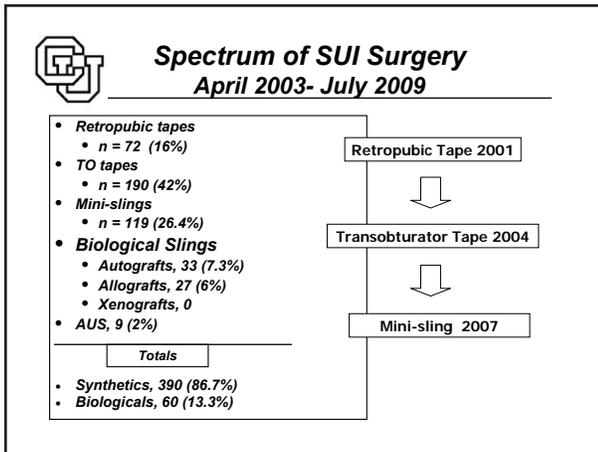
What I do and Why

Perspectives in Urology 2009

**Minimally Invasive Sling Surgery
Evolution of Polypropylene Tapes**

- **First generation**
 - retropubic placement
 - effective at 7 years f/u
 - uncommon, but serious complication (bladder, bowel, vascular)
- **Second generation**
 - transobturator placement
 - effective at 2 years f/u
 - rare, complication of thigh pain
- **Third generation**
 - mini-sling (8 cm)
 - minimal on efficacy
 - ? no complications







Challenges in Prostate Cancer: Why We Are 15 Years Behind Breast Cancer

~ David C. Beyer, MD

Challenges in Prostate Cancer: Why Are We 15 Years Behind Breast Cancer

David C. Beyer, MD, FACP, FACRO, FASTRO
 Arizona Oncology Services
 Phoenix, Arizona

Breast vs Prostate

- Cancer statistics and natural history
- Advocacy
- Research
- Treatment of primary
- Adjuvant hormonal treatments
- Adjuvant chemotherapy treatments

New Cancer Cases

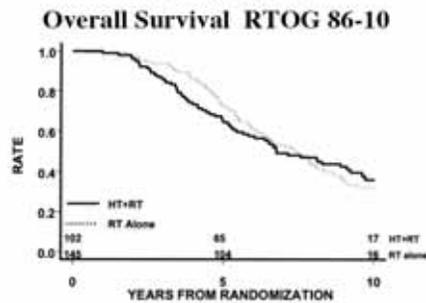
Prostate	234,460	33%		Breast	212,920	31%
Lung	92,700	13%		Lung	81,770	12%
Colon & Rectum	72,800	10%		Colon & Rectum	75,810	11%
Bladder	44,690	6%		Uterine	41,200	6%
Melanoma	34,260	5%		Non-Hodgkin Lymphoma	28,190	4%
All Sites	720,280			All Sites	679,510	

Jemal, A. et al. CA Cancer J Clin 2006;56:106-130

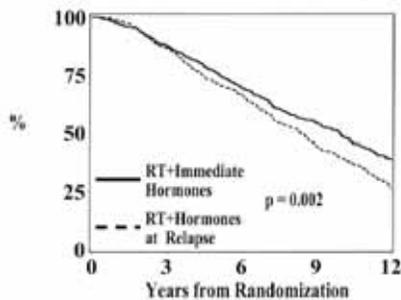
Adjuvant Tamoxifen

- Early Breast Cancer Trialists Collaborative Group (EBCTCG)
- 5 years adjuvant therapy
- In receptor positive patients:
 - Odds of recurrence ↓ 47%
 - Odds of death ↓ 26%

Does Early HT Compromise Late Salvage HT?



RTOG 85-31 Reduction in Mortality



Hormones for Prostate Cancer: Short vs Long Term

- RTOG 9202 (+)
 - Locally advanced PSA<150
 - T2 and >25cc, T3, T4
 - RT + Goserelin / Eulexin 2mos. prior and during
 - +/- 2 years Goserelin

Treatment Issues

- Breast
- ER/PR receptor assay
- Level I evidence
- Hormones
- AI's
- Chemotherapy
- Prostate
- Presumed sensitivity
- Level I evidence
- LHRH / Antiandrogen
- Chemotherapy (?)

Adjuvant Chemotherapy: Breast

- Standard therapy in 2009 for select patients
- Traditionally started promptly after primary surgical treatment

Timing of Chemotherapy: Breast Cancer



Shannon et al. JCO 21(20):3792-3797, 2003

Sequencing Chemo/Radiation in Breast Conserving Therapy

- Safe to administer XRT after chemo
- Early (<math>< 90</math> days) chemotherapy reduces local failure

Donato et al. Anticancer Res Mar-Apr 2004;24(2C):1303-1306

Clinical and Pathologic Characteristics of Prostate Cancer (including new markers such as PCA3)

~ M. Scott Lucia, MD

Prostate Cancer: Clinical and Pathological Characteristics



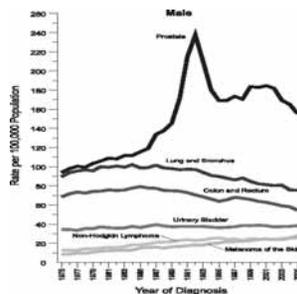
M. Scott Lucia, MD
 Associate Professor
 Chief of Genitourinary and Renal Pathology
 Director, Prostate Diagnostic Laboratory
 Dept. of Pathology
 University of Colorado Denver SOM

Prostatic Carcinoma - 2009¹

- >192,000 new cases expected
- 27,360 deaths expected
- Lifetime risk of prostate cancer in U.S.:
 - Diagnosis: ~17%
 - Death: ~3%
- More men die *with* prostate cancer than *of* it

1. Jemal A. et al. Cancer Statistics 2009. *CA Cancer J Clin* 2009;59:225-48.

Annual Age-adjusted Cancer Incidence Rates among Males and Females for Selected Cancers, United States, 1975- 2005

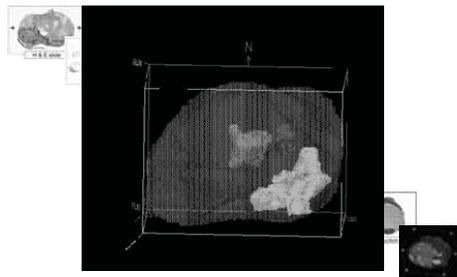


From Jemal, A. et al.
CA Cancer J Clin 2009;59:225-249.

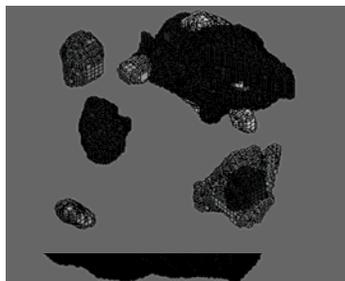
Copyright ©2009 American Cancer Society



3-Dimensional Reconstruction of Whole-Mounted Prostatectomy Specimens



3-Dimensional Reconstruction of Prostatectomy: Tumor Multifocality and Heterogeneity



Multifocality of 293 carcinomas from 151 prostates (< 1994)

Miller GJ, J Urol 152:1709, 1994

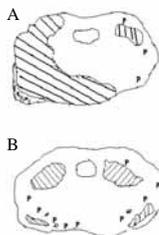
Tumors/Pt.	No. Pts. (%)	No. Tumors	Mean Tumor Vol. (cc)
1	66 (43.7)	66	6.52
2	47 (31.1)	94	1.48
3	25 (16.6)	75	1.01
4	8 (5.3)	32	0.59
5	4 (2.6)	20	0.40
6	1 (0.7)	6	0.22
Totals	151 (100)	293	

- Prostatectomies 1997-2006:
 - Solitary = 20 % (Mean vol = 2.14 cc)
 - Multifocal = 80% (range 2- 17 tumors)

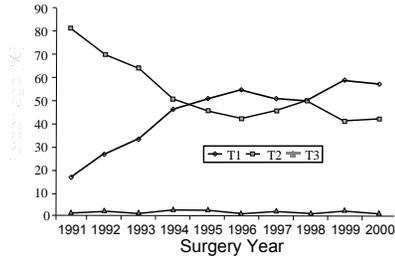
Lucia MS, Unpub

Representative Diagrams of Prostate Cancer and HGPIN in Early 1990s (A) and Present (B)

- A. Tumors were larger, more confluent and more advanced
- B. Tumors now smaller, more multifocal and more localized

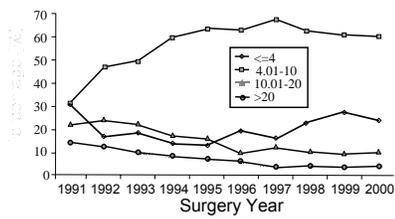


DoD CPDR National Database: Clinical T stage at diagnosis for patients who underwent prostatectomy



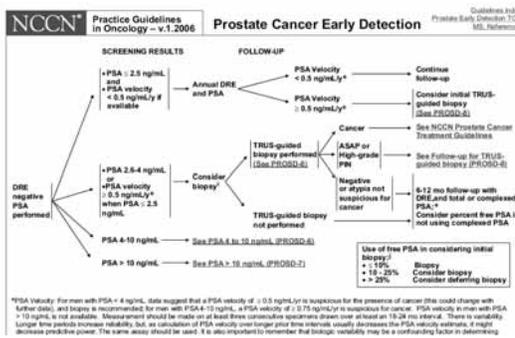
DoD = Department of Defense Moul JW, et al. Surgery 2002;132:213-9
CPDR = Center for Prostate Disease Research © 2002, Mosby, Inc.

DoD CPDR National Database: PSA level at diagnosis for patients who underwent prostatectomy



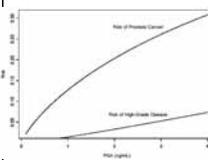
DoD = Department of Defense Moul JW, et al. Surgery 2002;132:213-9
CPDR = Center for Prostate Disease Research © 2002, Mosby, Inc.

NCCN Guideline For Prostate Cancer Screening



Prostate Cancer in "Normal" PSA (PCPT Placebo Arm)

PSA, overall & high-grade (Gleason 7+) prostate cancer			
PSA ng/ml	No. of men	No. (%) with prostate cancer	No. (%) of cancer with high-grade
≤ 0.5	486	32 (6.6)	4 (12.5)
0.6 - 1.0	791	80 (10.1)	8 (10.0)
1.1 - 2.0	998	170 (17.0)	20 (11.8)
2.1 - 3.0	482	115 (23.9)	22 (19.1)
3.1 - 4.0	193	52 (26.9)	13 (25.0)
Total	2950	449 (15.2)	67 (14.9)



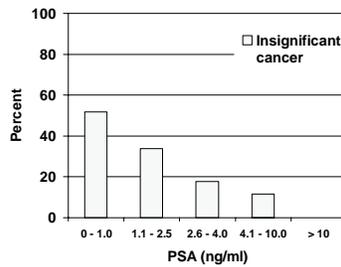
Thompson et al. JAMA 2005; 294: 66-70

PSA as a Marker for Prostate Cancer

PSA	Sensitivity	False positive rate
1.1	82.0	59.4
1.6	67.4	41.2
2.1	54.4	29.2
2.6	43.6	20.4
3.1	35.8	14.9
4.1	24.5	7.7
6.1	5.4	2.0
8.1	2.0	0.9
10.1	1.0	0.5

Thompson et al. JAMA 2005; 294: 66-70

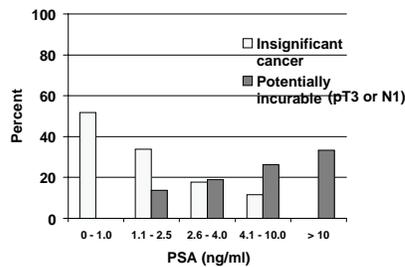
PCPT: PSA and Insignificant Cancer*



* GS≤6, <3 cores with cancer, no core with >50% tumor

Lucia MS, et al. Cancer Prev Res 2008;1:167-73.

PCPT: PSA and Insignificant Cancer*



* GS≤6, <3 cores with cancer, no core with >50% tumor

Lucia MS, et al. Cancer Prev Res 2008;1:167-73.

Prostatic Carcinoma: Issues for Screening and Detection

- Serum prostate specific antigen (PSA)
 - A continuum of risk over all values
- Digital rectal exam
 - Poor sensitivity
- Random biopsy schema
 - Sampling issues
 - Significant vs "Insignificant" tumors

Ideal Biomarker for Prostate Cancer

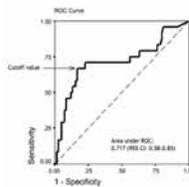
- Sensitive and specific for aggressive cancer
- When modulated, correlates with disease outcome
- Reproducible
- Quick and easy to assay
- Low cost
- Minimal invasiveness

New Biomarkers for Prostate Cancer Detection: PCA3

- First described in 1999 as DD3*
- Non-coding RNA
- Unknown function
- Prostate specific, highly overexpressed in more than 95% of prostate cancers
- Not detected in any other tissue or cancer

*Bussemakers *et al.*, Cancer Res 1999;59:5975-5979

RNA Analysis of PCA3 Gene in Urinary Sediments



- Ratio PCA3:PSA is used as a quantitative measure
- Ratio PCA3:PSA is consistently higher in samples from cancer patients

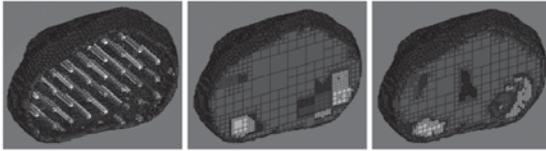
Hessels *et al.*, Eur Urol 2003;44:8-16

Validation Studies - PCA3

	Patients	Sensitivity	Specificity	Negative predictive value
Hessels <i>et al.</i> , 2003	108	67%	83%	90%
Tinzi <i>et al.</i> , 2004	158	82%	76%	87%
Fradet <i>et al.</i> , 2004	443	66%	89%	84%
Groskopf <i>et al.</i> 2006	122	69%	79%	

Hessels *et al.*, Eur Urol 2003;44:8-16
Tinzi *et al.*, Eur Urol 2004;46:182-186
Fradet *et al.*, Urology 2004;64:311-315
Groskopf *et al.* Clin Chem 2006;52: 1089-1095

Improved tumor sampling with saturation biopsies leads to improved detection and grading – implications for targeted therapy

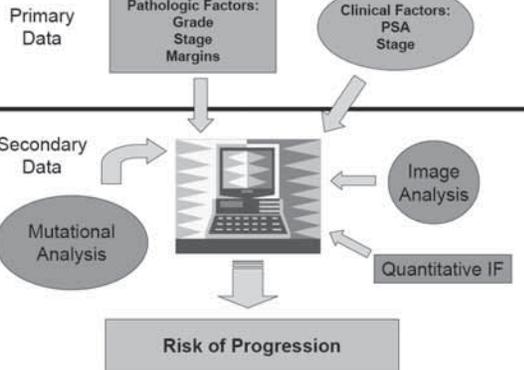
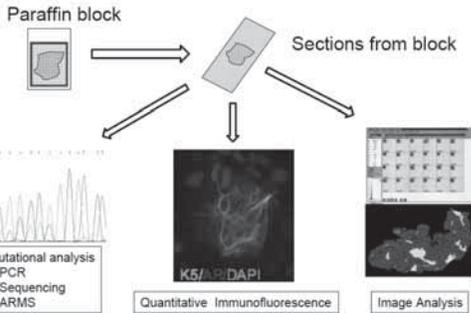


- Saturation grid-biopsy data (left)
- Reverse-reconstruction model (center)
- Actual RRP specimen (right)
- Model error: -15% for Gleason 3+4 tumor (right, 5.1cc)
+15% for Gleason 3+3 tumor (left, 0.093cc)

Crawford et al, *BJU Int* 96:999-1004, 2005

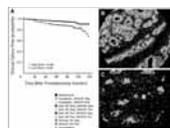
Systems Pathology

Definition: Analyzing the interrelationships of multiple elements (molecular and pathological) in a system rather than each one at a time



Systems Analysis Approach for the Prediction of Prostate Cancer Progression After Radical Prostatectomy*

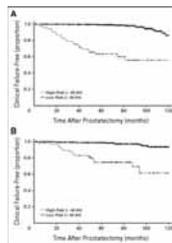
- Clinicopathologic: Grade, LN mets
- Image analysis: Pca gland lumen architecture, cytoplasm color/texture
- IF: AR, AMACR



CI=0.84

↑ Analysis of AR and AMACR

Kaplan-Meier curve demonstrating the classification of patients from the (A) training cohort and (B) validation cohort as being at low risk (blue line) or high risk (yellow line) for experiencing clinical failure (CF)



* Donovan, M. J. et al. *J Clin Oncol*; 26:3923-3929 2008

Copyright© American Society of Clinical Oncology

Chemoprevention Strategies

~ M. Scott Lucia, MD

Chemoprevention Strategies for Prostate Cancer



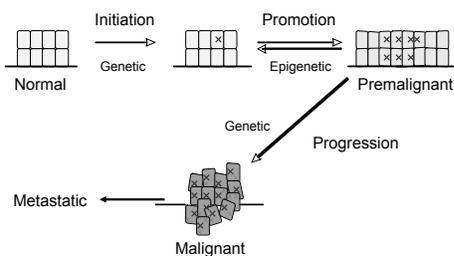
M. Scott Lucia, MD
Associate Professor
Chief of Genitourinary and Renal Pathology
Director, Prostate Diagnostic Laboratory
Dept. of Pathology
University of Colorado Denver SOM

Chemoprevention

The use of specific natural or synthetic agents, dietary or pharmacological, to reverse, retard or prevent the development or progression of cancer

Sporn 1976

Multistep Carcinogenesis



Chemoprevention Trials for Prostate Cancer Using 5ARI's

Prostate Cancer Prevention Trial (PCPT)

Primary Endpoint: To determine if **finasteride** administration for a period of seven years could reduce the period prevalence of prostate cancer.

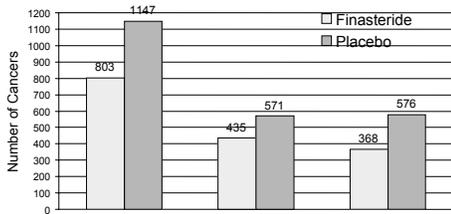
REduction by DUtasteride of prostate Cancer Events (REDUCE)

Primary Endpoint: To determine if **dutasteride** could reduce the likelihood of prostate cancer diagnosis on *repeat* biopsy after 2 and 4 years.

Design comparison between PCPT and REDUCE

	PCPT	REDUCE
Test agent	Finasteride (5mg/day)	Dutasteride (0.5 mg/day)
N	18,800	8200
Age at randomization	≥ 55	50-75
PSA at randomization	≤ 3 ng/ml	>2.5 and <10 ng/ml
Negative DRE	Yes	No
Negative baseline bx	No	Yes
Scheduled biopsies	At 7 yrs	At 2yrs and 4 yrs
Biopsy scheme	6 core (80%)	10 core
For-cause biopsies (↑PSA, +DRE)	Many	Few

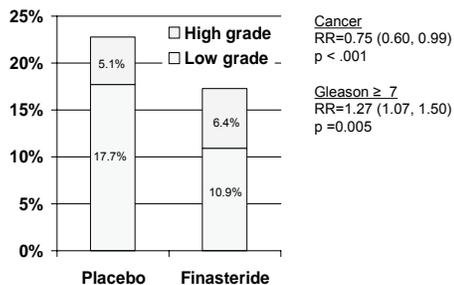
Prostate Cancer Prevention Trial



	Total Men Evaluated	Men with For-Cause Biopsy/Procedure	Men with End-of-Study Biopsy
Finasteride	4368	1639	3652
Placebo	4692	1934	3820

Thompson IM, et al. *NEJM* 2003.

Observed fractions of total subjects with low- and high-grade cancer in the PCPT

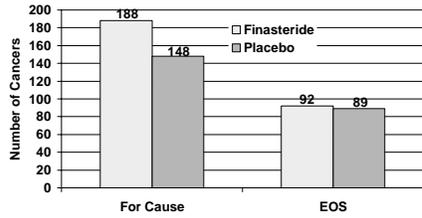


Cancer
RR=0.75 (0.60, 0.99)
p < .001

Gleason ≥ 7
RR=1.27 (1.07, 1.50)
p =0.005

Thompson IM, et al. *NEJM* 2003;349:211-20

Grade 7-10 Cancers diagnosed in PCPT



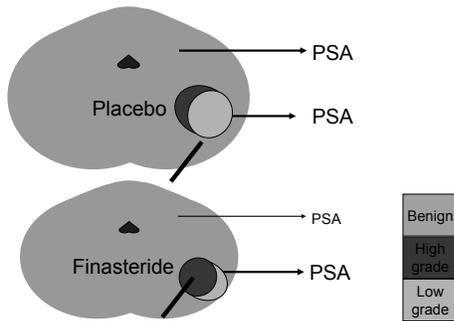
"For cause" = biopsy for ↑PSA and/or abnormal DRE
 "EOS" = end-of-study biopsy

Detection bias led to increased detection of high-grade cancer in PCPT

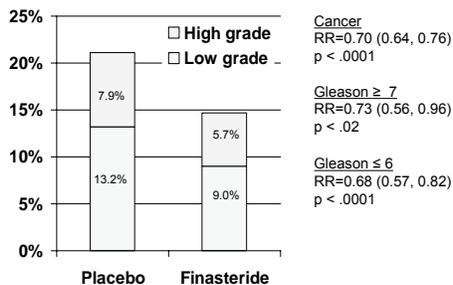
- Finasteride improved performance of PSA for cancer and high-grade cancer¹
- Finasteride increased sensitivity of DRE²
- Finasteride increased sensitivity of prostate biopsy for detection of high grade cancer by reducing prostate volume³

1. Thompson, I. M. et al. *J Natl Cancer Inst.* 2006;98:1128-1133
 2. Thompson IM, et al. *J Urol* . 2007;177:1749-52
 3. Lucia MS, et al. *J Natl Cancer Inst.* 2007;99:1375-83

Effect of finasteride on cancer detection



Estimated actual fractions of total subjects with low- and high-grade cancer after adjusting for bias



Cancer
 RR=0.70 (0.64, 0.76)
 p < .0001

Gleason ≥ 7
 RR=0.73 (0.56, 0.96)
 p < .02

Gleason ≤ 6
 RR=0.68 (0.57, 0.82)
 p < .0001

Redman MW, et al. *Cancer Prev Res* 2008;1:174-81

There are a lot of exciting things happening in the PLCO Trial
 Biorepository: More than 2.7 million specimens

Exam Cycle	Risk Factors	Usual Diet	Serum	Plasma	RBC	DNA	Viable Cells	Tumor Sample
Intervention Arm								
Baseline	X	X	X	X	X	X		
Year 1			X					
Year 2			X					
Year 3	X	X	X	X	X	X		X
Year 4			X	X		X		
Year 5			X	X	X	X		
2004-2013								x
Comparison Arm								
	X	X				X		X

**PLCO Prostate Subcommittee
 Thanks to participants**

Urologists

- G. Andriole, Chair
- C. Amling
- D. Crawford, V. Chair
- R. Grubb

Westat

- D. Carrick

- B. O'Brien
- L. Ragard
- T. Riley

IMS

- J. Ciapp
- B. Lake
- J. Mabie

B. Wilcox

Others

- D. Chia
- T. Church
- D. Reding

NCI

- C. Berg
- R. Hayes
- G. Izmerlian

- B. Kramer
- D. Levin
- A. Miller
- P. Pinsky
- P. Prorok



A special thanks to Barry Kramer and Phil Prorok for their leadership and guidance during the past 15 years

Prostate Biopsy

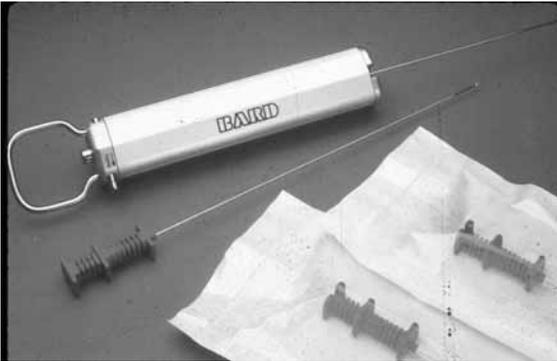
A prostate biopsy needle device in the hands of a Urologist !

Willet F. Whitmore Jr.

Prostate Biopsy

A prostate biopsy needle device in the hands of a Urologist !

Willet F. Whitmore Jr.



Prostate Cancer

prevalence
disease in a population

incidence
disease diagnosed in a
population

Prostate Cancer Prevalence

210 patients		4696 patients
0	20-29	0
0	30-39	0.2%
0	40-49	3.8%
29%	50-59	6.4%
30%	60-69	12.5%
40%	70-79	17.4%
67%	80-89	26.1%
100%	90+	
Franks 1954		Scott 1968

Prostate Cancer Prevalence

violent death series

Detroit

	Caucasian	Afro-American
20 - 29	0/6	0/28
30 - 39	6/26 23%	9/29 31%
40 - 49	11/29 38%	20/37 54%
		Sakr 1993

Prostate Cancer Prevalence

PSA	% positive	G 8, 9
< 0.5	32/486 6.6%	4/ 32 12.5%
0.6-1.0	80/791 10.1%	8/ 80 10%
1.1-2.0	170/998 17.0%	20/170 11.8%
2.1-3.0	115/482 23.9%	22/115 19.1%
3.1-4.0	52/193 26.9%	13/ 52 25%

Thompson NEJM 350:2239, 2004

Screening

AIMs

identify asymptomatic men
with aggressive, localized tumors,
treat them,
reduce morbidity, LUTs,
reduce metastases, [painful]
reduce mortality,

Prostate Cancer

indications for biopsy; biopsy
number of cores / lobe
number of cores containing cancer
% of tumor in all cores
Gleason patterns one and two
Gleason sum, biopsy 3+2+4 = 3+4
prostatectomy Gleason sum 3+2+4

Tumors 2009

incidence	mortality
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Tumors 2009

	incidence	mortality
prostate	192,280	27,360
lung	103,350	88,900
colo/ rectal	52,010	25,240
bladder	23,580	
	52,810	18,030p
non Hodgkin's	35,990	12,090l
melanoma	39,080	0,1801b

Tumors 2009

1992 325,000 + patients
prostate cancer; 40,000 deaths
180,000 to 220,000 patients/year
deaths down to 27,000 to 31,000
breast cancer; same incidence,
death rate; 40,000 patients/year

Tumors 2009

Why is the death rate lower ?
prostate specific antigen
screening [PSA + DRE]
radical prostatectomy*
conformal radiotherapy*
TRUS guided brachytherapy*
* all technical exercises

Prostate Biopsy

indications

80% PSA
20% abnormal digital rectal
exam

Prostate Biopsy

indications

181 patients

PSA	87	48.9%
nodule	13	7.3%
asymmetry	6	3.3%
hardness	3	1.7%

Prostate Biopsy

indications

181 patients

PSA	87	48.9%
PSA + nodule	27	14.1%
PSA + asymmetry	22	12.2%
PSA + hardness	23	12.7%

Treatments

diagnosis
does
not
mean
[local]
therapy !

Whole Mount Grading

580 patients
44% upgraded;
22% 2 or more;
29% same grade;
28% down graded;
12% 2 or more;
Crawford and Donohue 2002

Gleason 3+3

580 patients
3+3 173 patients, 3 cores
3+3 whole mount 47 patients
< 6 " 67 patients
7 " 49 patients
8-10 " 10 patinets
undergrading

Gleason 7

580 patients
G 7 173 patients, 3 cores
4+3 35 patients; 18 4+3 Gleason
9 < G7; 8 > G 7
3+4 66 patients; 36 3+4 Gleason
22 < G7; 8 > G 7
undergrading; overgrading



What's New in Advanced Disease (CRPC)?

~ Matthew Rettig, MD

What's New in Advanced Disease (castration resistant prostate cancer = CRPC)?

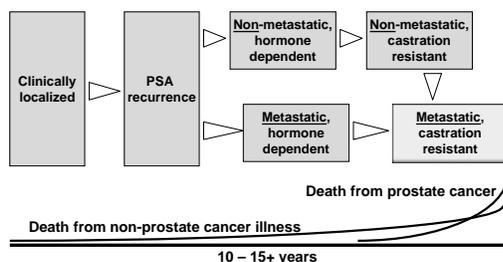
Matthew Rettig, MD
 Associate Professor
 Department of Medicine
 Division of Hematology-Oncology
 Department of Urology
 Medical Director, Prostate Cancer Program
 Institute of Urologic Oncology
 David Geffen School of Medicine at UCLA

Novel/Emerging Therapies

- Differentiating Agents
 - HDAC inhibitors (vorinostat)
- Immunotherapies
 - Sipuleucel (Provenge), ipilimumab (anti-CTLA4)
- Gene Therapy—Virus Based
 - Induce death, Enzyme/Prodrug, replace defective genes
- Targeting Aberrant Cell Signaling
 - ZD4054, oblimersen, etc
- Angiogenesis
 - Avastin, Aflibercept, Thalidomide
- AR targeting agents
 - MDV3100
 - Abiraterone
- Hedgehog inhibitor



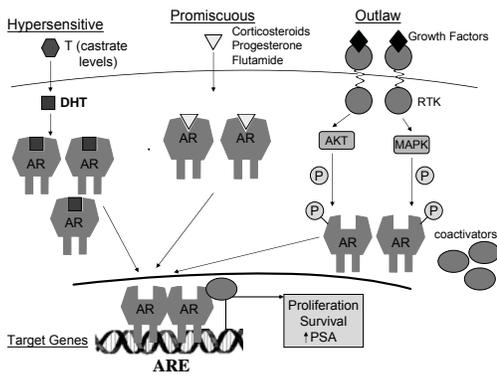
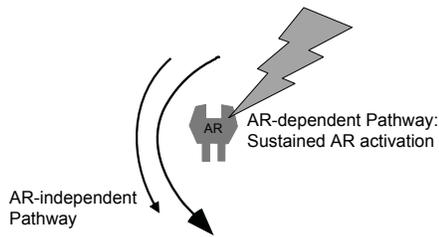
Clinical States of Prostate Cancer



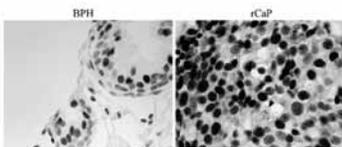
Mechanisms of Castration Resistance

- 1. AR-dependent
- 2. AR-independent

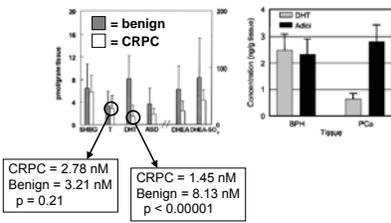
Mechanisms Giving Rise to CRPC



AR Expression in CRPC

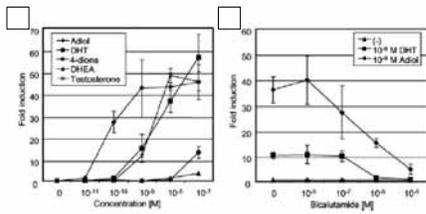


Intracellular Androgen Levels in CRPC



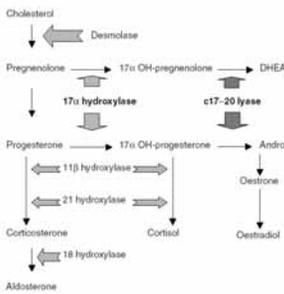
Clin Can Res 10:440, 2004.
 Can Res 64:765, 2004.

Activation of AR transcriptional activity by androgens

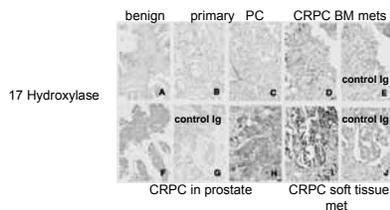


Can Res 64:765, 2004.

Biosynthesis of Androgens



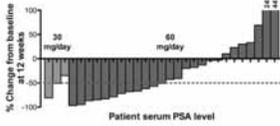
CRPC cells activate the androgen synthesis enzymatic pathway.



Cancer Res 66:2815, 2006.

MDV3100: Phase 1-2 results

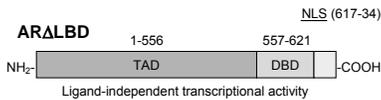
- 22/30 have PSA response, 12 of which were > 50% decline.



- Phase 3 has enrolled first patient in 9/09.

Science 324:787, 2009.

A Cautionary Note



J. Steroid Biochem Mol Biol. 41: 671-675, 1992.
 Cancer Res. 67:2007, 2007.
 Cancer Res. 68:5469, 2008.
 Cancer Res. 69:16, 2009.

Conclusions, Take Home Messages, and Other Comments

- CRPC is a lethal event.
- The AR represents a viable molecular target in at least a subset of CRPCs.
 - However, the biochemical and molecular events that lead to castration resistance are extremely complex and a simple therapeutic agent is not apt to be effective in all or perhaps even most cases.
- Innumerable drugs are in various stages of pre-clinical and clinical development, and incremental advances are anticipated. Major advances will require the identification and targeting of sentinel growth promoting molecular events.



An Update on Radiation Therapy for Prostate Cancer

~ David C. Beyer, MD

An Update on Radiation Therapy for Prostate Cancer

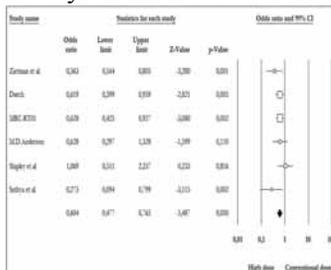
David C. Beyer, MD, FACR, FACRO, FASTRO
 Arizona Oncology Services
 Phoenix, Arizona

Objectives

- Review significant new data
- Identify leading trends in PCa

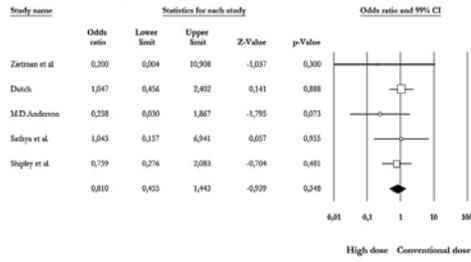
- 2009 Issues for:
 - Dose and Fractionation
 - Post-operative radiation
 - Role of hormones

XRT Dose Escalation (All Risk Groups) Meta-analysis of Biochemical Failure



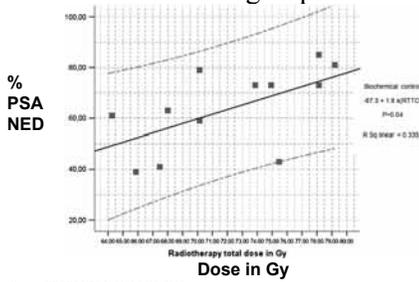
Viani, G. et al. IROBP V74(5):1405-1418, 2009

XRT Dose Escalation (All Risk Groups) Meta-analysis of PCa Specific Mortality



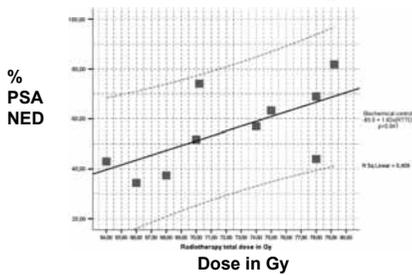
Viani, G. et al. JROBP V74(5):1405-1418, 2009

Regression Analysis All Subgroups



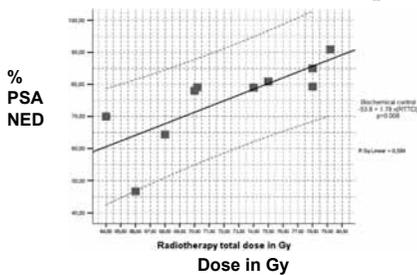
Viani, G. et al. JROBP V74(5):1405-1418, 2009

Meta-regression Analysis High-Risk Group



Viani, et al. JROBP V74(5):1405-1418, 2009

Meta-regression Analysis Intermediate-Risk Group



Viani, G. et al. JROBP V74(5):1405-1418, 2009

Hypofractionation 3 Year Results

	Control	Hypofractionated
PSA nadir <0.5	94%	100%
FBF	79%	87%
Late G2 GI toxicity	17%	16%
Late G2 GU toxicity	11%	14%

Arcangeli et al, IJROBP 75(3):S79, October 2009

Stereotactic Body Radiation Therapy SBRT for Prostate Cancer

- Considered **Investigational** in 2009
 - ASTRO SBRT Task Force
 - Noridian (Medicare) payment policy
 - ✓Varies by locale

Stereotactic Body Radiation Therapy SBRT

- Highly precise, and tight conformality
- Ablative doses
- ≤ 5 Fractions
- Image guidance / tracking
- Increased dose rate
- 725cGy x 5
- 900cGy x 4

SBRT Prostate Early “Phase II” Results

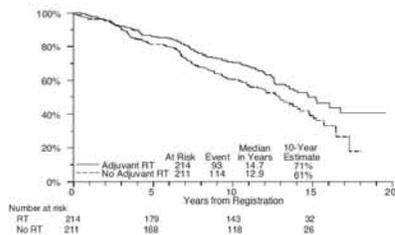
- 44 patients with 3 year bNED 78%
 - ✓Choi et al, IJROBP 69(3):s375 2007
- 40 patients with 4 year bNED 70%
 - ✓Madsen et al, IJROBP 67(4):1099-1105, 2007
- 10 patients with decreasing PSA at 4 months
 - ✓Fuller et al, IJROBP 69(3):s358, 2007
- 22 patients with low toxicity (18 f/u> 1 month)
 - ✓Mantz et al, IJROBP 69(3): s334, 2007
- 23 patients with 9% acute grade ≥2 toxicity
 - ✓Pawlicki et al, IJROBP Front Rad Ther Onc, 40:395-406, 2007

Phase III Trials: Adjuvant RT after RRP

	EORTC 22911		SWOG 8794		ARO 9402	
	RT	Observation	RT	Observation	RT	Observation
Eligibility	PSA < 10 with PT3a, PT3b, or positive surgical margin		PT3b, margin status, Prior hormone therapy		PT3b with undetectable postoperative PSA	
Standardization factors	Institution, PSA, PT3b, margin status				PT stage, margin status, Gleason score, Prior hormone therapy	
Number	302	303	214	211	108	133
Age (median)	65	65	64.1	65.8	N/A	N/A
Pre-op PSA (Median)	12.3	12.4	< 10 31% ≥ 10 49%	< 10 39% ≥ 10 47%	N/A	N/A
Post-op PSA (≤ 2)	89.8%	87.5%	45%	48%	100%	100%
Median follow-up	5 yrs	5 yrs	10.2 yrs	10 yrs	3.3 yrs	3.2 yrs
PSA free survival	74% at 5 years	52.8% at 5 years	71% at 5 yrs 52% at 10 yrs	44% at 5 yrs 26% at 10 yrs	81% at 4 years	68% at 4 years
CRP free survival	85% at 5 yrs	77.5% at 5 yrs	84% at 5 yrs 69% at 10 yrs	69% at 5 yrs 49% at 10 yrs	N/A	N/A
Metastasis-free survival	93.9% at 5 years	93.9% at 5 years	89% at 5 yrs 71% at 10 yrs	84% at 5 yrs 62% at 10 yrs	N/A	N/A
Freedom from ADT	N/A	N/A	93% at 5 yrs	93% at 5 yrs	N/A	N/A
Overall survival	92.3% at 5 yrs	93.1% at 5 yrs	90% at 5 yrs 74% at 10 yrs	89% at 5 yrs 66% at 10 yrs	N/A	N/A

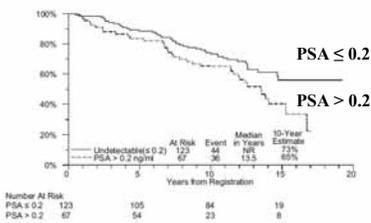
Bolla, M. et al. J. Clin. Oncol. 2002; 20: 1567-1575.
Pacholke, H et al, J. Urology, 2004, 06, 020: 982-986

SWOG 8794 Update Metastasis-free Survival



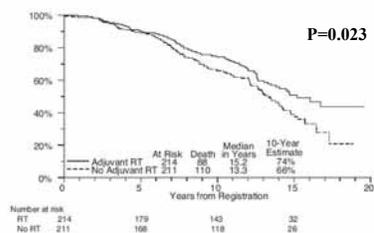
Thompson, I. et al. The Journal of Urology. 2009. V 181: 956-962

Adjuvant Radiotherapy Metastasis-free Survival Post Operative PSA



Thompson, I. et al. The Journal of Urology. 2009. V 181: 956-962

SWOG 8794 Overall Survival



Thompson, I. et al. The Journal of Urology. 2009. V 181: 956-962

18th Annual

PERSPECTIVES IN UROLOGY
POINT COUNTERPOINT 2009

Saturday, November 7, 2009

Ballroom E-F

The Scottsdale Plaza

Scottsdale, Arizona



Agenda	Saturday, November 7	Page
	7:15 – 8:00 am Continental Breakfast in Exhibit Hall	
	8:00 – 8:20 am Chemotherapy for Urological Cancers ~ Matthew Rettig, MD	17.1
	8:20 – 8:25 am Questions & Answers	
Prostate Conditions		
	8:25 – 8:55 am Increasing Awareness, Diagnosis, and Treatment of BPH, LUTS, and EP ~ E. David Crawford, MD	18.1
	8:55 – 9:25 am Point-Counterpoint Are We Ignoring Level One Evidence by Not Prescribing Appropriate Medical Therapy? ~ E. David Crawford, MD Alternative Medicine Should Be the Choice ~ Mark A. Moyad, MD, MPH	19.1
	9:25 – 9:35 am Questions & Answers	
Hypogonadism		
	9:35 – 10:05 am Increasing Awareness, Diagnosis, and Treatment of Hypogonadism ~ Jacob Rajfer, MD	20.1
	10:05 – 10:35 am Point-Counterpoint: Late Onset Hypogonadism (LOH) We are Under-diagnosing and Treating Men with LOH ~ Jacob Rajfer, MD LOH is a Non-existent Disease ~ Robert E. Donohue, MD	21.1 21.1 21.8
	10:35 – 10:45 am Questions & Answers	
	10:45 – 10:55 am Break in Exhibit Hall	
Complementary Alternative Medicine		
	10:55 – 11:55 am Fad Diets and Dietary Supplements for Urology Patients: What Works and What's Worthless ~ Mark A. Moyad, MD, MPH	22.1
	11:55 – 12:10 pm Pills and Tests: What Should I (the urologist) Be Taking and Getting? ~ Mark A. Moyad, MD, MPH	23.1
	12:10 – 12:30 pm Point-Counterpoint: Why Every Man Should Be Offered Chemoprevention for Prostate Cancer ~ E. David Crawford, MD Chemoprevention Is Not for Every Man ~ Mark A. Moyad, MD, MPH	24.1 24.1 24.12
	12:30 – 12:45 pm Questions & Answers	
	12:45 pm Meeting Adjourns	

Testicular Cancer

- Adjuvant chemotherapy for stage I and II markedly reduces recurrence risk, but does not affect overall survival because salvage therapy of patients managed by observation is effective.
- Metastatic disease: chemo is curative.
 - Good risk: 90% cure.
 - Intermediate risk: 70% cure.
 - Poor risk: 50% cure.

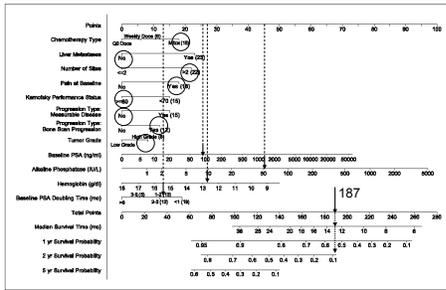
Testicular germ cell tumors risk stratification system
Seminomas
Good risk
All of the following:
Any primary site
No nonpulmonary visceral metastases
Normal serum AFP
Intermediate risk
All of the following:
Any primary site
Nonpulmonary visceral metastases present
Normal serum AFP

Non-seminomatous germ cell tumors
Good risk
All of the following:
Testicular or retroperitoneal primary tumors
No nonpulmonary visceral metastases
Serum AFP < 1000 ng/mL, beta-hCG < 5000 mIU/mL, and LDH < 1.5 times upper limit of normal
Intermediate risk
All of the following:
Testicular or retroperitoneal primary tumors
No nonpulmonary visceral metastases
Intermediate level of any of the following:
AFP 1000 to 10,000 ng/mL,
beta-hCG 5000 to 50,000 mIU/mL, or
LDH 1.5 to 10 times upper limit of normal
Poor risk
Any of the following:
Mediastinal primary, or
Nonpulmonary visceral metastases, or
Serum AFP > 10,000 ng/mL, or
Serum beta-hCG > 50,000 mIU/mL, or
LDH more than 10 times upper limit of normal

Prostate Cancer

- No established role for chemotherapy in the neoadjuvant/adjuvant setting.
- Metastatic disease:
 - Docetaxel improves OS
 - Median OS improved 2-3 mos.
 - Reduces risk of death by ~ 25%.
 - Mitoxantrone
 - No affect on survival.
 - Improves QOL of patients with bone pain.

CRPC Nomogram



Clin Cancer Res 2007;13(21) November 1, 2007 6396

Case 2 (continued)

Date	Case History	PSA
8/2007	• Chemotherapy (docetaxel) initiated.	95.1
9/2007	• Bone pain resolved. • No significant chemotherapy-related toxicity.	31.5
10/2007		8.6
11/2007		4.6
12/2007		1.6
1/2008	• Bone scan: no evidence of progression.	0.8
5/2008	• Chemotherapy completed (10 of 10 planned cycles).	0.5

Survival by PSA Decline from TAX 327

	Median Survival (months)
PSA normalization (n=115)	33.3
≥ 90% PSA decline (n=106)	26.6
≥ 50% PSA decline (n=460)	22.4
≥ 30% PSA decline (n=591)	21.6
Any PSA decline (n=730)	20.7
No PSA decline (n=259)	11.7

Armstrong, AJ et al. J Clin Oncol 2007; 25 (18S Part 1 of II):237S (abstract and oral presentation 5009).

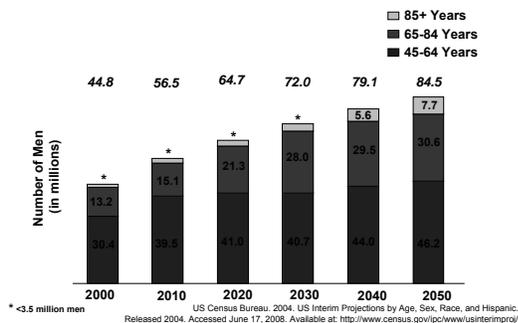
Case 2

Date	Case History	PSA
?	Progression	↑↑
	No established therapy for docetaxel-resistant CRPC.	
	↓	
	Clinical trials.	



The Burden of EP in the United States (US)

Population Growth of Men At-Risk for EP



Prevalence of EP

- EP affects 50% of men over age 50 and 90% of men over the age of 80^{1,2}
- In a recent survey of men over age 50 in the United States³
 - 25% reported moderate to severe symptoms of EP
 - 55% of those consulting a doctor were diagnosed with EP

EP is significantly underreported and underdiagnosed^{1,3}

1. AUA guideline on management of benign prostatic hyperplasia (2003). *J Urol*. 2003; 170:530-47.
2. Berry S. *J Urol*. 1984;132:474-79.
3. Roehrborn C, et al. *Prostate Cancer and Prostatic Dis*. 2006;9:30-4.

Economic Burden of EP

- In 2000, the direct cost of EP reached \$1.1 billion in the US alone (not including outpatient pharmaceuticals)
 - Medical services at hospital inpatient and outpatient settings
 - Emergency departments and physician office visits
- In a 2-year period, outpatient prescription drugs for EP were estimated to cost \$194 million a year*



*from 1996-1998

Wei J, et al. *J Urol*. 2005;173:1256-61.

Natural History of Untreated EP Progression

Male patient, age 55 years:
symptomatic EP, PSA = 1.5 ng/mL, negative for prostate cancer



55 years old PV: 30 mL PSA = 1.5 ng/mL
 60 years old PV: >40 mL
 65 years old PV: >50 mL
 70 years old PV: >61 mL

Disease progression can increase the risk of AUR and prostate-related surgery^{1,2}

Figure based on Roehrborn C, et al. *J Urol*. 2000;163:13-20.
 1. Kaplan S. *Weill Medical College of Cornell University Reports on Men's Urologic Health*. 2006;1(1):1-8.
 2. Roehrborn C, et al. In: *Campbell's Urology*, 8th ed. Saunders; 2002:1297-336.

Overview and Outcomes of AUR

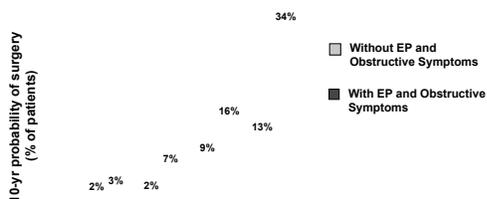
- Common urological emergency^{1,2}
 - Greater resistance to urine flow
 - Bladder over-distention
 - Can have neuropathic causes
- Outcomes of AUR^{2,4}
 - Inability to urinate with increasing pain
 - Visits to the emergency room
 - Emergency catheterization
 - Urinary tract infection
 - Continuing failure to spontaneously void
 - Surgery



AUR is a painful, time-consuming, and feared condition that often results in emergency catheterization¹

1. Fitzpatrick J, et al. *BJU Int*. 2006;97 (Suppl 2):16-20.
 2. Choong S, et al. *BJU Int*. 2000;85:198-201.
 3. Roehrborn C, et al. In: *Campbell's Urology*, 8th ed. Saunders; 2002:1297-336.
 4. Roehrborn C, et al. *Rev Urol*. 2001;3:107-02.

Risk of EP-Related Surgery in Men with EP



Baltimore Longitudinal Study of Aging
 N = 1057

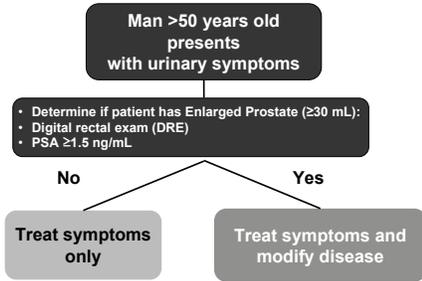
Arrighi H, et al. *Urology*. 1991;38 (suppl):4-8.

Summary of Progressive Disease

- Age, severity of urinary symptoms, PSA and prostate volume are predictors of clinical progression of EP
- Disease progression increases the risk of AUR and EP-related surgery
 - Men 70 to 79 years of age are up to 3 times more likely to have AUR
 - Men with a baseline prostate volume >30 mL are at greater risk for AUR, as are men with greater PSA and symptom severity at baseline
- AUR is a painful condition that results in emergency catheterization
- As men age, their risk for developing EP, and progressing to AUR and prostate-related surgery increases

Diagnosing EP

A Practical Algorithm for the Diagnosis and Management of EP



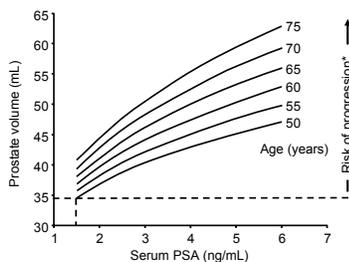
Adapted from Figure 3, entitled "Practical Algorithm for the treatment of EP in primary care" in Kaplan S. *Weill Medical College of Cornell University Reports on Men's Urologic Health*. 2006;1(1):1-8.

Symptom Assessments for EP

- American Urological Association Symptom Index (AUA-SI)¹
 - 7 item, patient-rated questionnaire to evaluate symptom severity
 - Scaled 0-5, with a maximum score of 35:
 - ≤7 mild symptoms
 - 8-19 moderate symptoms
 - 20-35 severe symptoms
- International Prostate Symptom Score (IPSS)²
 - Same 7 questions as the AUA SI, with the addition of a disease-specific quality of life question

1. Barry M, et al. *J Urol*. 1992;148:1558.
2. AUA guideline on management of benign prostatic hyperplasia (2003). *J Urol*. 2003;170:530-47.

Serum PSA ≥ 1.5 ng/mL Can Predict Prostate Enlargement and Risk of Progression



PSA = prostate-specific antigen
Adapted from Roehrborn CG et al. *Urology*. 1999;53:581-589.
*Crawford ED et al. *J Urol*. 2006;175:1422-1427.

Treatment Options: AVODART - A 5AR Inhibitor

- Dutasteride (AVODART)
 - Dual Type I and II inhibitor
 - Dual 5ARI blocks the conversion of testosterone to DHT by competitively inhibiting both Type I and Type II pathways



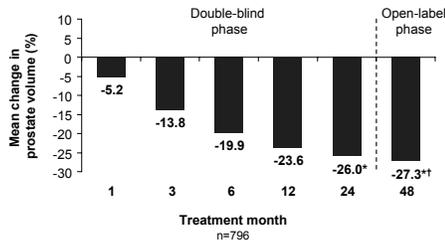
The clinical benefit of more complete DHT suppression has not been established.

Prescribing Information for AVODART, 2008.

AVODART®
(dutasteride) - Phase III
Data:
Reducing Size,
Symptoms, and Risk

AVODART Reduces Size

Pooled Results from Three Randomized, Placebo-controlled, 2-year Clinical Studies Followed by 2-year Open-label Extension Phase of AVODART 0.5 mg daily

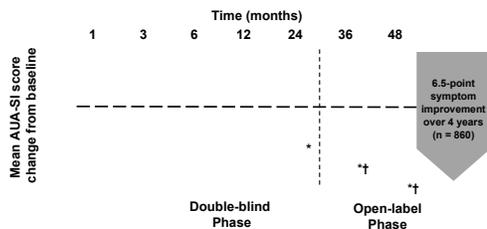


*P < 0.001 between treatment groups; †p < 0.07 vs month 24

Debruyne F, et al. Eur Urol. 2004;46:488-94.

AVODART Reduces Symptoms

Pooled Results from Three Randomized, Placebo-controlled, 2-year Clinical Studies with 2-year Open-label Extension Phase with AVODART 0.5 mg daily



*P < 0.001 between treatment groups
†P < 0.001 vs month 24

Debruyne F, et al. Eur Urol. 2004;46:488-94.

CombAT Major Entry Criteria

Age	≥50 years
EP diagnosis	Diagnosis by history and DRE
IPSS	≥12 (moderate-to-severe symptoms)
Prostate volume	≥30 cc by TRUS
Serum PSA	1.5 – 10.0 ng/mL
Q _{max}	>5 and ≤15 mL/sec (moderate-to-severe impairment)
Minimum voided volume	≥125 mL (based on two voids at screening)

DRE = digital rectal exam; TRUS = transrectal ultrasound; Qmax = maximum urinary flow.
Roehrborn C, et al. J Urol. 2008;179:616-21.
 Siami P, et al. Contemp Clin Trials. 2007;28:770-9.

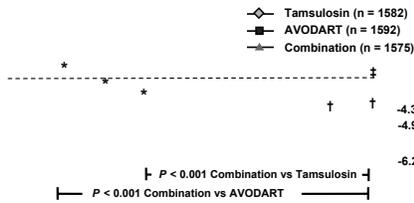
CombAT Patient Characteristics at Baseline

	All Patients N=4844	Combination* n=1610	AVODART n=1623	Tamsulosin n=1611
Mean age (years)	66.1	66.0	66.0	66.2
Caucasian ethnicity (%)	88	88	88	87
Mean IPSS score (points)	16.4	16.6	16.4	16.4
Mean prostate volume (cc)	55.0	54.7	54.6	55.8
Mean Qmax (mL/sec)	10.7	10.9	10.6	10.7
Mean serum PSA (ng/mL)	4.0	4.0	3.9	4.0
Previous 5ARI use (%)	11	11	12	11
Previous alpha blocker use (%)	50	50	51	51

*AVODART plus tamsulosin Roehrborn C, et al. J Urol. 2008;179:616-21.

CombAT: Reduction in Urinary Symptoms

IPSS - Adjusted Mean Change From Baseline (LOCF)¹

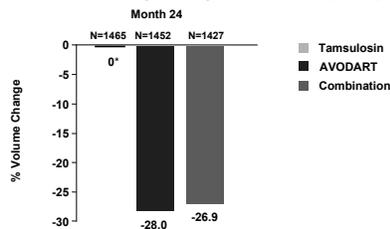


LOCF = last observation carried forward
 *P < 0.001 in post hoc analysis for tamsulosin vs. AVODART as monotherapy²
 †P < 0.05 in post hoc analysis for AVODART vs. tamsulosin as monotherapy²
 ‡Patients generally perceive a 3-point change in the AUA-SI score as meaningful³

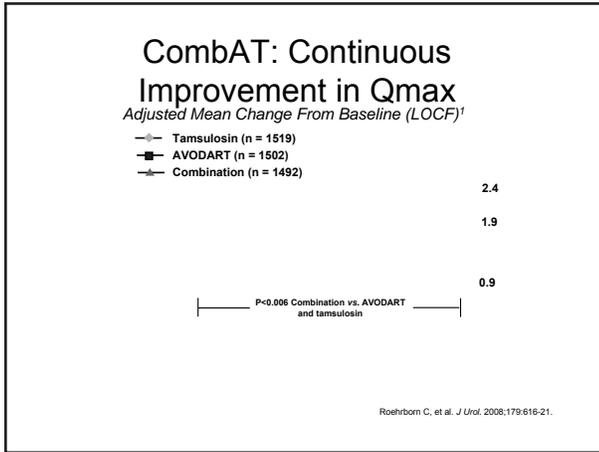
1. Roehrborn C, et al. J Urol. 2008;179:616-21.
 2. Data on file, GlaxoSmithKline.
 3. Barry J, et al. J Urol. 1995;154:1770-74.

CombAT: Reduction in Total PV

Adjusted Mean Percentage Change from Baseline (LOCF)



*P < 0.001 Combination vs. tamsulosin Roehrborn C, et al. J Urol. 2008;179:616-21.



Most Common Drug-related Adverse Events* - CombAT

	Combination n = 1610	Tamsulosin n = 1611	AVODART n = 1623
Erectile dysfunction	7.4%	3.8%	6.0%
Retrograde ejaculation	4.2%	1.1%	0.6%
Libido decreased	3.4%	1.7%	2.8%
Ejaculation failure	2.4%	0.8%	0.5%
Semen volume decreased	1.8%	0.8%	0.3%
Loss of libido	1.7%	0.9%	1.3%
Dizziness	1.6%	1.7%	0.7%
Breast enlargement	1.4%	0.8%	1.8%
Nipple pain	1.2%	0.3%	0.6%
Breast tenderness	1.0%	0.3%	1.0%
Discontinued due to drug-related AEs	5%	3%	3%

*Drug-related AEs occurring in ≥1% of subjects within any treatment group.
Roehrborn C, et al. J Urol. 2008;179:616-21.

CombAT Summary

- Clinical trial in >4,800 men with moderate to severe lower urinary tract symptoms and enlarged prostate
- The CombAT study demonstrated a benefit for combination therapy over monotherapies in the first 12 months of therapy.
- Significant improvement in urinary symptoms and prostate size with combination therapy at 24 months

2.4 mL/sec

IPSS Qmax PV

6.2 points 26.9%

Roehrborn C, et al. J Urol. 2008;179:616-21.

PSA in Relation to the Prostate

- PSA production and use in EP¹
 - DHT stimulates the growth of glandular epithelial cells in the prostate, which produce high levels of PSA¹
 - Predictive of prostate volume in men with EP²
- PSA is prostate-specific, not cancer-specific
- Prostate cancer cells also produce PSA³
- PSA ≥1.5 ng/mL suggests EP⁴

1. Schalken J. BJU Int. 2004;93 (suppl 1):5-9.
2. Roehrborn C, et al. Urology. 1999;53:581-9.
3. Balk S, et al. J Clin Oncol. 2003;21:383-91.
4. Kaplan SA. Weill Medical College of Cornell University Reports on Men's Urologic Health. 2006;1(1):1-8.





Increasing Awareness, Diagnosis, and Treatment of Hypogonadism

~ Jacob Rajfer, MD

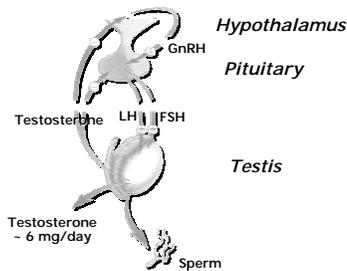
HYPOGONADISM

DEFINITION: PRODUCTION OF SEX HORMONES AND GERM CELLS IS INADEQUATE (ENDOCRINE SOCIETY)

DEFECT OF THE REPRODUCTIVE SYSTEM THAT RESULTS IN LACK OF FUNCTION OF THE GONADS (Wikipedia)

REDUCTION IN TESTICULAR FUNCTION
(www.nature.com/nrg/journal/v2/n4/glossary/nrg0401_245a_glossary.html)

FUNCTION OF TESTIS



Adapted from Bagatell CJ, Bremner WJ. *N Engl J Med*. 1996;334:707-714.

FUNCTION OF TESTIS

1. SPERMATOGENESIS
 - A. BEGINS AT PUBERTY
 - B. CONTRIBUTES TO ABOUT 80% OF TESTIS VOLUME
 - C. DECREASES WITH AGING (FSH may increase)
2. TESTOSTERONE PRODUCTION
 - A. BEGINS TO INCREASE AT PUBERTY
 - B. PRODUCES ABOUT 6 mg of T per day adult
 - B. DECREASES WITH AGING (LH may increase)

Prevalence of Study-Defined Testosterone Deficiency in Older Men

Study	Ages	N	Serum total testosterone (mg/dL)	Prevalence
Lungimayr	50-87	817	<300	11.4%
Tenover	20-100	300	<317	22% (80-100y) 36% (80-100y)
Tenover (unpublished)	60-83	379	<350 <300 <250	36% 19% 8%
Morley (unpublished)	75-101	77	<245	33%

What is the most common cause of hypogonadism in men > 50 y age

- HIV
- Obesity
- Aging
- Hyperprolactinemia
- Medications

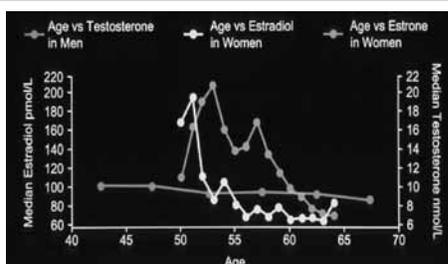
CAUSES OF HYPOGONADISM

- > PRIMARY TESTICULAR FAILURE
- > HYPOGONADOTROPIC HYPOGONADISM (KALLMANN'S SYNDROME, PITUITARY ADENOMA)
- > TRAUMA
- > IDIOPATHIC
- > OBESITY
- > SEVERE SYSTEMIC ILLNESS (INCLUDING HIV)
- > MEDICATIONS
- > CHANGES IN GnRH, PROLACTIN, CORTISOL, AND THYROID HORMONES
- > NORMAL AGING

GnRH=gonadotropin-releasing hormone

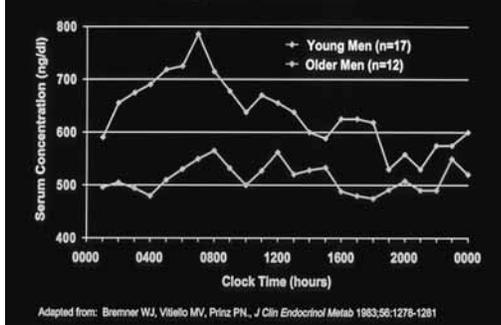
Winters S.J. *Arch Fam Med.* 1999;8:257-263.
Tenover J.L. *Endocrinol Metab Clin North Am.* 1998;27:969-987.

T in Men and E2 in Women During the Middle Years

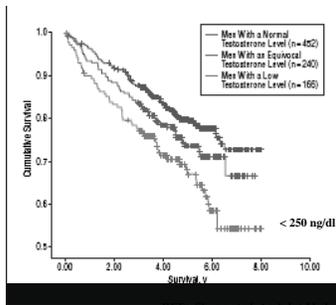


Massachusetts Women's Health Study (1981-1996) and Massachusetts Male Aging Study (1986-1989)

Hourly Serum Testosterone Profiles in Normal Young and Older Men



LOW T & MORTALITY



SERUM T & MORTALITY

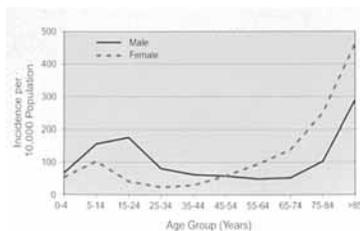
n = 794, AGE X = 73.6y, 11.8 y f/u, 538 deaths
Rancho Bernardo, CA, pop based study

sT < 241 ng/dl had a > 40% greater mortality if sT > 370 ng/dl
It predicted increased CV and Respiratory but not cancer death

REF: Laughlin et al: JCEM 93:68-75, 2008

Long-term Consequences of Andropause

Annual Fracture Incidence



Donaldson LJ, et al. J Epidemiol Community Health. 1990;44:241-245.

DIAGNOSTIC TESTOSTERONE TESTING

(IF T LEVEL IS OR SUSPECTED TO BE LOW)

Additional Tests:

- **LH and FSH**
 - To ascertain whether cause is primary or secondary
- **Serum prolactin**
 - High prolactin levels may suggest presence of pituitary tumor

BENEFITS OF T – TX OF HYPOGONADISM (LOW T)

- Preserve or improve bone mass
- Increase muscle mass, rearrange fat
- Increase strength, stamina and physical function
- Improve libido and mood, HRQoL
- **Possibly** decrease cardiovascular risk

(MOST DATA ARE IN YOUNG MEN)

REF: Snyder et al, 1999, 2001; Sih et al, 1997; Kenny et al., 2001, 2002

ANDROGEN R_x OLDER MEN

1. BMD -spine  8% over 3 yrs
-hip  3% over 3 yrs

2. Lean Body Mass  8% over 3 yrs

3. Body Fat  15% over 3 yrs

REF: Adapted from Tenover. *Int J Androl.* 1999;22:300.

How long after starting TRT will a hypogonadal symptom start to improve

- 3 months
- 6 months
- 9 months
- 12 months.

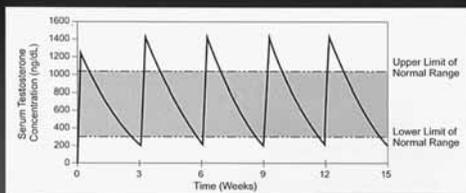
CONTRAINDICATIONS OF TESTOSTERONE REPLACEMENT THERAPY IN MEN

- KNOWN OR SUSPECTED PROSTATE CANCER
- MALE BREAST CANCER
- KNOWN OR SUSPECTED SENSITIVITY TO INGREDIENTS USED IN TESTOSTERONE THERAPY SYSTEMS
- ELEVATED HEMOCRIT

ANDROGEN PREPARATIONS

- ORAL
- BUCCAL
- PARENTERAL
- TRANSDERMAL PATCH
- TRANSDERMAL GEL

Testosterone Enanthate 250 mg Administered IM Every 3 Weeks



Behre HM et al. In: Testosterone: Action, Deficiency, Substitution. Berlin, Germany: Springer-Verlag; 1996:329-348

ANDROGEN PREPARATIONS

TRANSDERMAL PATCH

- **Testoderm (scrotal)** - Delivers 4-6 mg testosterone daily
- **Testoderm TTS (arm/torso/thigh skin)**
Delivers 5 mg testosterone daily
- **Androderm (arm/torso/thigh skin)**
Delivers 2.5-5 mg testosterone daily

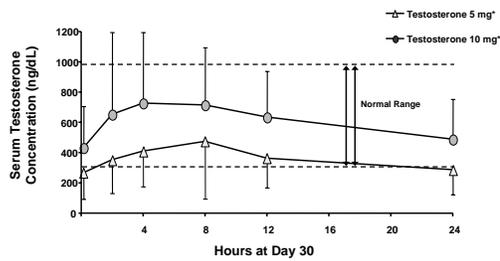
ANDROGEN PREPARATIONS

TRANSDERMAL GEL

- ANDROGEL OR TESTIM 1%
(ARM/TORSO SKIN)
5 G/DAY

Testosterone 1% Gel

Testosterone Concentration (Day 30)



Steidle C, et al. *J Clin Endocrinol Metab.* 2003;88:2673.

*Approx. delivered testosterone dose

CLOMIPHENE CITRATE

WORKS WHEN LH IS LOW

EFFECTIVE AS A Q O D PILL (25 – 50 mg)

MINIMAL SIDE EFFECTS

DOES NOT SUPPRESS SPERMATOGENESIS

CHECK SERUM T IN 2-3 WEEKS

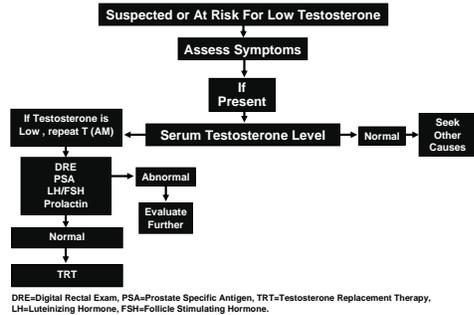
Rajfer J; Personal experience

TRT : NOT RECOMMENDED

hCG, DHEA, DHEAS, DHT

http://www.uroweb.org/fileadmin/user_upload/Guidelines/14%20Hypogonadism.pdf

Diagnosis and Treatment Algorithm for Testosterone Deficiency



Patient Monitoring with Testosterone Replacement Therapy

Baseline, Pre-therapy:	Testosterone levels Hgb and Hct PSA level DRE IPSS
Day 30:	Testosterone levels
Day 90:	Hgb and Hct PSA level DRE IPSS
Repeat Day 90 Measures:	Month 9 and every 6-12 months thereafter

Hgb=Hemoglobin, Hct=Hematocrit, PSA=Prostate-Specific Antigen, DRE=Digital Rectal Exam, IPSS=International Prostate Symptom Score.

LOH

LOH: underdx. & undertx

LOH is a syndrome characterized primarily by:

- (1) The easily recognized features of **diminished sexual desire (libido) and erectile quality** and frequency, particularly nocturnal erections.
- (2) Changes in **mood** with concomitant **decreases in intellectual activity, cognitive functions, spatial orientation ability, fatigue, depressed mood and irritability.**
- (3) **Sleep disturbances.**
- (4) **Decrease in lean body mass** with associated diminution in muscle volume and strength.
- (5) **Increase in visceral fat.**
- (6) **Decrease in body hair and skin alterations.**
- (7) **Decreased bone mineral density** resulting in **osteopenia, osteoporosis** and increased risk of bone fractures.

Ref: ISA*, ISSAM**, and EAU recommendations
http://www.uroweb.org/fileadmin/user_upload/Guidelines/14%20Hypogonadism.pdf

**A Ten-Year Safety Study of the Oral
Androgen Testosterone Undecanoate**

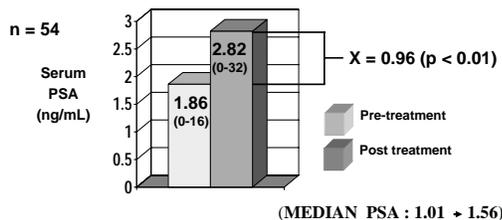
N = 33/35 men followed for 10-year minimum; 8/33 >50 y age

- No gynecomastia
- No liver abnormalities
- No prostate abnormalities
- 2/8 > 50y age showed slight decrease in urine flow
- Levels of T remained stable
 - No liver enzyme activation

REF: Gooren. J Androl. 1994; 15: 212-215.

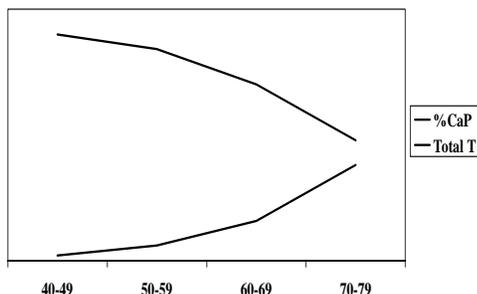
**Effect of Testosterone Supplementation
on Serum PSA**

Dose = 200-300 mg, Q2-4wks Mean F/U = 30.2 mos
6 biopsies (11%), 1 PCa Mean Age = 60.4 yrs



Gerstenbluth RE, et al. J Androl. 2002; 23:922-926.

CaP Prevalence Increases as T Levels Decline



**Case series: reports of clinically apparent
tumor diagnosed in men while on TRT**

	TRT (months)	Patients	Prostate Cancer
Hajjar, 1997	24	45	-
Sih, 1997	12	17	-
Dobs, 1999	24	66	3
Snyder, 1999	36	54	1
Snyder, 2000	36	18	0
Wang, 2000	6	76	0
Kenny, 2001	12	34	0
Wang, 2004	36	123	3
Total		433	7 (1.6%)

Effects of Exogenous Testosterone on PSA Levels

166 hypogonadal men
3 years of 1% testosterone gel
mean PSA increase of 0.37 ng/ml
3 men diagnosed with cancer (1.8%)

NOTE: THE PSA RISE OCCURS IN THE FIRST 6 MONTHS OF TREATMENT AND REMAINS STABLE THEREAFTER

Swerdlloff et al. Aging Male 2003;6:207

Is the incidence in Hypogonadal men different?

- 345 “hypogonadal” men (<300 ng/dl)
 - PSA ≤ 4: 15% positive biopsy
 - Markedly suppressed T level: 20% positive biopsy
 - Low T and PSA≥2.0: 30% positive biopsy
- Is this any different than the “baseline” established in PCPT?

Rhoden & Morgentaler. JUrol,2003

High Levels of Circulating Testosterone Are Not Associated With Increased Prostate Cancer Risk: A Pooled Prospective Study

- N = 708 men (Finland, Norway, Sweden) with prostate cancer
- N = 2,242 men without prostate cancer
- Mean lag time from blood draw to diagnosis was 14 years.
- Decrease in risk of prostate cancer for increasing levels of:

Total Testosterone	OR	0.80
SHBG	OR	0.76
Free Testosterone	OR	0.82

Statlin, et al. Int J Cancer 2004; 108: 418-424

Testosterone Replacement in Hypogonadal Men With Prostatic Intraepithelial Neoplasia (PIN)

75 hypogonadal men (TT <300ng/dL) after 12 mo TRT

	<u>With PIN</u>		<u>Without PIN</u>
	PSA		
Before TRT	1.49		1.53
After TRT	1.82		1.78
	Biopsy for ↑ PSA		
Bx +	1		0
Bx -	2		4

Overall, one cancer in 75 men (1.3%). No sig difference with PIN

Rhoden et al. J Urol. 2003; 170: 2348-2351

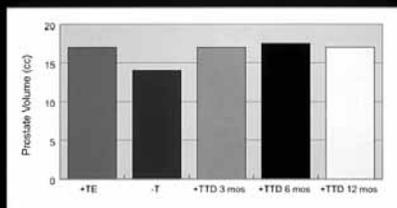
EFFECTS OF TRT ON PROSTATE

- PBO (n = 19) vs T (n = 21: TE 150 mg/2 wk) x 6 mo., TRUS + Bx @ baseline and 6 mo.
- T: 282 → 640 ng/dl (@ 6 mo); no diff PBO
- No increased CA with T tx
- No difference in pT or pDHT with TRT
- No change in PSA, genes for prostate growth

44-78y

REF: Marks et al., JAMA 2006;296:2351-61

Mean Prostate Volume +/- Treatment With Testosterone Enanthate (TE) or Transdermal Patch (TTD)



TRT and PSA

T trials have *inconsistently* shown a rise in PSA- the mean increase has been 0.3-0.43 ng/mL.

Study	Duration mo	Increase in PSA	
		Placebo	Testosterone number/t
Hajjar et al. (1997) ¹⁰	24	-	-
Sih et al. (1997) ⁹	12	0/15	0/17
Dobs et al. (1999) ¹¹	24	-	3/33
		-	0/33
Snyder et al. (1999) ⁸	36	7/54	13/54
Snyder et al. (2000) ⁶	36	-	-
Wang et al. (2000) ²⁰	6	-	0/76
		-	1/73
		-	4/78
Kenny et al. (2001) ⁷	12	3/33	8/34

Duval reported no significant PSA changes in 50 men treated for over 5 years. (Aging Male, 2001)

TRT and BPH?

- Results of studies are conflicting or insignificant
- No well-designed study yet done
- What we have so far:
7 studies of 3-36 months' duration conclude:
 - Prostate volume No change
 - IPSS No change
 - Average urine stream No change

Gettman M, et al. AUA Update Series 2001

• *Despite decades of research there is no compelling evidence that T has a causative role in prostate cancer, that men with higher T levels are at greater risk of prostate cancer or that treating hypogonadal men with androgens increases the risk of converting the biological behaviour of prostate cancer*

T & SLEEP APNEA

THERE IS LACK OF EVIDENCE TO SUPPORT ANY LINK BETWEEN OSA AND TRT

REF: Hanafy HM J Sex Med 4:1241-6, 2007.

ANDROGENS AND CV SYSTEM

Age = 51 y, n = 25 in each group; case control study for plasma total T; no TRT.

- **Lipid metabolism**
- **Insulin sensitivity**
- **Coagulation factors**
- **Vascular responsiveness**

DATA ARE INCONCLUSIVE AT THIS TIME

Simon D. JCEM 82:682-685, 1997

Androgens And Coronary Artery Disease

- 430 references
- "Cross-sectional data have suggested coronary heart disease can be associated with low T in men"
 - But no independent association in prospective studies
- "Based on current evidence, the therapeutic use of T in men need not be restricted by concerns regarding cardiovascular side effects"
- Hypoandrogenemia in men are associated with:
 - Visceral obesity
 - Insulin resistance
 - Low HDL cholesterol
 - Elevated: Triglycerides, LDL cholesterol

Wu and von Eckardstein. Endocrine Reviews. 2003; 24: 183-217

Effects of Testosterone on Serum Lipid Profile in Middle Aged-Men: A Meta-Analysis

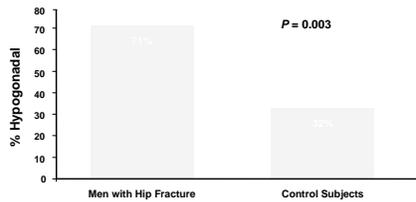
Hypoandrogenemia in men are associated with:
 Visceral obesity
 Insulin resistance
 Low HDL cholesterol
 Elevated: Triglycerides, LDL cholesterol

- Review of randomized- controlled trials (#29) OF TRT
- n = 1,083
- Mean age 64.5 yrs
- **Total and LDL chol ↓**
- **HDL Chol mixed:**
 - Small ↓, esp. in men with higher testosterone
 - Do not give supraphysiological levels

Isidori, et al. Clinical Endocrinology 2005; 63: 280-293

Hip Fractures in Aging Males

Increased Hypogonadism With Hip Fractures



Jackson JA et al. Am J Med Sci. 1992;304(1):4-8.

**Elderly Population >65
% of the Total**

Continents	1950	2000	2025	2050
Europe	8.2	14.6	20.2	25.8
North America	8.2	12.4	18.5	21.5
Latin America	3.7	5.4	9.6	16.7
Asia	4.1	5.8	9.6	15.9
World	5.2	6.8	10.0	15.1

U.N. Data

Conclusions

Testosterone Therapy is Safe In:

- Benign prostate disease (BPH)
- Risk of prostate cancer
 - Men receiving testosterone therapy
 - Men with high normal levels of T
 - Men at higher risk for prostate cancer (PIN)
- Effect on lipids and cardiovascular disease

Low Testosterone May Be Unsafe For:

- Incidence of prostate cancer
- Prognosis of prostate cancer
- Prevention of cardiovascular disease
- Prevention of osteoporosis / fractures
- Overall longevity ?



Point-Counterpoint: Late Onset Hypogonadism (LOH)

We are Under-diagnosing and Treating Men with LOH
~ *Jacob Rajfer, MD*

LOH is a Non-existent Disease
~ *Robert E. Donohue, MD*

Late Onset Hypogonadism

LOH: underdx. & undertx

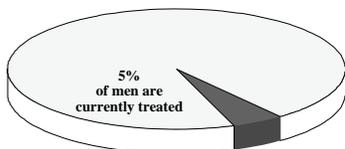
LOH is a syndrome characterized primarily by:

- (1) The easily recognized features of **diminished sexual desire (libido) and erectile quality** and frequency, particularly nocturnal erections.
- (2) Changes in **mood** with concomitant **decreases in intellectual activity, cognitive functions, spatial orientation ability, fatigue, depressed mood and irritability.**
- (3) **Sleep disturbances.**
- (4) **Decrease in lean body mass** with associated diminution in muscle volume and strength.
- (5) **Increase in visceral fat.**
- (6) **Decrease in body hair and skin alterations.**
- (7) **Decreased bone mineral density** resulting in **osteopenia, osteoporosis** and increased risk of bone fractures.

Ref: ISA*, ISSAM**, and EAU recommendations
http://www.uroweb.org/fileadmin/user_upload/Guidelines/14%20Hypogonadism.pdf

PREVALENCE OF HYPOGONADISM

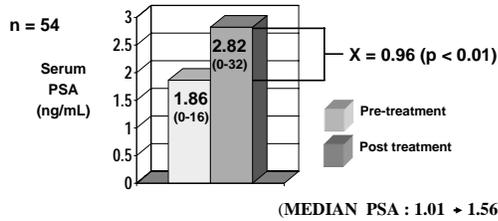
4 TO 5 MILLION MEN WITH HYPOGONADISM



US Food and Drug Administration Updates. Skin patch replaces testosterone. Available at:
http://www.fda.gov/fdac/departs/196_upd.html. Accessed January 19, 2004.

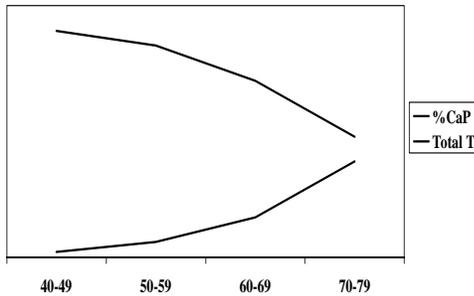
Effect of Testosterone Supplementation on Serum PSA

Dose = 200-300 mg, Q2-4wks Mean F/U = 30.2 mos
 6 biopsies (11%), 1 PCa Mean Age = 60.4 yrs



Gerstenbluth RE, et al. *J Androl.* 2002; 23:922-926.

CaP Prevalence Increases as T Levels Decline



Case series: reports of clinically apparent tumor diagnosed in men while on TRT

	TRT (months)	Patients	Prostate Cancer
Hajjar, 1997	24	45	-
Sih, 1997	12	17	-
Dobs, 1999	24	66	3
Snyder, 1999	36	54	1
Snyder, 2000	36	18	0
Wang, 2000	6	76	0
Kenny, 2001	12	34	0
Wang, 2004	36	123	3
Total		433	7 (1.6%)

Effects of Exogenous Testosterone on PSA Levels

166 hypogonadal men
 3 years of 1% testosterone gel
 mean PSA increase of 0.37 ng/ml
 3 men diagnosed with cancer (1.8%)

NOTE: THE PSA RISE OCCURS IN THE FIRST 6 MONTHS OF TREATMENT AND REMAINS STABLE THEREAFTER

Swerdlow et al. *Aging Male* 2003;6:207

Is the incidence in Hypogonadal men different?

- 345 “hypogonadal” men (<300 ng/dl)
 - PSA ≤ 4: 15% positive biopsy
 - Markedly suppressed T level: 20% positive biopsy
 - Low T and PSA≥2.0: 30% positive biopsy
- Is this any different than the “baseline” established in PCPT?

Rhoden & Morgentaler. JUrol,2003

High Levels of Circulating Testosterone Are Not Associated With Increased Prostate Cancer Risk: A Pooled Prospective Study

- N = 708 men (Finland, Norway, Sweden) with prostate cancer
- N = 2,242 men without prostate cancer
- Mean lag time from blood draw to diagnosis was 14 years.
- Decrease in risk of prostate cancer for increasing levels of:

Total Testosterone	OR	0.80
SHBG	OR	0.76
Free Testosterone	OR	0.82

Statlin, et al. Int J Cancer 2004; 108: 418-424

Testosterone Replacement in Hypogonadal Men With Prostatic Intraepithelial Neoplasia (PIN)

75 hypogonadal men (TT <300ng/dL) after 12 mo TRT

	<u>With PIN</u>		<u>Without PIN</u>
	PSA		
Before TRT	1.49		1.53
After TRT	1.82		1.78
	Biopsy for ↑ PSA		
Bx +	1		0
Bx -	2		4

Overall, one cancer in 75 men (1.3%). No sig difference with PIN

Rhoden et al. J Urol. 2003; 170: 2348-2351

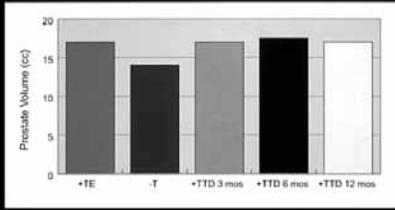
EFFECTS OF TRT ON PROSTATE

- PBO (n = 19) vs T (n = 21: TE 150 mg/2 wk) x 6 mo., TRUS + Bx @ baseline and 6 mo.
- T: 282 → 640 ng/dl (@ 6 mo); no diff PBO
- No increased CA with T tx
- No difference in pT or pDHT with TRT
- No change in PSA, genes for prostate growth

44-78y

REF: Marks et al., JAMA 2006;296:2351-61

Mean Prostate Volume +/- Treatment With Testosterone Enanthate (TE) or Transdermal Patch (TTD)



TRT and PSA

T trials have *inconsistently* shown a rise in PSA- the mean increase has been 0.3-0.43 ng/mL.

Study	Duration mo	Increase in PSA	
		Placebo	Testosterone
		number/t	number/t
Hajar et al. (1997) ¹⁰	24	—	—
Sih et al. (1997) ⁹	12	0/15	0/17
Dobs et al. (1999) ¹¹	24	—	1/33
		—	0/33
Snyder et al. (1999) ⁸	36	7/54	13/54
Snyder et al. (2000) ⁶	36	—	—
Wang et al. (2000) ²⁰	6	—	0/76
		—	1/73
		—	4/78
Kenny et al. (2001) ⁷	12	3/33	8/34

Duval reported no significant PSA changes in 50 men treated for over 5 years. (Aging Male, 2001)

TRT and BPH?

- Results of studies are conflicting or insignificant
- No well-designed study yet done
- What we have so far:
7 studies of 3–36 months' duration conclude:
 - Prostate volume No change
 - IPSS No change
 - Average urine stream No change

Gettman M, et al. AUA Update Series 2001

• *Despite decades of research there is no compelling evidence that T has a causative role in prostate cancer, that men with higher T levels are at greater risk of prostate cancer or that treating hypogonadal men with androgens increases the risk of converting the biological behaviour of prostate cancer*

Testosterone trials

adverse outcomes

Erythrocytosis

T treated men were four times as likely to experience a rise in hematocrit above 50%.

Testosterone trials

adverse outcomes

The frequency of cardiovascular events, sleep apnea or death did not differ significantly between groups.

Cardiovascular risk

30 trials; 1642 men

Low Testosterone

inconsequential changes in BP and glycemia; lipid profile shows

Cholesterol [-0.22],

HDL [-0.04],

LDL [0.06]

Trig [-0.27]

Cardiovascular risk

30 trials; 1642 men

Currently available evidence weakly supports the inference that T use in men is not associated with important cardiovascular effects. We need large, randomized, clinical trials of men at risk for CVD.

Haddad Mayo CI Pro 82: 29., 2007

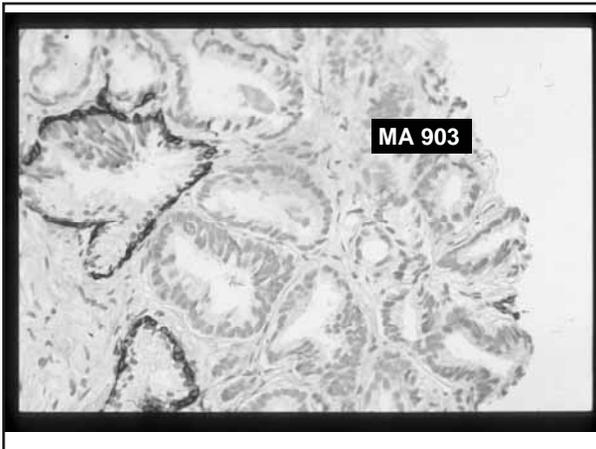
Thompson

Google

Prostate Cancer Risk Calculator

risk 44%

high grade 14%



Racemase and P⁶³ stains

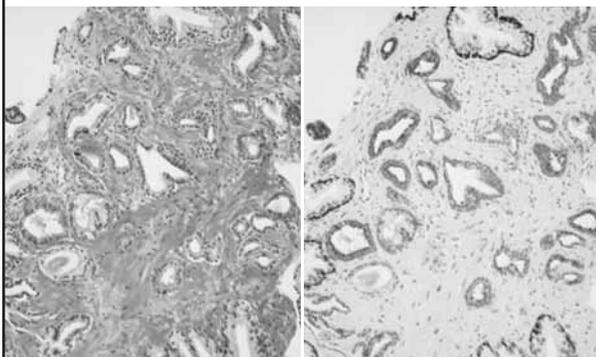
MA 903 - basal cell cytoplasm;
benign, 2 layer prostate glands
no basal layer = malignancy

Racemase - cytoplasmic epithelial
cell; stains = malignancy

P⁶³ - basal cell nuclei, basal cells
present, stain = benign gland

R +, P⁶³ - = Ca;

AMACR + p63 in PCa



Prostate Biopsy

The future
 Djavan's technique
 Thompson's risk calculator
 tumor localization technique
 PCA 3

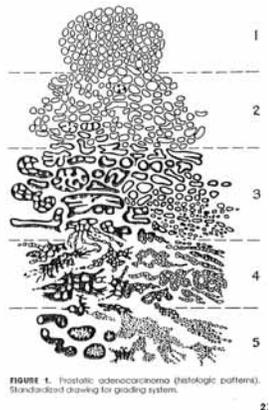
Prostate Biopsy Oct 2000 – September 2007

percentage positive

#	pos / total	percentage
3 cores	106 / 433	24.4%
4 cores	115 / 407	28.2%
5 cores	152 / 449	33.8%
6 cores	154 / 418	36.8%
7 cores	128 / 364	36.2%

Biopsy Results

technique altered
 7/01/07 to 11/28/2007; 41+ / 165, 25%
 technique corrected
 12/01/07 to 3/30/08; 77+ / 273, 28%
 technique re-corrected; re-re-corrected
 March 08 46%; October 08 50%
 April 08 41%;
 BUT 31 / 85 36% 4-6; 37 / 100 37% 7-9,08





E=Exercise
Aerobic vs. Weight Lifting

<u>HEALTH AREA</u>	<u>AEROBIC</u>	<u>WT. LIFTING</u>
Bone Health		Yes!!!
Burn Fat/Metab	Yes!!!	Yes!!!
Strength		Yes!!!
Glucose/Insulin	Yes!!!	Yes!!!
Lipids + hs-CRP	Yes!!!	
HR/BP at rest	Yes!!!	
Mental Health	Yes!!!	Yes!!!
Overall Survival	Yes!!!	Yes!!!

Braith RW, Stewart KJ. Circulation 113:2642-2650, 2006.



AMERICAN GINSENG

Rx for Fatigue?!-Maybe! N=282!

(Barton DL, et al. Mayo Clinic. Abstract 9001, page 493s, ASCO, 2007, Brief Fatigue Inventory)

8 wk data

ENDPT	Placebo	750 mg/d	1000 mg/d	2000 mg/d
BFI-sub	---	---	---	Best
BFI	---	---	---	Best
Scale	---	---	Best	Best
Physical	---	---	Best	Best
% Perceived	---	---	Best	Best (25-27%)
% Satisfied	---	---	Best	Best (34%)



F=FATIGUE
(Summary)

- Lifestyle Option=Weight-Lifting
- American Ginseng-1000-2000 mg/day-New possibility?
- Rx=Provigil (modafanil=100-200 mg/d)

Barton DL et al: ASCO/AUA-2007

Moyad MA et al: Sem Prev Alt Med-2007



F=FIBER
(internal
Anti-Aging)

- 20-30 Grams
Per day for:
- Acid Reflux
 - BP
 - Cholesterol
 - Constipation
 - Diverticulitis
 - Glucose
 - Hem..
 - PSA
 - Prebiotic!!
 - Weight Loss...



SOLUBLE
(VISCOUS)
FIBER SHOULD
BE INCREASED!

WHAT ABOUT
INSOLUBLE
FIBER?
(All-Bran, Flax...)



Moyad MA, et al. No BS Health Advice, 2009. & Anderson JW, et al. Nutr Rev 2009; 67:188-205.

Flaxseed-Presurgical Rand Trial (30 grams--6 wks pre-surg, n=161)

	Placebo	Flaxseed	Low-Fat	Flax+LF
TC (mg/dl)	+9	-26	-46	-37
LDL	-14	-17	-29	-21
Weight	+0.3 kg	-1.3 kg	-1.7	-1.1
Pathology	---	Sign Ki-67	----	Sign Ki-67

Demark-Wahnefried W, et al. Cancer Epidemiol Biomarkers Prev 2008;17:3577-3587.
George SL, et al. Abstract 1510, pg 63S, ASCO, 2007



F=Flaxseed

(2-3 Tablespoons pre/post surgery)

GOOD NEWS	BAD NEWS
FIBER	FIBER (golden?)
OMEGA-3	PILLS/OIL
PLANT ESTROGENS	CHIA SEEDS ARE HERE!!
HEART HEALTHY	
CHEAP/Powdered/grounded	

Ki-67. Sesame seed?

Demark-Wahnefried W, et al. Cancer Epidemiol Biomarkers Prev 2008;17:3577-3587. & Moyad MA



F=Fruits & Veggies (Pills)? MORE is not MORE

- WHEL=Women's Healthy Eating & Living
- Treated for early-stage breast cancer
- 7.3 years (n= >3000)
- Veggies, fruit, fiber & low-fat

Bottom Line=NOTHING!

Pierce JP, et al. JAMA 298(3):289-298, 2007.



Remember the Obesity Epidemic?

BEVERAGE	CALORIES (8 oz)
Acai Juice	150-200
Cranberry/Grape Juice	140-160
Pomegranate Juice	140-160
Tomato/Carrot	50-60
Light Beer	70-80
Beer/Wine/Hard Liquor	100-150 (Low-carb diet)

Moyad MA. Dr. Moyad's Diet Book. 2008.

Calories=Antioxidants!





Expenditures

- Prostate- 8 billion 11.2%
- Lung- 9.6 billion 13.3%
- Breast 8.1 billion 11.2%

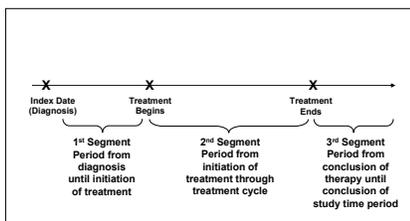
Presentation Outline

- Study Design
- Research Objectives
- Results
- Next Steps

Selection Criteria

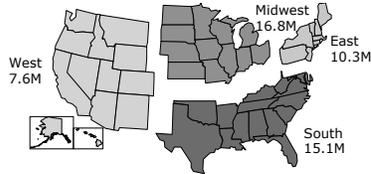
- **Inclusion Criteria**
 - Men ≥ 40 years of age
 - Index date occurs during the enrollment period
 - Continuously eligible for at least 18 months (6-month pre-period and a minimum 12-month post-period)
- **Exclusion Criteria**
 - Members with ICD-9 claims for any other cancer

Measurement Segments



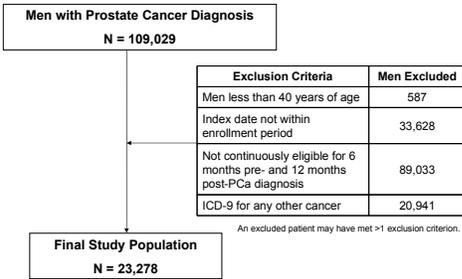
Data Sources

- PharMetrics
 - Data from over 85 health plans and 45 million lives
 - Mostly a commercial population (80%)
 - Timeframe of the dataset is 1995 to present (approximately a 6-month lag)



8

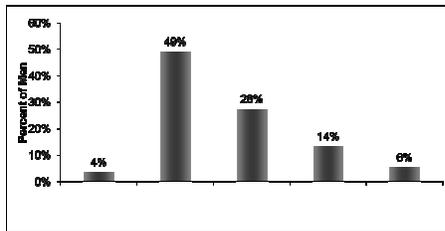
Patient Selection



9

Age

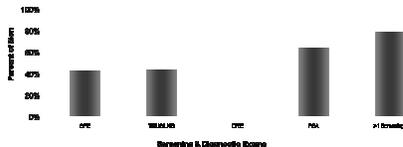
Mean age = 61.2 years



10

Screening & Diagnostics

80% of men had screening/diagnostic exam(s) in the 6-month pre-period through the cancer index date. Men had PSA most often.

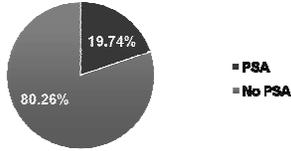


*35% had 1, 16% had 2, and 30% had ≥3 screening or diagnostic exams
DRE - Digital Rectal Exam, PSA - Prostate Specific Antigen, SPE - Surgical Pathological Exam, TRUS - Transrectal Ultrasound, LNB - Lymph Node Biopsy

11

Screening & Diagnostics

80% of men had a PSA test at some time in the database.

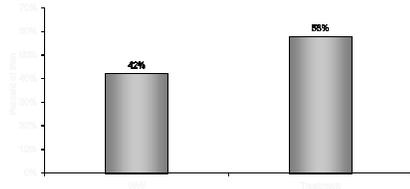


N=23,278
PSA - Prostate Specific Antigen

12

Treatment or Watchful Waiting?

More than half of the men that were diagnosed with prostate cancer received some treatment during the follow-up period.

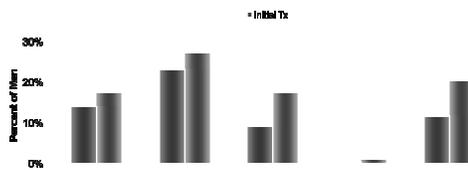


N=11,227
WW - Watchful Waiting

13

Type of Treatment

Of men that were treated, the most common treatment was surgery.

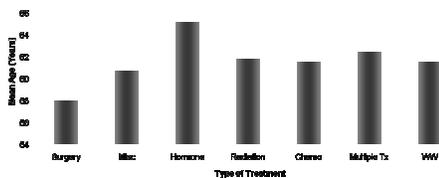


The percentages add to more than 100% as there were patients that received more than one treatment
*Misc=ketoconazole, aminoglutethimide, and any corticosteroid

14

Characteristics of Treatment Cohorts

Men receiving surgery as their initial treatment were younger.

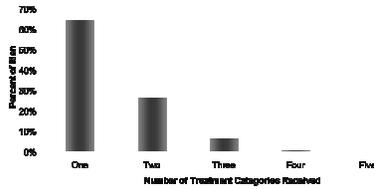


WW - Watchful Waiting

15

Number of Treatments

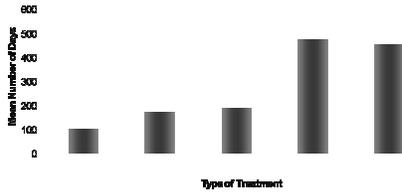
Of men that were treated, the majority received one type of treatment.



16

Time to Treatment

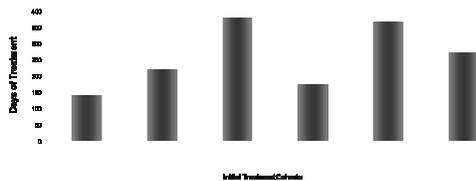
Of all men that received treatment, surgery occurred closest to diagnosis, and miscellaneous treatments occurred furthest from diagnosis (1.31 years).



17

Average Duration of Treatment

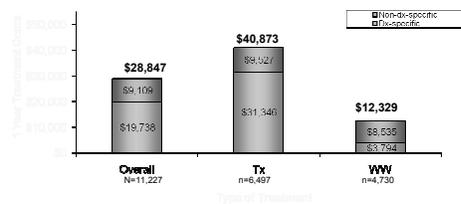
Mean days from first to last treatment ranged from 141 days for surgery cohort to 381 days for hormone therapy cohort.



18

Average Annual Cost per Patient

Patients with prostate cancer cost \$28,847 in the 1 year following diagnosis. Those who received any treatment were more costly.

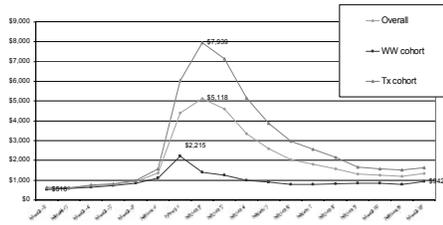


Costs were calculated from diagnosis through 1 year
WW - Watchful Waiting

19

Average Total Monthly Medical Costs

Costs peak in the month following diagnosis and are highest for patients who receive treatment

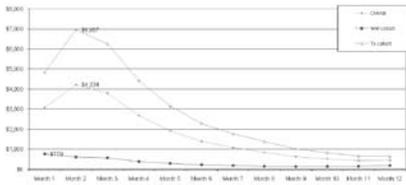


WW – Watchful Waiting

20

Average Prostate Cancer-specific Monthly Medical Costs

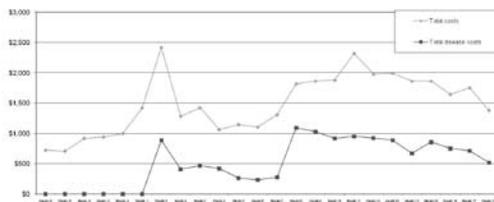
Disease-specific costs account for a high proportion of total costs



WW – Watchful Waiting

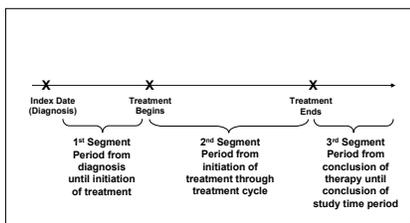
21

Average Monthly Medical Costs: Patients Starting Therapy at ≥8 Months



22

Measurement Segments



23

Summary

- The majority of men receive one type of treatment.
- Surgery was the most common treatment. It was received by the youngest men and resulted in the highest costs and most clinical events.
- Annual costs, regardless of treatment pattern, were \$30K per patient in the year following diagnosis.
- Costs peaked in the month following diagnosis.
- The watchful waiting cohort had the lowest costs and fewest clinical events.

28

Why Prostate Cancer Prevention?

- Significant public health risk
 - 186,000 new cases and 26,000 deaths yearly (2008)
- Risk factors (age, race, genes) are not modifiable
- Benefit of screening on mortality is unproven
- Therapy is associated with morbidity
 - That Leaves Prevention

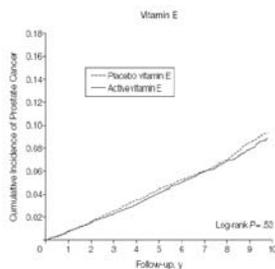
Prostate Cancer Diet & Exercise Risk Factors

- May **Increase** Risk
 - Fat / Red Meat
 - Cooking methods
 - Dairy/Calcium
 - Smoking
 - Total Calories, Body size
- May **Decrease** Risk
 - Plant-based Foods/ Vegetables
 - Tomatoes
 - Cruciferous
 - Soy/Legumes
 - Specific Nutrients
 - Selenium
 - Vitamin E
 - Carotenoids/Lycopene
 - Total Antioxidants
 - Fish / Marine Omega 3 Fatty acids
 - Moderate to Vigorous Exercise



Courtesy J. Chan, UCSF

Vitamin E and Prostate Cancer Physicians Health Study II



N = 14,641

Gaziano et al, JAMA (in press)

Effect of Dutasteride on Cancer in BPH Trials

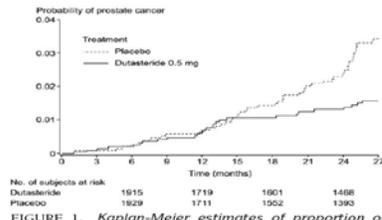
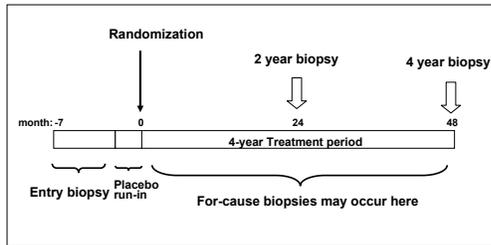


FIGURE 1. Kaplan-Meier estimates of proportion of subjects experiencing a prostate cancer adverse event with onset after randomization (study population).

Andriole et al, Urology 64: 537, 2004

REDUCE Schema



Andriole et al, J Urol 172:1314, 2004

REDUCE and PCPT Study Design Differences

Parameter	REDUCE	PCPT
Study drug	AVODART 0.5 mg daily	Finasteride 5 mg daily
Study duration	4 years	7 years
Number of patients	8,250	18,882
Age (years)	50 to 75	≥ 55
Baseline biopsies	Yes (1 negative biopsy)	No
Follow up (planned) biopsies	Year 2 and Year 4 (mandatory)	Year 7 (recommended)
PSA entry criteria	2.5 - 10 ng/mL if 50-60 years; 3 - 10 ng/mL if > 60	≤ 3 ng/mL
Location	International	United States

Note: Due to the differences in study design and patient population, comparisons of the results from REDUCE and PCPT cannot be made.

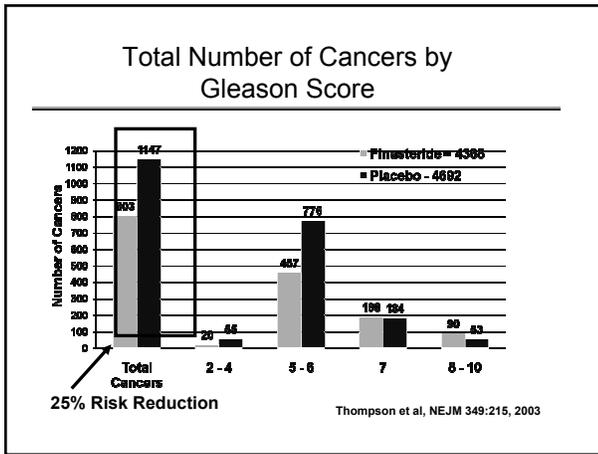
1. Thompson M et al. NEJM 2003;349(3):215-224. 2. Andriole G et al for the REDUCE Study Group. J Urol 2004;172:1314-1317. 3. Ciorella L.G. Curr Opin Uro 2005;15:2932. 4. Musquera M et al. Expert Reviews 2008;8(7):1079-1079.

REDUCE: Primary endpoint (analysis ongoing)

Dutasteride reduced the risk of prostate cancer over 4 years by **23%**
 $p < 0.0001$
 (857 placebo vs 659 dutasteride)

Note: Analysis of data from the REDUCE trial is ongoing. Once the analysis is complete, the results will be published.

Data on file, GlaxoSmithKline (ARI40006)



Statins and Prostate Cancer Risk

Risk Group	Risk Ratio
Any Px Cancer	1.09
Advanced Px Cancer	
Any use	0.51
Use < 5 yrs	0.60
Use > 5 yrs	0.26

Health Professionals Follow-up Study, N = 34,989
Platz et al, JNCI 98:1819-25, 2006

Prevention: What to Tell Patients

Historical Imperative for Prevention

- Superior doctors prevent the disease.
- Mediocre doctors treat the disease before evident.
- Inferior doctors treat the full blown disease.

Nai-Ching (2600 B.C. 1st Chinese Medical Text)

