

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*

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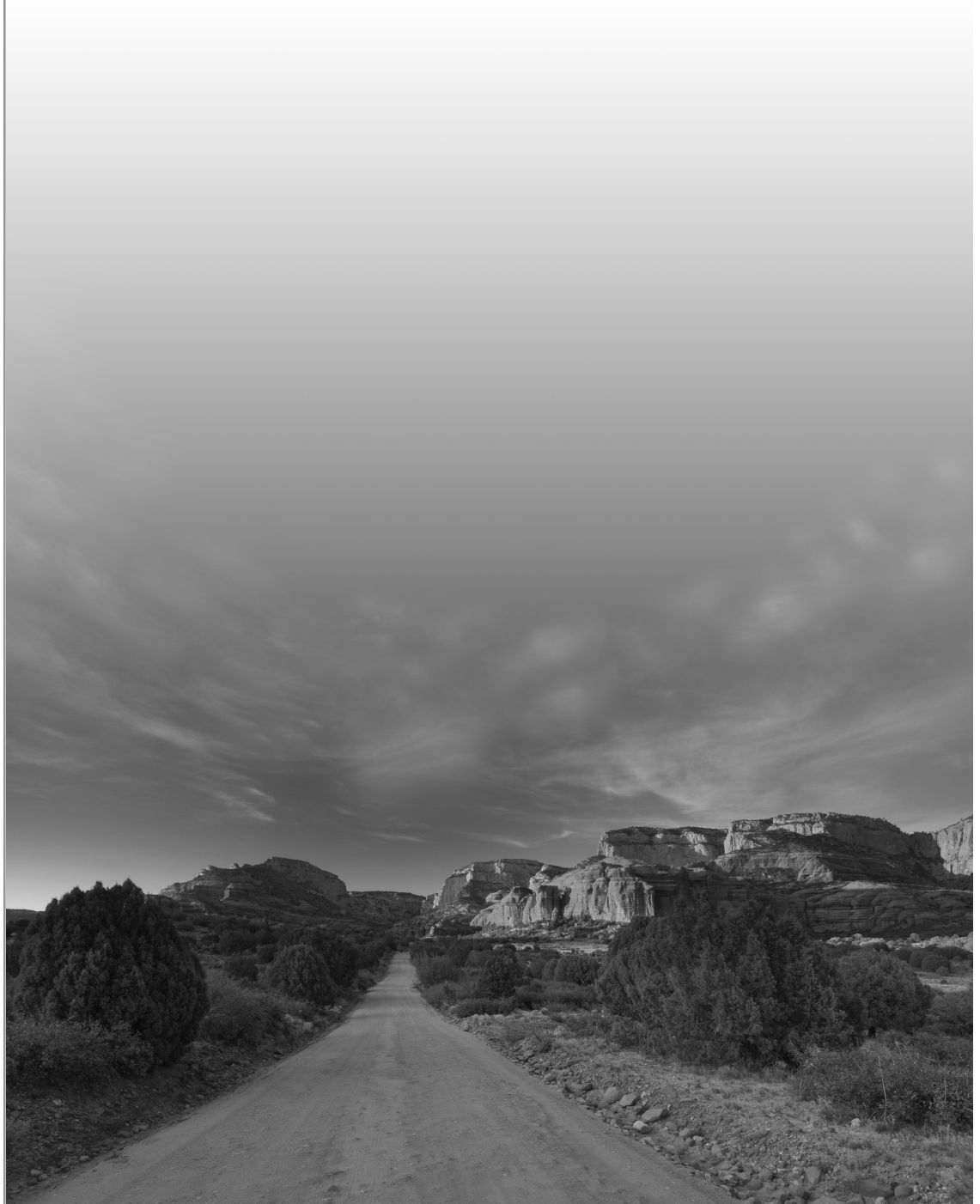
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## Introduction

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

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**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.

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**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.

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**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.

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**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 Guérin* (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.

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### **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.

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### **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.

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### **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

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### **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**

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**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

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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	
	<b>Bladder Cancer</b>	
	8:00 – 8:45 am A Case-based Approach to the Management of Bladder Cancer ~ Moderator: Robert Donohue, MD	6.1
	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 ~ Review of Existing Guidelines & International Recommendations ~ Donald L. Lamm, MD	7.1
	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 ~ Donald L. Lamm, MD	9.1
	10:35 – 10:45 am Questions & Answers	
	<b>Female Urology, Part II</b>	
	10:45 – 11:15 am The Spectrum of Stress Incontinence Surgery, 2009 ~ Brian J. Flynn, MD	10.1
	11:15 – 11:25 am Questions & Answers	
	<b>Clinical Challenges</b>	
	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	
	<b>Prostate Conditions</b>	
	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	
	<b>Hypogonadism</b>	
	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	
	<b>Complementary Alternative Medicine</b>	
	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**

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Thursday, November 5, 2009

Ballroom E-F

The Scottsdale Plaza

Scottsdale, Arizona



## Agenda

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6:00 – 8:00 pm      Registration

### Thursday, November 5

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~ 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

# The Role of Robotics in Urologic Surgery

~ Paul D. Maroni, MD

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## The Role of Robotics in Urologic Surgery

Paul D. Maroni, MD  
Assistant Professor  
Department of Surgery/Urology



University of Colorado at Denver



## Objectives

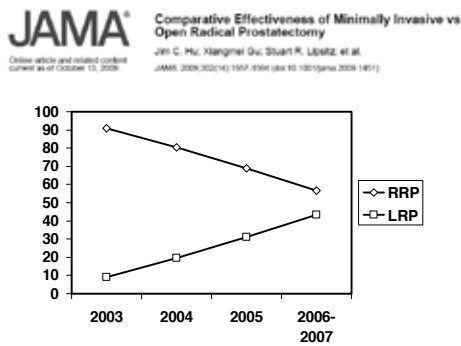
- Review history of robotics in surgery/urology
- Identify areas where robotic surgery can be useful.
- Avoid pitfalls of robotic surgery.
- Learn a responsible way to integrate into your practice.

## Brief history of robotic surgery

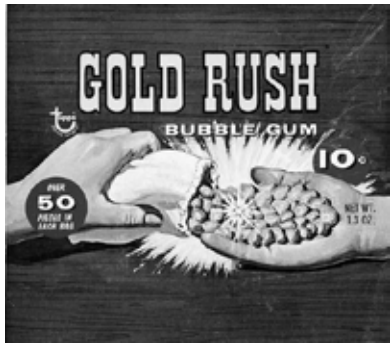
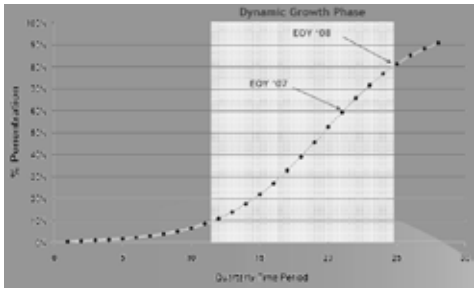
- “robot” coined by Karel Capek in 1921 from Czech word robota meaning forced labor
- 1985 – PUMA 560 used for brain biopsy
- 1987 – first robotic gall bladder removal
- 1988 – PROBOT for TURP
- Late 1980s – ROBODOC first FDA approved for hip surgery
- Late 1980s – NASA and US Army developed systems

Brief history of robotic surgery

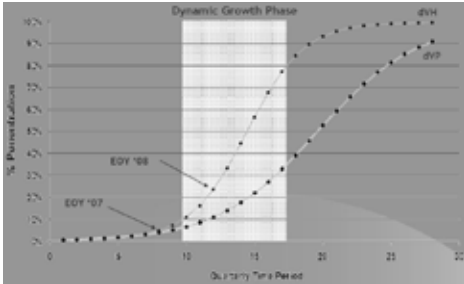
- 1993 – AESOP approved for surgery
- 1997 – daVinci begins use
- 1998 – ZEUS first fully robotic surgery (Computer Motion)
- 2000 – daVinci approved by FDA (Intuitive Surgical, Inc)
- 2003 – Computer Motion merged with Intuitive Surgical, Inc.



Adoption of robotic prostatectomy  
Market estimate



## Adoption of robotic hysterectomy Market estimate



## Gold or Bubble Gum

- |  |  |
|--|--|
| <ul style="list-style-type: none"> <li>■ Winners</li> <li>■ Early adopters</li> <li>■ Intuitive Surgical, Inc./ stockholders</li> <li>■ Late patients (?)</li> </ul> | <ul style="list-style-type: none"> <li>■ Losers</li> <li>■ Late/non adopters</li> <li>■ Healthcare system</li> <li>■ Early patients</li> </ul> |
|--|--|

## How are late patients helped?

- Forced most prostate surgeons to improve results/technique
- Regionalization
- or
- Identify processes of care in high volume hospitals and implement at lower volume centers

## Robotic procedures in Urology

- |  |  |
|--|--|
| <ul style="list-style-type: none"> <li>■ Radical prostatectomy</li> <li>■ Nephrectomy/partial</li> <li>■ Pyeloplasty</li> <li>■ Ureteral reimplant</li> <li>■ Cystectomy</li> <li>■ Adrenalectomy</li> <li>■ Simple prostatectomy</li> </ul> | <ul style="list-style-type: none"> <li>■ Bladder diverticulectomy</li> <li>■ Urinary diversion</li> <li>■ Pelvic lymph node dissection</li> <li>■ RPLND</li> <li>■ Inguinal lymph node dissection</li> </ul> |
|--|--|

### Lap versus robotic

- Would you close one eye while operating? NO
  - 3-dimensional view with robot
- Would you lock your wrists? NO
  - Wristed instrumentation with robot
- Would you prefer to move more precisely? YES
  - Motion scaling and tremor filtering with robot
- Would you rather be comfortable? YES
  - Ergonomic seated position with robot
- Would you prefer to be cost effective? YES
  - Don't use the robot for things safely done laparoscopically

### Robotic assisted partial nephrectomy

- AUA Guidelines
 

“... only a few small, single-institution reports offer limited information regarding this procedure, including whether robotic-assisted LPN offers any advantages over other forms of nephron-sparing surgery (NSS). At present there are insufficient data to evaluate outcomes.”

Guideline for Management of the Clinical Stage 1 Renal Mass. AUA 2009

### Healthy, clinical T1a enhancing renal mass

- **Standard: Complete surgical excision by partial nephrectomy is a standard of care and should be strongly considered.**
- Both open and laparoscopic approaches to PN can be considered.... LPN can provide more rapid recovery, although **this approach has been associated with increased warm ischemic times and an increased risk of urological complications including postoperative hemorrhage and urinary fistula.** ... a solitary kidney, preexisting renal dysfunction, hilar tumor, multiple tumors or predominantly cystic tumor are best managed with an open surgical technique. **With improved laparoscopic instrumentation and greater dissemination of expertise, improved outcomes and more widespread application of LPN is anticipated in the future.**

Guideline for Management of the Clinical Stage 1 Renal Mass. AUA 2009

#### Robot Assisted Partial Nephrectomy Versus Laparoscopic Partial Nephrectomy for Renal Tumors: A Multi-Institutional Analysis of Perioperative Outcomes

Brian M. Benway,\* Sam B. Bhayani,† Craig G. Rogers,† Lori M. Durlabon, Mariah N. Patel, Michael Lipton, Agnes J. Wang and Michael D. Stohrman†

J Urol September 2009

- 118 LPN, 129 RAPN – 3 surgeons
- No difference in OR time or positive margin rate (3.9% v. 1%)
- Less blood loss and warm ischemia time for RAPN (19.7 min v. 28.4 min)
- Similar post-op complications (10.2% v. 8.6%)
- Long-term oncologic outcomes unknown

### My opinion RAPN

- Still a difficult operation for the novice roboticist

ated with a learning curve. Unlike robotic pyeloplasty and prostatectomy, robotic partial nephrectomy places a time constraint upon the surgeon because of the need to minimize warm ischemia time [17\*].

- Little information on learning curve, but probably not as shallow as LPN

Shapiro et al Curr Opin Urol 2009

### Robotic assisted radical nephrectomy/nephroureterectomy

- No literature on RARN
- Probably no different than LRN

### Robotic assisted Ureteral Surgery: Pyeloplasty

	Patients	ORtime (min)	Comps. (%)	Success (%)	F/U (mo)
Palese	35	216	11	94	7.9
Gettman	9	138	11	100	4.1
Siddiq	26	245	12	95	6
Schwenner	92	108	4	97	39.1
Patel	50	122	nil	96	11.7

Adapted Leveillee and Williams Curr Opin Urol 2009

### Robotic assisted Ureteral Surgery: Ureteral reimplant

- Limited publications on this subject
- Leveillee and Williams Curr Opin Urol 2009
  - 8 patients with benign diseases
  - Mean follow-up 18 months
  - 1 recurrence treated successfully with balloon dilation
  - Psoas hitch and Boari flap still available

Opinion:

Will probably become widely accepted for benign and malignant disease (oncologic results unknown – Glinianski et al J Endourol 2009)



## Robotic assisted simple prostatectomy

- Technically feasible
- Case series x 2, 3 and 7 patients
- Millin's technique
- Modest EBL <600, 300 respectively
- 3-4 hours!!!

Opinion

Learn HoLEP. Probably not for robot.

Sotelo et al J Urol 2008, Yuh et al Can J Urol 2008

## Robotic assisted bladder diverticulectomy

- Little in literature
- Easy to do robotically
- Curl guidewire in diverticulum
- Unproven for cancer
- Can do PVP simultaneously

Opinion

Excellent training case. Quick and handles all comers. Not for malignancy yet.

## Robotic assisted lymph node dissections

- Pelvic
  - Well described and can do extended lymph node dissections, but tedious
- RPLND
  - Only 2 patients in PubMed
  - Expect more will come
- Inguinal LND
  - Believe it or not (Josephson et al Urology 2009)
  - Leave this to the few

## Medical Ethics

- |                      |                          |
|----------------------|--------------------------|
| ■ Commercial         | ■ Professional           |
| ■ Caveat emptor      | ■ Primum non nocere      |
| ■ Equal relationship | ■ Fiduciary relationship |
| ■ Self-interest      | ■ Self-sacrifice         |

- Practical constraints to practicing physician taking significant amount of time to learn new procedures.

$$Q_r$$

- 2 of first 10 patients at place I did fellowship had rectourethral fistula after prostatectomy
- Bad complications common
  - Urinary leaks
  - Incomplete prostate removal
- Promises not delivered
  - More incontinence and impotence

- Ongoing QI processes and M and M
- 1. Training pathway
  - Significant residency or fellowship experience
  - 3 proctored cases
  - Period of observation (10 cases)
- 2. Practice pathway
  - Device training – online, off-site certificate
  - 3 proctored cases
  - Period of observation (17 cases)
  - CME or advanced course

### University of Colorado Hospital Robotic Credentialing

3. Experience pathway
  - 20 cases as surgeon and 10 within last year.
  - List of complications
  - Verification of robotic privileges at other medical center
  - Supportive letter of recommendation from Chair of Surgery/Department.

### Ways for practicing physician to train

- Fellowship
  - 6 months to 3 years
  - Hands-on required
- Mini-fellowships
- Self-directed
  - Dry-lab
  - Courses – hand-on and video observation

### Prerequisites

- Experience with laparoscopy
- Understand an investment is necessary
- Discuss with partners (if any)
- Willingness to start slowly

### How to incorporate

- Case observation
- Video observation
- Basic training
  - Online module
  - Hands-on off-site certification
- Dry-lab time (very helpful)
- Honesty is the best policy/dispel myths/expectations
- Start with simpler procedures soon after training
  - Nephrectomy
  - Bladder diverticulectomy



## Point-Counterpoint: Robotic Surgery

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

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

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### ***Robotic prostatectomy? HYPE***

E. David Crawford, MD  
Professor of Surgery (Urology) and Radiation Oncology  
University of Colorado Health Sciences Center

#### ARS

Do you believe that the robot has  
significantly improved the care of  
patients undergoing a radical  
prostatectomy

1. yes
2. no

Just because you have a Ferrari does  
not make you a race car driver



Robot and LPR Primary Advantages

- Faster recovery – no lower abdominal incision
- Less blood loss – pneumoperitoneum
- Better preservation of the NVB – magnification
- Better Vesicourethral anastomosis – direct vision

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Robot

- Supposed improvement over lap
- 3-D up-close
- Wristed motions
- Tremor and movement scaling

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Conclusions

- A lot of marketing hype
- Skill trumps any technique  
Robot=RRP=RPP=Lap RRP  
There is no difference in any parameter with the robot (even blood loss)
- To much time wasted at meetings
- Has done nothing to advance care

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Marketing

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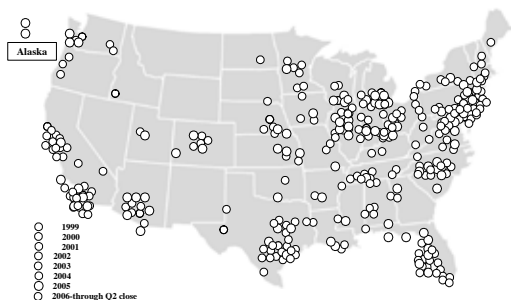
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### Da Vinci® Surgical System U.S. Installed Base 1999 – 2006 >350 now



### Boston Globe -continued

- "It's unbelievable how good it was," said Philip Bedard, 59, a Boxford construction company ..... "In five days I was back in the office, and in 10 days I was operating a backhoe."

The result - if a hospital does not have a robot you loose market share, even if not cost effective

### Prostate Cancer Surgery

Google: Prostate Cancer Treatment

<a href="http://www.rcog.com">www.rcog.com</a>	Comprehensive info from a world leader in treatment and research Prostate Cancer Surgery
<a href="http://www.laprp.com">www.laprp.com</a>	America's longest running program for lap prostate cancer surgery Prostatectomy
<a href="http://www.CityofHope.com">www.CityofHope.com</a>	Leading Treatment options including Robotic-Assisted Cancer Surgery

### Do an internet search for prostate cancer:

Web | CNN News | CNN Videos  
Web results for "prostate cancer" | Results 1-10 of 3,970  
Sponsored Links  
Prostate Health

[www.ProstateCare.com](http://www.ProstateCare.com) Important Information About  
Determining Your Prostate Health. Robotic prostate surgery

[www.StJosephsAtlanta.org](http://www.StJosephsAtlanta.org) Minimally invasive robotic surgery  
Saint Joseph's Hospital in Atlanta.



## Marketing

- You will be left out
- Hospital against hospital
- Mid size cities where there are 5 robots
- Hospitals loose money
- When is the last time you were detailed on a perineal prostatectomy?

'The ideal way to compare Robot,LPR, RRP,RRP is a randomized clinical study using common clinical pathways'

## In 2009

A man undergoing open RRP can expect:

- Uncomplicated surgical procedure
- A short and uneventful hospital stay
- The lack of allogeneic blood transfusion
- Early removal of the urinary catheter
- Full return to activity within 3 weeks
- Restoration of urinary continence within 3 weeks

### **Only long term problem is ED**

Shekarriz et al Urol Clin North Am

## Outcomes After Radical Prostatectomy: Ranked Order Based on Clinical Importance

- Cancer control
- Technical complications
- Postoperative complications
- Urinary continence
- Erectile function
- Cost
- Blood loss
- Timing of catheter removal
- Length of hospital stay
- Postoperative pain

Not the technique  
Robot, RRP, RPP, Lap

- Lap longer
- Robot less
- RRP less
- With experience all about the same

- Lap and robot less
- But experience trumps all

- No difference
- Perhaps more bladder neck contracture with lap/robot
- Disasters with Robot/Lap  
vascular injuries, rectal, anastomosis

## 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

Center	Approach	No Pts	Mean op time	Mean EBL	Transfusion %	Mean LOS	Complications	Positive Surgical Margin
Rassweiler et al <sup>1</sup>	TLRP	219	288	1100	30.1	12	19.6	21
		219	218	800	9.6	11	10.5	23.7
Goeman et al <sup>20</sup>	TLRP	165	240	678	1.2	6.7	9.1	23
Eden et al <sup>21</sup>	TLRP	100	238.9	310.5	2	3.8	8	16
Guillonneau et al <sup>5</sup>	TLRP	550	200	380	5.3	5.8	10	15
Cathelineau et al <sup>22</sup>	ELRP	600	173	380	1.2	6.3	11.5	17.7
Tuerk et al <sup>23</sup>	ELRP	174	169	176	0	1.67	9.9	14.5
Goeman et al <sup>20</sup>	ELRP	550	188	390	4.7	4.6	10.9	pT2 17.9 pT3 44.8 pT4 71.4
Eden et al <sup>21</sup>	ELRP	100	190.6	201.5	0	2.6	4	16
Stolzner et al <sup>24</sup>	ELRP	700	151	220	0.9	-	2.4	19.8
Menon et al <sup>25</sup>	RAR	1142	154	142	0	1.14	2.3	13
Patel et al <sup>2</sup>	RAR	200	141	75	0	1.1	2	10.5
Joseph et al <sup>26</sup>	RAR	325	130	196	0.09	-	9.8	13
Rassweiler et al <sup>1</sup>	ORP	219	196	1550	55.7	16	35.6	28.7
Zincke et al <sup>27</sup>	ORP	3170	-	600-1030	5-31	-	-	24
Lepor et al <sup>28</sup>	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
Rapaport et al <sup>1</sup>	TLRP	438	94% (3 mos)	90.3% (12 mos), 95.9% (18 mos)
Guillonneau et al <sup>2</sup>	ELRP	350	p12a 92.3% (36 mos) p12b 86.9% (31 mos)	82.3% No pad (12 mos)
Geerman et al <sup>3</sup>	ELRP	350	p12 89.7% (3 yr) p13 58.6% (3 yr)	91% (24 mos)
Steinberg et al <sup>4</sup>	ELRP	700	Not reported	92% complete (12 mos) 98% 1 pad or less
Memon et al <sup>5</sup>	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
Mikhail et al <sup>6</sup>	RARP	100	Not reported	84% return to baseline function (12 mos) 89% subjective continence (12 mos)
Dink et al <sup>7</sup>	RARP	300	95% (8.7 mos)	88% (12 mos)
Kim et al et al <sup>8</sup>	RARP	305	97% (6 mos)	90% (6 mos)
Camlona et al <sup>9</sup>	ORP	1325		93% BNS 68% UNSS 47%
Geary et al <sup>10</sup>	ORP	458		80.1% No pads 8.1% 1 - 2 pads 6.6% 3 - 5 pads 2.4% totally incontinent
Leandri et al <sup>11</sup>	ORP	620		65% complete control 71% w/ 0-NS

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 <sub>2</sub> Disease	pT <sub>3</sub> Disease	
Open radical prostatectomy					
Legge <sup>a</sup>	New York University	1000	2.9	33.2	2000-2005
Baumgartner et al	Emory Hospital	77	2.3		1999-2001
Klein et al	Cleveland Clinic	152	7.4	28.6	1994-1996
Laparoscopic radical prostatectomy					
Rapaport et al	University of Heidelberg	438	9.7	37.1	1999-2002
Guillonneau et al	Montebello Institute	1000	15.5	31.1	1998-2002
Memon et al	Honey Ford	100	0	40	2001-2002
Ruiz et al	Hennrichs	330	16.3	44.3	2000-2002
Baumgartner et al	Emory Hospital	85	7.8		1999-2001

<sup>1</sup>Unpublished 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	580	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

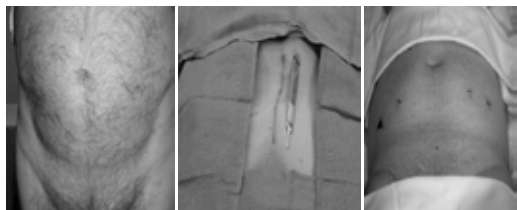
RPP

Modify how you do your standard RRP

## LAP RRP

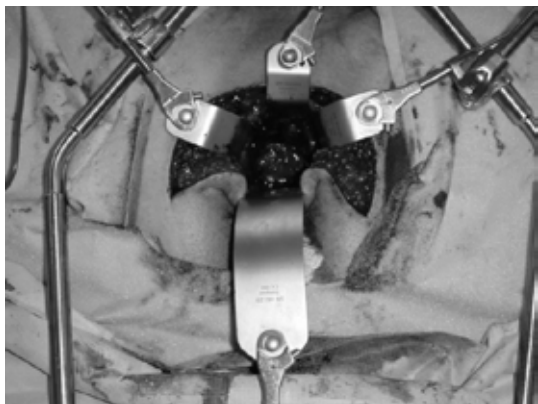
- Most European and many US Centers use Lap alone and have excellent results
  - Learning curve for suturing
  - Visualization

RALP



- 1904 – Hugh Hampton Young
- 1947 – Retropubic approach
- 1969 – Jewett HJ
- 1982 – Elder et al

Survival approaching age- matched population



## Concerned about LN





### Advantages of a Perineal Prostatectomy

- Avoidance of an abdominal incision
- Avoidance of blood transfusion
- Apical dissection is facilitated and margin rate decreased ( 7% )

Weldon et al. J Urol -1995

- Ease of anastomosis – Watertight
- Early and immediate continence rates better
- Overall continence similar.

Weldon – J. Urol 1997, Bishoff – J. Urol 1998

### Advantages of a Perineal Prostatectomy

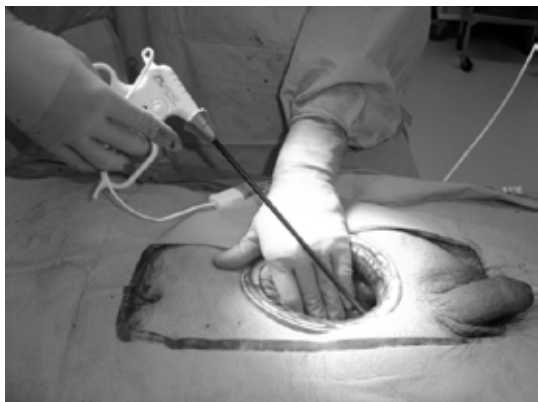
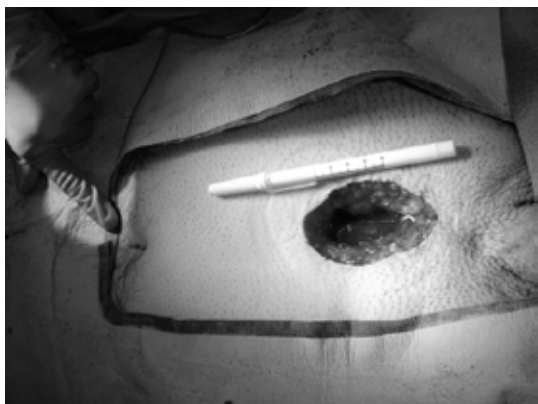
- Oral pain. No epidural or PCA
- Postoperative convalescence : Regular Diet Ambulation in 12 to 18 hours.
- Discharge same day or next.
- Outpatient series – only 12% wished >23 hr stay  
Ruiz-Deya et al. J urol. 2001.
- Prior surgery and obesity
- Potency: theoretical advantage due to better visualization but no clear evidence.
- [WWW.medscape.com/viewarticle/551746](http://WWW.medscape.com/viewarticle/551746)

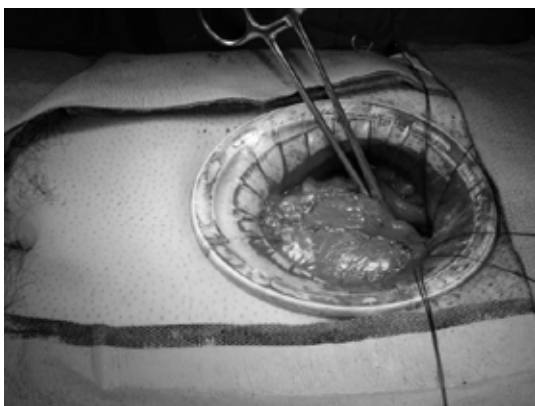
## Perineal

Surgeon

Similar results as Robot, Lap,  
RRP

Go home the same day





### The Incision



**From:** Stacy Childs <stacychilds@yahoo.com>  
**Date:** Wed, 20 Jun 2007 15:20:18 -0700 (PDT)  
**To:** "E. David Crawford M.D." <edc@edavidcrawford.com>  
**Subject:** "Your Patient"

Took his foley out today. Voids well, good sphincter control. He was driving at p.o. day #5, back at work at day #7. You're right, tiny incision. Impressive. Are you using all laparoscopic instruments and not fingers?

Stace

Stacy J. Childs, M. D.  
 (970) 870-6684 hm  
 (970) 871-9710 wk  
 (970) 870-6698 fx hm  
 (970) 871-9709 fx wk

### Postoperative complications Last 400 cases

	Number of patients
Bladder Neck Contracture	27
Meatal stricture	7
Wound Infection	3
bladder neck stricture	2
Bladder infection	2
Rectal Tear	1
Penile Pain	1
Epididitymis	2
Hydronephrosis	1
Penile pain	1
Hydroureteronephrosis	1
Suprapubic postoperative hematomas	1
wound granuloma	1

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

<i>Pathological Stage</i>	<i>Frequency</i>	<i>Cumulative %</i>
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

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

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

- A step sideways at best, rather than a step forward, this is not ESWL
- We are 15 years behind breast cancer, colorectal cancer, and radiation oncologist who treat prostate cancer
- The Robotic prostatectomy is an example why

- A step sideways at best, rather than a step forward, this is not ESWL
- We are 15 years behind breast cancer, colorectal cancer, and radiation oncologist who treat prostate cancer
- The Robotic prostatectomy is an example why



### 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.*

available at: [www.sciencedirect.com](http://www.sciencedirect.com)  
journal homepage: [www.europeanurology.com](http://www.europeanurology.com)



European Association of Urology

Review - Prostate Cancer

Vincenzo Fiorina<sup>a,\*</sup>, Giacomo Novara<sup>a</sup>, Walter Artibani<sup>a</sup>, Andrea Cestari<sup>b</sup>,  
Antonio Galfano<sup>c</sup>, Markus Graefen<sup>c</sup>, Giorgio Guazzoni<sup>b</sup>, Bertrand Guillemeau<sup>d</sup>,  
Mani Memon<sup>e</sup>, Francesco Montorsi<sup>f</sup>, Vishal Patel<sup>g</sup>, Jens Raschewler<sup>h</sup>, Hendrik Van Poppe<sup>i</sup>

- Published 2009 - 103 references

“...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).”

- Hu et al J Clin Oncol 2008 – need for salvage treatments – Medicare database
  - MRP 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	<i>P</i>
Overall	8.2	6.9	.35
Radiation	5.1	4.9	.67
Hormone	5.3	3.7	.21

Incontinence*	MIRP	RRP	<i>P</i>
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

### Is robotic assistance or laparoscopy necessary?

- Most metrics appear equal
- Device is costly
- Costs are important
- Why use it?

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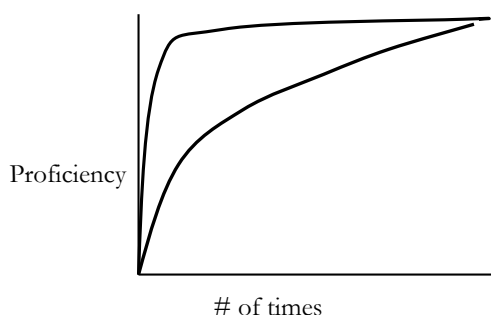
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### The learning curve




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### The learning curve

#### The Learning Curve for Coil Embolization of Unruptured Intracranial Aneurysms

Vincent Singh, Deepak R. Gnan, Randall T. Higashida, Christopher F. Dowd, Van V. Halbach, and S. Claiborne Johnston

*AJNR Am J Neuroradiol* 23:768-771, May 2002

- First 5 cases – 53% complications, after that 10%

#### Analysis of the Learning Curve in Telerobotic, Beating Heart Coronary Artery Bypass Grafting: A 90 Patient Experience

Richard J. Neuvick, MD, Stephanie A. Fox, RBCP, Bob B. Kiani, MD, Larry W. Sitt, MS, Reza Rayman, MD, Kojiro Kodera, MD, Alan H. Menkus, MD, and W. Douglas Bord, MD

- Ann Thorac Surg 2003 – 9 of first 18 with major complications, 9 of next 72 with major complications

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### Learning curve important for open radical prostatectomy

- All outcomes improve with surgeon experience
- Critical number 200-500 cases
  - Catalona et al J Urol 1999 (single surgeon)
  - Klein et al J Urol 2008 (multiple surgeons, 4 centers)
- Argument for regionalization
- Fellowship training may reduce the learning curve
  - Rosser et al Cancer 2006
  - First 66 patients post fellowship, same outcomes

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Learning curve robotic assisted  
radical prostatectomy

- Are patients hurt by the learning curve?

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Learning curve robotic assisted  
radical prostatectomy

- White et al Urol 2009
  - First 50 RARP compared to 50 historical RRP by same community surgeon (2005-2008)
  - Surgeon had performed >1200 RRP in career

	Margin positive	T2 (margin positive)
RRP	36%	34%
RARP	22%	19%

Adapted from White et al Urology 2009

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Learning curve robotic assisted  
radical prostatectomy

- Atug et al Eur Urol 2006
  - First 100 RARP divided into thirds
  - 3 advanced laparoscopic surgeons

#	1-33	34-66	67-100
+ margin	45.4%	21.2%	11.7%
T2 + margin	38.4%	13.7%	3.6%

Adapted from Atug et al Eur Urol 2006

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Learning curve robotic assisted  
radical prostatectomy

- Patel et al J Urol 2005 (positive margins – PSM)
  - First 100 – 13%
  - Second 100 – 8%
  - T2 – 5.7%
- Ahlering et al Urology 2004 (PSM)
  - First 45 – 35%
  - Next 60 – 16.7%
  - Next 60 - T2 – 4.5%

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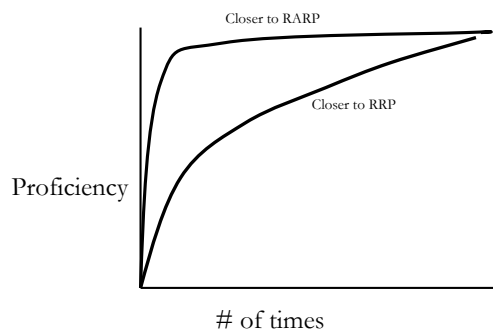
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### The learning curve

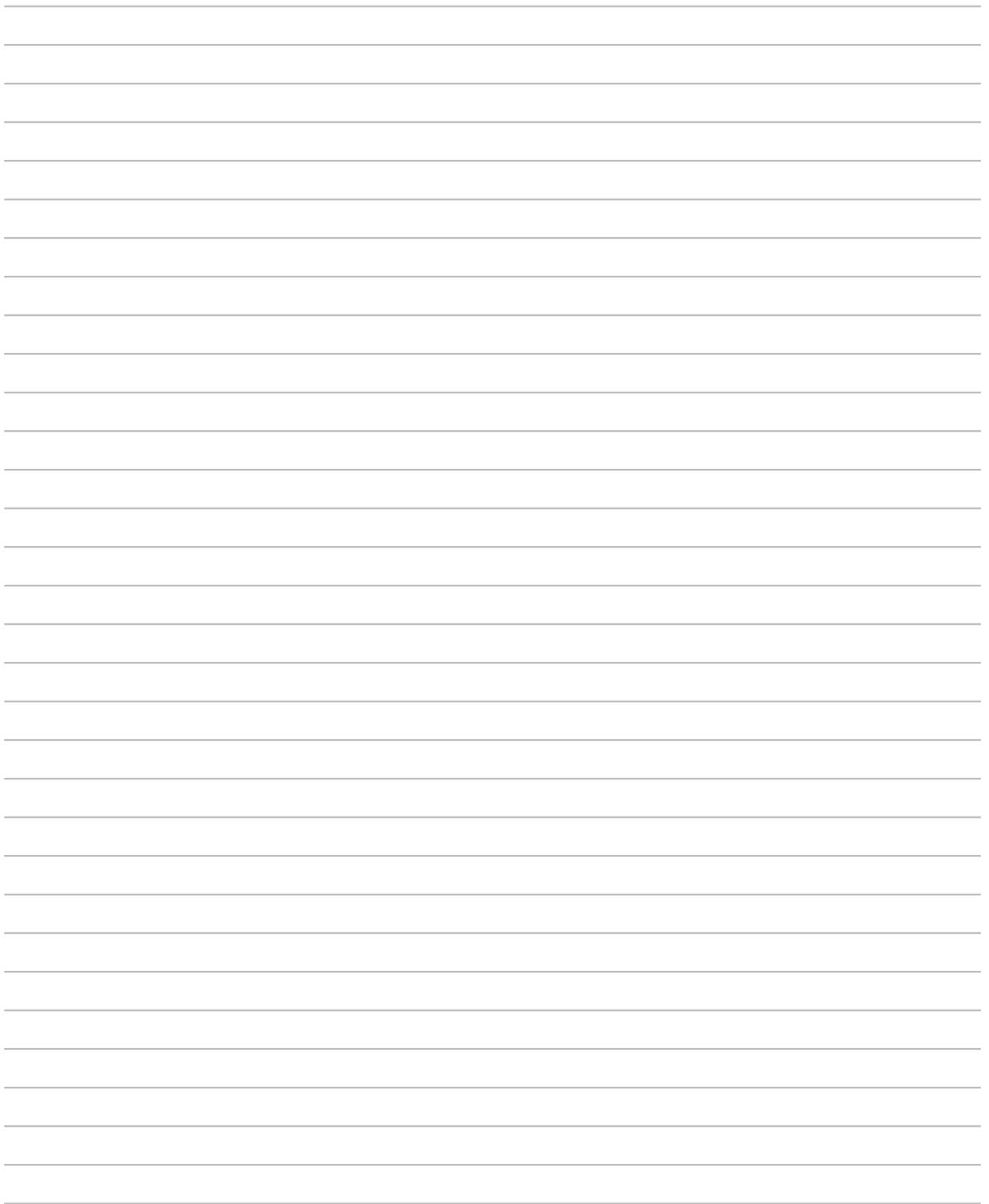


### Cost issues

- Technological costs decrease with time
- Must calculate in context of other treatments for PCa
  - RT highest cost (Crawford et al, presented at SCS AUA, 2009)
- Incremental cost will decrease as other specialties use more frequently

### Why robot assisted radical prostatectomy?

- Patients deserve the procedure with the steepest learning curve (and hopefully proficiency is achieved in training).
- It allows what only a few could do well to be done by a wider array of surgeons.



# Histologic Subtypes of Renal Cell Carcinoma

~ M. Scott Lucia, MD

## Histologic Subtypes of Renal Cell Carcinoma



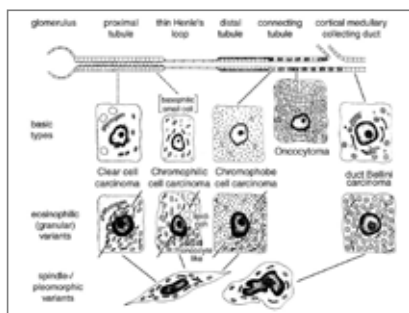
M. Scott Lucia, MD  
Associate Professor  
Chief of Genitourinary and Renal Pathology  
Director, Prostate Diagnostic Laboratory  
Dept. of Pathology  
University of Colorado Denver SOM

## 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, Scirrhous, 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.

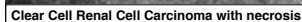
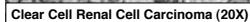
## The Mainz Classification 1986



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

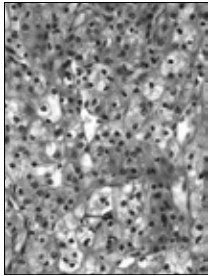
Tumor type	Freq	Histopathology	Cytogenetics
Clear cell RCC	70%	-Clear cytoplasm -Alveolar, tubular and cystic architecture -Vascular stroma	-3p, +5q, -6q, -8p, -14q
Chromophil RCC	15%	-Papillary architecture -eosinophilic, low N/C (type I) -eosinophilic, high N/C (type II)	Trisomy 7, 17, -Y, +3q
Chromophobe RCC	5%	-Solid architecture -Pale or granular cytoplasm -Prominent cell membranes -Occ. Bizarre nuclei	-1, -2, -6, -10, -13, -17, -21
Collecting duct Carcinoma	1-2%	-Medullary location -Tubuloglandular architecture -Hobnail cells -Desmoplastic stroma	-1q, -6p, -8p, - 13q, -21q

1. Kovacs et al. J Pathol 1997;183:131-3.

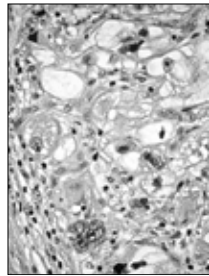


## Fuhrman grading predictive of outcome

Fuhrman grade II



Fuhrman grade IV



## Clear Cell RCC - Cytogenetics

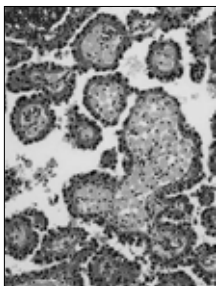
- Abnormalities involving VHL gene (3p25.3) (tumor-suppressor gene):
  - Deletion (3p-)
  - Translocation (3;6, 3;8, 3;11)
  - Somatic mutation or hypermethylation (80% RCC)
  - In both sporadic (95%) and familial (4%) RCC
- Familial, associated with VHL (Von Hippel-Lindau) syndrome:
  - Hemangioblastomas of the cerebellum and retina
  - Bilateral renal cysts
  - Multiple RCCs (nearly all, if they survive older age)

## VHL Gene

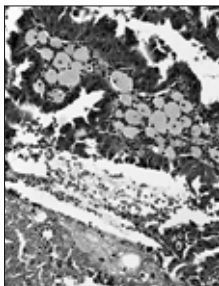
- VHL protein part of ubiquitin ligase complex
  - Degrades hypoxia-inducible factor (HIF-1)
  - Degrades insulin-like growth factor-1 (IGF-1)
- Loss/ mutation results in:
  - High levels of HIF-1 (stimulates angiogenesis via VEGF and TGF- $\beta$ )
  - Upregulation of IGF-1 (stimulates cells growth)

## Papillary RCC

Basophilic (Type I)



Eosinophilic (Type II)



Papillary RCC

- Hereditary and sporadic forms
  - Hereditary usually multifocal and bilateral
- Most common cytogenetic abnormalities:
  - Trisomy 7, 17 (hereditary and sporadic forms)
  - Loss of Y in male patients (sporadic form)
- Protooncogene locus on chromosome 7 (cMET):
  - Tyrosine kinase receptor for HGF
  - Mutated in some sporadic cases

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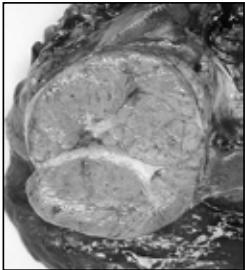
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Chromophobe renal cell carcinoma

- 5% of RCC
- Gross appearance:
  - Solid tumor
  - Mimics oncocytoma
- Derived from intercalated cell of collecting duct
- Numerous mitochondria and mitochondria-derived cytoplasmic vesicles



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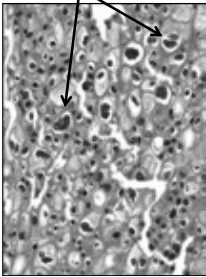
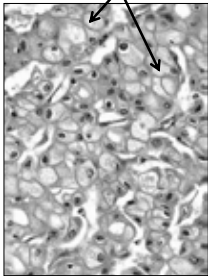
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Chromophobe renal cell carcinoma

Fuhrman grading not reliable

Prominent cell membranes

Bizarre atypical nuclei



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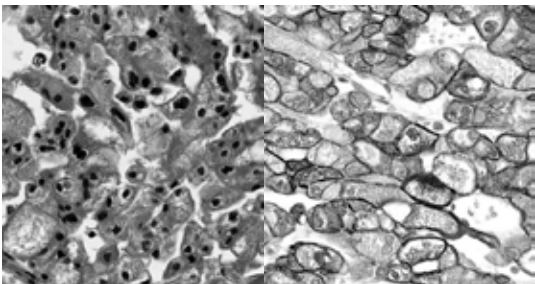
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Chromophobe RCC

Eosinophilic variant

CD117 Expression



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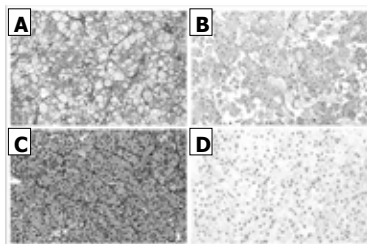
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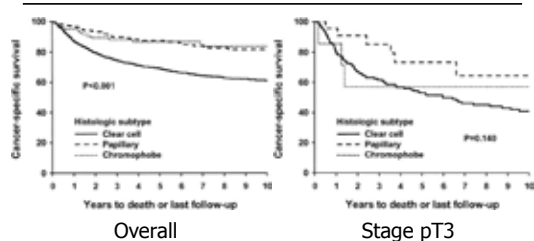
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A. Chromophobe RCC      B. Chromophobe RCC Colloidal iron  
C. Oncocytoma            D. Oncocytoma Colloidal iron

## Cancer-specific survival among clear cell, papillary and chromophobe RCC

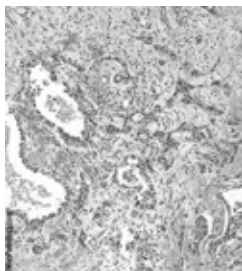


Cheville, J. et al. Amer J Surg Pathol 2003;27:612-624

Wolters Kluwer | OvidP Copyright © 2009 Wolters Kluwer

## Carcinoma of the Collecting Ducts of Bellini (Collecting Duct Carcinoma)

- Centrally located
  - Medullary origin
- Derived from principal cell of collecting duct
- Usually present in advanced stage and higher grade
- Medullary carcinoma
  - Aggressive variant of CDC that occurs in young black males with sickle cell trait



## 2004 World Health Organization Classification of Renal Cell Tumors

Expanded on Mainz and Heidelberg classifications to account for cytogenetics, behavior, and associated conditions

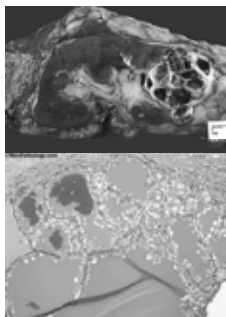
- Clear cell RCC
- Multi-focal clear cell RCC (VHL gene mutation, good prognosis)
- Papillary RCC (Type I=basophilic, good prognosis; type II=eosinophilic, worse prognosis)
- Chromophobe RCC
- Carcinoma of the collecting ducts of Bellini
- Renal medullary carcinoma
- Xp11 translocation carcinoma
- Carcinoma associated with neuroblastoma
- Mucinous, tubular, and spindle cell carcinoma
- Renal cell carcinoma, unclassified
- Papillary adenoma
- Oncocytoma

Expanded on Mainz and Heidelberg classifications to account for cytogenetics, behavior, and associated conditions

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  - Xp11 translocation carcinoma
  - Carcinoma associated with neuroblastoma
  - Mucinous, tubular, and spindle cell carcinoma
  - Renal cell carcinoma, unclassified
- 
- Papillary adenoma
  - Oncocytoma

- Good prognosis
- Most low grade (Fuhrman I or II)
- Usually stage I or II
- Mets not reported
- VHL mutations



Expanded on Mainz and Heidelberg classifications to account for cytogenetics, behavior, and associated conditions

- Clear cell RCC
  - Multi-focal clear cell RCC (VHL gene mutation, good prognosis)
  - Papillary RCC (Type I=basophilic, good prognosis; type II=eosinophilic, worse prognosis)
  - Chromophobe RCC
  - Carcinoma of the collecting ducts of Bellini
  - Renal medullary carcinoma
  - Xp11 translocation carcinoma
  - Carcinoma associated with neuroblastoma
  - Mucinous, tubular, and spindle cell carcinoma
  - Renal cell carcinoma, unclassified (5% of RCC)
- 
- Papillary adenoma
  - Oncocytoma

- The classification of renal cell carcinomas is expanding
- Classification has morphological and cytogenetic basis
- Proper classification important for prognosis

## Point-Counterpoint: Small Renal Masses

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

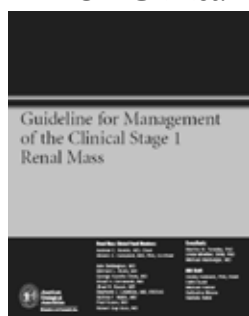
Best to Watch ~ *Donald L. Lamm, MD*

### Point-Counterpoint: Small Renal Masses Best to Remove

Paul D. Maroni, MD  
Assistant Professor  
Department of Surgery/Urology



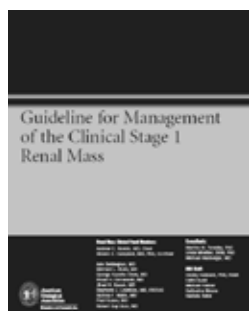
### AUA Clinical Guidelines 2009



Index 1 patient: SRM  
and healthy

- **Standard** – Partial nephrectomy if able
- If PN not feasible, then radical nx
- Cryo, RFA, and surveillance are **options**

### AUA Clinical Guidelines 2009



Index 1 patient: SRM  
and not healthy

- **Standard** – Partial nx or radical nx
- Cryo, RFA, and surveillance are **recommendations**

Small renal mass  
Best to remove

- Definition – enhancing renal mass ≤4cm (clinical T1a)

SRMs - Best to remove

- Why?
- Minimal risk
  - Effective treatment
  - A real medical threat
  - Improvements in peri-operative care

Risk of partial nephrectomy



	# Pts	Size	Compl.	Medical	Leak
Open	2756	3.2	21.3%	10%	3.9%
Lap	1062	2.7	21.4%	9.6%	4.2%

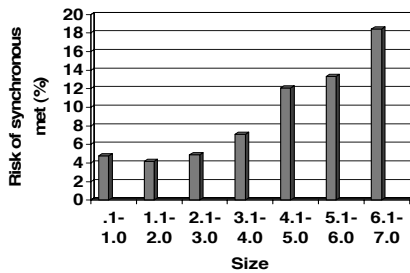
Adapted from Porpiglia et al Eur Urol 2008

Contemporary reality

- 1-3 day hospital stay (even with open surgery)
- 3-4 weeks of convalescence
- 98% 10-yr cancer specific survival
  - 100% with smaller tumors?
- ~4% local recurrence

*Exceptionally low-risk in healthy patients with excellent cancer control*

### Cancer risk



Adapted from Lughezzani et al J Urol 2009

### Cancer Risk

- Crispin et al Cancer 2009
  - 173 patients with enhancing renal mass on AS
  - 24 month median f/u
  - 1.3% developed metastasis
  - 15% exhibiting growth still had benign tumors
- Development of metastasis in 2-yr  
as high as 10-yr CSS for PN.  
Growth a poor indicator of cancer.***

### Cancer Risk

Growth Kinetics of Renal Tumors/Crispin et al

low risk of disease progression, the excellent oncologic outcomes obtained with prompt surgical intervention continue to indicate that extirpative therapy in acceptable candidates should remain standard. Identification of clinical, radiographic, pathologic, and molecular correlates of a tumor's biologic potential is essential to avoid potential overtreatment of otherwise indolent asymptomatic tumors.

### Real-life case

- 1987 – 63 yo male with abnormality on IVP in upper pole of right kidney
- 2004 – 81 yo male has 3-4cm mass identified in upper pole of right kidney. Cardiologist told him his cardiac risk was too high. Urologist told him his heart would kill him first.
- 2005 – 4cm – continue to watch
- 2006 – 5cm – continue to watch

- 2007 – 7cm, losing weight. Thinking more seriously about surgery. Saw cardiologist, PCP – all said not to operate.

MANAGEMENT OF RENAL MASSES IN PATIENTS  
MEDICALLY UNSUITABLE FOR NEPHRECTOMY—NATURAL  
HISTORY, COMPLICATIONS, AND OUTCOME

GAYN W. A. LAMB, TAMAR J. BRONWISCH, PAUL VASEY, and MICHAEL J. ARCHERSON

- 36 patients with renal masses 3.5-20cm in size (median 6)
- 23 had biopsy confirming RCC
- No deaths from cancer progression
- Generally slow growth (0.4cm/year)

- 2007 – 7cm, losing weight. Thinking more seriously about surgery. Saw cardiologist, PCP – all said not to operate.
- 2008 – 10 cm, flank pain. Local spread to liver and lung.
- August 2008 – dead from kidney cancer.

- How old is too old?
- How ill is too ill?

- Mortality 5.6% at one year

Example: Hypertrophic cardiomyopathy

- In hospital death – 6.7%

Ballotta et al Minerva Med 2009; Hreybe et al Clin Cardio 2006

- Do not discount surgery with the “eye-ball” test.
- Consultation with cardiologist and anesthesiologist.
- Balance surgical risks and cancer risks.
- Growth not indicative of cancer, but probably of malignant potential.



### Needle Biopsy of SRM

- Old Concept: Risk of bleeding, risk of seeding; necrosis, false negative biopsy common.
- New Concept (the facts):
  - Small cores or FNA rarely produce bleeding or AV fistula
  - Only 6 reported cases of tumor seeding (<0.01%); none recently with canula technique, small needles
  - FNA and core biopsies are accurate with experience: (97% sensitivity, 100% specificity)

Rodriguez, Sem Urol Oncol. 1995; Jewitt, Urol. Clin N Amer. 2008

### Does Delay Affect Outcome?

Rais-Bahrami: BJU Int. 103:1355-8, 2009

- 32 with SRM, mean 2cm; 5 yr follow
- 3 or more month delay (mean 16 months) in LPN compared with standard
- Mean growth .56cm/yr
- No increase in operative complications, blood loss or time.
- No local or distant recurrence

### How Effective is Cryoablation of SRM?

Stein: J Endourol. 22:2433-9, 2008.

- 30 SRM underwent lap cryoablation
- 84% had no enhancing mass at 3 months
- 90% by 6 months, only 1 (3%) of these 3 persisted by 9 months
- Lap partial nephrectomy on this mass showed no remaining carcinoma
- 100% short term (one year) complete response.
- Residual enhancement by 9 months may not indicate failure

### Meta-analysis: Cryo vs RFA

Kunkle: Cancer. 113:2671-80, 2008

- 47 series, 1375 SRM's
- Local progression: Cryo 5%, RFA 13% ( $p<.0001$ )
- Repeat ablation: 1% Cryo, 8% RFA ( $p<.0001$ )
- Metastasis: 1% Cryo, 2.5% RFA ( $p=0.06$ )
- Response criteria and short term follow up favor cryoablation over radio frequency ablation, though RFA is more frequently done percutaneously



## Female Urology “Potpourri”

~ Brian J. Flynn, MD

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### **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



## UTI

### Asymptomatic Bacteriuria

- generally does not require screening or treatment except in pregnancy
- risk of subsequent pyelonephritis in pregnancy increases to 28%
- treatment does not decrease incidence of positive follow-up cultures and may increase resistance
- no treatment is indicated until the patient becomes symptomatic

Perspectives in Urology 2009

## UTI

### Acute Uncomplicated Cystitis

#### Short Course

- female, young
- acute symptoms
- lack of systemic symptoms
- duration < 48 hours
- infrequent recurrence
- availability for reliable f/u

#### Extended Course

- male, older
- systemic toxicity
- concomitant diseases
- recurrence
- nosocomial
- tract abnormalities
- lack of follow-up

Perspectives in Urology 2009

## UTI

### Acute Uncomplicated Cystitis

- duration of treatment
  - Single dose v. 3 day v. longer
  - Single dose therapy has lost favor as recent evidence suggests lower cure rates and higher recurrence
  - 3 day regimen is generally preferred in relatively healthy adults
- can treat empirically without culture results in appropriate candidates

\* Clin Infect Disease 1999;29:745

Perspectives in Urology 2009

## UTI

### Acute Uncomplicated Cystitis

- Single-dose treatment
  - TMP/SMX DS x 2 tablets
  - Ciprofloxacin 500 mg x 1
  - Fosfomycin x 1 dose
- Three day treatment
  - TMP/SMX DS BID
  - Ciprofloxacin 250 mg BID\*
  - Other Beta-lactams
- Longer course may be used

\* Clin Infect Disease 1999;29:745

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UTI  
Complicated Cystitis

- patients predisposed to recurrent infection or treatment failure
- anatomic or functional factors
- DM, pregnancy
- h/o pyelonephritis
- men > 50 years of age
- urine culture necessary
- oral fluoroquinolone 1st line
- 10-14 day course

\* Clin Infect Disease 1999;29:745

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UTI  
Recurrent: Same or organism or different\*

- symptomatic UTI that follows clinical resolution of an earlier UTI
- common in post-menopausal women
  - residual urine
  - changes in microflora
- college women
  - 27% experience at least 1 Cx proven recurrent UTI within 6 months of tx

\* Orenstein R, et al: Am Fam Physician 1999

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UTI  
Prophylactic/Suppressive/Self-Start ABX  
Therapy

If a women experiences > 3 UCx proven UTIs/year

- Options
  - postcoital abx therapy if occurs following sex
  - self-start (3-day) therapy if no causal relation
  - suppressive abx therapy if more severe infections
- Suppressive abx therapy x 3 -6 months, stop then re-asses
  - Nitrofurantoin 50 mg daily
  - Bactrim DS ½ tablet daily
  - TMP 100 mg daily
  - Norfloxacin 200 mg daily

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Vulvovaginal Candidiasis  
'Vaginal Yeast Infection'

- Uncomplicated VVC Treatments
  - short courses of treatment (1-3 days) adequate for most uncomplicated cases; improved compliance
  - Clotrimazole 1% cream 1 applicator intravaginally for 7-14 days
  - Clotrimazole 500 mg vaginal tablet x 1 dose
  - Terconazole 6.5% ointment one applicator x 1 dose
  - Terconazole 0.4% cream one applicator QD x 3 days
  - Terconazole 80 mg vaginal suppository x 3 days
  - Fluconazole 150 mg tablet PO x 1 dose

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**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 ulcer)  
 Vascular catheter-associated infection  
 Serious gastrointestinal "acute events"  
 Foreign object retained after surgery  
 Air embolism  
 Blood incompatibility  
 Falls and trauma  
 Manifestations of poor glycemic control  
 Endemic keratoconjunctivitis  
 Neuroleptic malignant syndrome  
 Hypoglycemia, severe  
 Secondary diabetes with ketoacidosis or hyperosmolality  
 Deep venous thrombosis 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  
 Intrigene pneumonia  
 Legionnaire disease  
 Tuberculosis

\* 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

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**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

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**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

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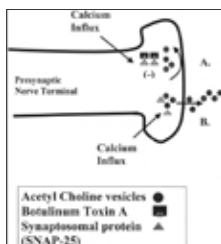
## Perspectives in Urology 2009

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### 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

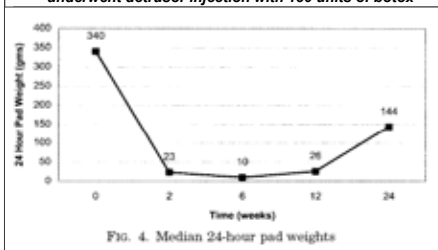


FIG. 4. Median 24-hour pad weights

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

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- Perspectives in Urology 2009

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**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/CPP or neurologic condition) refractory to anti-muscarinics

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**Management of Pelvic Organ Prolapse**

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**Anatomy of Vaginal Support  
POP Location <sup>1</sup>**

- |                      |     |
|----------------------|-----|
| • 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% <sup>2-6</sup> |

<sup>1</sup> Olsen et al. *Obstet and Gynecol* 1997;89:501-506<sup>2</sup> Shull et al. *Am J Obstet Gynecol* 1992;166:1764-1768<sup>3</sup> Holley et al. *South Med J* 1995;88:547-549<sup>4</sup> Samuelsson et al. *Am J Obstet Gynecol* 1999;180:299-305<sup>5</sup> Shull et al. *Am J Obstet Gynecol* 2000;183:1365-1373<sup>6</sup> Weber et al. *Int Urogynecol J Pelvic Floor 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<sup>1,2</sup>
- 60% of the recurrences are at the same site<sup>3</sup>
- 32.5% of the recurrences are at a different site<sup>3</sup>

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

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**PROLIFT System: Early Outcome Data<sup>1</sup>**

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. Dysfn.-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 Dysfn-1	2 (4.7%) S=N/A	6 mo.	35 (81.4%)

<sup>1</sup>IUGA – Fallon - 2006 Abstracts all published in: Int Urogynecol J 2006;<sup>1</sup>**PROLIFT System: Early Outcome Data<sup>1,2</sup>**

Author	# Pts	Mean Age	Site	Complications	Exposure	Length of Follow Up	"Success" (≤ Stage II)
Groenen MJC et al. (Netherlands) <sup>1</sup>	26	61	A-6 P-10 T-10	Vd.dysfn-5	1 (3.8%) S=N/A	2 mo.	26 (100%)
Perscheier M et al. (Austria) <sup>1</sup>	80	N/A	N/A	Cystotomy-2 Hematomas-2	8 (10%) S=5 (50%)	N/A	N/A
Rivera JM et al. (USA) <sup>2</sup>	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 dysfn- 6.7%	34 (6.2%) S=12 (2.6%)	6 mo.	81.4-100%

<sup>1</sup> IUGA – Fallon - 2006 Abstracts all published in: Int Urogynecol J 2006;17(S.2):S212<sup>2</sup> AUGS 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

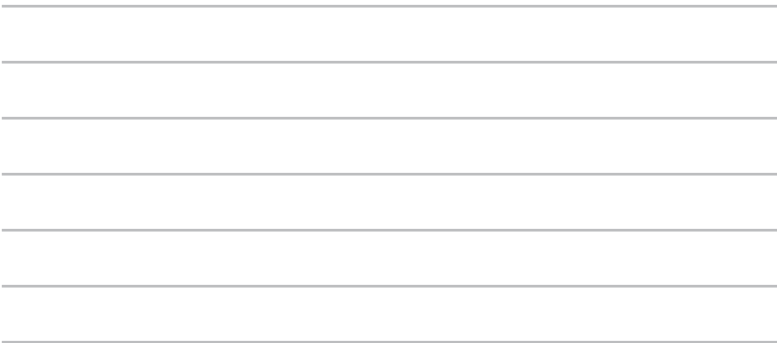
\* Jia x et al: BJOG 2008

**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

\* Jia x et al: BJOG 2008

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### 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)

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### 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

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### 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

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### 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

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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

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Management of Complications of  
SUI and Prolapse Surgery

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Complications  
What could happen?

Intraoperative

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

Postoperative

- Erosion/extrusion
- Fistula
- Urinary retention
- Pain
- Osteitis Pubis
- Infection
- Voiding dysfunction
- Failures

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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<sup>\*</sup>

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

<sup>\*</sup> Bemelmans BLH and Chapple, CR: Cur Opin Urol Urol 2003  
<sup>†</sup> Meschia M, et al: IntUrogynecol J Pelvic Floor Dysfunct 2001  
<sup>‡</sup> Giri SK, et al: Urol 2007

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### Graft Complication

#### CU Criteria for Simple v. Complex Graft Complications

	Simple	Complex
Mesh Type	Type 1 mesh	Type 2, 3, 4 mesh especially if mesh has been withdrawn from market
Timing to presentation	early < 6 weeks	delayed ≥ 6 weeks
Location of extrusion	suture line	remote from suture line
Depth of mesh	deep	embedded in vaginal wall, "cobblestone vagina"
Prior excisions	none	≥ 1
Associated inflammation	none/minimal	obvious purulence
Affected organ	vagina only	bladder, urethra, rectum

Terlecki RT and Flynn BJ: AUA update series 2010

### Vaginal Wall Mesh Erosion

#### Predisposing Factors

##### Etiology

Ischemia, infection, iatrogenic

##### Patient characteristics

- Elderly
- Post-menopausal
- Radiation
- Vaginal infection

##### Surgical factors

- Button holes
- Unrecognized trocar injury
- Hematoma, infection, wound closure
- Mesh too superficial in vaginal wall

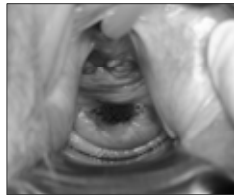
Terlecki RT and Flynn BJ: AUA update series 2010

### Vaginal Wall Mesh Extrusion

#### Diagnosis

##### Diagnosis

- High index of suspicion
  - vaginal bleeding > 6 wks
  - dyspareunia
  - 'scratchy vaginal wall'
  - partner pain on intercourse ('hispareunia')
- Meticulous follow-up
  - 6 wks, 3 mos, 1 yr and PRN
- Clear plastic speculum



Terlecki RT and Flynn BJ: AUA update series 2010

### Vaginal Wall Mesh Extrusion Prevention During Prolapse Surgery

#### Intra-operative

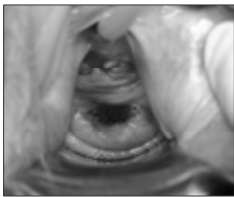
- generous hydrodissection
- transverse incisions
- careful tissue handling
- full-thickness dissection
- avoid button holes, trocar injury
- avoid incision over the vaginal cuff
- avoid concomitant hysterectomy
- avoid redundancy of mesh, no tension
- proper incision closure
- do not excise redundant vaginal wall

Terlecki RT and Flynn BJ: AUA update series 2010

Vaginal Wall Mesh Extrusion  
Initial Management

Initial Management

- pelvic rest
- avoid heavy lifting
- antibiotics?
- vaginal estrogen
- local mesh excision or “trimming” in clinic



Terlecki RT and Flynn BJ: AUA update series 2010

Vaginal Wall Mesh Extrusion  
Conservative Management

Retrospective review of the management of 4 vaginal wall mesh extrusions after SPARC sling in a single institution

- 2 patients presented with vaginal discharge
- 1 of which stated her partner had pain during intercourse
- 2 patients were asymptomatic
- Each patient was observed conservatively
- At 3 months postoperatively all 4 had complete spontaneous epithelialization over the mesh
- No patient developed had SUI, urgency or obstruction

Kobashi, KC and Govier, FE: J Urol 2003

“In my personal experience in management of more than 50 vaginal wall erosions I have seen only 1 erosion heal spontaneously.”

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Vaginal Wall Mesh Extrusion  
Management in Prolapse Cases

Minor Extrusion (<8 weeks post-op)

If mesh non-redundant below plane of vaginal wall defect

- Vaginal estrogen
- Local mesh excision in clinic
- Pelvic rest, avoid heavy lifting

Large (> 2 cm), Recurrent

Late Erosion (> 8 weeks)

- Excision of exposed mesh
- Raise 1 cm rim around exposed area
- Vigorous washout with bacitracin, betadine
- 2-layer closure (4-0 PDS running stitch, 4-0 PGA Mattress stitch)
- Consider alloderm for severe vaginal wall loss

Terlecki RT and Flynn BJ: AUA update series 2010

Urethral Erosion  
Prevention

Patient Selection

Avoid the use of mesh in patients with

- XRT, infected field, neurogenics, diverticulum
- Occlusive slings

Urethra obstruction

Postop

- Do not delay urethrolisis
- Avoid urethral dilation

Terlecki RT and Flynn BJ: AUA update series 2010

Handwritten notes area with horizontal lines.

### Urinary Tract Sling Erosion

#### Urethrolisis: Contemporary Outcomes

Study	No.	Type	Management	Outcome
Kobashi et al 1999	7/34	ProteGen	Sling removal Marius (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 3/3	Nonsynthetic Synthetic	Sling incision Sling removal Marius (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

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### 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

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### Institutional Sling Extrusion Data April 2003-Present


Vaginal Wall extrusion and urinary tract erosion

**Vaginal wall extrusion/pain**


- retropubic tape 1 of 72 (1.4%)
- TVT-O, 4 of 190 (2.1%)
- TVT-S, 1 of 119 (0.8%)
- Biological PVS, 0 of 60
- AUS, 0 of 9

**Urinary tract erosion**

- retropubic tape 1 of 72 (1.4%)
- TVT-O, 1 of 190 (0.5%)
- TVT-S, 0 of 119
- Biological PVS, 0 of 60
- AUS, 0 of 9



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### 2010 SUFU Abstract: MANAGEMENT OF POLYPROPYLENE MESH COMPLICATIONS (VAGINAL WALL EXTRUSIONS AND URINARY TRACT EROSIONS) AFTER SURGERY FOR SUI AND POP

Flynn BJ et al, Denver, CO

39 patients that underwent mesh explantation due to recurrent vaginal wall extrusions and/or urinary tract erosions performed by BJF (2003-2009) were analyzed

- treatment based upon CU algorithm for mesh complications
- patients classified as “simple” or “complex” graft complication
- simple graft complications treatment
  - in office partial mesh excision
  - OR excision, washout, and primary closure
- complex graft complications treatment
  - near total mesh excision, washout, repair of the urinary tract/vaginal wall, and concomitant placement of biological graft

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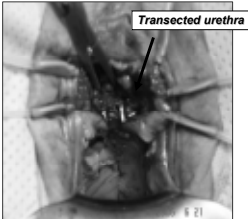
### Polypropylene Mesh Complication Algorithm Location and Severity

Minor (n = 17)	Severe (n = 22)
<div>Vaginal wall extrusion</div> <div><ul style="list-style-type: none"><li>Partial mesh excision</li><li>Primary vaginal wall closure</li></ul></div> <div>Recurrent (n = 4)</div>	<div>Recurrent vaginal wall extrusion or urinary tract erosion</div> <div><ul style="list-style-type: none"><li>Abd/vag mesh explant</li><li>Urethral/bladder repair</li><li>Biological re-implant</li></ul></div>

Terlecki RT and Flynn BJ: AUA update series 2010

### Polypropylene Mesh Complication Algorithm Operative Technique for Severe Graft Complication \*

- Abdominal/vaginal removal of mesh straps
- total explant of retropubic tapes, mini-slings
- removal of vaginal portion of TOT, prolapse mesh
- Urinary tract repair



- Biological re-implant
  - autologous RF PVS for slings
  - alloderm for prolapse kits
- 12 Fr foley (10-14 days) if urinary tract erosion

\* Flynn BJ et al: SUFU 2010

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### 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 assess 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

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### 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



18th Annual

**PERSPECTIVES IN UROLOGY**  
**POINT COUNTERPOINT 2009**

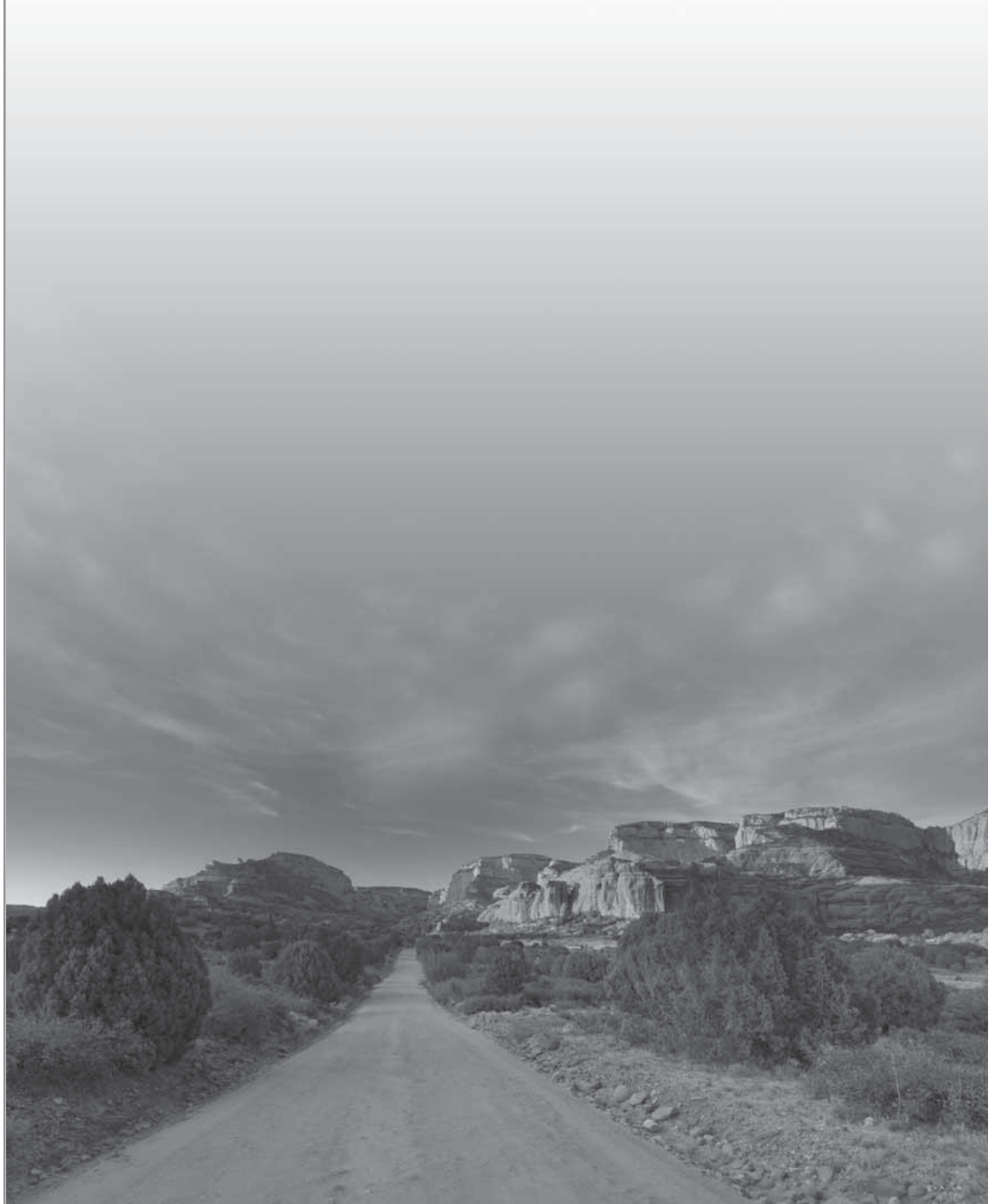
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Friday, November 6, 2009

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

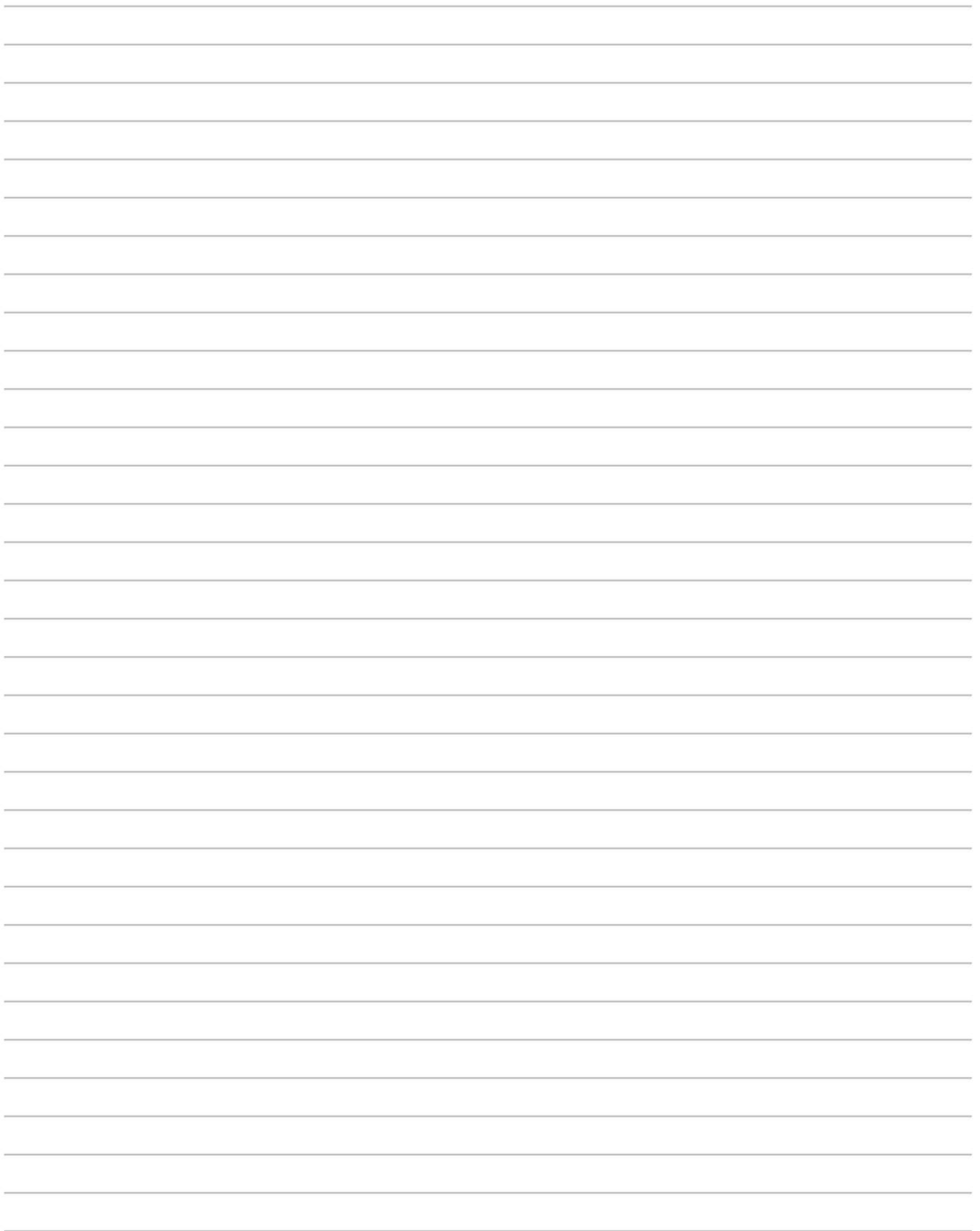
Clinical Challenges

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	



## Panel: A Case-based Approach to the Management of Bladder Cancer

~ Moderator: Robert Donohue, MD

Panel: David C. Beyer, MD • E. David Crawford, MD

Donald L. Lamm, MD • Paul D. Maroni, MD

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### TCC Cases

Robert E. Donohue M.D.  
Denver VAMC  
University of Colorado

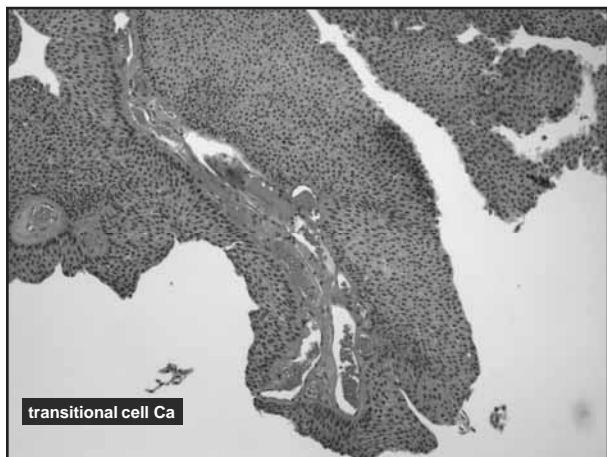
### Bladder cases

ChRx immediately post-op  
second look  
BCG instillation induction and maintenance  
N+, LE+,  
fever,  
restart,  
Drug Eluting Stents  
diverticulum  
T2 1] reTRBT 2] bCh Rx 3] Cystectomy 4]  
Bladder preservation 5] neo-adjuvant Ch Rx  
+ cystectomy

### Bladder cases #1

65 - gross hematuria  
CT extensive tumor  
1<sup>st</sup> TURBT – incomplete TURBT  
resected 50%; slides 1 / Ta  
2<sup>nd</sup> TURBT – resect remainder  
only small am't; slides 1 / Ta  
3<sup>rd</sup> TURBT – second look,  
slides; negative for tumor

~ Moderator: Robert Donohue, MD | Panel: David C. Beyer, MD • E. David Crawford, MD • Donald L. Lamm, MD • Paul D. Maroni, MD



**65 - gross hematuria**  
**CT extensive tumor**  
**1<sup>st</sup> TURBT – incomplete TURBT**  
**resected 50%; slides 1 / Ta**  
**2<sup>nd</sup> TURBT – resect remainder**  
**only small am't; slides 1 / Ta**  
**3<sup>rd</sup> TURBT – second look,**  
**slides; negative for tumor**

HARRY W. HERR

*From the Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York*

**J.U. 162: 24, 1999**

## Panel: A Case-based Approach to the Management of Bladder Cancer

~ Moderator: Robert Donohue, MD | Panel: David C. Beyer, MD • E. David Crawford, MDDonald L. Lamm, MD • Paul D. Maroni, MD

### REPEAT TRANSURETHRAL RESECTION TO EVALUATE BLADDER TUMORS

TABLE 1. Comparison of bladder tumor stage after first and second transurethral resections

Stage at First Transurethral Resection	No. Pts.	No. Stage at Second Transurethral Resection (%)			
		T0	Ta/Tis	T1	T2
Tis	20	8 (30)	8 (40)	4 (20)	2 (10)
Ta	18	5 (28)	7 (39)	5 (28)	1 (5)
T1:	58	13 (22)	15 (26)	14 (24)	16 (28)
Muscle	35	9 (26)	11 (31)	10 (29)	5 (14)
No muscle	23	4 (17)	4 (17)	4 (17)	11 (49)
T2	54	12 (22)	7 (13)	3 (6)	30 (55)
Totals	150	36 (24)		114 (76)	



## Bladder cases #1

65 - gross hematuria  
instillational chemotherapy  
after each resection ?  
“second” look ?  
q 3 or 6 month follow-up ?

### Management of Low Grade Papillary Bladder Tumors

Harry W. Herr, S. Machele Donat and Victor E. Reuter

From the Departments of Urology and Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York

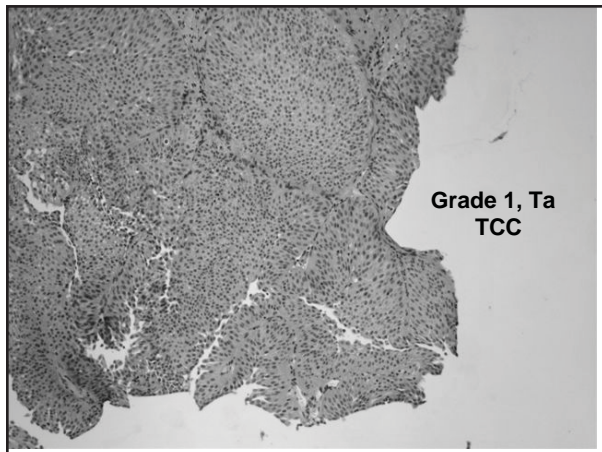
JU 178: 1201, 2007

## 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

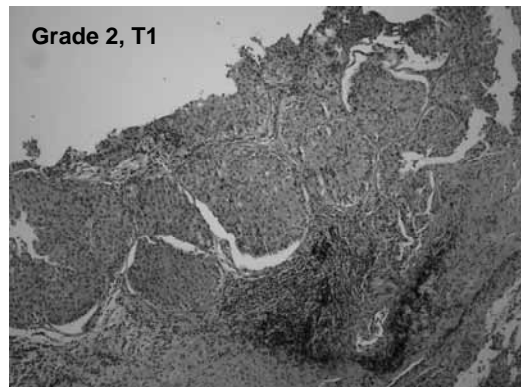
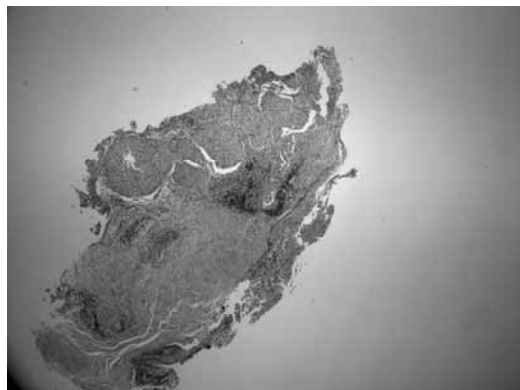
## Bladder cases #3

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 ?

**71 – 2000 - gross hematuria, smoker,  
TURBT 1-2 / Ta  
BCG x 2years,  
Oncovite x 4 years  
no recurrence  
LFTs abnormal – 2004  
Ampulla of Vater tumor,  
Whipple, Miami**

**75 - 2005**  
recurrent tumor, 1 / Ta  
LFTs are normal, NED surgery

**78 - 2008**  
recurrent tumor, 2 / T1



## 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

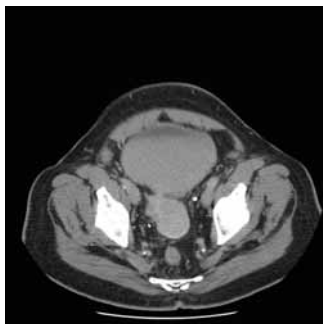
diverticulum, tumor

co-morbidities

Hpt, DM II, overweight, diverticulitis

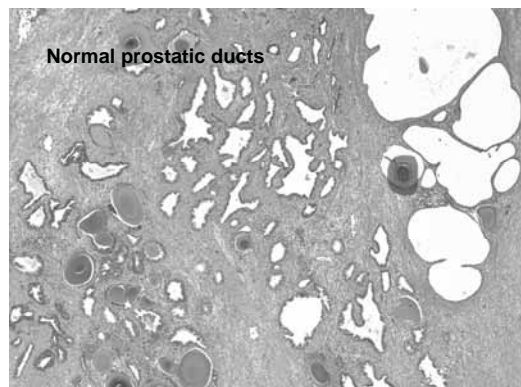
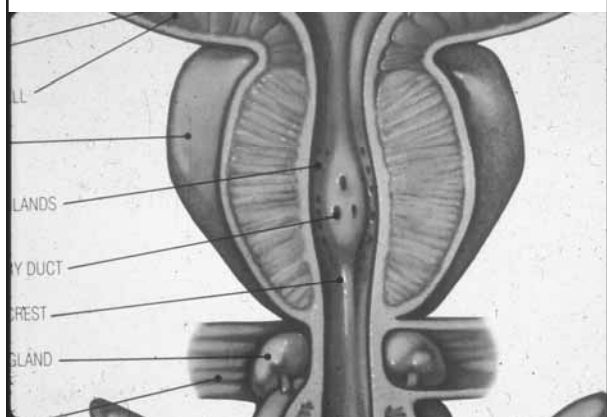
TURBT; diverticular tumor, 2/T1

bladder mapping, negative



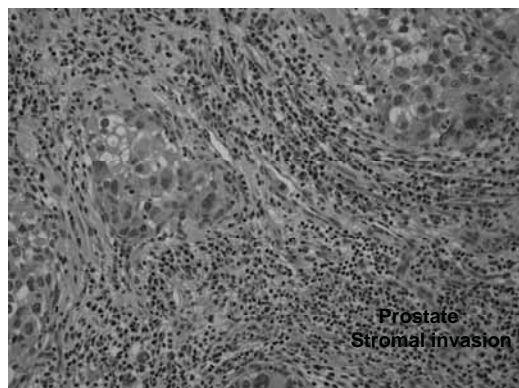
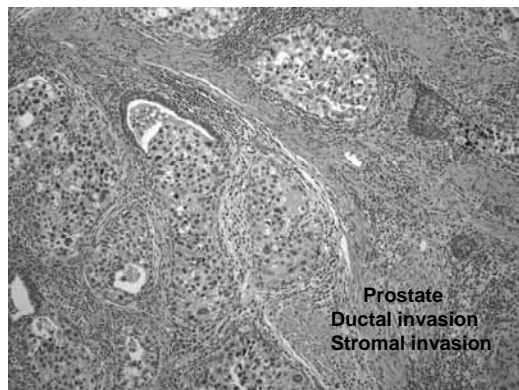
**bladder mapping negative**  
**Where do we take biopsies ?**  
**How many ? Technique ?**  
**what about prostatic urethra ?**  
**WHERE ?**

**distal prostatic urethra**  
**WHY ?**  
**ductal invasion ?**  
**stromal invasion ?**  
**stromal invasion has a terrible**  
**prognosis !**



## Panel: A Case-based Approach to the Management of Bladder Cancer

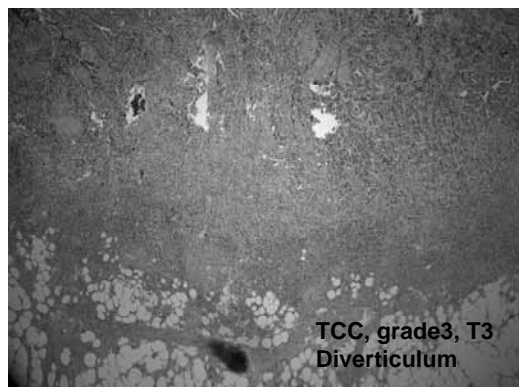
~ Moderator: Robert Donohue, MD | Panel: David C. Beyer, MD • E. David Crawford, MD • Donald L. Lamm, MD • Paul D. Maroni, MD



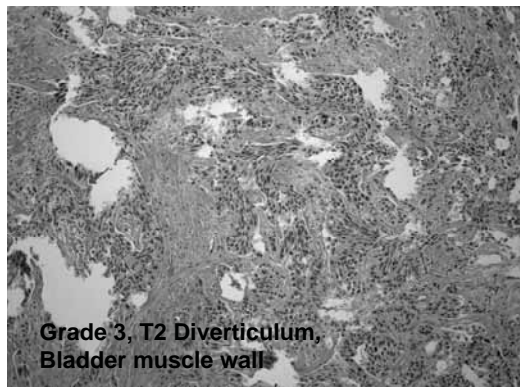
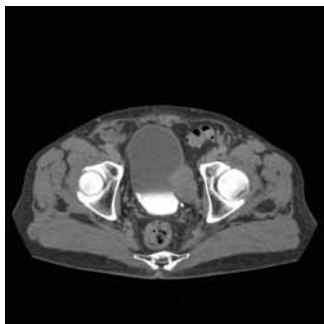
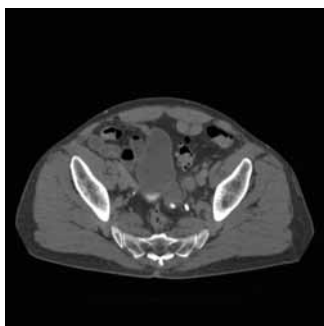
### Bladder cases #5

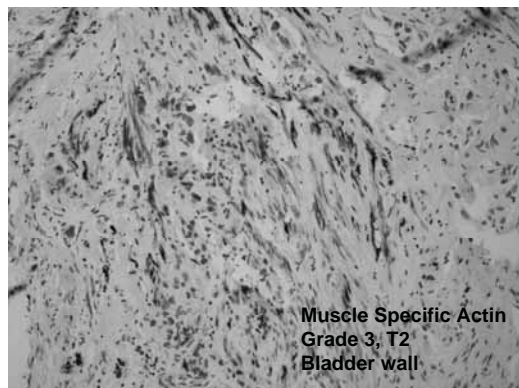
options

cystectomy vs partial cystectomy  
nodes to be done,  
tumor is on one side, extent LN  
requirements for partial  
first tumor  
cystoscopy, bladder negative  
bladder mapping negative



**62 gross hematuria for 4 months**  
**2 diverticula**  
**inferior diverticulum – stone**  
**superior diverticulum –**  
**extensive tumor exiting**  
**the neck of the diverticulum**  
**into the bladder**





## Bladder cases #6

62 gross hematuria for 4 months  
2 diverticula  
tumor into the bladder; 2 / T2  
not a candidate for partial cyst  
lymph node dissection extent ?

## Bladder cases #6

62 gross hematuria for 4 months  
diverticulum tumor but tumor  
extends into the bladder; 2 / T2  
not a candidate for partial cyst  
lymph node dissection extent  
more nodes, negative, better ?  
“ “ positive nodes, better ?  
proximal nodes positive,  
distal nodes, IMA, neg, Yes

## Bladder cases #7

57 year old male  
coronary artery disease  
drug-eluting stents, DES, April 2008  
Plavix and Aspirin for one year  
gross hematuria August 2008  
cystoscopy and cytology  
November 2008  
single papillary tumor



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**Bladder cases #7**

What to do ?  
bleeding to death  
see patient yourself  
bleeding is 3 RBCs/ hpf  
What to do ?  
is bleeding to death ?  
how is risk assessed ?  
at 1 month, 3 months, 8 months ?

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**Bladder cases #7**

What to do ?  
waited for year  
uneventful TURBT  
vs  
TURBT within year; 40% mortality  
as months progress from DES  
placement, mortality from  
coronary thrombosis lessens.

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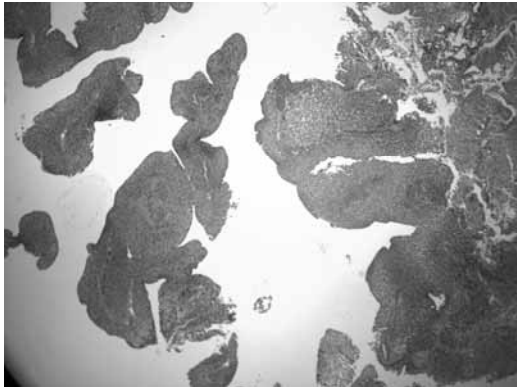
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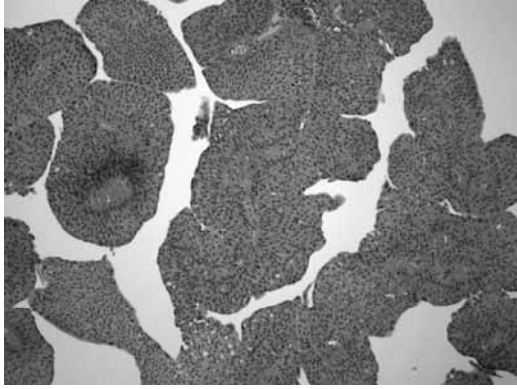
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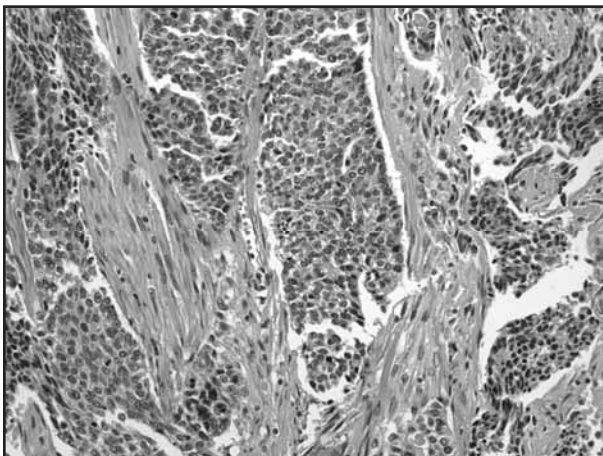
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## Bladder cases #8

55 - gross hematuria,  
long history of smoking,  
cytology positive,



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

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**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

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**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 ?

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

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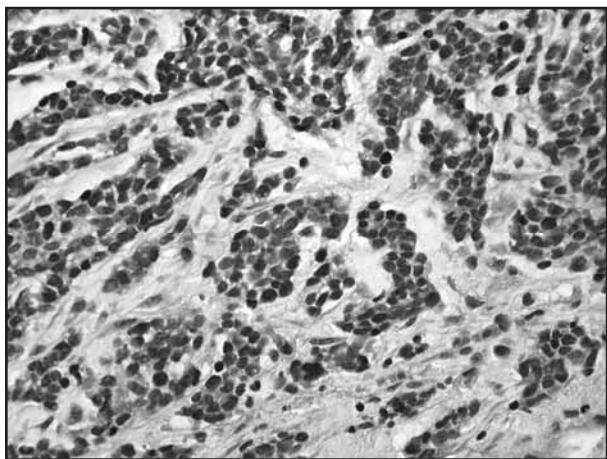
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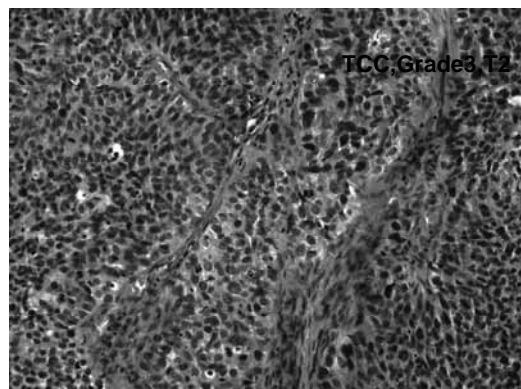
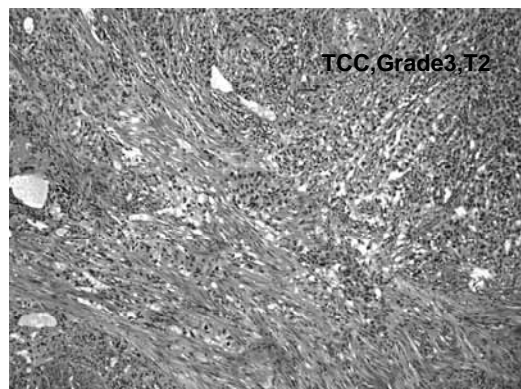
## Bladder cases #9

55, bartender  
extensive tumor  
TURBT  
small cell carcinoma  
neo-adjuvant ChRx  
What therapy ?  
transitional cell therapy or  
small cell therapy ?

## Bladder cases #9

55, bartender  
neo-adjuvant small cell ChRx  
cis-platinum and VP 16  
complete response  
radical cystectomy, ileal conduit  
pathology pTo ;  
follow-up ?

**64, gross hematuria Grade 3 / T2  
terrible candidate for surgery  
350 pounds, CABG x 6,  
3 packs a day and refuses  
to quit or even lessen smoking**



## Bladder cases #10

64, gross hematuria Grade 3 / T2  
options

repeat TURBT

chemotherapy

cystectomy

bladder preservation

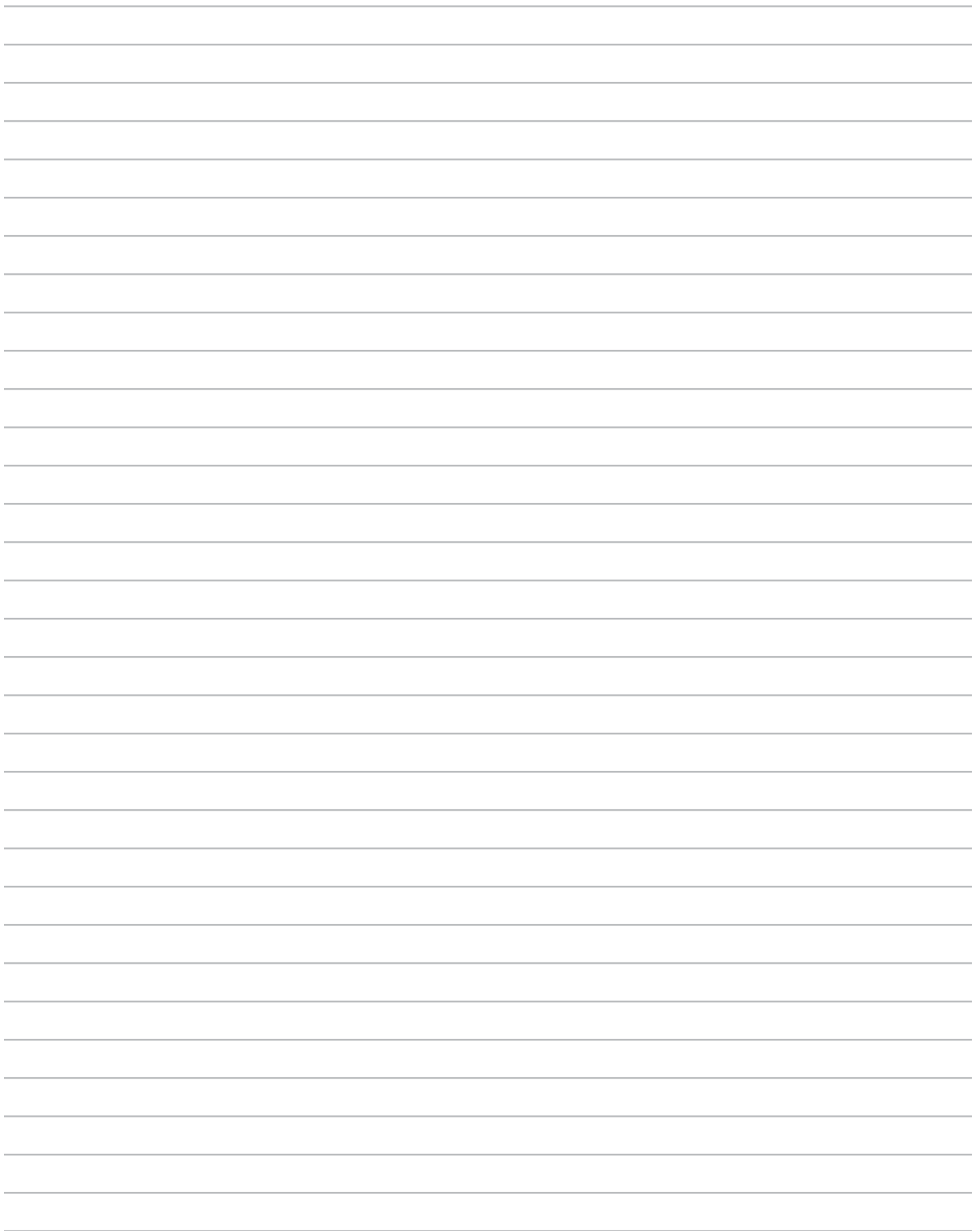
ChRx + ChXRT

neo-adjuvant ChRx + cystectomy

## Bladder cases #10

64, gross hematuria Grade 3 / T2  
repeat extensive TURBT  
negative for tumor

Patient elected surveillance !



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

~ Donald L. Lamm, MD

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### 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

Low-Risk		Definitions	Intermediate-Risk	High-Risk
<b>EAU</b>	G1-2Ta	Mult G2Ta, G1T1, sol G2T1	Mult G2T1, G3Ta-T1, CIS	
<b>FICBT</b>	Low-grade Ta	Rec or mult Low Grade	High-grade Ta, all T1, CIS	
<b>NCCN</b>	G1-2Ta	G3Ta, solitary G1-2T1	Multifocal T1, G3T1	
<b>AUA</b>	Small, low-grade Ta	Mult or large low-grade Ta	High-grade Ta, all T1, CIS	
<b>IBCG</b>	Sol low-grade Ta	Rec or mult low-grade Ta	All High grade, T1 and CIS	
<b>Risk:</b>	<b>Rec: moderate Prog: low</b>	<b>Rec : mod to high Prog: low to mod</b>	<b>Rec: high Prog: high</b>	

- Low risk: Immediate postop chemotherapy. BCG is NEVER given immediately postop!
- Intermediate risk: Immediate postop chemo; chemotherapy x6 previously recommended. Now 3 wk. maintenance BCG: Level 1 evidence
- High Risk: BCG immunotherapy, cystectomy for failure

- Second hand smoke, pesticides, diesel fuel and organic chemical exposure, as well as excessive exposure to dyes should be avoided.
- Water reduces BT risk, but only if free of arsenic and insecticides.
- Fruit and vegetables: reduce carcinogenic DNA adducts in urine.
- Soy: genistein is excreted in the urine in active form and kills 7/8 human BT cell lines in vitro.
- Broccoli: only 3 servings a month reduced BT risk up to 50% in 3 independent studies.
- Garlic: randomized controlled murine trial in my lab demonstrated that oral garlic supplement significantly reduced MBT2 growth and cancer death.
- High dose vitamins A, B6, C and E plus zinc significantly reduced BT recurrence (40%) in pts with suboptimal BCG, but not optimal maintenance.

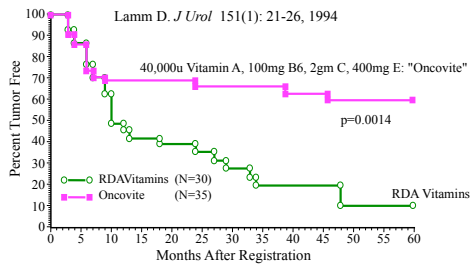
Group	Inc d2	Vol d35	Survival d50
Saline:	18 (90%)	4047	4 (20%)
BCG:	3 (15% <sup>***</sup> )	390 <sup>***</sup>	15 (75%) <sup>***</sup>
AS5mg:	17 (85%)	4670	3 (15%)
AS50mg:	14 (70%)	2563 <sup>**</sup>	8 (40%)
AS 500mg:	12 (60%)	1644 <sup>***</sup>	10 (50%) <sup>*</sup>

\*P<.05; \*\*P<.025; \*\*\*P<.001

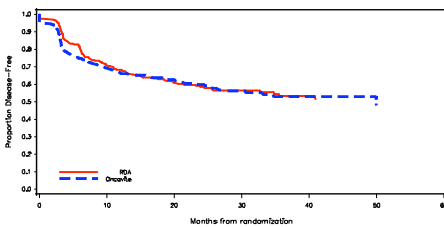
Lamm DL: J Nutr. 2001;131:1067S

## Kaplan Meier Estimate of 5 Year Tumor Free Rate

In Patients Receiving Vitamin Supplement and BCG Therapy  
For Bladder Carcinoma



## Efficacy Results – Disease Free Interval BCG + RDA vs BCG + Oncovite



## Comparison of Guidelines for Intermediate Disease

EAU (Multifocal G2Ta, G1T1, solitary G2T1)

- TURBT; Single, immediate post-operative instillation of chemotherapy followed by:
  - 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)

- TURBT; Single immediate post-operative instillation of chemotherapy
- Adjuvant intravesical therapy: First-line: intravesical chemotherapy < 6 months (grade B). Second-line: BCG (grade A)

NCCN (G3Ta, solitary G1–2T1)

- TURBT>Observe or Intravesical therapy
- BCG (preferred) (category 1) or Mitomycin (category 2A)

AUA (Multifocal and/or large volume low-grade Ta or recurrent low-grade Ta)

- TURBT, Intravesical BCG or mitomycin C (recommendation)
- Maintenance BCG or mitomycin (option)

IBCG: 3 week maintenance BCG based on Level 1 evidence from EORTC

## 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

Comparison of Guidelines for High Risk Disease

- EAU (Multiple G2T1, G3Ta-T1 )
- 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)
    - Multiple recurrent high-grade tumours
    - High-grade T1 tumours
    - High-grade tumours with concomitant CIS
- CIS: Intravesical BCG plus maintenance for at least 1 year (grade A)
- Assess response at 3 months: If no response:
    - 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)

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Comparison of Guidelines for High Risk Disease

- FICBT (High-grade Ta; T1 or CIS)
- Second-look TURBT and bladder mapping biopsies in 2-4 weeks for Ta or T1 (grade B)
  - If residual tumor is found: Re-resection and one immediate instillation of chemotherapy
    - Followed by 6-week BCG induction and 1-3 years of BCG maintenance (grade A)
- NCCN (T1, G3)
- Complete Resection: BCG preferred (category 1) or mitomycin (category 2A); Consider cystectomy
  - Uncertain Resection: Repeat resection or cystectomy
    - If positive: BCG (category 1) or cystectomy (category 2A)
    - If negative: BCG (category 1) or mitomycin (category 2A)
  - Any CIS/Tis: Complete resection followed by intravesical BCG
- AUA and IBCG (High-grade Ta, T1 and/or CIS)
- \* Repeat resection if lamina propria invasion without muscularis propria in specimen prior to intravesical therapy (standard)
  - Induction BCG followed by maintenance (recommendation)
  - Cystectomy (option)

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Can BCG Delay or Prevent  
Progression in Superficial Bladder Cancer ?  
Sylvester R: J Urol. Nov., 2002

- Meta-analysis of 24 studies, 4863 patients randomized to BCG vs surgery alone (2), BCG maintenance (3), chemotherapy (14), or other immunotherapies (5).
- 2.5 year median follow (max 15)
- 82% Ta, T1, 37% G1, 55% G2, 8% G3; 18% CIS
- 78% received maintenance BCG, 10-30 Rx over 18 weeks to 3 yrs.

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Progression

Treatment	Progression
• No BCG	304/2205 (13.8%)
• BCG	260/2658 ( 9.8%)
Difference	4.0%
Odds ratio (OR)	0.73
Odds reduction	27% (95% CI: 11%-40%)
P Value	0.001

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## Progression: Maintenance BCG

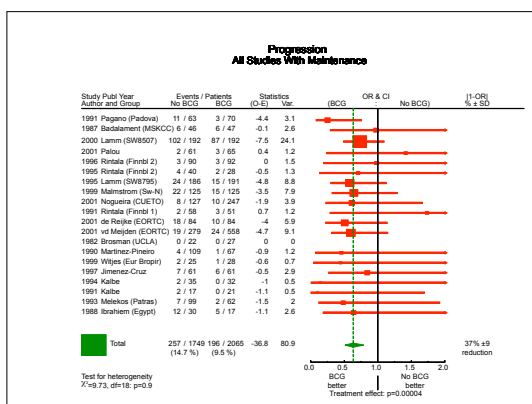
Patients  
OR

No Maint 1049 10.3% 10.8%

1.28  
Maintenance 3814 14.7% 9.5%

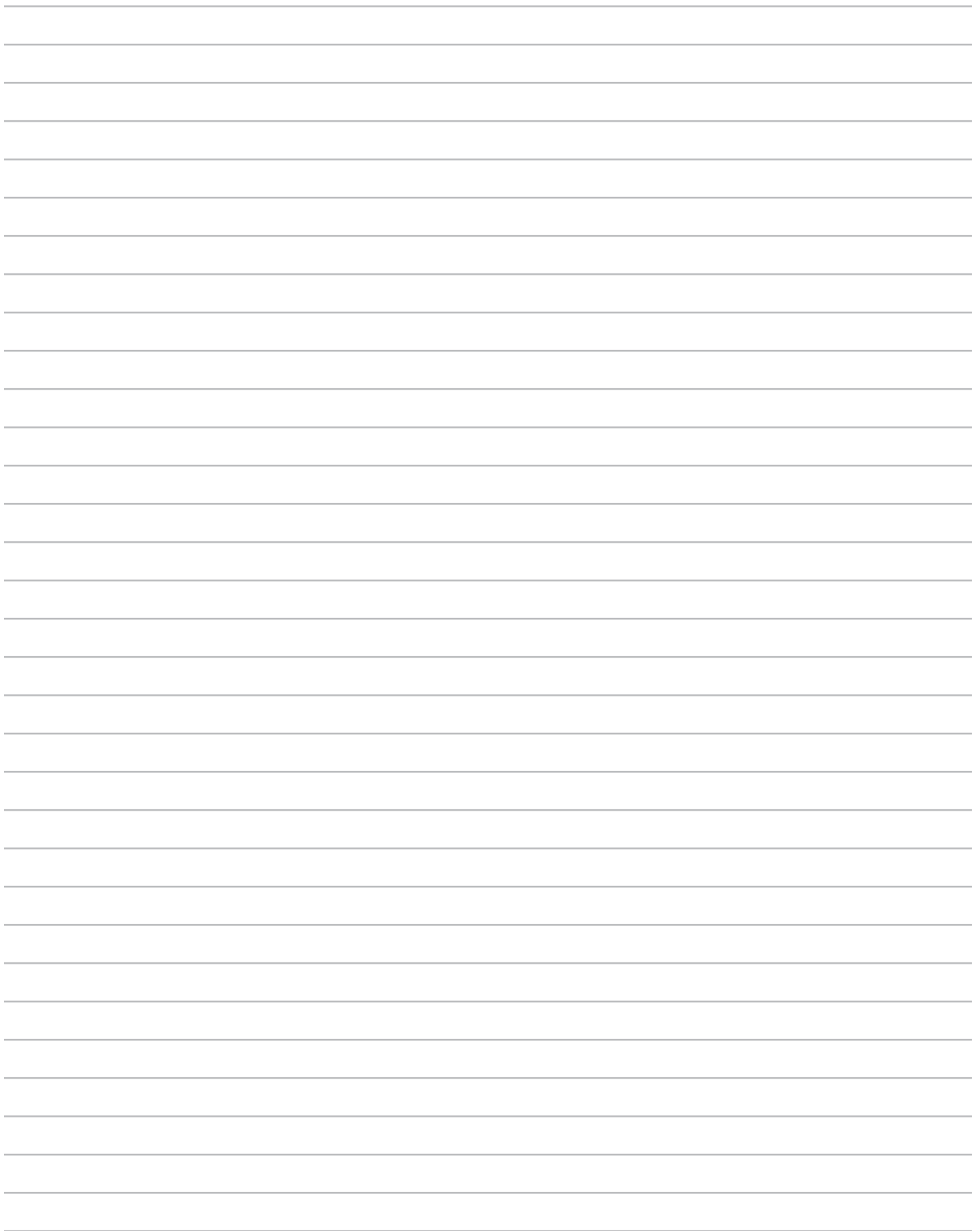
0.63  
Test for heterogeneity:  $P = 0.008$

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



## 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.



*Document*

# 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,<sup>a</sup> Donald Lamm,<sup>b</sup> Maurizio Brausi,<sup>c</sup> Mark Soloway,<sup>d</sup> Joan Palou,<sup>e</sup> Andreas Böhle,<sup>f</sup> Marc Colombel,<sup>g</sup> Hideyuki Akaza,<sup>h</sup> Roger Buckley,<sup>i</sup> J Alfred Witjes<sup>j</sup>

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<sup>g</sup>Department of Urology, Claude Bernard University, Hôpital Edouard Herriot, Lyon, France

<sup>h</sup>Department of Urology, University of Tsukuba, Tsukuba, Japan

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<sup>j</sup>Department 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
<b>EAU</b>	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)
<b>FICBT</b>	Low-grade Ta	Low-grade Ta with high-risk factors for recurrence or recurrent low-grade Ta tumors	High-grade Ta, all T1, CIS
<b>NCCN</b>	G1-2Ta	G3Ta, solitary G1-2T1	Multifocal T1, G3T1 (CIS listed separately)
<b>AUA</b>	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

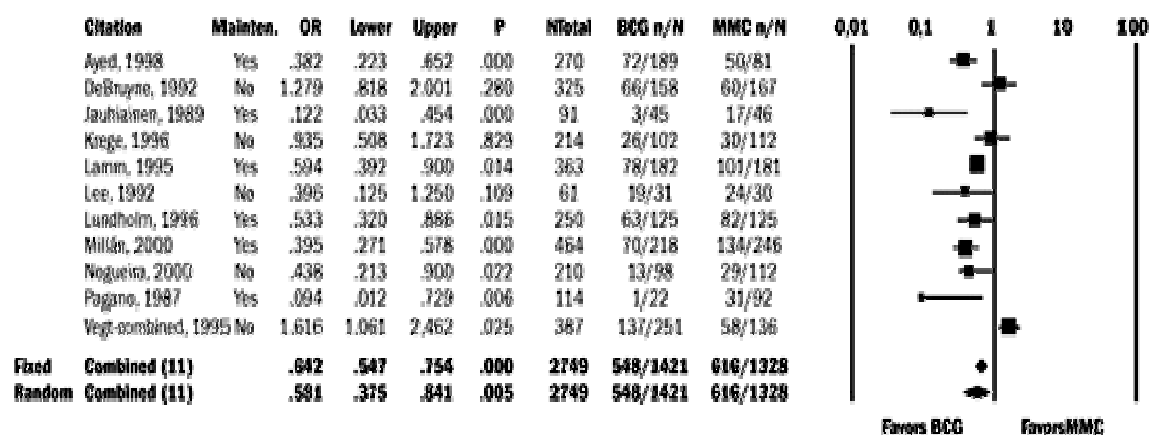
maintenance schedule versus induction Epirubicin. In that study of 957 intermediate risk patients followed for 9.2 years time to first recurrence ( $p < 0.0001$ ), time to distant metastases ( $p = 0.03$ ), and overall ( $p = 0.02$ ) and disease-specific survival ( $p = 0.03$ ) were all significantly 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
<b>EAU</b>	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"> <li>• TURBT</li> <li>• Single, immediate post-operative instillation of chemotherapy followed by: <ul style="list-style-type: none"> <li>– Induction BCG plus maintenance (at least 1 year) (grade A), or</li> <li>– Maintenance intravesical chemotherapy (grade A) of 6-12 months (grade B)</li> </ul> </li> </ul>
<b>FICBT</b>	Multiple low-grade Ta	<ul style="list-style-type: none"> <li>• TURBT</li> <li>• Single immediate post-operative instillation of chemotherapy</li> <li>• Further adjuvant intravesical therapy: <ul style="list-style-type: none"> <li>– First-line: intravesical chemotherapy &lt; 6 months (grade B)</li> <li>– Second-line: BCG (grade A)</li> </ul> </li> </ul>
	Recurrent low-grade Ta	<ul style="list-style-type: none"> <li>• Office fulguration only in select patients with &lt; 5 small (&lt; 0.5 cm) low-grade recurrent tumours and negative cytology (grade C)</li> <li>• Formal TURBT if clinical doubt that tumour is low-grade, cytology positive, or change in tumour appearance has occurred (grade C)</li> <li>• Adjuvant intravesical therapy (see above)</li> </ul>
<b>NCCN</b>	G3Ta, solitary G1-2T1	<ul style="list-style-type: none"> <li>• TURBT &gt; Observe or</li> <li>• Intravesical therapy <ul style="list-style-type: none"> <li>– BCG (preferred) (category 1)</li> <li>or</li> <li>– Mitomycin (category 2A)</li> </ul> </li> </ul>
<b>AUA</b>	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"> <li>• TURBT</li> <li>• Intravesical BCG or mitomycin C (recommendation)</li> <li>• Maintenance BCG or mitomycin (option)</li> </ul>

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

Follow up regimens vary according 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 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.

## Point-Counterpoint: Radiation & Bladder Cancer

**Radiation Has No Role in the Treatment of Any Stage of Bladder Cancer**

*~ Robert E. Donohue, MD*

**Radiation Plays a Major Role in Certain Stages of Bladder Cancer**

*~ David C. Beyer, MD*

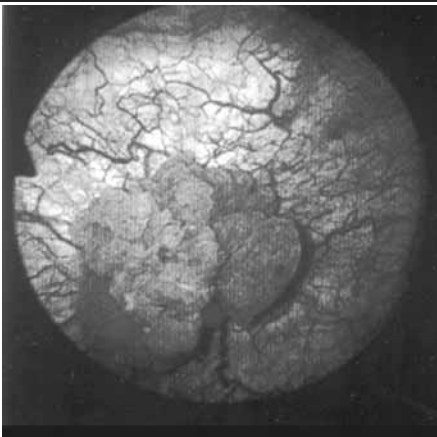
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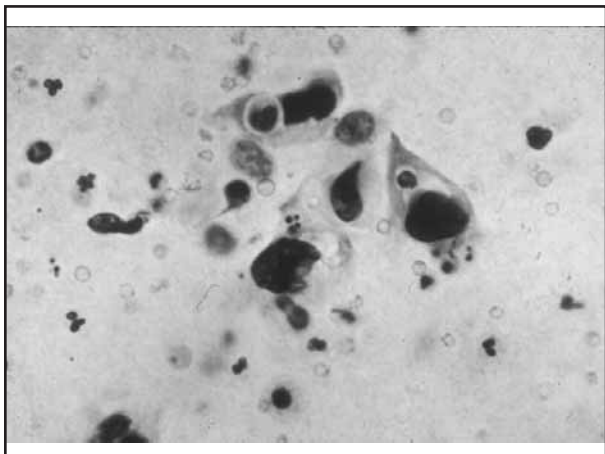
**Radiation Therapy;  
no role in management  
of bladder cancer**

Robert E. Donohue M.D.  
Denver VAMC  
University of Colorado

**TURBT  
classic**

hematuria  
cystoscopy / cytology ?  
upper tract study  
cystoscopy / cytology ?  
TUR resection, bladder mass





## Bladder Tumors 2009

incidence 70,980

male 52,810

female 18,170

mortality 14,330

male 10,180

female 4,150

## Transitional Cell Carcinoma

85% superficial carcinoma-in-situ

Ta epithelium

T1 LP invasion

15% invasive

85% recur 15% no recurrence

70% same stage, grade

30% increase in either or both

## TURBT classic

bimanual examination,

resection of tumor[s] to the

bladder wall, minimum cautery

cold cup of base, +/- M. propria

resection of deeper tissue [muscle?]

bladder mapping, carcinoma-in-situ

## **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  
Stage the others  
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  
modern**

1999 Herr – second look, 2 – 6 wks,  
all referrals  
2004 Herr – office fulguration,  
Lidocaine, urethra  
2007 Herr – low grade, papillary TCC  
advantages,

**THE VALUE OF A SECOND TRANSURETHRAL RESECTION IN  
EVALUATING PATIENTS WITH BLADDER TUMORS**

HARRY W. HERR

*From the Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York*

**J.U. 162: 24, 1999**

**REPEAT TRANSURETHRAL RESECTION TO EVALUATE BLADDER TUMORS**

TABLE 1. Comparison of bladder tumor stage after first and second transurethral resections

Stage at First Transurethral Resection	No. Pts.	No. Stage at Second Transurethral Resection (%)			
		T0	Ta/Tis	T1	T2
Tis	20	6 (30)	8 (40)	4 (20)	2 (10)
Ta	18	5 (28)	7 (39)	5 (28)	1 (5)
T1:	58	13 (22)	15 (26)	14 (24)	16 (28)
Muscle	35	9 (26)	11 (31)	10 (29)	5 (14)
No muscle	23	4 (17)	4 (17)	4 (17)	11 (49)
T2	54	12 (22)	7 (13)	3 (6)	30 (55)
Totals	150	36 (24)			114 (76)

**Herr**

**second look TURBT  
76%\* persistent tumor**

first TURBT		repeat TURBT	
T1	T0	T2	
35 muscle	9 [26%]	5* [14%]	
23 no muscle	4 [17%]	11* [49%]	
T2	12* [22%]	30 [55%]	

## **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



## Muscle Invasive TCC

currently

high grade, T1 disease

with negative M. propria

T2 disease,

aggressive wide re-TURBT

cystectomy

chemotherapy

bladder preservation

## Bladder Preservation

T1, high grade, T2

options

aggressive wide re-TURBT

cystectomy

chemotherapy

bladder preservation

Chemotherapy +  
radiosensitizing agent =EBRT

## Bladder Preservation

T1, high grade, T2

options

aggressive wide re-TURBT

cystectomy

chemotherapy

bladder preservation

Chemo + Chemosensitizing EBRT

## Bladder Preservation

T1, high grade, T2

cystectomy – negative LN

50-60% pT0,T1,T2; 75-85% 5 year

20-30% T3a-b, perivesical fat, T4,

45-55% 5 year

- positive LN

20-30% any pT, pN1-3 25-35% 5 year

## Bladder Preservation

aggressive wide re-TURBT

20% local control

selected patients, better

T2a

external beam radiotherapy-6,000 Gy

50% likelihood of bladder control

20 – 40 % survival

## Bladder Preservation

external beam radiotherapy

50% likelihood of bladder control

20 – 40 % survival

subsequent randomized trials

improved local control

BUT

not survival

## Bladder Preservation

T1, high grade, T2

Chemotherapy + ChXRT

parameters

solitary, early stage lesion,

no hydronephrosis,

no palpable mass,

no multifocal disease or c-i-s

no disease outside the bladder

non- constricted bladder volume

## Bladder Preservation

T1, high grade, T2

Chemotherapy + XRT

parameters

transitional cell carcinoma,

aggressive TURBT,

adequate renal function,

favorable – T2,

neo-adjuvant Ch Rx, pTo @ TURBT

## Bladder Preservation

T1, high grade, T2  
Chemotherapy + ChXRT  
discordance between  
clinical and pathologic staging  
staging  
visual appearance, cytology, TURBT  
at cystectomy, 33% tumor Scher  
BUT  
ChRx 38%, post MVAC, pTo Grossman

## Bladder Preservation

111 patients, T2,T3  
60 patients, [ 54%], pTo @ TURBT  
43 bladder sparing  
28 TURBT  
15 partial  
32, 74% alive; 25,58% bladder intact  
17 radical cystectomy  
65% 10 year survival Herr

## Bladder Preservation

104 patients T2 to T4a  
3 courses of Paclitaxel,  
Carbo-platin and Gemcitabine,  
Restaging TURBT in 74 patients  
34 / 74 were pTo  
10/34 immediate cystectomy  
6/10 persistent tumor 60%  
re-TURBT is flawed significantly White

## Bladder Preservation

53 patients, T2,T3,T4  
TURBT  
CMV – 2 courses  
external beam 40Gy + CDDP  
8 cystectomy; 34 CRT; 11other Rx  
24, alive and well, NED, 45%  
31, functioning bladder, no T2, 58%  
28, CR to chemo, 89% NED bladder  
Kaufmann 1993



## Bladder Preservation

opponents  
metachronous bladder tumors  
multifocal tumors are present  
risk 50 – 60% new tumor  
50% muscle invasive  
25-30% non-muscle  
TURBT plus BCG  
urinary diversion is more difficult !

## Bladder Preservation

XRT technique  
supine and bladder empty  
40 – 45 Gy bladder + true pelvis  
biopsy and cytology, negative  
cone-downed to cystoscopically  
identified tumor site  
positive  
or cystectomy

## Bladder Preservation

RTOG 99-06  
Paclitaxel + CDDP + standard XRT  
vs  
hyperfractionated XRT  
4 courses  
Gemcitabine + CDDP Kaufman  
CR 87% 2 years; 69% intact bladder  
or Gemcitabine + XRT only Kent Sanger

## Bladder Preservation

RTOG 99-06, T2- T4a  
Paclitaxel + CDDP +  
hyperfractionated XRT  
reTURBT < T1  
4 courses  
Gemcitabine + CDDP





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

- No modern surgery / XRT randomized trial
- Generally offered to poor surgical risk patients

- National Bladder Cancer Cooperative Group
- 70 patients with medical contraindications to surgery
- Cisplatin + 64.8 Gy XRT
  - 70% complete response
  - 57% 4 year survival
    - ✓ 57% for responders
    - ✓ 11% non responders

Shipley et al., JAMA 258:931, 1987

- TUR + Chemotherapy
  - ~ 20-30 response rates
- TUR + Chemotherapy + XRT
  - ~74% response rates

Srouigi & Simon, J Urol, 1994; 151:593  
Given et al. Urology. 1995; 46:499

### Radiation Alone May Be Inadequate

- 459 patients
- T1-T4
- Generally poor surgical risk
- 60-70 Gy with no chemo
- 5 year survival:
 

Overall	36%
Cause Specific	56%
Failure Free	33%

Tonoli et al; Clin Oncol, 2006 18(1):52-59

### RTOG 85-12

- Candidates for Cystectomy
- 40Gy + Platinum
  - Evaluate response
    - ✓ Consolidation 24Gy + platinum
    - ✓ Cystectomy
- 66% CR
- 40% Freedom from Local Recurrence
- 40% Bladder preservation
- 73% Freedom from Invasive Recurrence

Tester, Porter, Asbell. IJROBP 1993, 25:783-790

### Phase II Combined Modality

- 53 Cystectomy candidates
- TURBT / Chemo / XRT
- Evaluate at 40 Gy
  - 36 boost 24.8 Gy
  - 15 early salvage surgery
- 48% 5 year survival
- 58% bladder preservation
- 81% functioning bladder in patients with CR

Kaufman et al., NEJM 329:1377: 1993

### XRT + Brachytherapy for Bladder Cancer <5cm

- 122 patients
  - 94 men
  - 81 pT2
  - 103 Grade 3
- 10.5-40 Gy XRT with Cystotomy 10 days later
- 20-70 Gy Brachytherapy

Blank et al; IJROBP 2007, 69(2):454-458



## 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

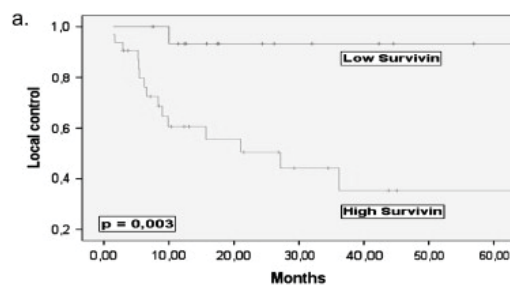
Weiss, C. et al. J Clin Oncol 24:2318-2324, 2009

## Survivin in Bladder Cancer

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

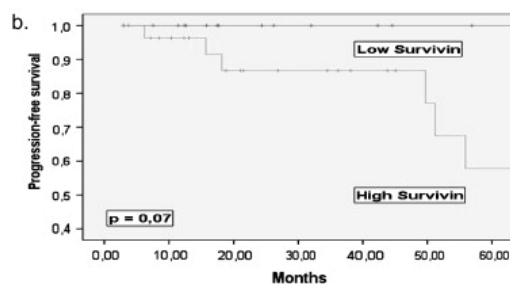
Weiss, C. et al. IJROBP V74(5): 1455-1460, 2009

## 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

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

Hoskin, P. et al. IJROBP, V73(5): 1425-1431, 2009

Hoskin, P. et al. *IJROBP*, V73(5): 1425-1431, 2009

Hoskin, P. et al. IJROBP. V73(5): 1425-1431, 2009

## HypoFractionated ChemoRadiation

- Retrospective 26 patients, median age 80
- 37.5-40.0 Gy in 15 fractions + Platinum
- TCC or squamous cell (1)
- 39%  $\geq$  cT3
- Median survival 13.3 mos.
- Acute toxicity
  - GI 52%
  - GU 36%
  - Hematologic 36%

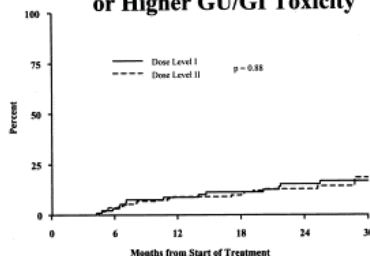
Ash, Welch, Winquist, Bauman; IJROBP 2007 69(3):S340

## Toxicity XRT+ Brachytherapy

- Acute: Ileus, PE, Wound Dehiscence
- Late: 90% Bladder preservation
  - 5% "urinary function deterioration"
  - 3% "crippled bladder"
- 17 second cancers
  - ✓ Only 1 in pelvis

Blank et al; IJROBP 2007, 69(2):454-458

## Toxicity RTOG 94-06 (68.4-79.2 Gy) RTOG 9406: Time to Late Grade 2 or Higher GU/GI Toxicity



Michalski et al, IJROBP 46(2):391-402; 2000

## Primary XRT for Bladder Cancer

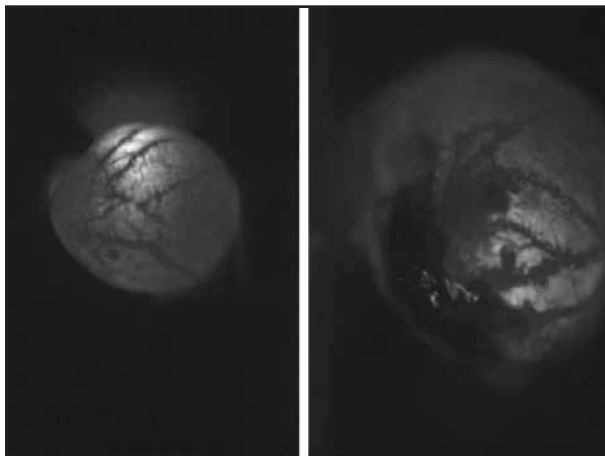
- Option for non-surgical candidates
- Option for surgical candidates desiring bladder preservation
- ~50% long term disease free survival
- >70% CR
- In RTOG studies 2/3 completed therapy with intact functioning bladder

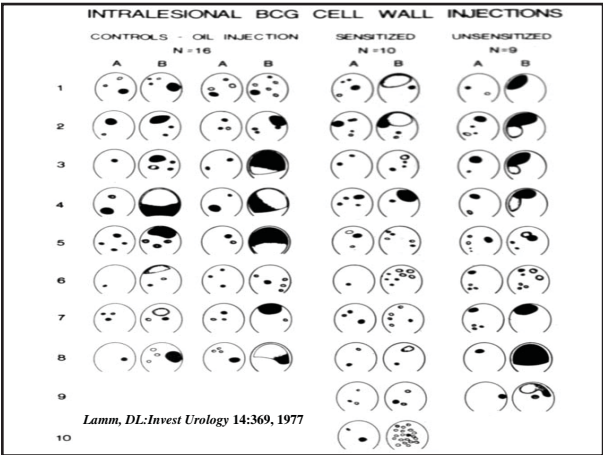
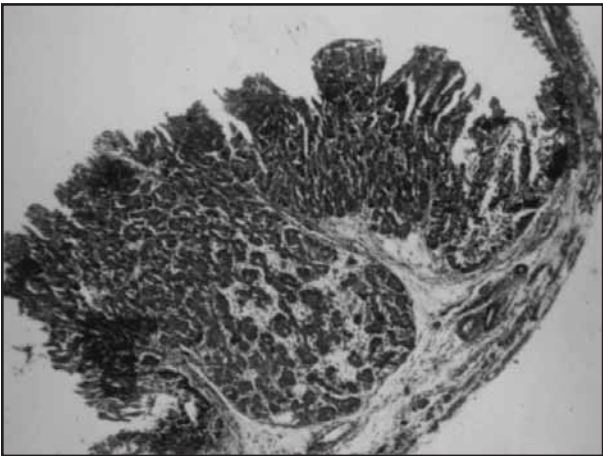
Shipley et al. Urology 2002;60:62-67



~ Donald L. Lamm, MD

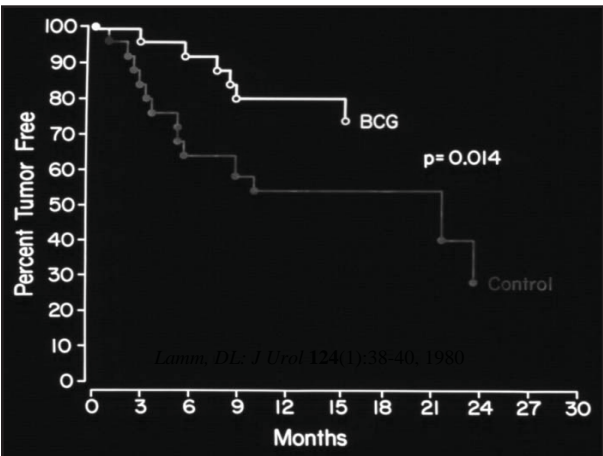
## BCGOncology.com

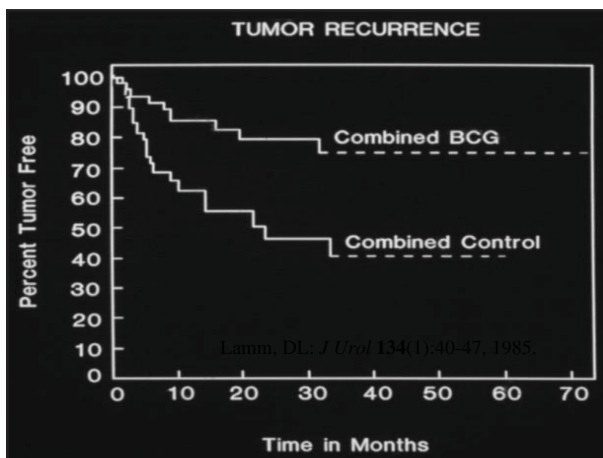




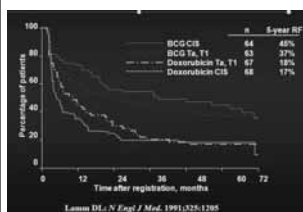
### BCG in Bladder Cancer

- 1976: Morales- 12 fold reduction in recurrence in 9 bladder cancer patients
- 1977: Lamm reports success in controlled animal studies of bladder cancer
- 1980: Lamm reports successful randomized clinical trial
- 80's-90's: Multiple comparison studies show BCG to be superior to chemotherapy

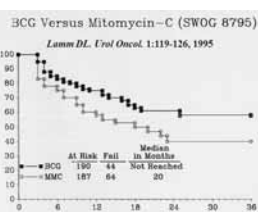




## BCG vs Chemotherapy



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



BCG reduces recurrence by 11% vs Mitomycin C

## BCG Present

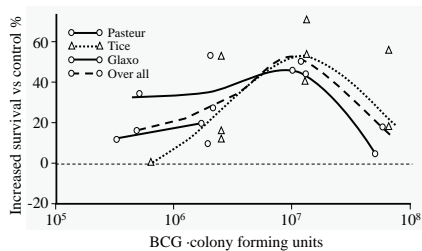
- BCG efficacy established as superior to chemotherapy
- Risk versus benefit and optimal schedule- questions remain
- Benefit in reducing progression and mortality questioned

## What is the best BCG regimen?

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

BCG Dose-Response in Murine TCC

Too little or too much BCG reduces effect



Lamm DL: *J Urol*. 128: 1104-1108, 1982

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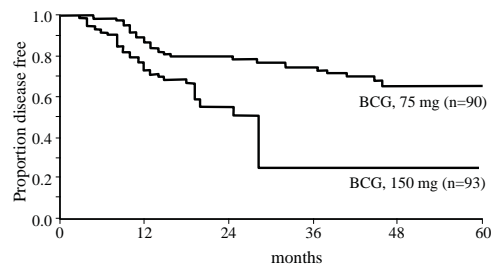
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Low-Dose Versus High-Dose BCG



40% reduction in recurrence with 50% Pasteur BCG

Pagano F: *Eur Urol*. 27: 19-22, 1995.

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6 Weekly Induction BCG is Suboptimal, *as is 6+6 Instillations*

- 6 week BCG:  
20/55(36%) Ta,T1; 12/32(37%) CIS; **37% NED**
- 6 + 6 week BCG:  
19/29(65%) Ta,T1; 11/18(61%) CIS; **64% NED**

2 year follow up; uncontrolled

Kavoussi LR: *J Urol*.139:935,1988

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6+6 versus other schedules

- 64% NED 2 years, no better than 6 week induction or monthly maintenance.
- Immune stimulation peaks at 6 weeks during the initial course and at 3 weeks with subsequent courses.
- The 4th, 5th and 6th instillation of a second course can suppress the immune response.

DeBoer EC, 1994

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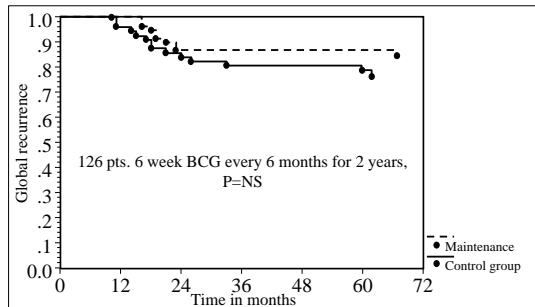
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## Repeated 6 week Maintenance BCG Palou J: J Urol. 165:1488,2001

- 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

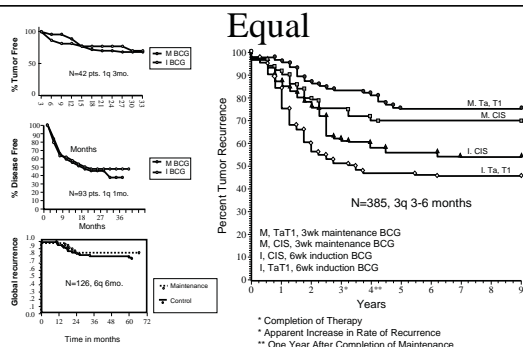


## Second Induction Course of BCG

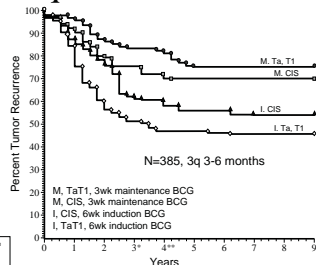
Author	N	R	R%	TTR
Bretton	28	18	64%	21 mo
Hurle	13	6	46%	27 mo
Kohjimoto	16	6	38%	35 mo
Yamada	31	20	64%	36 mo
Bui	11	6	54%	84 mo
O'Donnell	40	19	47%	26 mo*
Nadler	66	39	59%	45 mo
Total:	205	114	56%	21-84 mo

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

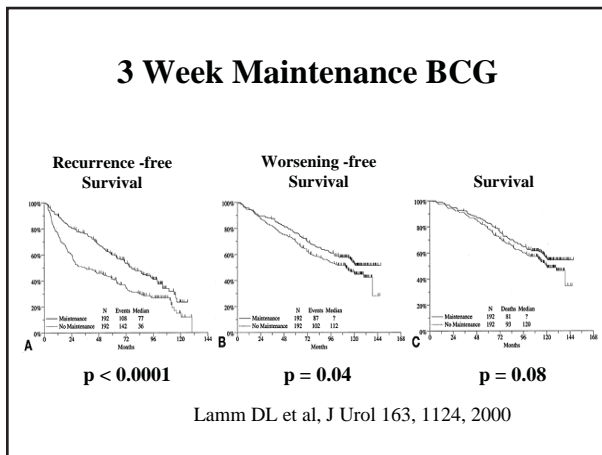
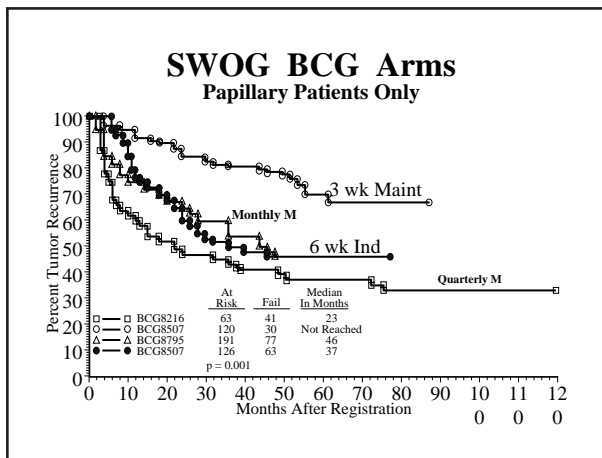
## BCG Maintenance: Not Created



Equal



\* Completion of Therapy  
\* Apparent Increase in Rate of Recurrence  
\*\* One Year After Completion of Maintenance



Can BCG Delay or Prevent  
Progression in Superficial Bladder Cancer ?  
Sylvester R: J Urol. Nov., 2002

- Meta-analysis of 24 studies, 4863 patients randomized to BCG vs surgery alone (2), BCG maintenance (3), chemotherapy (14), or other immunotherapies (5).
- 2.5 year median follow (max 15)
- 82% Ta, T1, 37% G1, 55% G2, 8% G3; 18% CIS
- 78% received maintenance BCG, 10-30 Rx over 18 weeks to 3 yrs.

## Progression

Treatment	Progression
• No BCG	304/2205 (13.8%)
• BCG	260/2658 ( 9.8%)
Difference	4.0%
Odds ratio (OR)	0.73
Odds reduction	27% (95% CI: 11%-40%)
P Value	0.001

### 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

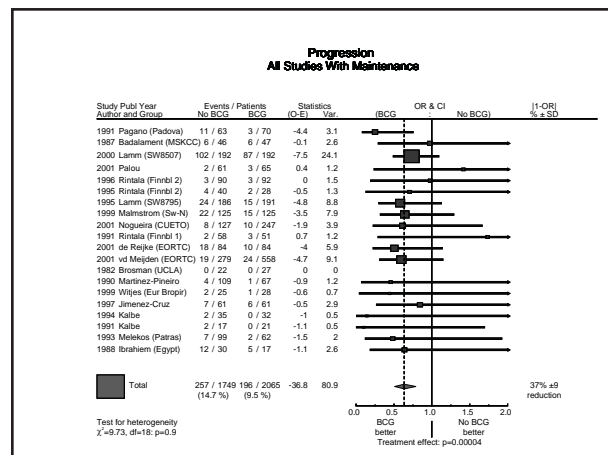
Although their prognosis is different, the size of the treatment effect was similar in papillary tumors and CIS

### 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%,  $p = 0.00004$ .



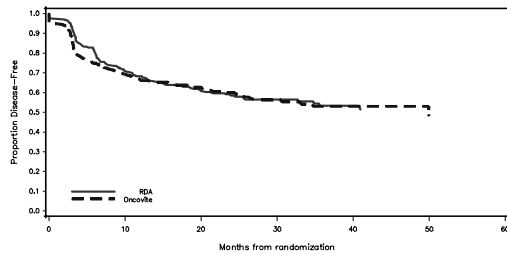
### Long-Term Efficacy of Epirubicin, BCG and BCG plus Isoniazid in Intermediate and High Risk Ta,T1 Bladder Cancer

- 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



### Efficacy Results – Disease Free Interval BCG + RDA vs BCG + Oncovite



32

### What about **percutaneous** BCG?

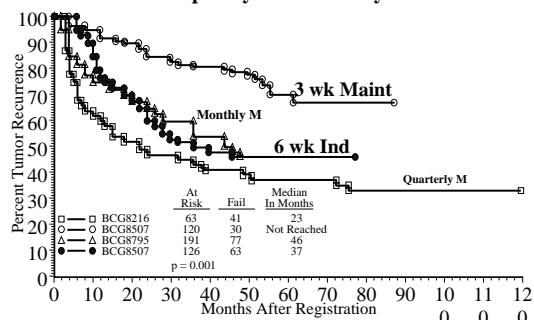
#### BCG, Scar Formation and Mortality

- Several studies show a positive correlation between BCG vaccination in childhood and a reduction in mortality.
- Hazard ratio for death in those with a BCG scar is 0.55(0.32-0.96), and is lowest in girls: 0.31 (0.11-0.88)

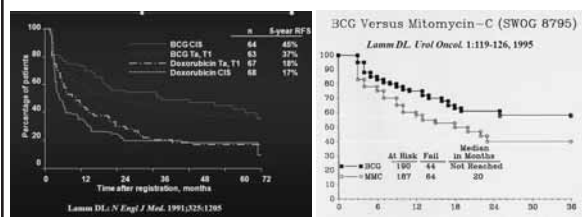
Roth A 6: Epidemiology. 2006, 562-8.

### How long should 3 week maintenance BCG be continued?

#### SWOG BCG Arms Papillary Patients Only



BCG vs Chemotherapy



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

BCG reduces recurrence by 11% vs Mitomycin C

15 Year Follow-up  
BCG Without Maintenance  
143 Ta, 73 T1 patients

	Progression	Ca Death
23 Ta G1	5%	0
125 Ta G3	39%	26%
73 T1 G3	56%	38%

\*10 yr: 69% rec/progression, 25% upper tract TCC (32% fatal), 24% urethral (44% fatal)

Herr. J. Urol, 2000 and \*JCO, 1998

CIS increases risk of extravesical TCC

- In 192 cystectomy specimens, CIS increased the risk of **prostatic** involvement 12-15 fold: from 4.5% to 31% (35% for multi-focal TCC)\*
- Zincke: 9% of pts with bladder CIS develop **upper tract** TCC post cystectomy, v 2.6% T2-T4 TCC without CIS (1984). Solsona: 25% of 138 pts with CIS v 2.3% of 786 with Ta, T1 and 2.9% of 179 T2 or greater patients (1997)

\*Nixon RG. J Urol. 2002;167:502-5

Maintenance BCG Schedule

Week	Month	Year
2 3 6 9 12 15 18 21 24 30 36	4 5 6 7 8 9 10 11 12	
cysto	x x x x x x x x x x	x x x x x x x x x x
BCG		
X6		
BCG	x x x x x x x x x x	
x3		

### Maintenance BCG Reduces the Death in Cystectomy Patients

- 501 evaluable pts randomized to induction vs 3 wk BCG at 3,6,12,18,24,30, and 36 months
- Neither stage (T2 vs Tis/T1, P=0.18, NS) nor delay in cystectomy reduced survival
- 3wk BCG **significantly** reduced mortality in **failure/cystectomy** pts: HR 0.37, p=0.017

### 3 Week Maintenance BCG Reduces Death in Cystectomy Pts

- 501 evaluable pts randomized to induction vs 3 wk BCG at 3,6,12,18,24,30, and 36 months
- Neither stage (T2 vs Tis/T1, P=0.18, NS) nor delay in cystectomy reduced survival
- 3wk BCG **significantly** reduced mortality in **failure/cystectomy** pts: HR 0.37, p=0.017

Lerner S: J Urol. (2007), 177: 1727

### Maintenance BCG Reduces the Incidence of Prostate Cancer

Lamm. J Urol 161:285, 1999

- 385 bladder cancer pts randomized to 6wk induction vs induction + 3 wk maintenance
- With 8+ yr follow up, second primary Ca developed in 23% of induction & only 13% of those on maintenance BCG (P<0.014)
- Prostate Cancer reduced from 14 (6.9%; 3 C, 3 D) to 5 (3.3%; 1C, P=0.04)

### Conclusions

- Current preparations are not significantly different in efficacy, and attempts to breed “superior BCG” have been unsuccessful.
- Molecular engineering, however, with insertion of human cytokine genes such as IL-2 or interferon gamma are very promising

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

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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.

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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.

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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

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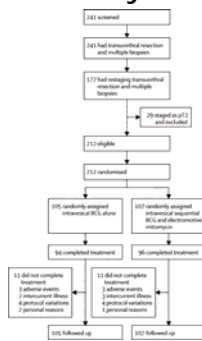
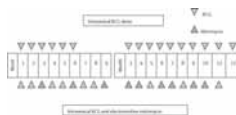
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What's New?

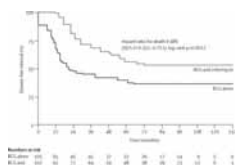
What's Needed?

## BCG & Electromotive Mitomycin

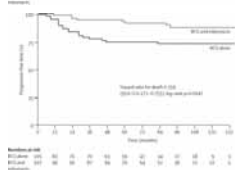


Di Stasi SM, et al. *Lancet Oncol.* 2006;7:43-51.

## BCG & Electromotive Mitomycin



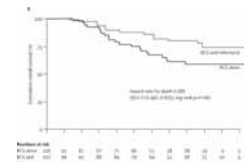
**Disease-free Survival**



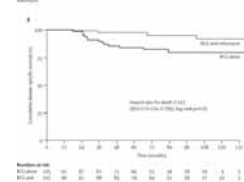
**Progression-free Survival**

Di Stasi SM, et al. *Lancet Oncol.* 2006;7:43-51.

## BCG & Electromotive Mitomycin



**Overall Survival**

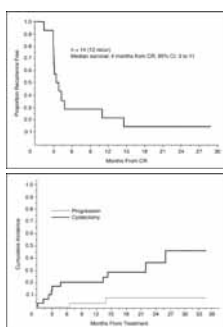


**Disease-specific Survival**

Di Stasi SM, et al. *Lancet Oncol.* 2006;7:43-51.

## 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

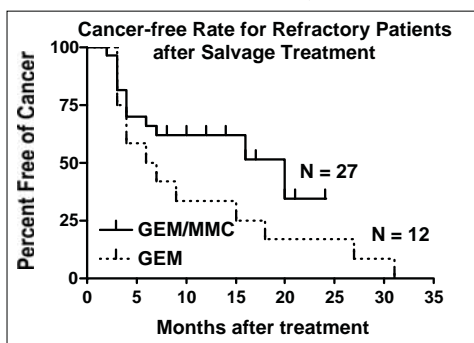
Mike O'Donnell, 2006

## Vesicant Profile of Chemotherapeutic Agents

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

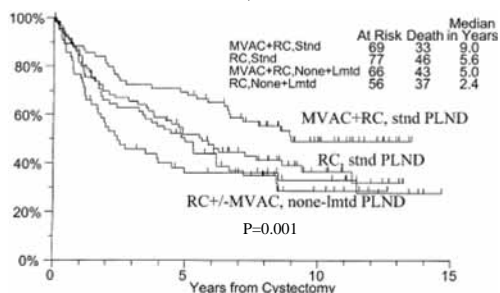
Mike O Donnell, 2006, MD Anderson Bladder Cancer Meeting

## Conclusions

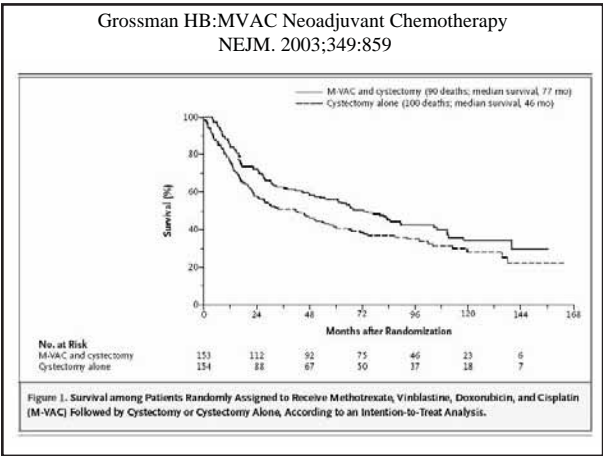
- Surgery Counts! Extend resection, send margin, then roller-balling base and edges (?); or re-resect
- Immediate postoperative chemotherapy: standard
- Concentrated chemo for low risk, BCG for high
- 3 week maintenance BCG, not repeated 6 weeks
- High grade: carefully follow upper tracts and prostate. 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

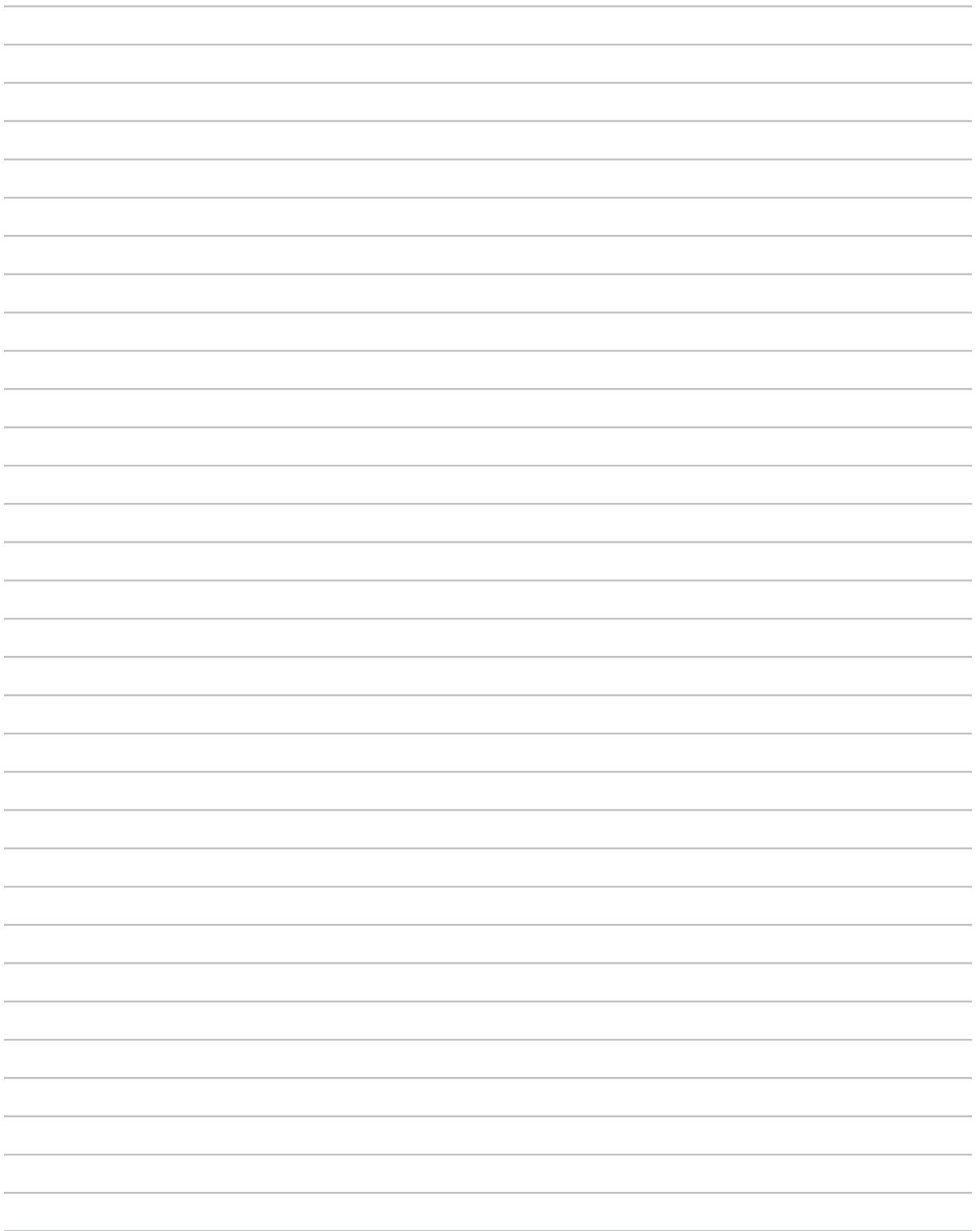
Herr HW: JCO, 2004 172:1286



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







# The Spectrum of Stress Incontinence Surgery, 2009

~ Brian J. Flynn, MD

## ***The Spectrum of SUI Surgery, 2009 The Midurethral Sling Evolution***

**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

## ***Spectrum of SUI Surgery Objectives***

- Review the midurethral tension-free sling evolution
- Review tension-free tape approaches and outcomes
  - retropubic
    - vaginal → abdominal, 'bottom-up'
    - abdominal → vaginal, 'top-down'
  - transobturator
    - vaginal → thigh, 'inside-out'
    - thigh → vaginal, 'outside-in'
  - single incision sling ('mini-sling')
- Head to head RCTs
- Procedure selection
  - my algorithm

Perspectives in Urology 2009

## ***Background***

Perspectives in Urology 2009

Out

- Proximal urethra
- Tension
- Biological materials
- Gortex, marlex

Trends

In

- Mid-urethra
- Transobturator
- Tension-free systems
- Polypropylene mesh

"Loosely applied mid-urethral slings are the new gold standard for female SUI. Whether these should be composed of synthetic or bio-material can only be determined after comparative randomized controlled trials." \*

\* Bemelmans, BLH and Chapple, CR: Cur Opin Urol 2003  
Perspectives in Urology 2009

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1996

TVT™

- ribbon-like mesh placed via an incision under the mid-urethra, 'bottom-up'

Ulmsten, U, et al: Int Urogynecol 1996

2001

SPARC™

- ribbon-like mesh placed via an incision under the mid-urethra 'top-down'

Statskin D, 2001

2003

TOT

- transobturator 'outside-in' insertion of polypropylene mesh

Delorme, E, et al: Eur Urol 2004

2004

TVT-O™

- transobturator 'inside-out' insertion of polypropylene mesh

De Leval, J: Eur Urol 2004

2006

Mini-sling

- 1.1 x 8 cm polypropylene tape placed vaginally, with 'no exit site'

Perspectives in Urology 2009

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Knitted

Woven

Non Knitted, Non Woven

Alexander 1967 ; Larson et Harrower 1978 Law et Ellis 1991 ; Elek et Conen 1957 ; Neel 1983

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Dietz, HP: Mechanical properties of urogyn implant materials. Int Urogynecol 2003

Elasticity

Gynemesh demonstrated low stiffness, easy deformability, and permanent elongation, with the AMS sling showing similar results. Moalli et al. 2008

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10.2

PERSPECTIVES IN UROLOGY: POINT- COUNTERPOINT • November 5–7, 2009 • The Scottsdale Plaza • Scottsdale, Arizona

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

**FDA** 10/20/08

**>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

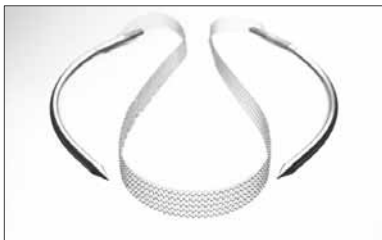
**"Serious Complications with Mesh Use in PFR and SUI Repair"<sup>†</sup>**

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

**Retropubic Tapes  
First Generation TVT**

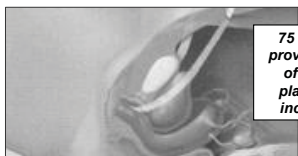
Perspectives in Urology 2009

**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 uroynamically 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

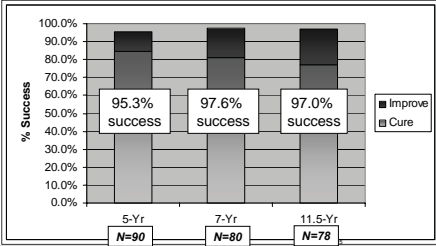
Tension-Free Vaginal Tape  
Overview of "Level I Evidence"

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 <sup>5</sup>	3 years <sup>9</sup>	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 <sup>10</sup>	N/A	1 year <sup>11</sup>

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 †

- Outcome
- 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

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\*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†

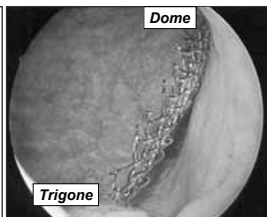


\* Minaglia S, Klutke C, Klutke, J: Urol 2004  
† Azam J, et al: J Urol 2001

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

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### Question

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

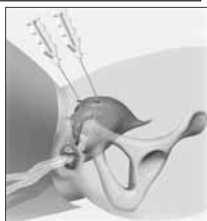
- A. Yes, I have had one personally
- B. Yes, one of my partners
- C. Yes, the other group
- D. Yes, the other specialty
- E. No

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## Complications

**140 patients underwent SPARC for SUI, hematocrit was measured on POD #1 in the last 57 patients regardless of EBL \***

- 4 required transfusion
- 1 patient had a large retropericardic hematoma requiring drainage
- 1 bowel perforation required small bowel resection



\* Kobashi, KC and Govier, FE: J Urol 2003

Perspectives in Urology 2009

## ***Spectrum of SUI Surgery***

### ***Technical Pearls for Sling Placement***

Retropubic TVT- Doug Hale, MD

- 1.5 cm incision, full thickness
  - push – spread technique
  - place catheter guide with tension on catheter
  - visualize what is happening
  - avoid sulcus – look for “bridge”
  - trocar parallel to floor unless proximal sling placement
- perforate perineal membrane
  - retract 1cm
  - handle parallel to floor
  - avoid trocar tip movement
  - keep contact with bone
  - look for tenting, flash of blood, fluid pooling along trocar
  - pull sling to contralateral leg, not straight out
  - 70 degree scope mandatory with full bladder

Perspectives in Urology 2009

## Transobturator Tapes

### Second Generation TVT

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***TVT how does it work?***  
***DeLancey's Hammock Hypothesis***

***In the normal continent female, 'increases in urethral closure pressure during a stress maneuver arise because the urethra is compressed against a hammock-like supporting layer, rather than the urethra being truly intra-abdominal'***



\* DeLancey, JOL: Am J Obstet Gyencol 1994

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 Urolyn 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



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### 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)



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### TVT-Obturator 'Inside-Out'

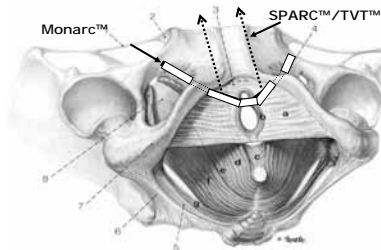
107 patients with SUI that underwent transobturator inside-out insertion of polypropylene mesh were retrospectively reviewed \*

- 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

Monarc® Mesh Position



Perspectives in Urology 2009  
Reiffenstahl, Platzer & Knapstein

Transobturator Tape  
Overview of “Level I Evidence”

Transobturator Devices	GYNECARE TVT® Obturator	Monarc™	Obtrix®	Align TO®
Total RCTs	9	4	0	0
Longest Follow-Up in Any Published Study	3 years <sup>12</sup>	2 years <sup>13</sup>	N/A	N/A

Transobturator Devices	Uretex TO®	Aris TOT®	Desara®*	T-Sling®*
Total RCTs	0	0	0	0
Longest Follow-Up in Any Published Study	N/A	N/A	N/A	N/A

\*Desara® and T-Sling® have multiple placements

Transobturator Tape  
Results of RCTs

Liapis A et al.: Int Urogynecol J. 2008  
But I et al.: Int Urogynecol J. 2008

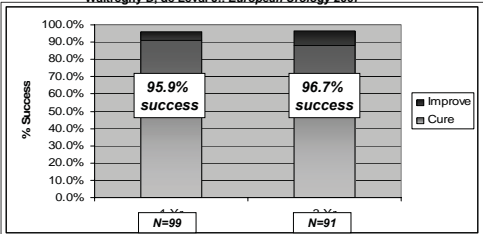
	Liapis (12 mo) <sup>12</sup>		But (4 mos) <sup>21</sup>	
	GYNECARE TVT® Obturator System	AMS Monarc®	GYNECARE TVT™ Obturator	AMS Monarc™
Obj Cure	95%*	94%*	98%	97%
Sub Cure	80%	77%	N/A	N/A
Erosion	N/A	N/A	0%	0%
Bladder Perf	0%	0%	N/A	N/A
Urethral Perf	0%	2%	N/A	N/A
Pt Satisf VAS	N/A	N/A	91%	89%

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Transobturator Tape  
3-year follow-up

Follow-up for 91 of the original 102 patients from the investigator's original data, 3-year minimum follow-up

\*Waltregny D, Reul O, Mathantu B, et al.: J Urol 2006  
†Waltregny D, de Leval J.: European Urology 2007



Mid-term cure rates similar to traditional TVT

**TOT Complications****Bladder Injury During 'Outside-In' Approach \***

TOT using Mentor™ tape in 120 cases  
(Uratape in 60, Obtape in 60) with 1-year minimum follow-up

- 13 vaginal wall injuries recognized at the time of surgery
- 3 delayed vaginal wall extrusions
- Three perforations of the urethra and one of the bladder occurred during the learning phase
- In 2 of 3 cases of urethral injury re-intervention was necessary for tape removal when the injury was unrecognized

"It is certainly of importance to put a finger into the midline vaginal incision to protect the urethra from the tunneler. To avoid vaginal perforation, it is also of importance to take care of a good sulcus dissection at the upper lateral vaginal wall. These observations enabled us to continue our series without the need to perform cystoscopy."

\* Roumegue' re T, et al: EU 2005  
Perspectives in Urology 2009

**TVT-Obturator****'Inside-Out'**

136 patients with SUI treated with TVT-R were randomized against  
131 patients treated with TVT-O\*

• **Short-term cure:**

- TVT = 98.5%
- TVT-O = 95.4%

	TVT	TVT Obturator
Bladder Perforation	1	0
Vaginal Perforation	2	3
Hematoma	1	0
Pain (thigh/groin)	2 (1.5%)	21 (16%)

\*Trademark  
Perspectives in Urology 2009  
Nilsson CG et al. Int Urogynecol J. 2006

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

TVT-O Mark Walters, MD

- know the obturator anatomy
- high stirrups with buttock to end of table
  - especially in obese women
- hydrodissection
- 2 cm mid-urethral vaginal incision
- limited dissect. to pubic ramus
  - little bigger than TVT
- exit at level of clitoris lateral to the labia major, below the adductor longus tendon
- empty bladder
- proper alignment of helix
- then bilat passage
- cystoscopy
  - 1 bladder perf in 1150 cases)
- tension over Kelly clamp loosely
  - no gap to the urethra
  - tighter than TVT
  - looser than TVT-Secur

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**Single-Incision Slings or 'Mini-Sling'**  
**Third Generation TVT**

Perspectives in Urology 2009

### ***Simplify the procedure***

- *simpler and less-invasive techniques*
  - *minimal passage through tissues*
  - *less anesthesia*
  - *further reduce procedure time*
  - *eliminate external incisions*

***Decrease morbidity and convalescence***

- **maximum safety**
  - Less material left behind in the patient
  - Eliminate mesh lateral to obturator
- **potential for quicker return to normal activities for the patient**

Perspectives in Urology 2009

**Simple, outpatient procedure done under local anesthesia**

### ***Sling Design***

- **dimensions 8 cm x 1.1 cm**
- **laser cut**
- **no exit point**
- **unique fixation technique**

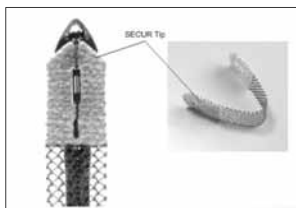
### Procedure Advantages

- *less dissection and pain*
- *less bleeding*
- *no risk of bowel, nerve ureteral injury*
- *decreased risk of urethral obstruction*
- *ability to do a cough test*



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### Fixation Tips



- *secures sling without anchors*
- *fleece absorbed within 90 days*
- *fixation is then provided by the mesh*
- *similar material used in dental implants*

- 2 cm absorbable fixation tips of fleece-like material sandwich the mesh at the tips
- absorbable tips are made of Vicryl (polyglactin 910) suture yarn and PDS (polydioanone)

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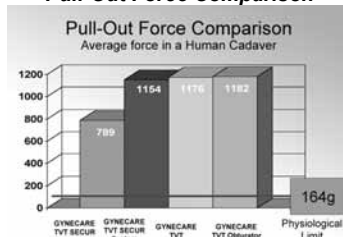
### Hammock position

U position

**Same kit may be used to place the tape in either position**

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### 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/m<sup>2</sup>

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

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

Convalescence

- mean operative time 34 minutes
- all patients discharged same day without catheter
- all patients returned to daily activity in < 7 days

Complications

- no to urethra, bladder, bowel, or neural injury
- 0 vaginal mesh extrusion



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

TVT-S

- 34 of 55 (62%) patients
- mean f/u 5 (1-13) months
- EBL = 16 ml
- 28 of 34 (82%) patients cured
  - 25 patients, 0 pads
  - 3 patients, 1 ppd
- 6 of 34 patients failed
- 1 case (2.9%) of obstruction
  - sling lysis at 6 weeks
  - now voiding
  - continence maintained

TVT-S + Concomitant Procedure

- 21 of 55 (38%) patients
- mean f/u 5 (1-13) months
- POP surgery in 16
- 19 of 21 (90%) patients cured
  - 25 patients, 0 pads
  - 3 patients, 1 ppd
- 2 of 21 patients failed
- 4 cases (19%) of obstruction
  - sling lysis in 4
  - now voiding
  - continence maintained

Flynn BJ et al: AUGS 2009

Perspectives in Urology 2009



MiniArc Single-Incision Sling System™  
Proposed Advantages

Simple, outpatient procedure done under local anesthesia

Kit Design

- dimensions 8.5 cm x 1.1 cm
- slim Needle Design
  - 2.3mm diameter
- ergonomic Handle
- blunt, bladeless tip

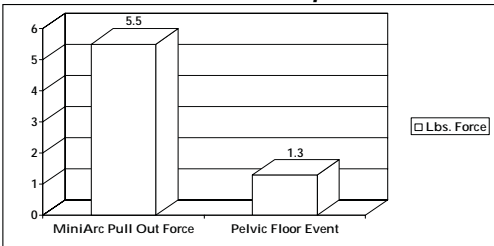
Procedure Advantages

- single, small vaginal incision
- no mesh beyond obturator
- same proven materials and trajectory as Monarc
- easy to Perform



Perspectives in Urology 2009

MiniArc Single-Incision Sling System™  
Pull-Out Force Comparison



MiniArc demonstrated equivalent pull-out force to Monarc (AMS data on file) in cadavers

Perspectives in Urology 2009

## ICS 2009: MiniArc Multicenter Prospective Single-Arm Trial

Michael Kennelly, Dirk DeRidder and Steve Siegel, ICS 2008

151 patients underwent MiniArc Sling

- demographics
  - mean age 51 (32-79) years
  - mean BMI 27.6 kg/m<sup>2</sup>
  - mean parity = 2
- procedural
  - 44% general anesthesia
  - 56% local anesthesia
- mean pain score at discharge
  - 0.78 ± 1.23
- estimated blood loss
  - Median = 25mL
- mean length of stay
  - Median = 2.8 hours
- intra-operative complication
  - 1 (0.7%) vaginal wall perf

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## ICS 2009: MiniArc Multicenter Prospective Single-Arm Trial

Michael Kennelly, Dirk DeRidder and Steve Siegel, ICS 2008

## 6 Week Follow-up Results

## 6 month Efficacy

N=149 Subjects	
Median Pain Score	0
Mean Pain Score	0.3 ± 0.9
Recommend to a friend	95.3%
Cured/improved	94.7%
Not improved	5.3%

- CST negative in 94% (68/72)

- Mean 1-hr pad weight test
  - baseline = 26.5 ± 38.1 gm



- 6 months = 5.2 ± 28.5 gm (n=80)

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Single-Incision (Mini) Sling  
Tensioning Recommendations

- 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 after inserting the second tip
- tension both sides together
- CST is vital for success
- MiniArc
  - only push forward as to not disengage needle from mesh
- TVT-s
  - easier to push in further than to try to pull out

Perspectives in Urology 2009

Single-Incision (Mini) Sling  
Overview of "Level I Evidence"

Single-Incision Devices	GYNECARE TVT SECUR™	MiniArc™	Contasure	Solyx
Total RCTs	0	0	0	0
Longest Follow-Up in Any Published Study	1 year <sup>32</sup>	6 months <sup>33</sup>	N/A	N/A

Single-Incision Devices	Ajust	Prefyx-PPS™	Minitape®	Needless™
Total RCTs	0	0	0	0
Longest Follow-Up in Any Published Study	N/A	N/A	N/A	N/A

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

### Spectrum of SUI Surgery RCT TVT® v. Monarc® in Patients with SUI

Barber, M. et al.: OB Gyn 2008

- N=170 women from 3 centers with USUI
- Mean f/u 18.2 months
- Exclusion
  - Detrusor overactivity
  - Previous sling surgery

#### Conclusion

"...Monarc TOT is not inferior to TVT for the treatment of stress urinary incontinence and results in less bladder perforations..."

Perspectives in Urology 2009

### Spectrum of SUI Surgery RCT TVT® v. Monarc® in Patients with SUI

Barry et al.: Int Urogynecol J 2007

- Australian multi-center randomized prospective study
- 140 women with 3 month f/u

#### Conclusion

"...Transobuturator tape [Monarc] appears to be as effective as the retro-pubic tape [TVT] in the short term, with a reduction in the risk of intra-operative bladder injury, shorter operating time, decreased blood loss and quicker return to normal activities..."

Perspectives in Urology 2009

### Spectrum of SUI Surgery RCT TVT® v. Monarc® in Patients with SUI

Laurikainen et al; Ob Gyn 2007

- N=273, 7 centers in Finland
- Cure = negative cough stress test
  - 98% in TVT v. 95% in TOT
- Return of normal voiding = PVR<100
  - 6 hours in TVT v. 9 hours in TOT
- Groin pain hospital stay was greater in TOT

TOT was not found to be inferior to TVT with respect to efficacy but had more groin pain

Perspectives in Urology 2009

### Spectrum of SUI Surgery

#### Retrospective Comparison of PVS, TVT and TOT in ISD

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• 273 women with ISD                             <ul style="list-style-type: none"> <li>• VLPP &lt; 60 cm H2O or</li> <li>• MUCP &lt; 20 cm H2O</li> </ul> </li> <li>• Follow up at 24 months</li> <li>• Cure = subjective absence of sx &amp; -CST                             <ul style="list-style-type: none"> <li>• PVS= 87%</li> <li>• TVT=87%</li> <li>• TOT= 35%</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• N=164, 2 hospitals</li> <li>• Cure = absence of SUI on UDS</li> <li>• Secondary outcomes                             <ul style="list-style-type: none"> <li>• Sx stress</li> <li>• Surgical complications</li> <li>• QOL questionnaires</li> </ul> </li> <li>• Urodynamic testing at 6 months                             <ul style="list-style-type: none"> <li>• TVT-21% leakage (79% cure)</li> <li>• TOT-45% leakage (55% cure)</li> </ul> </li> </ul> |
|--|---|

Jeon et al AJOG 2008

Schierlitz et al. Ob-Gyn 2008

TOT was found to be inferior to PVS and TVT with respect to efficacy in patients with ISD

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)

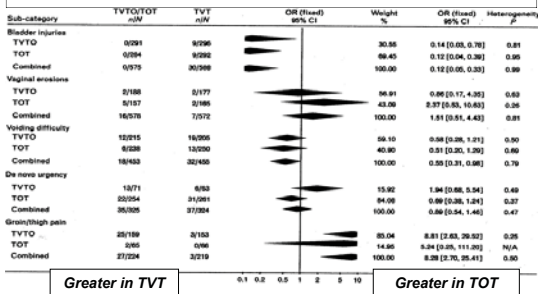
- Baseline characteristics were similar
- Relative risk of postoperative SUI 3 months after surgery was 2.85 in all patients when Monarc was compared to TVT
- RR was 0.56 if MUCP > 42 cm H2O
- RR was 5.89 if MUCP < 42 Cm H2O

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



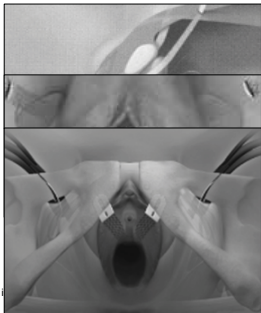
Latthe PM: Curr Opin in Obstet Gyn 2008

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





### Spectrum of SUI Surgery April 2003- July 2009

- **Retropubic tapes**
    - n = 72 (16%)
  - **TO tapes**
    - n = 190 (42%)
  - **Mini-slings**
    - n = 119 (26.4%)
  - **Biological Slings**
    - Autografts, 33 (7.3%)
    - Allografts, 27 (6%)
    - Xenografts, 0
  - **AUS, 9 (2%)**
- Totals**
- Synthetics, 390 (86.7%)
  - Biologicals, 60 (13.3%)

Retropubic Tape 2001



Transobturator Tape 2004

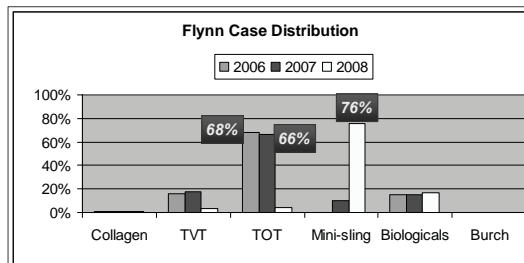


Mini-sling 2007



### Flynn Spectrum of SUI Surgery 2006 - 2008

Primary procedure for SUI in 2008 is Mini-Sling  
replacing TOT 2006-07



### Institutional Sling Extrusion Data April 2003-Present

GU tract erosion data of mesh, silicone and biologicals

- **Vaginal wall extrusion/pain**
  - retropubic tape 1 of 72 (1.4%)
  - TVT-O, 4 of 190 (2.1%)
  - TVT-S, 1 of 119 (0.8%)
  - Biological PVS, 0 of 60
  - AUS, 0 of 9
- **Urinary tract erosion**
  - retropubic tape 1 of 72 (1.4%)
  - TVT-O, 1 of 190 (0.5%)
  - TVT-S, 0 of 119
  - Biological PVS, 0 of 60
  - AUS, 0 of 9



Perspectives in Urology 2009

### 2010 SUFU Abstract: MANAGEMENT OF RECURRENT VAGINAL WALL EXTRUSIONS AND URINARY TRACT EROSIONS AFTER INCONTINENCE AND PROLAPSE SURGERY

Flynn BJ et al, Denver, CO

Retrospective review in 82 patients that underwent explantation  
of an eroded device due to recurrent vaginal wall extrusions  
and/or urinary tract erosions

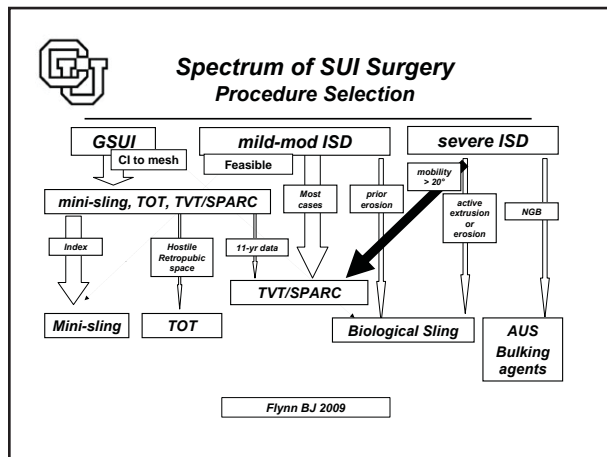
- removal of exposed/eroded sling material, sutures and prolapse mesh by a single surgeon at CU since 2003

- **Type of material**
  - Suspension sutures/plegets n = 5 (5.9%)
  - Xenografts n = 10 (11.8%)
  - Retropubic tapes n = 15 (18.3%)
  - TOT n = 29 (35.6%)
  - Mini-sling n = 2 (2.4%)

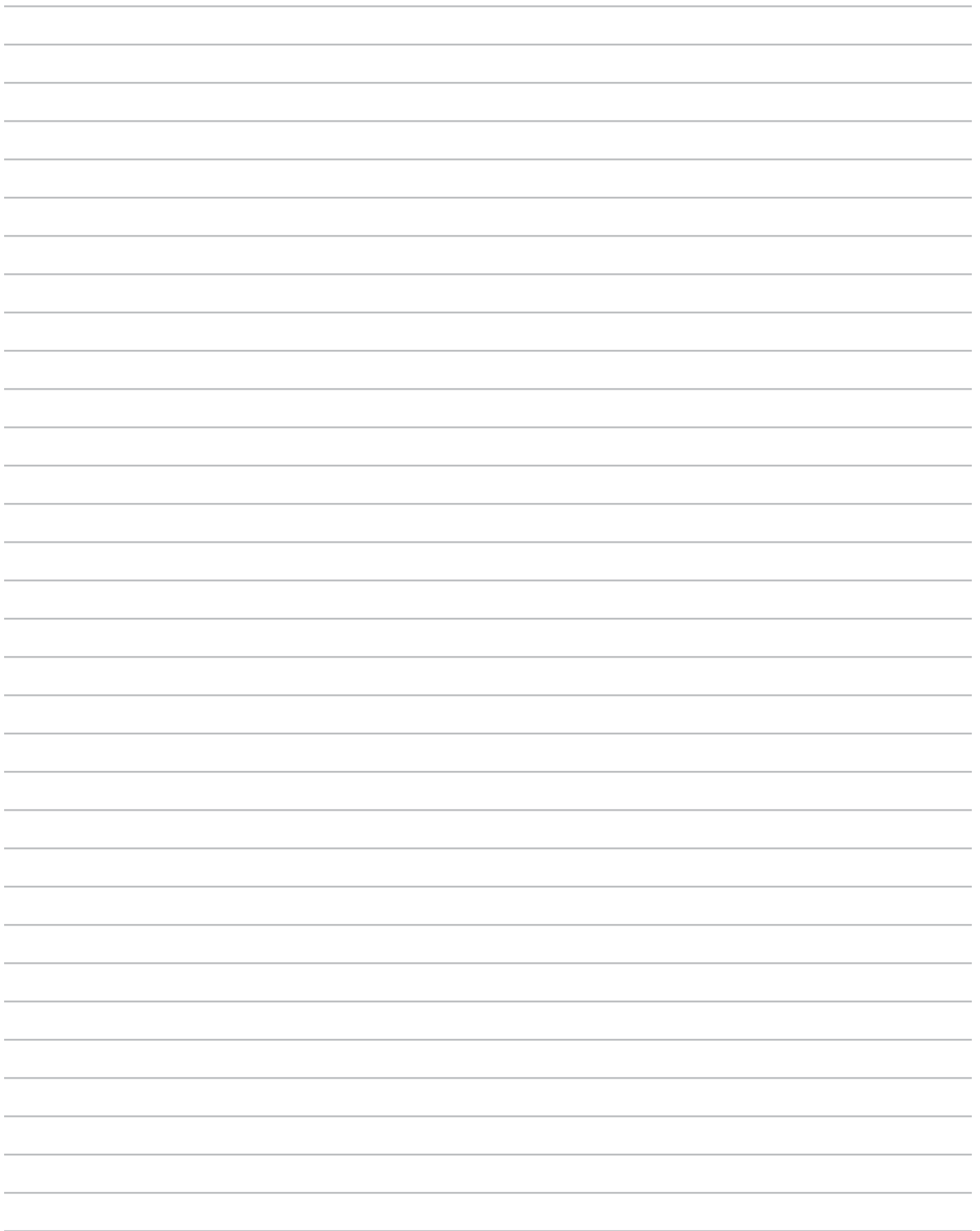
- Prolapse kits n = 17 (20.7%)
- ASC n = 4 (4.9%)

Flynn BJ et al: SCAUA 2007









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

~ David C. Beyer, MD

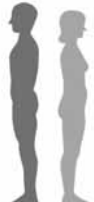
## Challenges in Prostate Cancer: Why Are We 15 Years Behind Breast Cancer

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

Lung	90,330	31%		Lung	72,130	26%
Colon & Rectum	27,870	10%		Breast	40,970	15%
Prostate	27,350	9%		Colon & Rectum	27,300	10%
Pancreas	16,090	6%		Pancreas	16,210	6%
Leukemia	12,470	4%		Ovary	15,310	6%
All Sites	291,270			All Sites	273,560	

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

		Birth to 39 (%)	40 to 59 (%)	60 to 69 (%)	70 and Older (%)	Birth to Death (%)
Breast	Female	.5	4.1	3.8	7.1	13.2
Prostate	Male	.01	2.7	7.2	14.5	17.9

DevCan Software, Probability of Developing or Dying of Cancer Software, Version 6.0. Statistical Research and Applications Branch, National Cancer Institute, 2005. <http://srab.cancer.gov/devcan>.

Stage	Group 1 (%)	Group 2 (%)
Localized	63	64
Regional	29	35
Distant	6	9

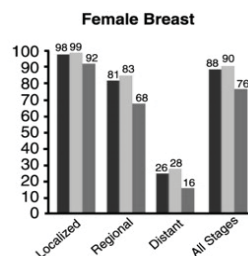
Ries LAG, Eisner MP, Kosary CL. et al.  
[http://seer.cancer.gov/csr/1975\\_2002/](http://seer.cancer.gov/csr/1975_2002/).

**Prostate\***

Category	Black Bar (%)	Grey Bar (%)
Localized	91	91
Distant	5	7

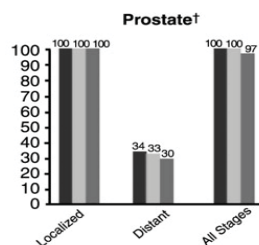
Ries LAG, Eisner MP, Kosary CL. et al.  
[http://seer.cancer.gov/csr/1975\\_2002/](http://seer.cancer.gov/csr/1975_2002/).

## Five-year Survival by Stage: Breast



Ries LAG, Eisner MP, Kosary CL, et al.  
[http://seer.cancer.gov/csr/1975\\_2002/](http://seer.cancer.gov/csr/1975_2002/)

## Five-year Survival: Prostate



Ries LAG, Eisner MP, Kosary CL, et al.  
[http://seer.cancer.gov/csr/1975\\_2002/](http://seer.cancer.gov/csr/1975_2002/)

## Studying Cancer Correlated with:

- **Diet**
  - Fat
  - Fiber
- **BMI**
- **Vitamin A, E, C**
- **Selenium**
- **Alcohol**
- **Caffeine**

Diseases of the Breast, Harris et al, Lippincott-Raven 201-215, 1996

## One Day on Google

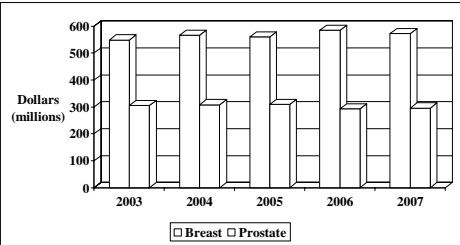
- **Breast cancer:** 7,700,000 hits
- **Prostate cancer:** 12,000,000 hits
  
- **Komen:** 42,800,000 hits
- **Us Too International:** 204,000,000 hits

Google, accessed October 15, 2009

Funding



NCI Research Funding



<http://obf.cancer.gov/financial/historical.htm>

Models for Breast Cancer Spread

- **Halsted**
  - Orderly spread
  - + Node instigator of DM
  - RLN barrier to spread
  - Bloodstream of little significance
  - Local/Regional disease
  - Extent of surgery matters
- **Systemic**
  - No orderly pattern
  - + Node indicator of DM
  - RLN ineffective barrier
  - Bloodstream very important to spread
  - System disease
  - Local/Regional therapy secondary

Halsted, J. J. Hopkins Hosp Bull, 1895 4:297  
Fisher, Breast Cancer Res Treat 1981; 1:17

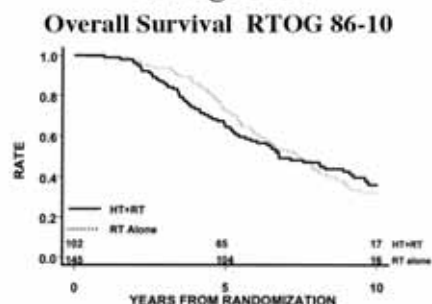
Treatment Issues

- **Breast**
  - ER/PR receptor assay
  - Level I evidence
- **Prostate**
  - Presumed sensitivity
  - Level I evidence

## Adjuvant Tamoxifen

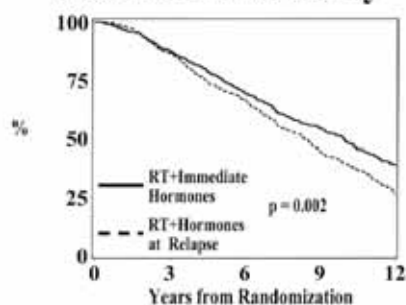
- Early Breast Cancer Trialists Collaborative Group (EBCTCG)
- 5 years adjuvant therapy
- In receptor positive patients:
  - Odds of recurrence ↓ 47%
  - Odds of death ↓ 26%

## Does Early HT Compromise Late Salvage HT?



Shapley et al. JROBP, 2002, 54(5):1302-1310

## RTOG 85-31 Reduction in Mortality

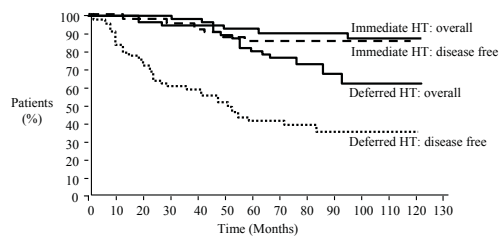


Pilepich et al. JROBP 61(15):1283-1290, 2003

## 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

### RP and Pelvic Lymphadenectomy in Node-Positive Patients +/- Hormones



Messing EM, et al. *N Engl J Med*. 1999;341:1781-1788.

Fraction Surviving

Time (Years)

elderly AD

radiated

$p=0.00$

### 313 Patients

Kestin, Vicini, Martinez; JROBP, 2004, 60(2):453-462

	Disease Free Survival	bNED	Local Control	Survival	Survival Gleason 8-10
STAD	34%	21%	87%	78%	69%
LTAD *	54%	46%	94%	79%	80%

\* ↑↑ GI toxicity

Hanks et al. UROBP 2000 ASTRO

	Disease Free Survival	bNED	Local Control	Survival
STAD	18%	65%	84%	50%
LTAD	13%	45%	91%	51%
p	0.001	<0.001	0.002	0.25

Hanks et al. UROBP, 2006, 66(3 Supplement):815 2006

### Are Hormones Beneficial in the Era of Dose Escalation?

- **RTOG 0815**
- **Intermediate risk patients**
- **Dose escalation**
  - XRT 79.2 Gy (IGRT ok)
  - XRT 45 Gy + HDR 21 Gy / 2 Fx's
  - XRT 45 Gy +  $^{125}\text{I}$  110 Gy (or  $^{103}\text{Pd}$  100Gy)
- **+/- 6 months TAB**
- **1520 patients**

<http://rtog.org/members/protocols/0815/0815.pdf>

### Available Hormone Options

- |                       |                       |
|-----------------------|-----------------------|
| • Tamoxifen           | • DES                 |
| • Fareston            | • Bicalutamide        |
| • Arimidex            | • Flutamide           |
| • Aromasin            | • Nilandrone          |
| • Femara              | • Leuprolide          |
| • Megestrol           | • Goserelin           |
| • Halotestin          | • Degarelix           |
| • Bicalutamide        | • Surgical castration |
| • Leuprolide          |                       |
| • Surgical castration |                       |

<http://www.webmd.com/breast-cancer/hormone-therapy-overview>

### Hormone Induced Flair

- Worsening pain, bone scan, labs, etc.
- 2-21 days
- 3-20%

Plotkin, et al, JAMA, 1978; 240:2644

### Treatment Issues

- |                        |                        |
|------------------------|------------------------|
| • Breast               | • Prostate             |
| • ER/PR receptor assay | • Presumed sensitivity |
| • Level I evidence     | • Level I evidence     |
| • Hormones             | • LHRH /               |
| • AI's                 | Antiandrogen           |



### Sequencing of Tamoxifen and Radiation in Breast Cancer

- 1646 women for breast conservation
- 500 received TAM
  - 254 up front
  - 241 after XRT
- No difference in outcomes or toxicity

Ahn et al. J Clin Oncol 2005;23(1):17-23

### Adjuvant Chemotherapy in Prostate Cancer

- RTOG 0521
- High risk
  - Gleason  $\geq 7$
  - PSA  $<150$
- XRT 72-75.6 Gy
- 2 years LHRH + Antiandrogen
- +/- 6 cycles Docetaxel/Prednisone started 28 days after XRT
- Reached 600 patient accrual target

<http://rtog.org/members/active.html> Accessed Oct 2006

### Adjuvant Docetaxel Following RP Phase II RTOG 0621

- Post Prostatectomy
  - Gleason  $\geq 7$  and PSA nadir  $>0.2$  ng/ml
  - Gleason  $\geq 8$  and Stage  $\geq T3a$  (any PSA nadir)
- Accrual 76 patients
- TAB 6 months
- XRT 66.6 Gy (at 8 weeks)
- Docetaxel  $75\text{mg}/\text{m}^2$  q21days x 6 cycles

### Treatment Issues

- |                                       |                        |
|---------------------------------------|------------------------|
| • Breast                              | • Prostate             |
| • ER/PR receptor assay                | • Presumed sensitivity |
| • Level I evidence                    | • Level I evidence     |
| • Hormones                            | • LHRH /               |
| • AI's                                | Antiandrogen           |
| • Chemotherapy                        | • Chemotherapy (?)     |
| • No blood marker                     | • PSA                  |
| • Genetic markers predict sensitivity | • Limited markers      |

Zhang, M. et al. *IJROBP*. V73(4): 1033-1042, 2009.

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

~ M. Scott Lucia, MD

### Prostate Cancer: Clinical and Pathological Characteristics



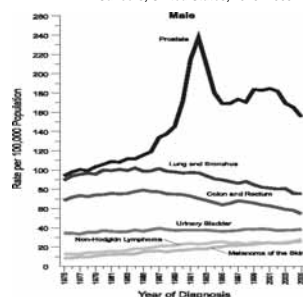
M. Scott Lucia, MD  
Associate Professor  
Chief of Genitourinary and Renal Pathology  
Director, Prostate Diagnostic Laboratory  
Dept. of Pathology  
University of Colorado Denver SOM

### Prostatic Carcinoma - 2009<sup>1</sup>

- >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



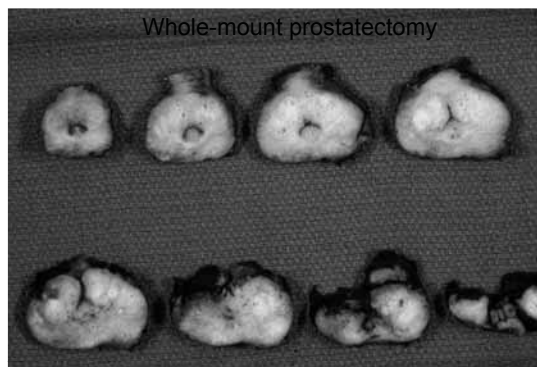
From Jemal, A. et al.  
*CA Cancer J Clin* 2009;59:225-249.

Copyright ©2009 American Cancer Society

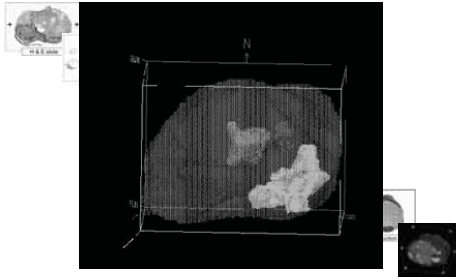


Copyright ©2009 American Cancer Society

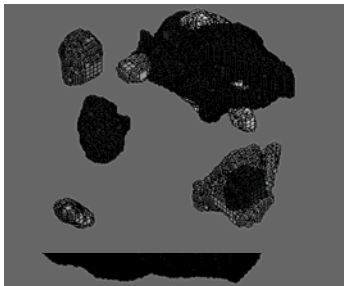
- Shift in pathological characteristics
- Shift in clinical presentation
- Shift in treatment paradigms
  - Recognition that not all cancers need treatment
  - New approaches for low-risk cancer
    - Active surveillance
    - Targeted focal therapy
- Need for improved diagnostic tools and approaches
  - Differentiate "significant" vs "insignificant" tumors
  - Earlier diagnosis of aggressive cancers



### 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 G.J., J Urol 152:1709, 1994

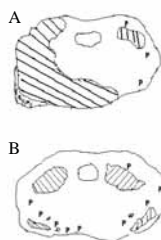
Tumors/Pt.	No. Pts. (%)	No. Tumors	Mean Tumor Vol. (cc)
1	66 (43.7)	66	6.52
2	47 (31.1)	94	1.48
3	25 (16.6)	75	1.01
4	8 (5.3)	32	0.59
5	4 (2.6)	20	0.40
6	1 (0.7)	6	0.22
Totals	151 (100)	293	

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

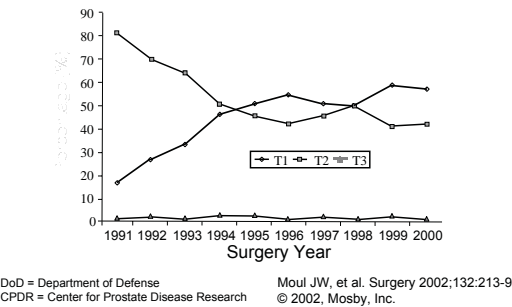
Lucia MS, Unpub

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

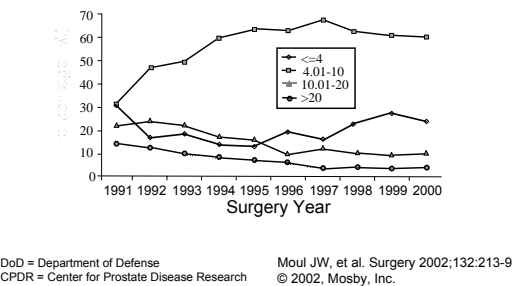
- Tumors were larger, more confluent and more advanced
- Tumors now smaller, more multifocal and more localized



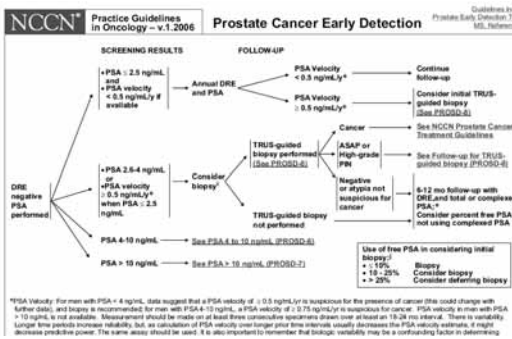
DoD CPDR National Database: Clinical T stage at diagnosis for patients who underwent prostatectomy



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

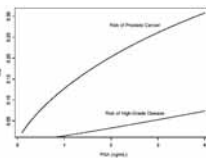


NCCN Guideline For Prostate Cancer Screening



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)



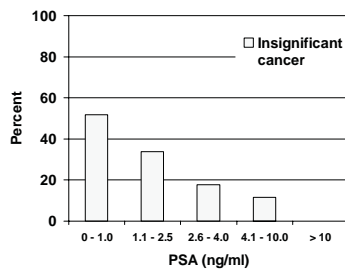
Thompson et al. JAMA 2005; 294: 66-70

### 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

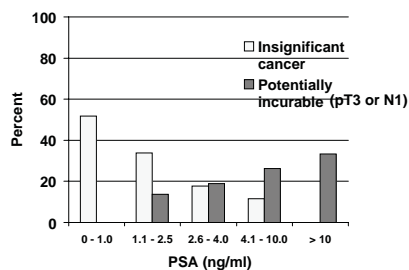
### PCPT: PSA and Insignificant Cancer\*



\* 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\*



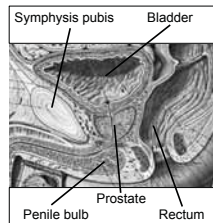
\* GS≤6, <3 cores with cancer, no core with >50% tumor

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

- Prostate in pelvic “blind spot”
- Limited imaging available
- Access to prostate through rectum
- Difficult to access anterior prostate
- Biopsies random
  - ~50-70% sensitive
  - Many cancers aren't life threatening



From: *Anatomy: A Regional Atlas of the Human Body*, Clemente CD, 2<sup>nd</sup> Ed., Urban & Schwarzenberg, Baltimore, 1981.

- Cancer sampling is a function of tumor volume: prostate volume
- Negative biopsy  $\neq$  no cancer
- Biopsy grade may be inaccurate
- Biopsy is a poor staging tool

- *Has consequences for choice and effectiveness of therapy*
  - Expectant management
  - Targeted focal therapy

Gleason Score on Biopsy	Gleason Score at Radical Prostatectomy (RP)			
	2-5	6	7	8-10
2-5	10	28	8	1
6	12	100	43	0
7	1	13	38	3
8-10	0	3	5	7
Increased at RP	83/272 (30.5%)			
Unchanged at RP	155/272 (57.0%)			
Decreased at RP	34/272 (12.5%)			

**Proportion of high grade cancer at RP initially detected at biopsy = 53/105 (50.5%)**

Lucia MS, et al. *JNCI* 2007; 99:1375-83

- 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
- *Need new approaches to assess tumor aggressiveness*

### Ideal Biomarker for Prostate Cancer

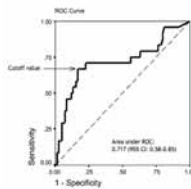
- Sensitive and specific for aggressive cancer
- When modulated, correlates with disease outcome
- Reproducible
- Quick and easy to assay
- Low cost
- Minimal invasiveness

### 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

Nakanishi, H et al. J Urol 2008;179:1804-9. Used with permission.

- Histologic type and grade
- Pathologic stage
- Margin status
- Tumor volume
- Biomarkers/molecular determinants?
  - Systems pathology – can we improve on traditional pathology?

## Stamey TA, et al. JAMA. 1999;281:1395-400. Copyrighted 1999 American Medical Association

Log-rank,  $p < 0.001$ 

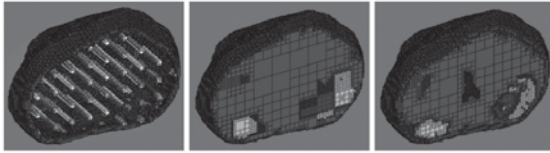
A. Organ-confined, margin negative

Rampersaud EN, et al. J Urol 2008;180:571-76  
© 2008 American Urological Association

Log-rank,  $p < 0.001$ 

B. ECE and/or margin positive

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



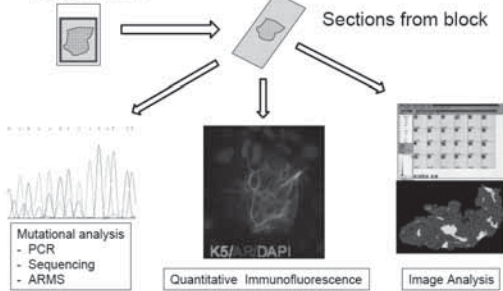
- Saturation grid-biopsy data (left)
- Reverse-reconstruction model (center)
- Actual RRP specimen (right)
- Model error: -15% for Gleason 3+4 tumor (right, 5.1cc)  
+15% for Gleason 3+3 tumor (left, 0.093cc)

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

Paraffin block



Primary  
Data

Pathologic Factors:  
Grade  
Stage  
Margins

Clinical Factors:  
PSA  
Stage

Secondary  
Data

Mutational  
Analysis

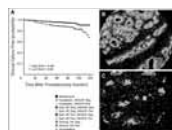
Image Analysis

Quantitative IF

Risk of Progression

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

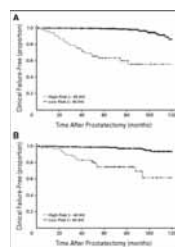
- Clinicopathologic: Grade, LN mets
- Image analysis: Pca gland lumen architecture, cytoplasm color/texture
- IF: AR, AMACR



↑ Analysis of AR and AMACR

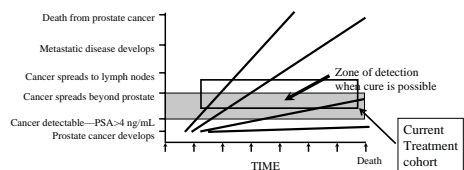
Kaplan-Meier curve demonstrating the classification of patients from the (A) training cohort and (B) validation cohort as being at low risk (blue line) or high risk (yellow line) for experiencing clinical failure (CF)

CI=0.84



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

Copyright© American Society of Clinical Oncology



$$\text{Metastatic Potential} = p \times T$$

**p** = phenotype (biologic aggressiveness)

- Assessed by grade (other?)

**T** = time

- Reflected by volume, stage
- Assessed by ? – to be determined

## Chemoprevention Strategies

~ M. Scott Lucia, MD

### Chemoprevention Strategies for Prostate Cancer



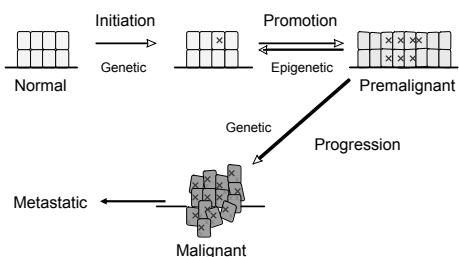
M. Scott Lucia, MD  
Associate Professor  
Chief of Genitourinary and Renal Pathology  
Director, Prostate Diagnostic Laboratory  
Dept. of Pathology  
University of Colorado Denver SOM

### 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



Characteristics of Prostate Cancer that support a role for chemoprevention

- Disease of aging (oxidative stress? Inflammation? epigenetic events)
- Long latency
- Putative precursor lesion
- Early dependence on androgen
- Susceptibility to oxidative damage:
  - High prevalence of GSTP1 hypermethylation<sup>1</sup>
  - Overexpression of COX-2<sup>2</sup>
- Altered growth factor responsiveness

1. Lee WH, et al. Proc Natl Acad Sci U S A 1994;91:11733-7

2. Aparicio Gallego G et al. Clin Transl Oncol 2007;9:694-702

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Early Events in Prostatic Carcinogenesis

The diagram illustrates the progression of early events in prostatic carcinogenesis. It shows a series of prostate gland cross-sections. The first two are normal. The third shows 'PIN' (Prostatic Intraepithelial Neoplasia). The fourth shows 'CAP' (Carcinoma in Situ). Above the glands, boxes for 'Androgens' and 'Growth regulatory imbalance' have arrows pointing to the progression. Below the glands, a horizontal bar shows the progression from normal to PIN to CAP. The CAP bar is shaded with a gradient, indicating increasing severity.

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Prostate Cancer – Risk Factors

- Age
- Family history
- Intact Androgen Axis
- Diet
  - High fat (oxidative stress? alteration of hormone balance? arachidonic acid?)
  - Low selenium/ antioxidants/ isoflavonoids
- Geographic locale
  - Western cultures (diet)
  - Low UV light exposure (vit D)
- Prostatitis (oxidative stress?)
- African-American ethnicity (androgens? vit D?)

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Candidate Chemopreventive Agents for PCa

- Hormonal agents
  - 5 $\alpha$ -reductase inhibitors (eg. Finasteride, Dutasteride)
  - Antiandrogens/ LHRH antagonists (eg. Flutamide, leuprolide)
  - SERM's (eg. Tamoxifen, raloxifene, toremifene, SERM-3)
- Phytoestrogens and Protein Kinase Inhibitors
  - Isoflavonoids (eg. Genestein, silibinin)
  - Angiogenesis inhibitors (eg. SU-101)
- Antiproliferative or Differentiating Agents
  - Vitamin D analogs
  - Retinoids (eg. 4-HPR, 9cis-retinoic acid)
  - Polyamine inhibitors (eg. DFMO)
- Anti-inflammatory Agents
  - COX-2 inhibitors (eg. Celecoxib, sulindac sulfone)
  - Statins
- Antioxidants
  - Vitamin E (SELECT)
  - Selenium (SELECT)
  - Carotenoids (eg. Lycopene)

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## Candidate Chemopreventive Agents for PCa

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  - Statins
- Antioxidants
  - Vitamin E (SELECT)
  - Selenium (SELECT)
  - Carotenoids (eg. Lycopene)

## Hormonal Agents

Antiandrogens/ 5 $\alpha$ -reductase inhibitorsRationale

- Androgen major regulator of growth and differentiation
  - Basis for androgen ablation therapy
- Males castrated < 40 yrs age don't get clinical prostate cancer<sup>1</sup>
- Males with 5 $\alpha$ -reductase deficiency don't get prostate cancer<sup>2</sup>
- Racial differences in androgen metabolism<sup>3</sup>

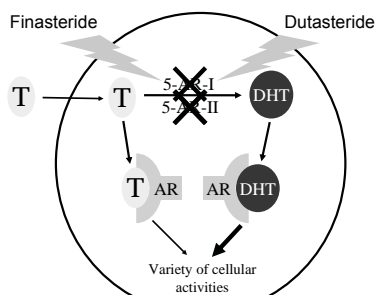
1. Moore RA. Surgery 1944.
2. Imperato-McGinley J et al. Science 1974.
3. Ross RK et al. Cancer Res 1998.

## Hormonal Agents for Prostate Cancer Chemoprevention

Limitations

- Side effects! (hot flashes, gynecomastia, sexual dysfunction, weakness, etc.)
  - LHRH agonists
  - Androgen receptor antagonists
- Candidates for prevention generally healthy with active physical & sexual lives
  - Must maintain acceptable QOL
- 5 $\alpha$ -reductase inhibitors (5ARI's)
  - Favorable side effect profile
  - Treatment for BPH

## 5ARI's: Mechanism of Action



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.

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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

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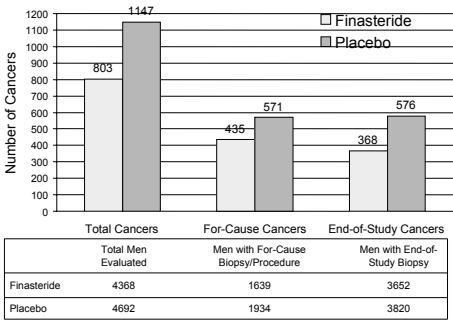
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Prostate Cancer Prevention Trial



Thompson IM, et al. *NEJM* 2003.

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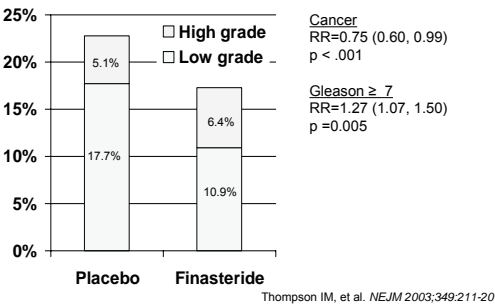
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Observed fractions of total subjects with low- and high-grade cancer in the PCPT



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

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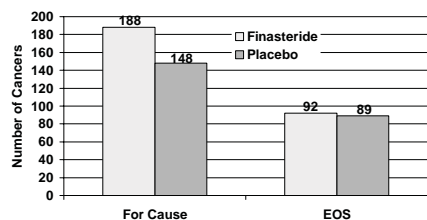
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## Grade 7-10 Cancers diagnosed in PCPT



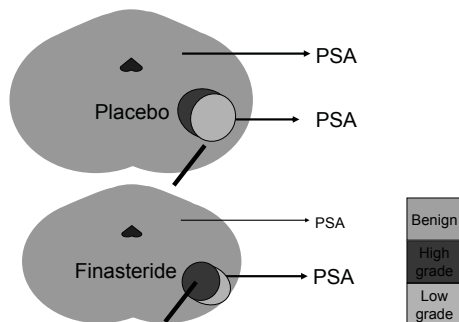
"For cause" = biopsy for ↑PSA and/or abnormal DRE  
 "EOS" = end-of-study biopsy

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

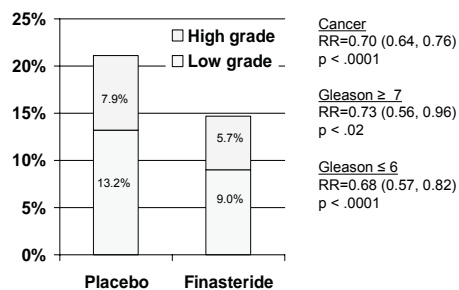
- Finasteride improved performance of PSA for cancer and high-grade cancer<sup>1</sup>
- Finasteride increased sensitivity of DRE<sup>2</sup>
- Finasteride increased sensitivity of prostate biopsy for detection of high grade cancer by reducing prostate volume<sup>3</sup>

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



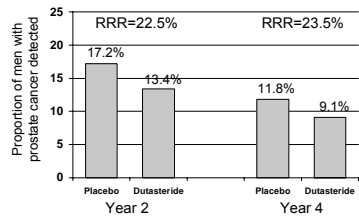
Cancer  
 RR=0.70 (0.64, 0.76)  
 p < .0001

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

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

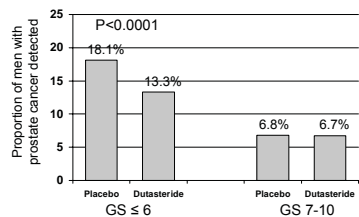
Redman MW, et al. *Cancer Prev Res* 2008;1:174-81

REDUCE Primary Results



Gleason 7-10: Placebo = 6.8%  
Dutasteride = 6.7%  
Andriole G. AUA 2009  
Used with permission

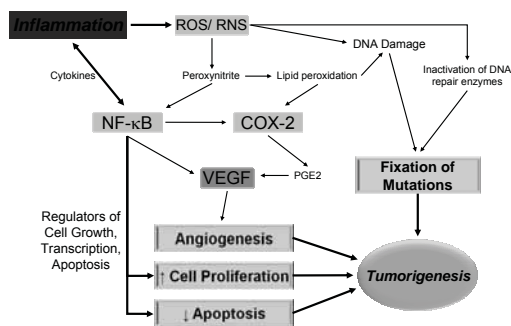
Gleason score (GS) distribution by treatment group in REDUCE



Andriole G. AUA 2009  
Used with permission

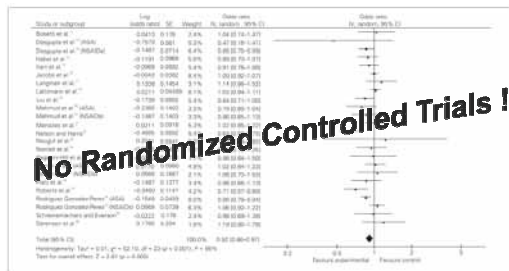
Future Directions for Prostate Cancer Chemoprevention: What next?

- Phytoestrogens (Phase II trials)
  - Inhibition of PKC, cell growth, angiogenesis
- Anti-proliferative agents (Phase II trials)
  - Vit D analogues, retinoids, DFMO
- Anti-inflammatory agents/ antioxidants
- Statins
  - Reduction of cholesterol
  - Anti-inflammatory



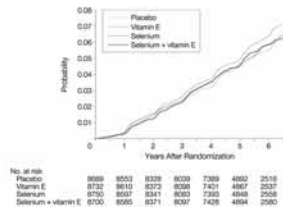
ROS=reactive oxygen species RNS=reactive nitrogen species  
COX-2=cyclooxygenase-2 VEGF=vascular endothelial growth factor

### Meta-analysis of effect of Non-steroidal anti-inflammatory drugs (NSAIDS) on prostate cancer risk



From: Jafari S. et al. Non-steroidal anti-inflammatory drugs and prostate cancer: A systematic review of the literature. CUAJ 2009;3:323-30.  
© 2009 Canadian Urological Association.

### The Selenium and Vitamin E Cancer Prevention Trial (SELECT): Cumulative Incidence of Prostate Cancer Detected Each Year by Intervention Group



Lippman, S. M. et al. JAMA 2009;301:39-51.  
© 2009 American Medical Association

JAMA



How do we identify those men who would benefit most?

- Patient desire?
- Positive family history?
- The REDUCE model?
  - Elevated PSA and negative biopsy
- Risk calculator/ nomogram?



## Point-Counterpoint:

**Early Detection of Prostate Cancer Is Not Valuable In a Lot of Men**

~ *E. David Crawford, MD*

**We Can't Go Backwards – Of Course Screening Has Saved Lives**

~ *Robert E. Donohue, MD*

### Screening does not impact mortality rates!

*E. David Crawford, MD*

Professor of Surgery (Urology) and Radiation Oncology  
Head, Urologic Oncology

E. David Crawford Endowed Chair in Urologic Oncology  
University of Colorado Health Sciences Center  
Denver, Colorado

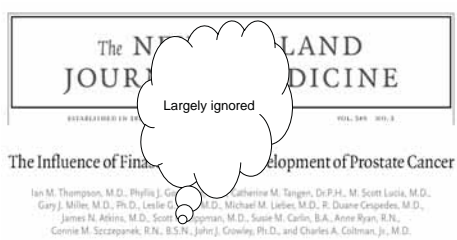


### 1989

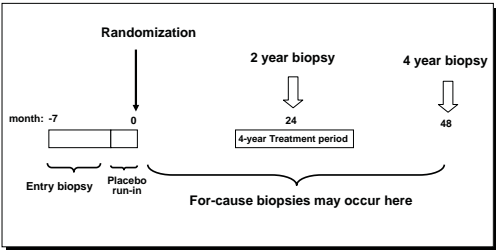
- Prostate cancer became the most common cancer in American Males
- And the second leading cause of death
- Options:
  - Do nothing
  - Prevention
  - Early detection
  - Improve outcome for advanced disease

### 1989-Fast forward, what happened?

Prevention: PCPT 25% reduction



REDUCE Schema  
to be presented



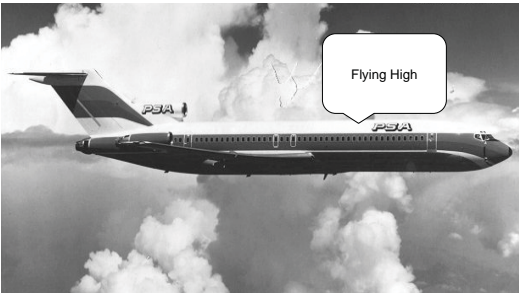
Andriole et al, J Urol 172:1314, 2004



Optimism that Screening Is Associated  
with a Fall in Mortality

- Fall in mortality now seen
  - SEER
  - Olmsted County
  - Evidence is conflicting, not strong enough to support public policy
  - Tyrol, Austria
- Mortality fall *not seen* where PSA screening not performed
  - Mexico—where little to no PSA screening is performed

PSA





## Untreated PCa Seldom Fatal in Elderly

The authors on these pages, report in their findings are based on data from the 2004 Surveillance, Epidemiology, and End Results (SEER) database, which was sponsored by the National Cancer Institute.

SEER database data with local and prostate cancer will also be used in the analysis. Dr. Crawford, an assistant professor at the University of California, San Francisco, and his colleagues report in their findings that the mortality associated with prostate cancer is not significantly higher than that associated with other causes of death in elderly men.

### Aggressive PCa Treatment Unsupported

Conservative management of low-risk malignancies is associated with very low long-term death rate

Dr. Crawford and his colleagues report in their findings that the mortality associated with prostate cancer is not significantly higher than that associated with other causes of death in elderly men. They also report that the mortality associated with prostate cancer is not significantly higher than that associated with other causes of death in elderly men.

Prostate Cancer Mortality	Other Causes of Death
10.5%	10.5%
10.5%	10.5%
10.5%	10.5%

Prostate cancer mortality greatly increased with high-grade tumors.

Renal and Urology News June 2005, April 2008

## The Clinical and Economic Burden of Prostate Cancer

- Number 1 cancer, 16% men, 3-4% death
- Cost 8 billion 11.2%
- First year of treatment cost \$40,873.20



## PROSTATE SCREENING 2009

### Organization

American Urological Association (AUA)

American Cancer Society (ACS)

Centers for Disease Control and Prevention (CDC)

U.S. Preventive Services Task Force (USPSTF)

American College of Preventive Medicine (ACPM)

### Recommendation

Men who are in good health: annual PSA testing starting at age 50, or 40 if high-risk (AA, or with a father, brother or son with prostate cancer).

Men who are in poor health: PSA testing starting at age 50, or 40 if high-risk (AA, or with a father, brother or son with prostate cancer).

Considers evidence "insufficient to determine whether the benefits outweigh the harms."

Discusses risks/benefits. The need for screening questionable in elderly men with other chronic illnesses and men with life expectancies of less than 10 years.

**Conflicting recommendations Updates expected**

## PLCO Cancer Screening Trial

- Multi-center randomized screening trial for:
  - Prostate
  - Lung
  - Colo-rectal
  - Ovarian
- 155,000 men and women aged 55-74
- Recruitment: 1993-2001
- Screening: 1993-2006
- Follow-up until 2015 by annual survey and mortality search



## PLCO Screening Centers



## Screening Interventions in PLCO Trial

- Prostate – Annual DRE x 4 and PSA x 6
- Lung – Annual Chest Xray x 4
  - Spiral CT for smokers
- Colon – FSG at years 1 and 6
- Ovary – TVU x 4 and CA125 x 6

## PLCO Screening Follow-up

- Intervention Arm:
  - Screening results reported to patient and PCP
  - “Community standard of care” applied to biopsy and treatment decisions
- Comparison Arm:
  - “Community standard of care”

## PLCO Study Endpoints

- Cause-specific mortality
- Outcomes of screening exams
- Incident and prevalent cancers

### Original Article Mortality Results from a Randomized Prostate- Cancer Screening Trial

Gerold L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb, III, M.D., Sandra S. Buys, M.D., David Chia, Ph.D., Timothy R. Chaneir, Ph.D., Mona N. Fouad, M.D., Edward P. Gelmann, M.D., Paul A. Kvale, M.D., Douglas J. Reding, M.D., Joel L. Weissfeld, M.D., Lance A. Yokochi, M.D., Barbara O'Brien, M.P.H., Jonathan D. Clapp, B.S., Joshua M. Rathmell, M.S., Thomas L. Riley, B.S., Richard B. Hayes, Ph.D., Barnett S. Kramer, M.D., Grant Izmirlian, Ph.D., Anthony B. Miller, M.B., Paul F. Pinsky, Ph.D., Philip C. Prorok, Ph.D., John K. Gohagan, Ph.D., Christine D. Berg, M.D., for the PLCO Project Team

N Engl J Med  
Volume 360(13):1310-1319  
March 26, 2009



#### Prostate Cancer Screening Fails to Provide Definitive Benefits

By Richard Chasen

March 23 (Bloomberg) — Prostate cancer screening may have a small number of  
benefits at best, while keeping many more men in state of confusion,  
according to studies in the U.S. and Europe that offered over survival benefit  
from the tests.

In one, an American research team detected no reduction in deaths with  
screening in a 15-year study involving a 10,000 men and women.



Los Angeles Times Opinion

Prostate cancer screenings: a second opinion

Prostate cancer screenings: a second opinion

Prostate cancer screenings: a second opinion

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Prostate cancer screenings: a second opinion

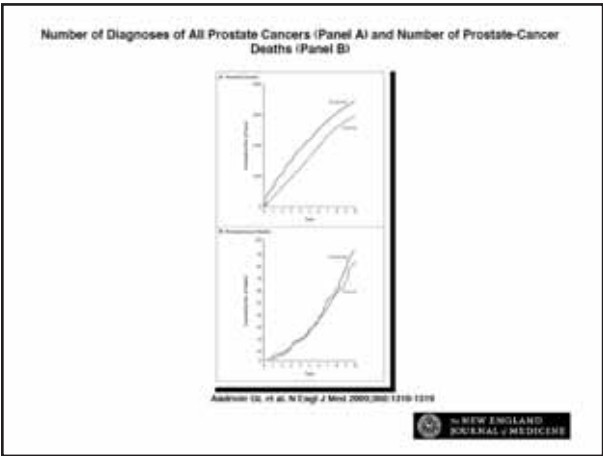
Prostate cancer screenings: a second opinion

#### Characteristics of the Subjects at Baseline

Characteristic	Screening Group (n=33,000)	Control Group (n=33,000)
Age		
< 50 yr	0.1	0.1
50-54 yr	1.1	1.1
55-59 yr	1.1	1.1
60-64 yr	1.1	1.1
65-69 yr	1.1	1.1
70-74 yr	1.1	1.1
75-79 yr	1.1	1.1
80-84 yr	1.1	1.1
85-89 yr	1.1	1.1
90-94 yr	1.1	1.1
≥ 95 yr	1.1	1.1
Marital status		
Married	98.1	98.1
Never married	1.1	1.1
Divorced	0.1	0.1
Widowed	0.1	0.1
Education		
Less than high school	1.1	1.1
High school graduate	1.1	1.1
Some college	1.1	1.1
College graduate	1.1	1.1
Postgraduate	1.1	1.1
Employment		
Employed	98.1	98.1
Unemployed	1.1	1.1
Retired	1.1	1.1
Health insurance		
Medicaid	1.1	1.1
Medicare	1.1	1.1
Private	1.1	1.1
Other	1.1	1.1
Health status		
Good	98.1	98.1
Fair	1.1	1.1
Poor	1.1	1.1
Very poor	1.1	1.1

Andriole GL, et al. N Engl J Med 2009;360:1310-1319





Tumor Stage, Histopathological Type, and Gleason Score for All Prostate Cancers at 10 Years, According to Method of Detection and Time of Diagnosis

Variable	Screening Group				Control Group	
	Screened (n=10,000)	Not Screened (n=10,000)	Screened (n=10,000)	Not Screened (n=10,000)	Screened (n=10,000)	Not Screened (n=10,000)
Overall	10,000	10,000	10,000	10,000	10,000	10,000
Stage						
I	1,000	1,000	1,000	1,000	1,000	1,000
II	2,000	2,000	2,000	2,000	2,000	2,000
III	3,000	3,000	3,000	3,000	3,000	3,000
IV	4,000	4,000	4,000	4,000	4,000	4,000
V	5,000	5,000	5,000	5,000	5,000	5,000
Histopathological Type						
Adenocarcinoma	9,000	9,000	9,000	9,000	9,000	9,000
Squamous	1,000	1,000	1,000	1,000	1,000	1,000
Sarcoma	1,000	1,000	1,000	1,000	1,000	1,000
Gleason Score						
6-7	1,000	1,000	1,000	1,000	1,000	1,000
8-9	2,000	2,000	2,000	2,000	2,000	2,000
10	3,000	3,000	3,000	3,000	3,000	3,000

Death Rates from Prostate Cancer per 10,000 Person-Years at 10 Years

Variable	Screening Group										Control Group									
	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
Overall	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000
Stage																				
I	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000
II	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000
III	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000
IV	4,000	4,000	4,000	4,000	4,000	4,000	4,000	4,000	4,000	4,000	4,000	4,000	4,000	4,000	4,000	4,000	4,000	4,000	4,000	4,000
V	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000

Causes of Death at 10-Year Follow-up

Cause	Screening Group		Control Group	
	n	(%)	n	(%)
Any†	2923	(29.2)	2923	(29.2)
Cancer‡	918	(9.18)	918	(9.18)
Ischemic heart disease	857	(8.57)	857	(8.57)
Stroke	337	(3.37)	337	(3.37)
Other circulatory disease	684	(6.84)	684	(6.84)
Respiratory disease	413	(4.13)	413	(4.13)
Digestive disease	341	(3.41)	341	(3.41)
Infectious disease	24	(0.24)	24	(0.24)
Endocrine or metabolic disease or immune disorder	155	(1.55)	155	(1.55)
Nervous system disease	139	(1.39)	139	(1.39)
Accidents	288	(2.88)	288	(2.88)
Other	138	(1.38)	138	(1.38)

### PLCO Trial Conclusions:

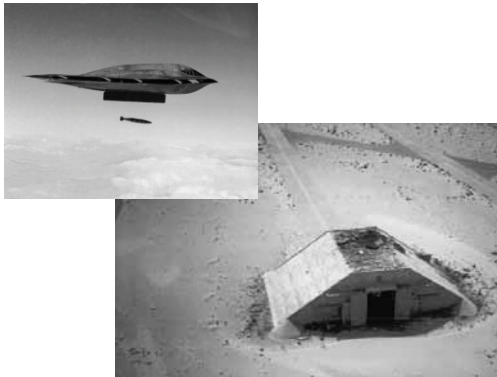
- 7-10 years, no difference in mortality
- Few CaP related deaths in either group- 92 screening and 82 control at 10 years
- Balance of benefits and harms unfavorable and does not support routine screening, at this time
- Even if mortality is shown to decrease, still significant harm to many men

### PLCO Trial Conclusions:

- First report-planned follow for at least 13 years, more to come
- Contamination-as high as 50%, could be a contributing factor, improved therapy could also be a contributing factor-
- PSA not the best test, far from it
- Need a better test and marker of progression

### Thoughts

- Screening doesn't work for all cancers: Lung, neuroblastoma, and not all breast cancers
- Need to separate diagnosis from treatment, clearly over treating men
- But, need to remember that 28,000 men died in 2008 of CaP
- We need to figure out who needs to be diagnosed and effectively treated.



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	
Year 4			X	X		X		
Year 5			X	X	X	X		
2004-2013								x
Comparison Arm								
	X	X				X		X

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

## **We can't go backwards: Screening has helped !**

**Robert E. Donohue M.D.  
Denver V.A. Medical Center  
University of Colorado**



## **Prostate Biopsy**

**“Is cure necessary;  
when it is possible ?”**

**“Is cure possible;  
when it is necessary ?”  
Willet F. Whitmore Jr.**

## **Prostate Biopsy**

**What is the most dangerous  
weapon in the world today ?**

**Willet F. Whitmore Jr.**



## 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,

**1930s perineal; 1937 rectal bx**

### PSA doubling time

**70 – 75 5.5 ng/ml**

**Crawford PCAW**

**Crawford PCAW  
JAMA**

## Moul

## 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

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
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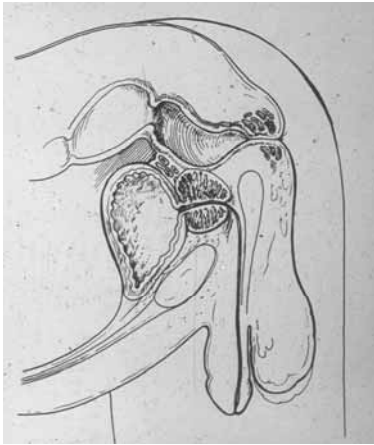
## Tumors 2009

	incidence	mortality
prostate	192,280	27,360
lung	103,350	88,900
colo/ rectal	52,010	25,240
bladder	23,580	
non Hodgkin's	52,810	18,030p
	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





## Rectal Exam

examiner comfort  
biopsy indications  
asymmetry  
nodule [s]  
hardness  
[diagram]

## Tumors 2009

234,460 new patients diagnosed  
213,358 confined  
radical prostatectomy  
30% plus ; insignificant cancer  
Patient is at low risk to develop  
life threatening disease  
Gleason 6 or less, p T2,

## Tumors 2009

screening is leading to  
unnecessary, expensive treatments,  
radical \$ 24,000; IMRT \$ 56,000  
anxiety,  
side effects,  
need for follow-up,  
quality of life issues, potency,  
urine continence,



## Screening 2009

### PLCO

76,693 men 50 to 74  
annual PSA 6 yrs and DRE 4 yrs  
85% PSA; 86% DRE  
bx; PSA > 4, abnormal DRE  
40 to 52% control PSA 1 and 6 years  
50s vs 44c deaths  
cancer diagnosis 2820s vs 2322c

## Screening 2009

### PLCO

large number pre-screened,  
culls out cancers,  
heavily contaminated, 40 to 52%,  
control group PSA testing

## Screening 2009

### PLCO

control group; 31% T1C @ RP  
25% screened; no curative therapy  
insufficient time for follow-up, 7 ys  
BIAS  
aggressive Rx, screened  
adjudicating committee, less CA  
as cause of death

## Screening 2009

### Klotz

300 patients  
diagnosis established  
active surveillance for  
< 65, PSA < 10, TiC, T2A  
>65, PSA < 15, T2B

**Klotz**  
**q 3 month PSA and DRE,**  
**at one year, repeat biosy,**  
**serial PSAs and DREs but**  
**repeat biopsy at 3 years**

**Klotz  
33%  
withdrew  
12% PSA  
3% DRE  
4% grade change  
13% anxiety**

**SEER data – less advanced disease  
Tyrol – three-fold decrease mortality  
Olmstead – mortality declined 22%  
USA and UK – early peak of age-  
adjusted mortality; USA declined  
faster because of PSA screening  
BUT Wales and England, mortality  
declined by 1.7%**

**BUT** Wales and England, mortality declined by 1.7%

**Seattle vs Ct; no difference in mortality [heavy PSA]**

**BIAS**  
deaths are incorrectly attributable to prostate cancer; deaths caused by another disease

## Screening 2009

American College of Physicians  
Ca of the Prostate – important  
Mortality benefits of screening and  
Rx are limited  
DRE and PSA false positive, negative  
Testing leads to invasive evaluation

## Screening 2009

American College of Physicians  
Aggressive therapy is necessary to  
benefit; death risk low,  
significant risk for chronic disease,  
Early detection can save lives  
Early Dx and Rx may avert  
cancer-related illnesses

## Screening 2009

initial visit; PSA and DRE  
results visit; need for biopsy,  
benefits and risks,  
individual patient's co-morbidities  
biopsy visit,  
biopsy results,  
treatment discussions,

## Screening 2009

initial visit; PSA and DRE  
results visit; need for biopsy,  
benefits and risks,  
individual patient's co-morbidities  
biopsy visit,  
biopsy results,  
treatment discussions,

**Guidelines 2009**

start at 40 years of age  
treat young, observe older  
PSA q 4 months  
vs  
repeat biopsy  
at 12- 24 months  
Active surveillance

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**Guidelines 2009**

Active surveillance  
well done biopsy necessary  
careful follow-up  
PSA > 1.2 in 40s, increased risk  
No BPH affect on PSA ?  
no decision on one PSA  
15-50% variability in PSA result  
antibiotics have no effect

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**Guidelines 2009**

Active surveillance  
Primary Care MDs; mortality  
elevated blood pressure  
diabetes mellitus  
controlled  
mortality falls in Ca P.  
Ca P is a chronic disease

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**Treatments**

radical prostatectomy  
external beam conformal RT  
TRUS guided brachytherapy  
watchful waiting  
active surveillance  
PSA and DRE serially  
repeat biopsy

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## 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

**Undergrading**

repeat biopsy now,  
4 studies; 20% variation  
repeat before entering active  
surveillance, Epstein  
saturation, mapping, 3D biopsy

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**Screening**

mortality rate has fallen from  
40,000 to 27,000 to 29,000 men  
PSA is one factor,  
abnormality on PE,  
on biopsy,  
on pathology  
does not equate to therapy!!!

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**Screening**

European study is flawed !  
PLCO study is flawed !  
We must continue to  
individualize each patient and  
include age, race, co-morbidities  
DRE, life span and other  
malignancies in deliberations

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**Screening**

One shoe does not fit all !!!

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## **Undergrading**

repeat biopsy now,  
4 studies; 20% variation  
repeat before entering active  
surveillance, Epstein  
saturation, mapping, 3D biopsy

## **Undergrading**

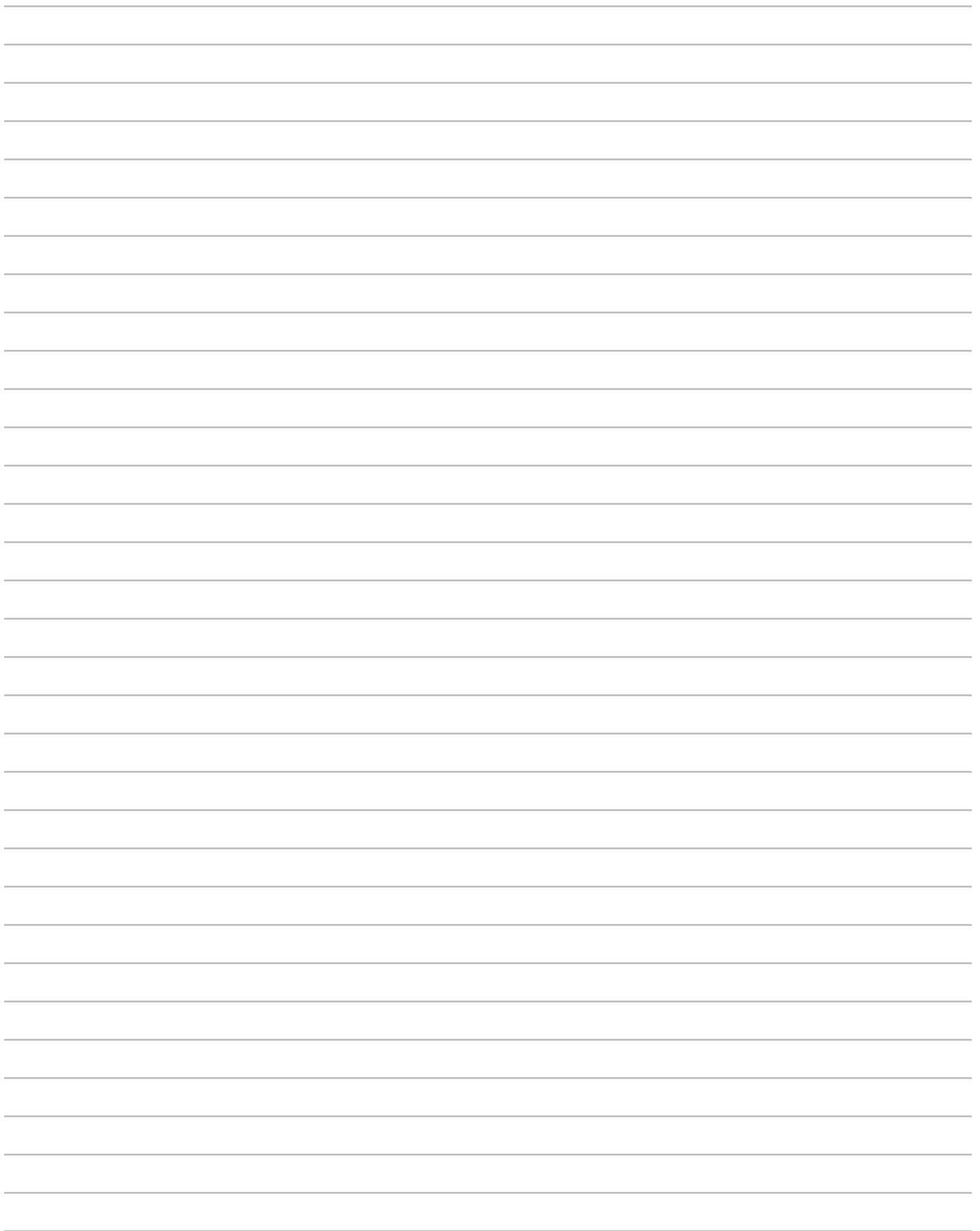
repeat biopsy now,  
4 studies; 20% variation  
repeat before entering active  
surveillance, Epstein  
saturation, mapping, 3D biopsy

## **Undergrading**

repeat biopsy now,  
4 studies; 20% variation  
repeat before entering active  
surveillance, Epstein  
saturation, mapping, 3D biopsy

## **Active Surveillance**

39 men  
Age 72.3 yrs; PSA 7.27; Gleason 6.08  
biopsy 5.8% tumor; 23.3 months  
PSA + DRE q 3m; biopsy 1 year  
39 – at least one PSA  
13 – repeat biopsy  
6 Gleason 6; 5 Gleason 7; 2 neg;  
7AS, 2 RP,XRT, 1 B, ! ????



## What's New in Advanced Disease (CRPC)?

~ Matthew Rettig, MD

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

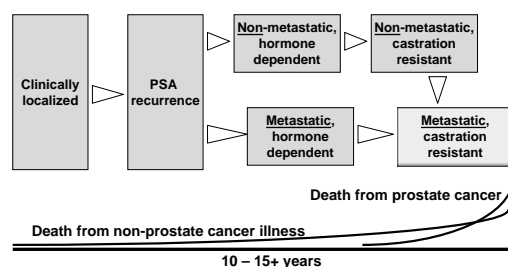
Matthew Rettig, MD  
Associate Professor  
Department of Medicine  
Division of Hematology-Oncology  
Department of Urology  
Medical Director, Prostate Cancer Program  
Institute of Urologic Oncology  
David Geffen School of Medicine at UCLA

### 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



Studies on Prostatic Cancer

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate<sup>®</sup>

Charles Huggins, M.D., and Clarence V. Hodges, M.D.  
*(From the Department of Surgery, the University of Chicago, Chicago, Illinois)*  
*(Received for publication March 22, 1941)*

Beatson, G. T.: On the Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a new Method of Treatment with Illustrative Cases. *Lancet*, ii:104, 1896.

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Huggins and Hormone Therapy

CHARLES HUGGINS

Endocrine-induced regression of cancers

*Nobel Lecture, December 13, 1966*

Charles Huggins, M.D. (1901-1997)



"We wanted to see if hormone therapy would do for elderly gentlemen what it would do for their best friends, elderly male dogs."

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The first series of patients with prostatic cancer treated by orchiectomy<sup>18</sup> comprised 21 patients with far advanced metastases; only 4 of them survived for more than 12 years. Despite regressions of great magnitude, it is obvious that there were many failures of endocrine therapy to control the disease but; on the whole, the life span had been extended by the novel treatments and there had been a decrease of man-pain hours.

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First recognition of CRPC.

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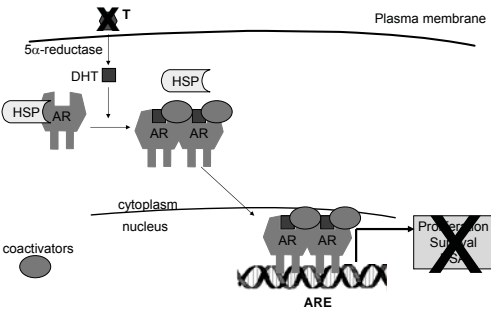
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AR Working Mechanism



The diagram illustrates the mechanism of Androgen Receptor (AR) signaling. At the top, Testosterone (T) is shown being converted to Dihydrotestosterone (DHT) by 5α-reductase. DHT then binds to the AR, which is initially associated with Heat Shock Protein (HSP). The DHT-AR complex moves into the nucleus, where it binds to the Androgen Response Element (ARE) on the DNA. This process is regulated by coactivators. The final outcome is the regulation of gene expression, indicated by a crossed-out 'X' and the text 'Regulation on Survival'.

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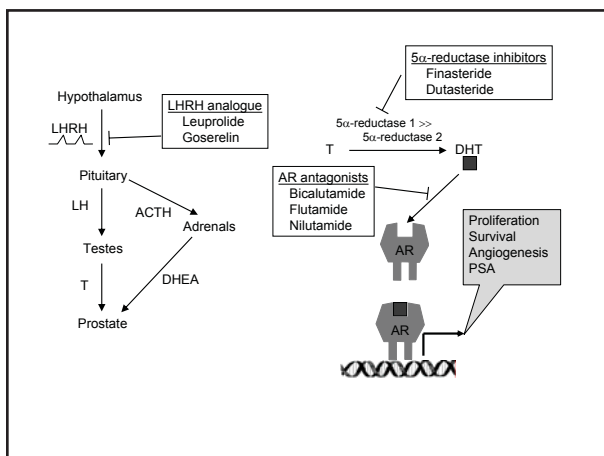
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## CRPC as the Preferred Terminology

- The terms androgen-independent prostate cancer (AIPC) and hormone refractory prostate cancer (HRPC) imply that additional hormonal manipulations will be ineffective, yet secondary and tertiary hormonal therapies may be effective.
- CRPC indicates some measure of progression of disease (i.e. biochemical, clinical or radiographic) despite castrate levels of circulating androgens.

## Current Management of Metastatic CRPC

- Median survival is 12-18 months.
- Secondary and tertiary hormonal manipulations are reasonable options:
  - Stop AR antagonist and observe for AR "withdrawal response."
  - Switch AR antagonist. (e.g. flutamide  $\Rightarrow$  bicalutamide).
  - Initiate ketoconazole.
  - Estrogens: high CV risk.
  - PSA response rates from 20-60%. No established survival benefit.
- Palliative management:
  - Spot radiation
  - radionuclide therapy
    - samarium 153
    - strontium 89
  - Bisphosphonates (zoledronate)

## Current Management of Metastatic CRPC

- Docetaxel-based chemotherapy is the only treatment that has been established to extend life expectancy in patients with *metastatic* CRPC.
  - extends median survival by 2-3 months.<sup>1,2</sup>
  - Well-tolerated and can be given irrespective of age.

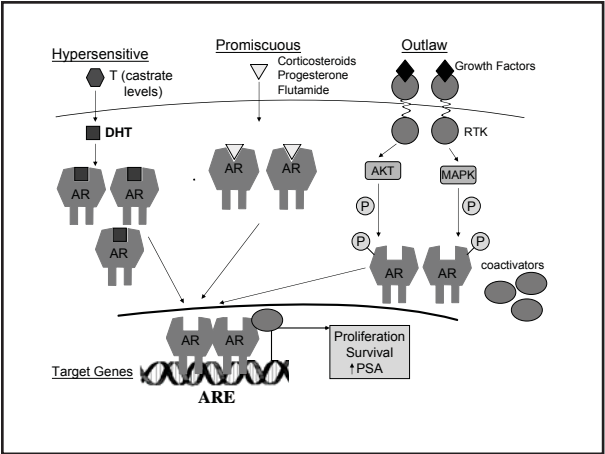
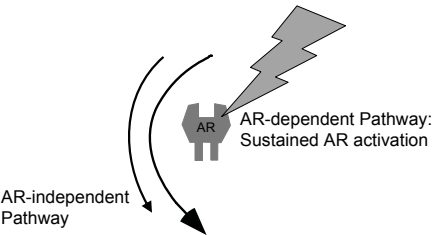
<sup>1</sup> NEJM 351:1502, 2004

<sup>2</sup> NEJM 351:1513, 2004

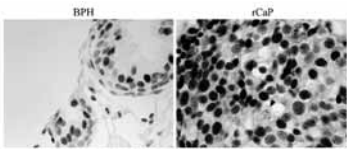
Mechanisms of Castration Resistance

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

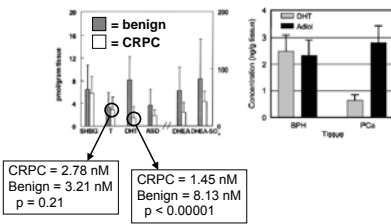
Mechanisms Giving Rise to CRPC



AR Expression in CRPC

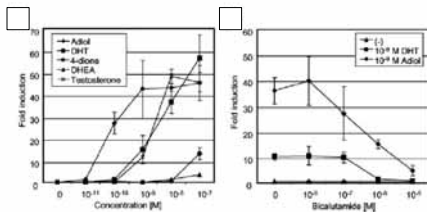


## Intracellular Androgen Levels in CRPC



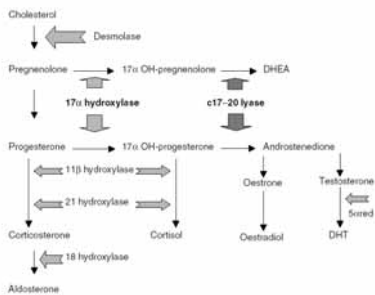
Clin Can Res 10:440, 2004.  
Can Res 64:765, 2004.

## Activation of AR transcriptional activity by androgens

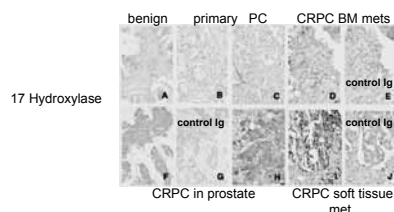


Can Res 64:765, 2004.

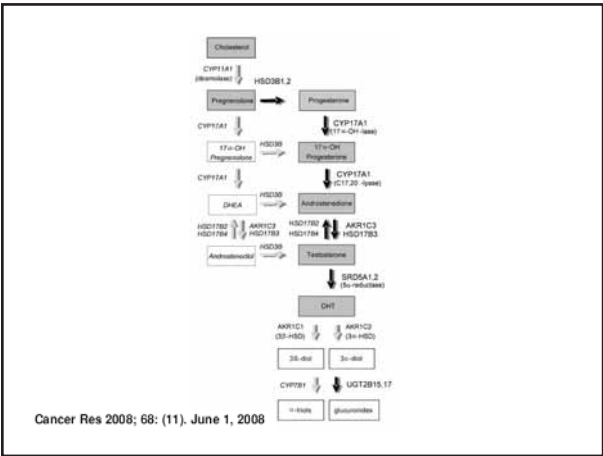
## Biosynthesis of Androgens



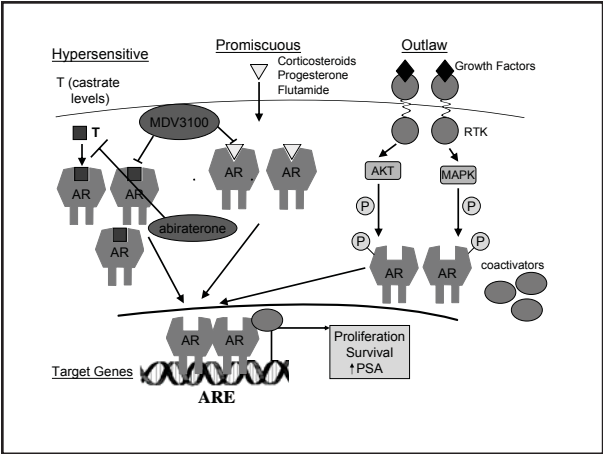
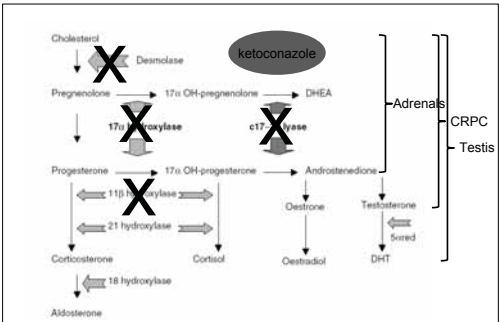
## CRPC cells activate the androgen synthesis enzymatic pathway.



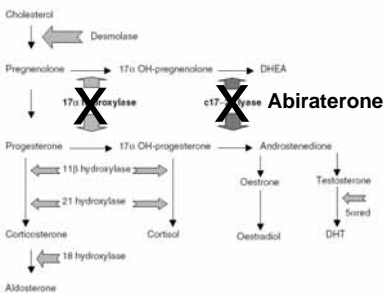
Cancer Res 66:2815, 2006.



Biosynthesis of Androgens



Inhibition Androgen Production



### Abiraterone Phase 2 CRPC: Chemo-Naive

- 27/44 (61%) have durable PSA declines  $\geq$  50%.
- 11/44 (25%) had  $\geq$  90% PSA decline.
- 21 patients with measurable disease.
  - 14/21 pts with objective partial response.
  - 7/21 pts with stable disease > 3 months.

### Abiraterone Phase 2 CRPC: Post-Docetaxel

- 14/28 patients with  $\geq$  50% PSA decline.
  - Median time to PSA progression ~ 6 months.
- 4/18 pts with measurable disease had PR.

### Phase 3 Study of Abiraterone: (post-chemotherapy metastatic CRPC)

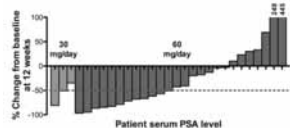
- Multinational, phase 3, placebo-controlled, double-blind study in patients with metastatic CRPC with progression after docetaxel-based chemotherapy.
  - 175 centers, 1158 patients.
- Randomization allocation 2:1. (abiraterone:placebo).
  - All patients receive prednisone 5 mg po bid.
- Primary endpoint = Overall Survival.
- Accrual completed.

### Phase 3 Study of Abiraterone: (pre-chemotherapy metastatic CRPC)

- Multinational, phase 3, placebo-controlled, double-blind study in asymptomatic or minimally symptomatic patients with metastatic CRPC who are chemotherapy naive.
- Primary endpoint = Progression-Free Survival.
- First patient enrolled in 2009.

## MDV3100: Phase 1-2 results

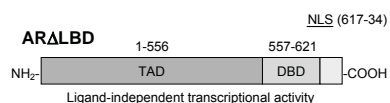
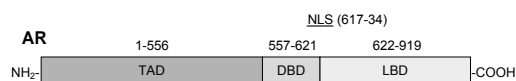
- 22/30 have PSA response, 12 of which were  $\geq 50\%$  decline.



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

Science 324:787, 2009.

## A Cautionary Note

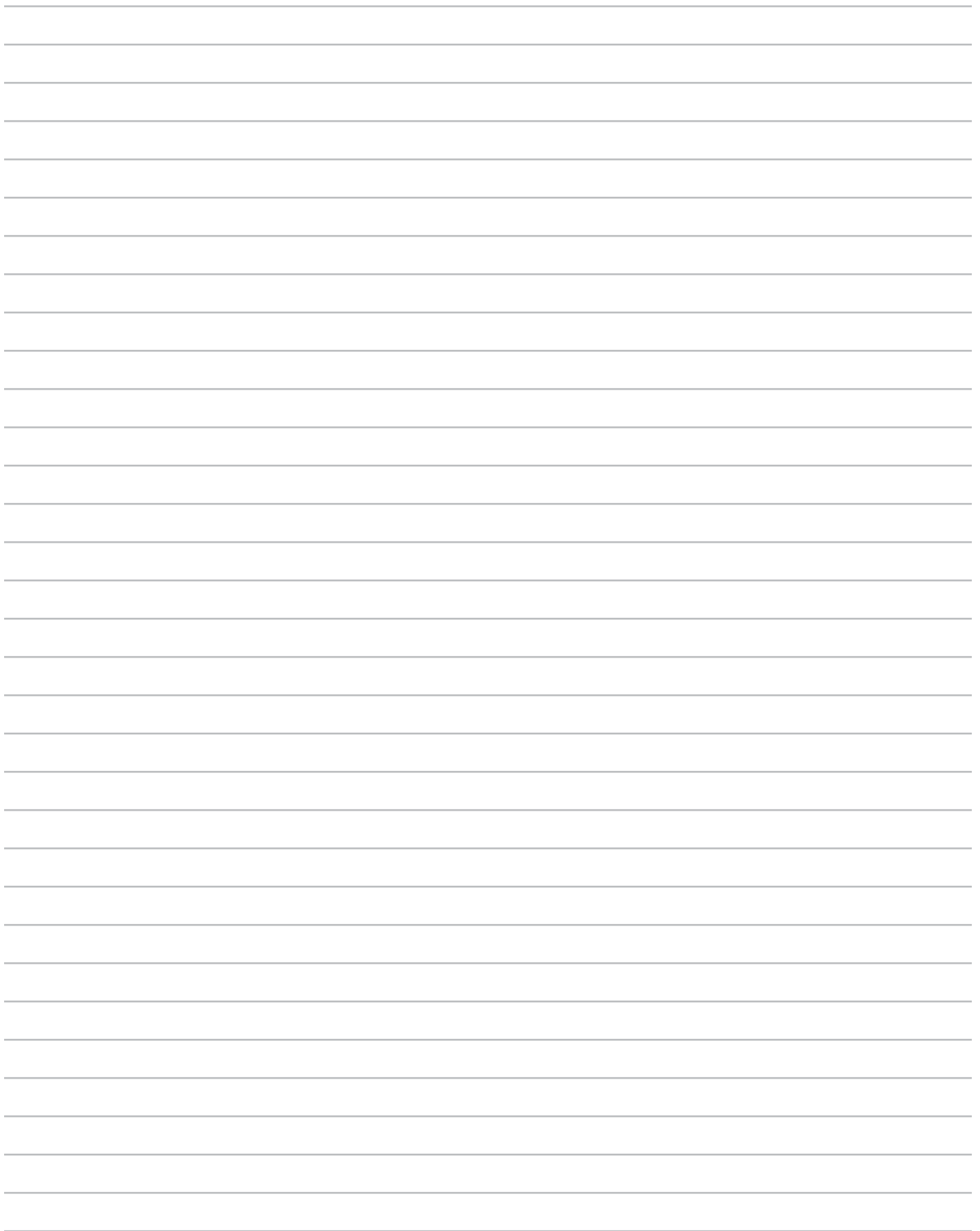


J. Steroid Biochem Mol Biol. 41: 671-675, 1992.  
Cancer Res. 67:2007, 2007.  
Cancer Res. 68:5469, 2008.  
Cancer Res. 69:16, 2009.

## 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

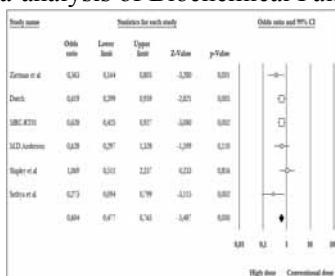
## An Update on Radiation Therapy for Prostate Cancer

David C. Beyer, MD, FACP, 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. UROBP V74(5):1405-1418, 2009

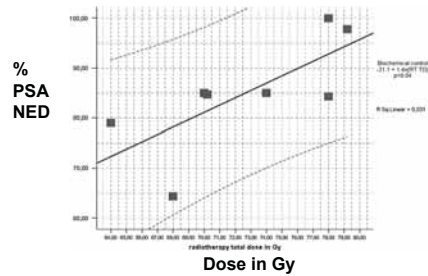
Viani, G. et al. IJROBP V74(5):1405-1418, 2009

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

Viani, et al. UROBP V74(5):1405-1418, 2006

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

### Meta-regression Analysis Low-Risk Group



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

### Meta-regression Analysis Projection for 100% "Cure"

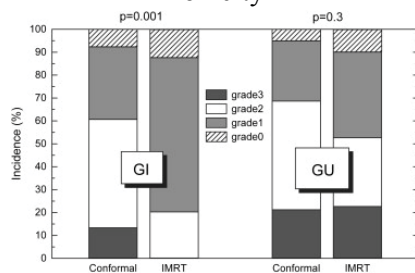
Low Risk	86.5 Gy
Intermediate Risk	90.4 Gy
High Risk	95.5 Gy

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

### Improvements in Technology

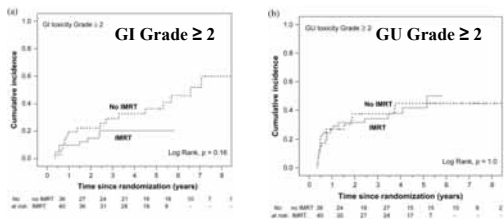
- IMRT allows greater precision in radiation delivery
  - Spare tissues adjacent to target
- IGRT allows greater accuracy in radiation delivery
  - "Hit" the target with each fraction
- Taken together should yield better cure and lower toxicity

### IMRT DOES Reduce Acute GI & GU Toxicity



Al-Mangani, A. et al. IJROBP V73(3): 685-691, 2009.

IMRT Reduces Late GI Toxicity



Al-Mamgani, A. et al. UROBP. V73(3): 685-691, 2009.

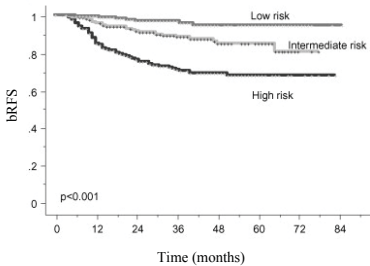
Fractionation = Daily Radiation

- Based on radiobiology principles
  - ✓  $\alpha/\beta$  ratio determines optimal daily dose
  - ✓  $\alpha/\beta$  ratio not precisely known for PCA nor for OAR
- Conventional wisdom
  - ✓ Prostate cancer  $\alpha/\beta \sim 10$
  - ✓ For any biologically effective dose, daily fractions of 1.8-2.0 Gy/day reduces late complications
  - ✓ Steady increase from 33Fx to 45 Fx or more
  - ✓ 6 1/2 to 9+ weeks

Radiobiology for Prostate Cancer

- But what if  $\alpha/\beta$  for prostate is  $< 3$ ??
- Then fewer fractions of higher daily dose =
  - Better or same cancer control
  - Fewer complications
  - Greater convenience
  - Better patient acceptance
  - Lower cost

Hypofractionated Radiotherapy  
70Gy = 250Gy x 28 Fx



Kupelian, PA. et al. UROBP. Aug 2007. V68(5); pp 1424-1430

## Hypofractionation in Prostate XRT

- Retrospective
- University of Wisconsin
- Patient choice (n=219)
  - 78 Gy / 2 Gy/day / 39 fractions / 55 elapsed days
  - 60 Gy / 3 Gy/day / 20 fractions / 33 elapsed days

Leborgne, F. et al. UROBP V74(5): 1441-1446, 2009

## Five-year Actuarial Rates of bNED

Risk Group	Hypo (n=89)	Standard (n=130)	p
Low risk	96%	98%	0.64
Medium risk	84%	84%	0.75
High risk	85%	87%	0.97

Leborgne, F. et al. UROBP V74(5): 1441-1446, 2009

## Late Complications Standard vs Hypofractionated XRT

Grade	Rectal		Bladder	
	Hypo	Standard	Hypo	Standard
1	22	17	1	2
2	4	5	2	2
3	1	1	2	1
4	0	1	0	0
5	0	0	0	0

Leborgne, F. et al. UROBP V74(5): 1441-1446, 2009

## Phase III Confirmatory Data

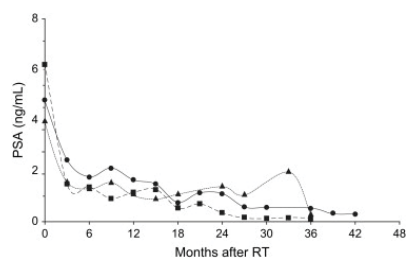
- Randomized trial
- National Cancer Institute, Italy
- 168 high risk patients
- 9 months TAB
  - 80 Gy / 40 Fx's / 8 weeks
  - 62 Gy / 20 Fx's / 5 weeks

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

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

- 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  $\geq 2$  toxicity  
✓Pawlicki et al, IJROBP Front Rad Ther Onc, 40:395-406, 2007

## PSA Bounce following SBRT



King, C. et al. UROBP. V73(4): 1043-1048, 2009.

## % With Urinary QOL after SBRT

QOL score (IPSS)	Baseline	3 months	1 year	2 year
0-1	51%	37%	44%	92%
2-3	41%	58%	52%	8%
4-5	8%	-	4%	-
6	-	5%	-	-

King, C. et al. UROBP. V73(4): 1043-1048, 2009.

## % With Rectal QOL after SBRT

QOL score (EPIC)	Baseline	3 months	1 year	2 year
0-1	89%	37%	46%	45%
2-3	11%	48%	50%	45%
4	-	16%	4%	9%
5	-	-	-	-

King, C. et al. UROBP. V73(4): 1043-1048, 2009.

Late Urinary & Rectal Toxicity  
on RTOG scale after SBRT

	RTOG grade				
	0	I	II	III	IV
Urinary, late % (no. patients)	30%	41%	24%	5%	-
Rectal, late % (no. patients)	51%	33%	15%	-	-

King, C. et al. UROBP. V73(4): 1043-1048, 2009.

King, C. et al. *UROBP*. V73(4): 1043-1048. 2009.

King, C. et al. *UROBP*. V73(4): 1043-1048. 2009.

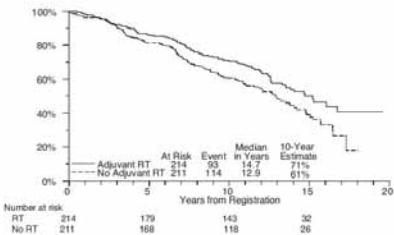
Boike et al. UROBP 75(3):S80, October 2009

Phase III Trials: Adjuvant RT after RRP

	EORTC 22911		SWOG 8794		ARO 9602	
High-risk	RT	Observation	RT	Observation	RT	Observation
Stratification factors	PT2, PT3, or positive surgical margin		PT3b, margin status, Prior hormone therapy		PT3b with undetectable PSA	
Number	302	303	214	211	108	135
Age (median)	65	65	64.1	65.8	N/A	N/A
Pre-op PSA	Median: 12.3	Median: 12.4	< 10: 31% ≥ 10: 49%	< 10: 33% ≥ 10: 47%	N/A	N/A
Post-op PSA (≤ 0.2)	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	52.0% at 5 years	71% at 5 years	44% at 5 years	81% at 4 years	60% at 4 years
Clinical progression-free survival	85% at 5 years	77.5% at 5 years	84% at 5 years	69% at 5 years	N/A	N/A
Metastasis-free survival	93.9% at 5 years	93.9% at 5 years	88% at 5 years	84% at 5 years	N/A	N/A
Toxicity from ADT	N/A	N/A	93% at 5 years	93% at 5 years	N/A	N/A
Overall survival	92.3% at 5 years	93.1% at 5 years	90% at 5 years	89% at 5 years	N/A	N/A

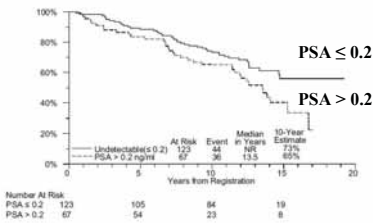
Bolla, M. et al. J. Clin. Oncol. 2002; 20: 281-286.  
Pacholke, H et al. J. Urology, 2004, 06, 020: 982-986

SWOG 8794 Update  
Metastasis-free Survival



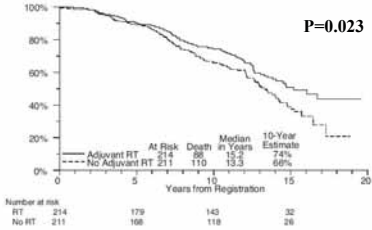
Thompson, I. et al. The Journal of Urology. 2009. V 181: 956-962

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



## EORTC 10 Year

	RT Alone	RT+LTAD	
Overall Survival	39.8%	58.1%	$p = 0.0004$
Clinical PFS	22.7%	47.7%	$p < 0.0001$
Distant PFS	30.2%	51.0%	$p < 0.0001$
PSA PFS	17.6%	37.9%	$p < 0.0001$

Bolla et al. *IJROBP* 72(1):s30-31, 2008

## EORTC 10 Year

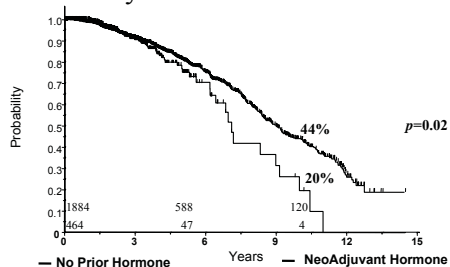
	RT Alone	RT+LTAD	
PC Mortality	31%	11.1%	$p < 0.001$
CV Mortality	11.1%	8.2%	$p = 0.75$
Pathologic Fracture	0	2	

Bolla et al. *IJROBP* 72(1):s30-31, 2008

## Impact of NHT on Mortality

- 1709 brachytherapy monotherapy patients
  - 786 NHT median 3.5 months
- All Cause Mortality (ACM)

	Hazard Ratio	$p =$
NHT	1.2	0.04
Age	1.1	0.001
Gleason $\geq 7$	1.2	0.05

Donsoretz et al. *IJROBP* 72(1): s39, 2008 and USA Today 9/24/2008Overall Survival  
by Hormone StatusBeyer et al. *IJROBP* 61(5):1299-1305, 2005

Nanda, A. JAMA. V302(8): 866-873. 2009

<http://rtog.org/members/protocols/0815/0815.pdf>

<http://rtog.org/members/protocols/0815/0815.pdf>

18th Annual

**PERSPECTIVES IN UROLOGY**  
**POINT COUNTERPOINT 2009**

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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	
	<b>Prostate Conditions</b>	
	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	
	<b>Hypogonadism</b>	
	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	
	<b>Complementary Alternative Medicine</b>	
	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	

## Chemotherapy for Urological Cancers

~ Matthew Rettig, MD

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### Chemotherapy for Urologic Cancers

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

- Q: What is Chemotherapy?
- A: In *oncologic* terms, chemotherapeutic agents are chemicals with varying mechanisms of action that influence cell survival by damaging DNA. May be:
  - Cytotoxic
  - Cytostatic

### Chemotherapy Schemes

- Adjuvant/neoadjuvant
- Palliative
- Survival benefit
- Curative
- Various roles in:
  - RCC
  - Bladder cancer
  - Testicular cancer
  - Prostate cancer

Chemotherapy Principles

- Very narrow therapeutic index.
- We do not understand why cancer cells are preferentially responsive to chemotherapeutic agents. In fact, the abundance of data suggest that for the vast majority of human malignancies, the converse is true. That is, certain normal cellular compartments are *more* sensitive to the effects of chemotherapy than cancer cells.

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RCC

- Chemotherapy has no role.

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Bladder Cancer

- Neoadjuvant (pre-op): combination chemotherapy improves OS.
  - ~5% improvement at 5 years.
  - Applies to all stages.
- Data in adjuvant (post-op) setting is controversial and less robust.
- Chemotherapy (cisplatin) plus radiation is a bladder-sparing option for tumors optimally debulked by TURBT with no clear decrement in OS.
  - Bladder spared in ~50% of cases.
  - Prognostic factors: performance status, visceral involvement, p53 mutations, ERCC1 mutations.

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Bladder Cancer

- Metastatic: Combination chemo improves OS.
  - ~12 mos vs. 6 mos for BSC.
  - Gemcitabine and cisplatin (GC) is “non-inferior” to MVAC, but less toxic.

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## 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
<b>Seminomas</b>
<b>Good risk</b>
All of the following:
Any primary site
No nonpulmonary visceral metastases
Normal serum AFP
<b>Intermediate risk</b>
All of the following:
Any primary site
Nonpulmonary visceral metastases present
Normal serum AFP

Non-seminomatous germ cell tumors
<b>Good risk</b>
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
<b>Intermediate risk</b>
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
<b>Poor risk</b>
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.

Case 1

Date	Case History	PSA
2/2006	• 55 yo AAM undergoes open RRP: Gleason 5+4 = 9/10, SVI (pT3b), PNI, SM-.	8.5
5/2006		1.2
7/2006	• LHRH analog initiated.	3.8
9/2006		0.8
12/2006	• Patient c/o bone pain, fatigue. • Bone scan: widespread bone mets. • CT abd/pelvis: RPLAN and liver mets. • CRPC diagnosed based on clinical and radiographic progression.	0.8

What is the next step?

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Case 1

Date	Case History	PSA
1/2007	• Liver biopsy → neuroendocrine (small cell) carcinoma. • Chemotherapy initiated (cisplatin/etoposide).	
3/2007	• Restaging CT abd/pelvis → partial response. • Chemotherapy continued for a total of four cycles.	
11/2007	• Restaging CT abd/pelvis → progression of liver mets. • Patient's performance status rapidly declines. • Referred for hospice care.	

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Case 2

Date	Case History	PSA
1991	• 62 yo WM. RRP: Gleason 4+4 = 8/10, pT2b.	6.2
1991-97		undetectable
1998	• Lupron/Casodex initiated.	3.7
1998-2007		undetectable
1/2007	• T = 4.0 ng/ml; CRPC diagnosed.	1.2
3/2007	• Casodex withdrawn.	4.8
5/2007	• Bone scan → widespread mets associated pain. CT abd/pelvis - • CRPC with clinical, radiographic and PSA progression. • Ketoconazole/hydrocortisone initiated.	11.8

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Case 2

Date	Case History	PSA
6/2007	• LFTs elevated → ketoconazole/hc d/c'd.	38.4
7/2007	• LFTs normalize.	85.2

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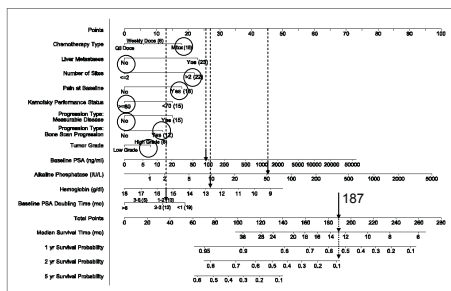
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## CRPC Nomogram



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.	31.5
	• No significant chemotherapy-related toxicity.	
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

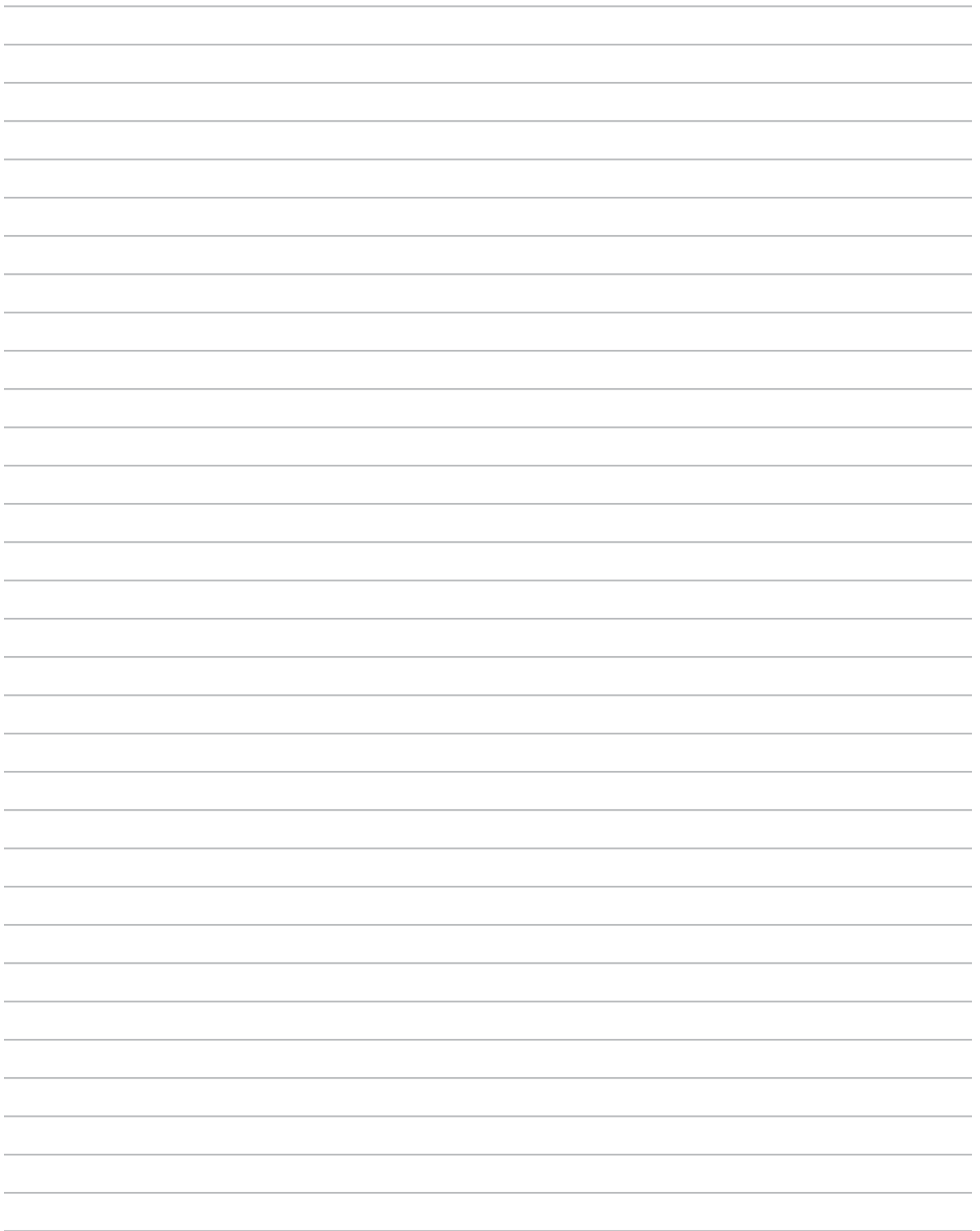
## Survival by PSA Decline from TAX 327

	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 I of II):237S (abstract and oral presentation 5009).

## Case 2

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



# Increasing Awareness, Diagnosis, and Treatment of BPH, LUTS, and EP

~ E. David Crawford, MD

## Introduction to Enlarged Prostate

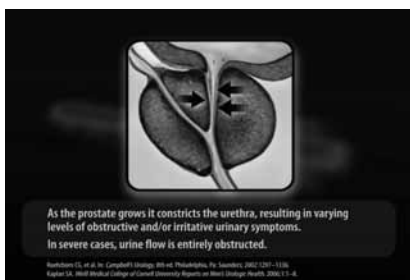
**E. David Crawford, MD**

Professor of Surgery (Urology) and Radiation Oncology  
Head, Urologic Oncology

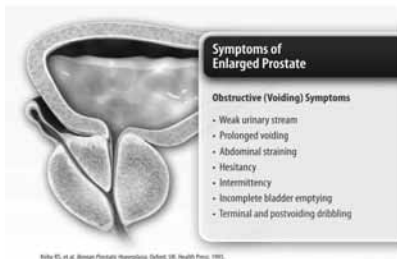
E. David Crawford Endowed Chair in Urologic Oncology  
University of Colorado Health Sciences Center  
Denver, Colorado



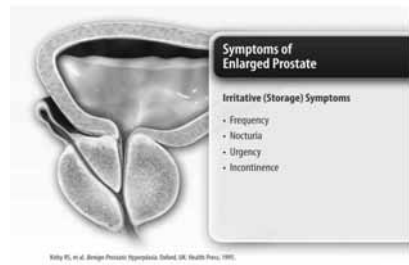
## What is Enlarged Prostate (EP)?



## Symptoms of Enlarged Prostate: Obstructive



Symptoms of Enlarged Prostate: Irritative



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Overview of DHT in the Development of EP

- The development and growth of the prostate gland depends on androgen stimulation.<sup>1</sup>
- In men, testosterone is converted to dihydrotestosterone (DHT),<sup>1</sup> a more potent androgen,<sup>2</sup> by 5-alpha-reductase (5AR) enzymes<sup>1</sup>
- In the prostate, two types of 5ARs exist: Type I and Type II.<sup>1</sup>
- It is known that DHT levels in the prostate remain high with aging, despite a decrease in the production of testosterone<sup>3</sup>

DHT is primarily responsible for the development of EP<sup>1</sup>

1. Steers W. Urology, 2001;58:17-24.  
2. Tindall D. J Urol, 2008;179:1235-42.  
3. Roehrborn C, et al. In: Campbell's Urology, 8th ed. Philadelphia, Pa: Saunders; 2002:1297-336.

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5ARs' Role in the Conversion of Testosterone to DHT



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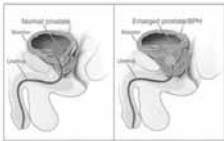
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Characteristics of EP

- Common prostate condition in men over 50<sup>1</sup>
- Prostate size ≥30 mL<sup>1</sup>
- Prostate-specific antigen (PSA) ≥1.5 ng/mL<sup>1</sup>
- Progressive disease<sup>1</sup>
- Major cause of urinary symptoms in older men<sup>2</sup>



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.

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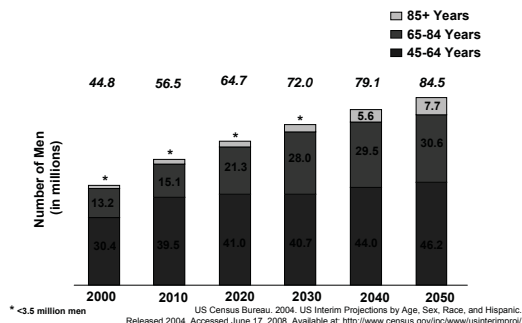
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## The Burden of EP in the United States (US)

### 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<sup>1,2</sup>
- In a recent survey of men over age 50 in the United States<sup>3</sup>
  - 25% reported moderate to severe symptoms of EP
  - 55% of those consulting a doctor were diagnosed with EP

**EP is significantly underreported and underdiagnosed<sup>1,3</sup>**

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

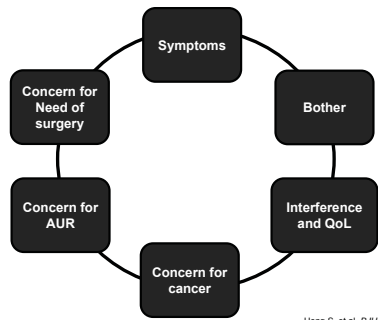
- In 2000, the direct cost of EP reached \$1.1 billion in the US alone (not including outpatient pharmaceuticals)
  - Medical services at hospital inpatient and outpatient settings
  - Emergency departments and physician office visits
- In a 2-year period, outpatient prescription drugs for EP were estimated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



\*from 1996-1998

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

The Personal Impact of EP



Hong S, et al. *BJU Int* 2005;95:15-19.

Summary of Disease Burden of EP

- The majority of men over age 50 are affected by BPH, which can include EP
- Considerably underdiagnosed and undertreated
- Economic and societal burden
- Can decrease quality of life
  - Creates strains on personal life
  - Interferes with daily activities
  - Causes concerns about AUR and prostate-related surgery

Enlarged Prostate:  
A Progressive Disease

Predictors of Clinical Progression of EP

	Age Progression	Symptoms	Prostate Volume	PSA
Olmsted County Study <sup>1,2</sup> (n = 2,115)	>50 years	Moderate-to-severe symptoms (AUA-SI >7)	>30 mL	≥1.4 ng/mL
Baltimore Longitudinal Study of Aging <sup>3,4</sup> (n = 1,057)	≥50 years	Obstructive symptoms	Clinical EP diagnosed by DRE	>1.4 ng/mL for 50-59 years*, >1.7 ng/mL for 60-69 years*
Medical Therapy of Prostatic Symptoms <sup>5</sup> (n = 737)	≥62 years	4-point increase in AUA-SI	≥31 mL	≥1.6 ng/mL

\*PSA level associated with prostate enlargement

1. Jacobsen S, et al. *J Urol*. 1997;158:481-7.  
2. Jacobsen S, et al. *J Urol* 1999;162:1301-1306.  
3. Aringhi H, et al. *Urology*. 1991;38 (suppl):4-8.  
4. Wright E et al. *J Urol*. 2002;167:2484-2488.  
5. Crawford E, et al. *J Urol*. 2006;175:1422-7.

## 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

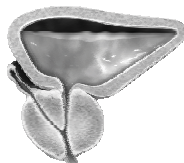
70 years old  
PV: >61 mL

**Disease progression can increase the risk of AUR and prostate-related surgery<sup>1,2</sup>**

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

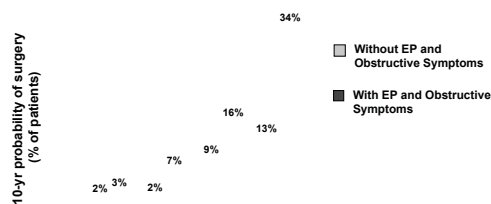
- Common urological emergency<sup>1,2</sup>
  - Greater resistance to urine flow
  - Bladder over-distention
  - Can have neuropathic causes
- Outcomes of AUR<sup>2-4</sup>
  - Inability to urinate with increasing pain
  - Visits to the emergency room
  - Emergency catheterization
  - Urinary tract infection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



**AUR is a painful, time-consuming, and feared condition that often results in emergency catheterization<sup>1</sup>**

1. Fitzpatrick J, et al. *BJU Int*. 2006;97 (Suppl 2):16-20.  
2. Choong S, et al. *BJU Int*. 2000;85:186-201.  
3. Roehrborn C, et al. In: *Campbell's Urology*, 8th ed. Saunders; 2002:1297-336.  
4. Roehrborn C, et al. *Rev Urol*. 2001;3:187-92.

## Risk of EP-Related Surgery in Men with EP



Baltimore Longitudinal Study of Aging  
N = 1057

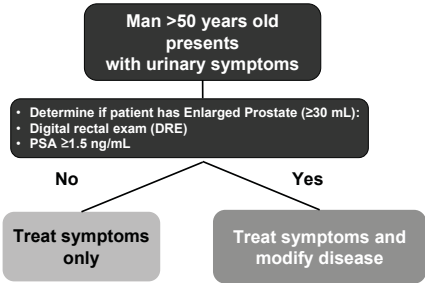
Arrighi H, et al. *Urology*. 1991;38 (suppl):4-8.

## 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



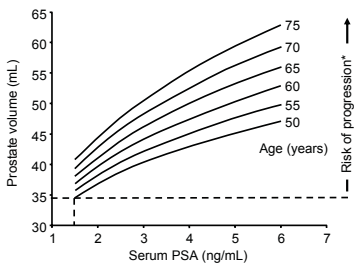
Adapted from Figure 3, entitled "Practical Algorithm for the treatment of EP in primary care" in Kaplan S. *Weill Medical College of Cornell University Reports on Men's Urologic Health*. 2006;1(1):1-8.

## Symptom Assessments for EP

- American Urological Association Symptom Index (AUA-SI)<sup>1</sup>
  - 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)<sup>2</sup>
  - 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.

## Arresting Disease Progression



**Symptom  
worsening<sup>1</sup>**



**Decreased  
urinary  
flow<sup>2</sup>**



**AUR<sup>3</sup>  
Prostate-  
related  
surgery<sup>4</sup>**

1. Samma A, et al. J Urol. 2002;168 (4 part 1):1446-52.  
2. Roberts R, et al. J Urol. 2000;163:107-13.  
3. Jacobson S, et al. Urology. 2001; (suppl 6A):5-16.  
4. Aringhi H, et al. Urology. 1991;38:4-8.

## Summary of EP Diagnosis

- Diagnosis involves assessment of symptom severity and determination of prostate volume
- The PSA test is an effective tool to estimate prostate size
- PSA of 1.5 ng/mL suggests a prostate volume  $\geq 30$  mL
- The goal of medical therapy should be to arrest disease progression and reduce the risk of long-term disease complications

## Pharmacologic Treatment Goals and Options for EP

## Treatment Options: Alpha Blockers


- Alpha blockers:<sup>1,2</sup>
  - Relax smooth muscle
  - Ease pressure on urethra and bladder
  - Improve urinary flow ( $Q_{max}$ ) and bothersome symptoms



1. Medical College of Cornell University Reports on Men's Urologic Health. 2006;1(1):1-8.  
2. McConnell J, et al. NEJM. 2003;349:2367-68.

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

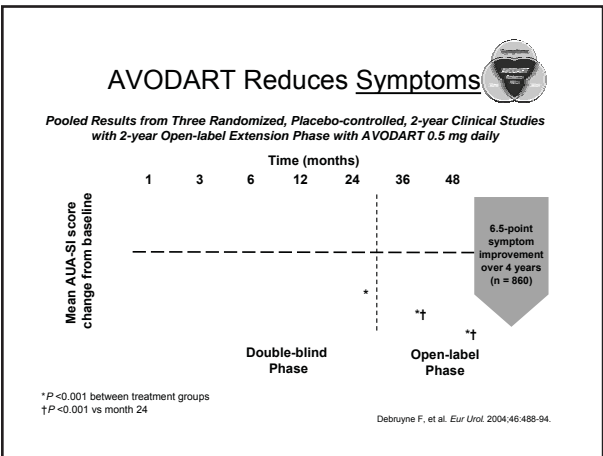
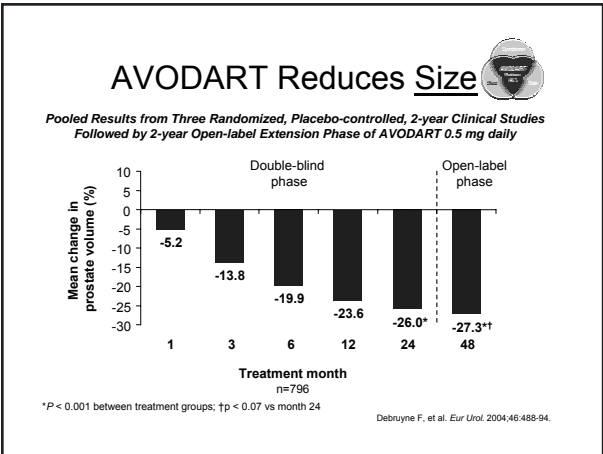


AVODART, a 5-alpha reductase inhibitor, inhibits both Type I and Type II 5-alpha reductase enzymes.

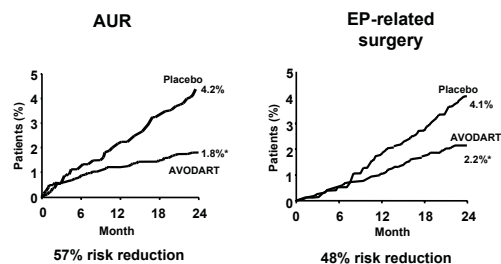
Prescribing Information for AVODART, 2008.

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

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

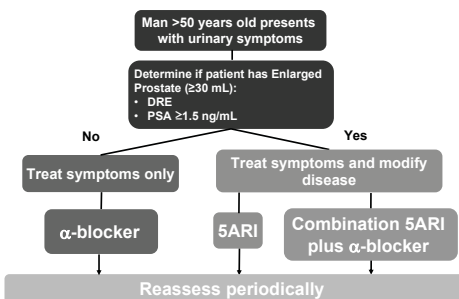


## AVODART Reduces the Risk



\*P<0.001 vs placebo.  
Results of 3 combined, double-blind, pivotal studies of 4325 men with BPH. Roehrborn C, et al. Urology. 2002;60:434-41.

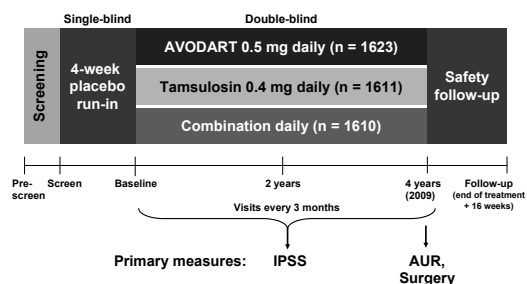
## A Practical Algorithm for the Treatment of EP in Primary Care



Adapted from Kaplan S. Weill Medical College of Cornell University Reports on Men's Urologic Health. 2006;1(1):1-8.

## Two-year Results From the Combination of AVODART and Tamsulosin (CombAT) Study

## CombAT Study Design



Roehrborn C, et al. J Urol. 2008;179:616-21.  
Siarni P, et al. Contemp Clin Trials. 2007;28:770-9.

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 <sub>max</sub>	>5 and ≤15 mL/sec (moderate-to-severe impairment)
Minimum voided volume	≥125 mL (based on two voids at screening)

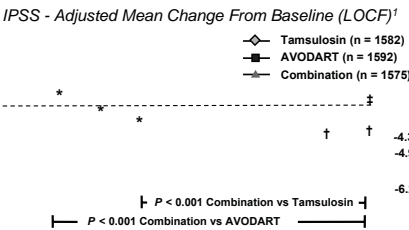
DRE = digital rectal exam; TRUS = transrectal ultrasound; Qmax = maximum urinary flow.  
Roehrborn C, et al. *J Urol*. 2008;179:616-21.  
Siami P, et al. *Contemp Clin Trials*. 2007;28:770-9.

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

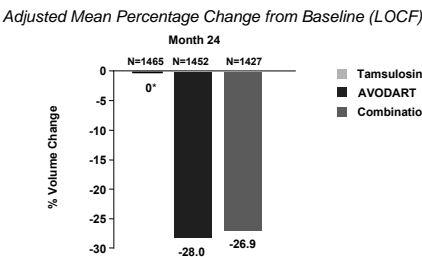
\*AVODART plus tamsulosin  
Roehrborn C, et al. *J Urol*. 2008;179:616-21.

CombAT: Reduction in Urinary Symptoms



LOCF = last observation carried forward  
\*P < 0.001 in post hoc analysis for tamsulosin vs. AVODART as monotherapy<sup>2</sup>  
†P < 0.05 in post hoc analysis for AVODART vs. tamsulosin as monotherapy<sup>2</sup>  
‡Patients generally perceive a 3-point change in the AUA-SI score as meaningful<sup>3</sup>  
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.

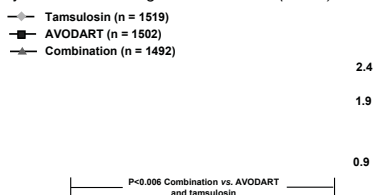
CombAT: Reduction in Total PV



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

## CombAT: Continuous Improvement in Qmax

Adjusted Mean Change From Baseline (LOCF)<sup>1</sup>



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

## Most Common Drug-related Adverse Events\* - CombAT

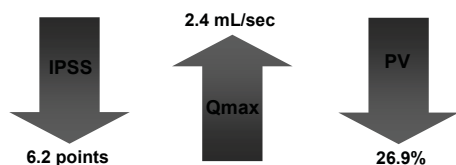
	Combination n = 1610	Tamsulosin n = 1611	AVODART n = 1623
Erectile dysfunction	7.4%	3.8%	6.0%
Retrograde ejaculation	4.2%	1.1%	0.6%
Libido decreased	3.4%	1.7%	2.8%
Ejaculation failure	2.4%	0.8%	0.5%
Semen volume decreased	1.8%	0.8%	0.3%
Loss of libido	1.7%	0.9%	1.3%
Dizziness	1.6%	1.7%	0.7%
Breast enlargement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

\*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

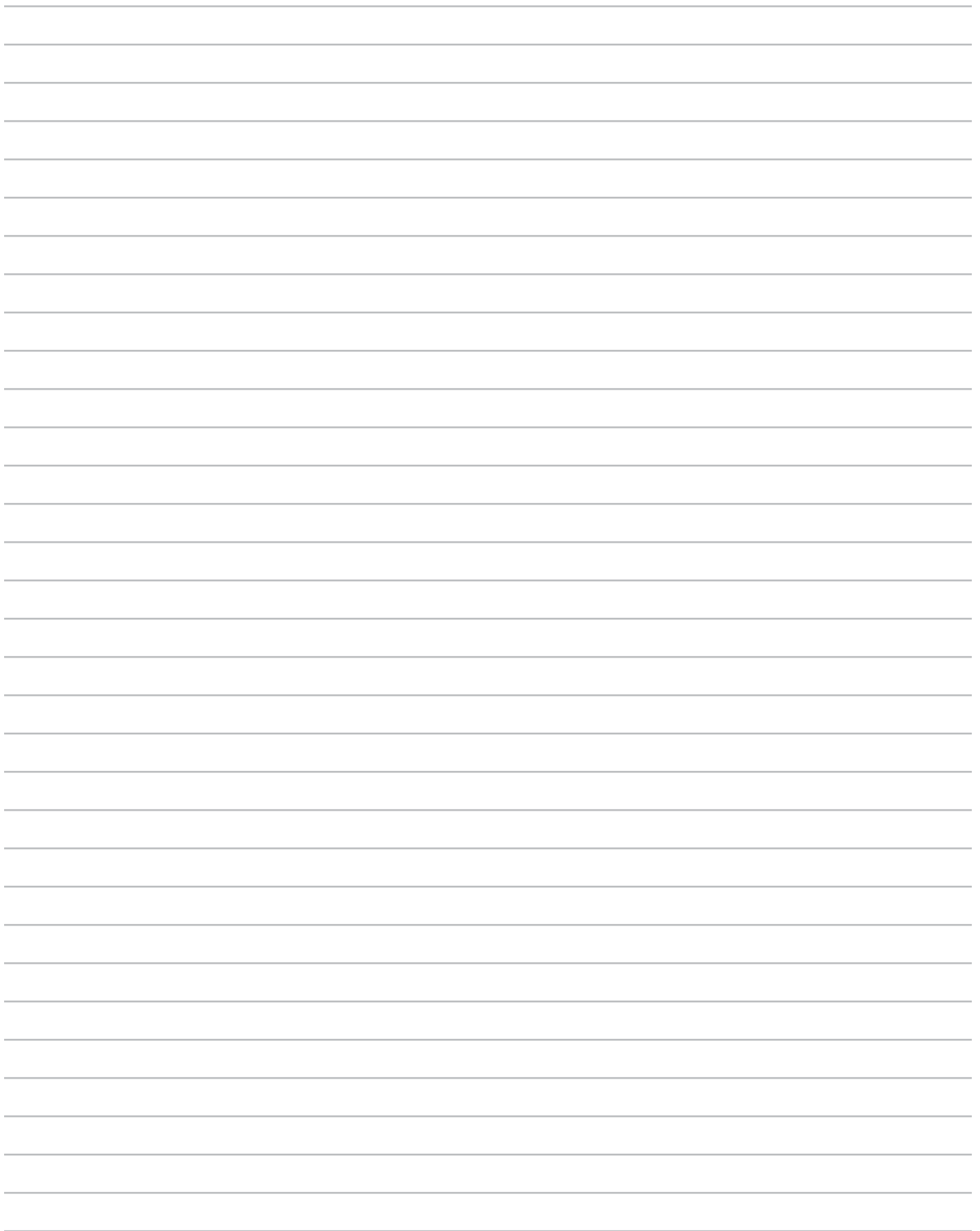


Roehrborn C, et al. J Urol. 2008;179:616-21.

## PSA in Relation to the Prostate

- PSA production and use in EP<sup>1</sup>
  - DHT stimulates the growth of glandular epithelial cells in the prostate, which produce high levels of PSA<sup>1</sup>
  - Predictive of prostate volume in men with EP<sup>2</sup>
- PSA is prostate-specific, not cancer-specific
- Prostate cancer cells also produce PSA<sup>3</sup>
- PSA ≥1.5 ng/mL suggests EP<sup>4</sup>

1. Schalken J. BJU Inter. 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.



## 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



## Health Professionals-II

- Total energy intake=51% increase
- Total dietary fat=No difference
- Increase in sympathetic activity?
- Increase in testosterone?
- Increase in abdominal obesity? Aromatization?

Bottom Line=Largest observational study.



## Diet & BPH

- Higher caloric consumption=Higher risk
- Higher meat consumption=Higher risk
- More omega-3 fatty acids=Lower risk
- More fruits & veggies=Lower Risk

Bottom Line=Heart healthy=Prostate Healthy!!!

Koskimaki J, et al. Scand J Urol Nephrol 34:46-50, 2000. Yang YJ, et al. Clin Biochem 32:405-409, 1999.



## Physical activity & BPH

- Health Professional Follow-up
- Walking=2-3 hours/wk=25% lower risk
- Total BPH (& surgery & symptoms)

Bottom Line=Walking/physical activity is good for your prostate.

Platz EA, et al. Arch Intern Med 158:2349-2356, 1998.



## Exercise vs. Zoloft®

- Duke Trial, n=156, MDD
- 4 months-exercise (3x), zoloft® (150 mg), both
- Baseline, 4 & 6 months post-study
- 50% reduction w/exercise

Bottom Line=Zoloft® fast-exercise more effective.

Blumenthal, et al. Arch Intern Med 159:2349-56,1999/ Babyak,et al. Psychosom Med 62:633-8, 2000.



Increase:  
-GH  
-DHEA  
-WBC...

- Increased Muscle Strength, No change in Fat Mass
- No bone loss at any site + No Hgb change!

Galvao DA, et al. (Spry N, Newton R...). *Pros Cancer Prostat Dis*. 2006.



Gioannucci E. et al: *Am J Epidemiol* 140:989-1002, 1994. Lee E. et al: *Br J Urol* 79:736-741, 1997.



Koskimaki J. et al: J Urol 159:1580-1582, 1998.



Hammarsten J, Hogstedt B: Eur Urol 39:151-158, 2001.



## Hyperinsulinemia/obesity & Urology

- BPH
- E.D.
- Prostate cancer
- Renal cell carcinoma (RCC)...

Bottom Line=Obesity epidemic=Urology case epidemic=Marriage of urology & preventive medicine.

Moyad MA: Urology January, 2002.



## BPH

### Supplements

- Saw palmetto (*Serenoa repens*=*Sabal serrulata*)
- Pygeum africanum (African plum)
- B-sitosterol (*Hypoxis rooperi*)
- Cernilton (*Secale cereale*=rye pollen)

Lowe FC, et al: Prostate 37:187-193, 1998. Moyad MA: Urol Clin N America, 2001.



## Plant extract components of BPH supplements

- Phytosterols
- B-sitosterol
- Alpha-5-sterols
- Alpha-7-sterols
- Campesterol
- Stigmasterol
- Lupenone

Lowe FC, et al: Prostate 37:187-193, 1998. Moyad MA: Urol Clin N America, 2001



## Plant extract components cont.

- Lupeol
- Terpenoids
- Fatty acids
- Lectins
- Plant oils
- Polysaccharides
- Flavonoids

Lowe FC, et al: Prostate 37:187-193, 1998. Moyad MA: Urol Clin N America, 2001





**Saw palmetto (meta-analysis)**

- Mean dose=320 mg/day
- No PSA change at this dose, 1-2% E.D. rate
- Use in Europe decreasing (Insurance???)

Bottom line=Mechanism of action???

Wilt TJ, et al: JAMA 280:1604-1609, 1998

**Saw palmetto-UCLA**

- N=44 (age 45-80), 6 months vs. placebo & finast.
- Clinical parameters not different from placebo
- Epithelial contraction

Bottom line=Mechanism of action???

Marks LS, et al: Urology 57:999-1005, 2001

**Saw palmetto-mild finasteride or dutasteride effect?**

	<u>Finasteride</u>	<u>Saw palmetto</u>
PSA	50% decrease	No change
DHT	70% decrease	No change
Testost.	10-20% increase	No change
Gland-vol.	20% decrease	No change
Epith. (%)	55% decrease	40% decrease
Gland-DHT	80% decrease	32-50% decrease
Gland-Tes.	5-10x increase	0-125% increase

Marks LS, et al: Urology 57:999-1005, 2001.

**Permixon® vs. Tamsulosin-I**

- 1 yr (n=542 from an n=704)
- 320 mg/day vs. 0.4 mg/day
- IPSS  $\geq$  10
- 11 European countries
- BMI=26-27
- Age=65 years

Debruyne F, et al. European Urology Annual Meeting, 2002.



### Permixon® vs. Tamsulosin-II

- Equivalent results
- IPSS=-4.4
- Qmax=similar=1.8-1.9 mL/s
- No diff in irritative vs. obstructive sympt improve
- PSA stable + prostate vol decline w/permixon
- Ejac. Disorders=0.6% vs 4.2%

Debruyne F, et al. European Urology Annual Meeting, 2002.



### Saw palmetto=hair tonic...?

- Inhibits 5-alpha reductase type II & I???
- Similar to propecia® & avodart®???
- Prostate cancer prevention=PCPT Trial???
- COX-inhibition???

Bottom line=millions in sales=an option

Moyad MA: Urol Clin N Am Feb, 2002.



### Pygeum africanum (meta-analysis)

- Extract-bark of African plum evergreen tree
- 18 randomized trials (n=1,562 men)-Tadenan®
- Mean study=64 days (range 1-4 months)-100 mg

Bottom Line=Modestly but significantly improves urologic symptoms & flow measures. Long term?

Ishani A, et al: Am J Med 109:654-664, 2000.



### B-sitosterol

- Extract of African star grass=Harzol®
- >70% dry weight=B-sitosterol (cholesterol?)
- 6 month trials (benefits up to 18 months)
- No effect on prostate size (stromal TGFbeta?)

Bottom Line=20 mg tid-symptoms not obstruction.

Berges RR, et al: BJU Int 85:842-846, 2000.



**Cernilton® (rye-grass pollen)**

- Prostatitis and/or BPH
- Not improve flow rates, residual vol., prost. size
- Improves symptoms-esp. nocturia (anti-inflamm)
- N=444 (2 trials) 3-6 months

Bottom Line=60 mg tid for prostatitis. BPH?

Macdonald R, et al: BJU Intl 85:836-841, 1999.

**Quercetin**

- Naturally occurring bioflavonoid
- High conc. in red wine, onions, green tea
- Anti-oxidant
- Tyrosine kinase inhib.
- Nitric oxide inhibitor
- Anti-inflammatory....(COX...)

Moyad MA: Urology January, 2001

**Quercetin trial**

- N=30
- 500 mg twice daily vs. placebo (1 month)
- Non-bacterial chronic prostatitis
- NIH chronic prostatitis symptom score

Shoskes DA: Urology 54:960-963, 1999

**Quercetin trial**

	<u>Placebo</u>	<u>Quercetin</u>
Age (yr)	43.5	46.2
Symp. Duration	11.5 yr	10.5 yr
Initial WBC/hpf	13.1	16.9
Final WBC/hpf	8.3	2.9
NIH symp. Score (pain,urin,QOL)	20.2 to 18.8	21.0 to 13.1 (significant)

Shoskes DA: Urology 54:960-963, 1999





### Lifestyle & ED

- N=1156, follow-up=8.8 yrs (Mass Male Aging)
- Ages 40-70
- Obesity status=significantly higher ED
- Physical activity=low ED risk (OR=0.5-0.8)
- Changes in smoking & alcohol=no effect

Derby CA, et al. Urology 56:302-306, 2000.



### Randomized Trial-I

- Italian Study
- Randomized, 2-yrs!!!, n=110 obese (BMI  $\geq 30$ )
- No diabetes, HTN, or dyslipidemia w/ED
- 21 or less on IIEF
- 55 men reduced calories, increase exercise

Esposito K, et al. JAMA 291:2978-2984, 2004.



### Randomized Trial-II

- Age=43, BMI=36-37
- ED score=13-14 (range=1-25)
- hs-CRP=3.3-3.4 mg/L

Esposito K, et al. JAMA 291:2978-2984, 2004.



### Randomized Trial-III

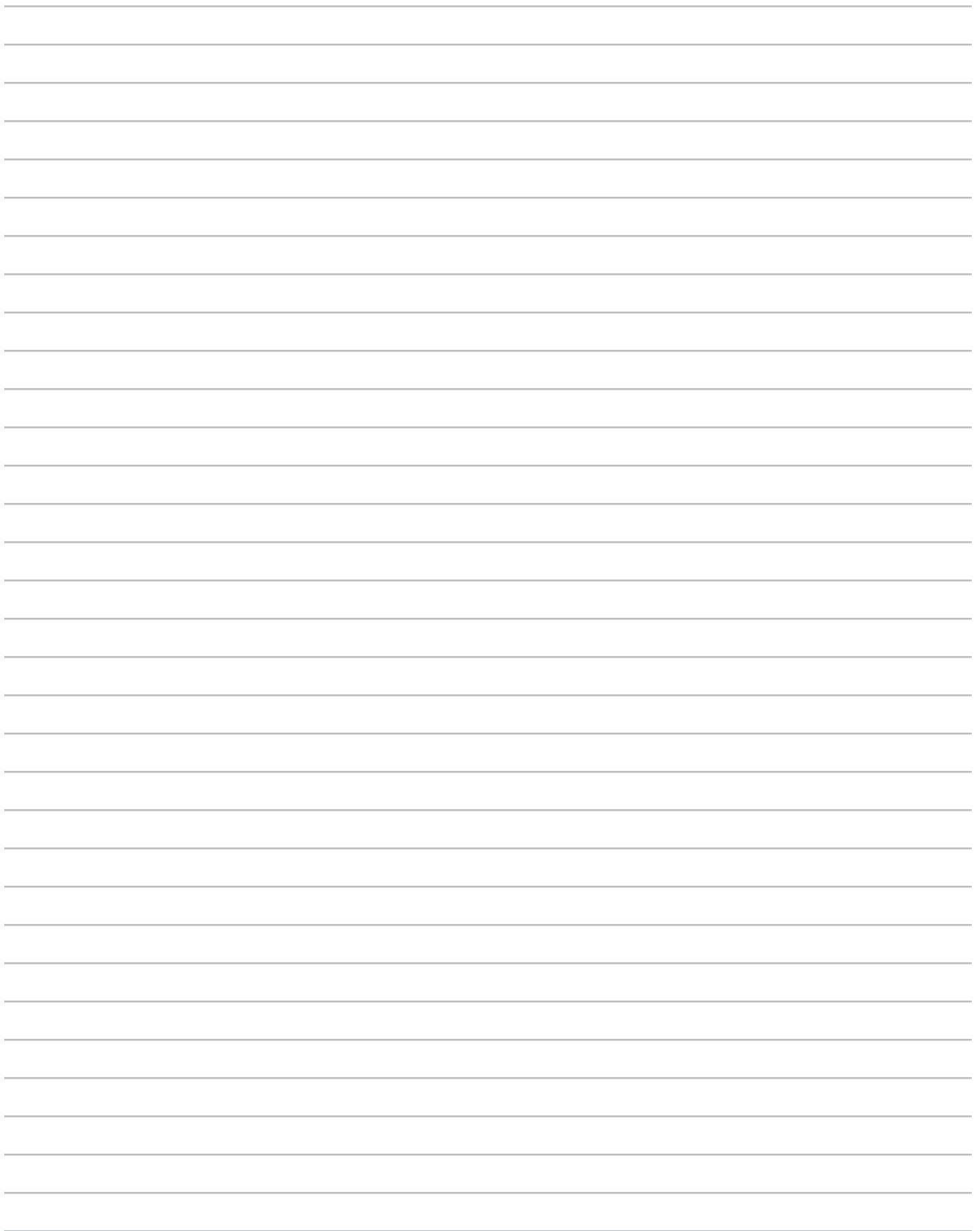
- BMI reduced 36.9 to 31.2
  - Exercise increase from 48 to 195 min/week
  - IIEF from 13 to 17 (17 men IIEF of 22 or more)
  - BMI, Exercise, & hs-CRP associated w/IIEF
  - hs-CRP=1.9 mg/L, HDL=48
- Bottom Line=WOW!!!

Esposito K, et al. JAMA 291:2978-2984, 2004.









# Increasing Awareness, Diagnosis, and Treatment of Hypogonadism

~ Jacob Rajfer, MD

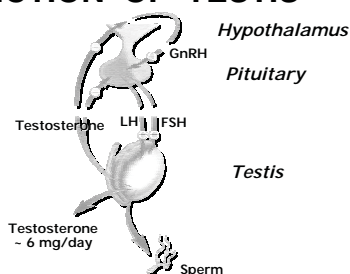
## HYPOGONADISM

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](http://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)

Ref: AACE Hypogonadism Task Force.  
*Endocrinol Pract.* 2002;8:439-456  
Morley JE et al. *Metabolism* 2000;49:1239-1242

Ref: AACE Hypogonadism Task Force.  
*Endocrinol Pract.* 2002;8:439-456  
Morley JE, et al. *Metabolism* 2000;49:1239-1242

- Definition of “low T” varies widely
- Most labs define “low T” based on lowest 2.5% of values
- Yet prevalence is >2.5%
- Most clinical trials use threshold values ranging from 325–400 ng/dL
- Each person may have his own individual threshold value

(SALIVARY T MEASUREMENT OK BUT NOT STANDARDIZED)

### 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

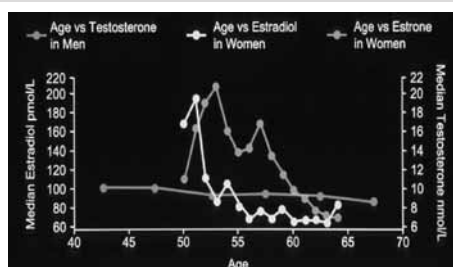
- > PRIMARY TESTICULAR FAILURE
- > HYPOGONADOTROPIC HYPOGONADISM (KALLMANN'S SYNDROME, PITUITARY ADENOMA)
- > TRAUMA
- > IDIOPATHIC
- > OBESITY
- > SEVERE SYSTEMIC ILLNESS (INCLUDING HIV)
- > MEDICATIONS
- > CHANGES IN GnRH, PROLACTIN, CORTISOL, AND THYROID HORMONES
- > NORMAL AGING

GnRH=gonadotropin-releasing hormone

Winters SJ. *Arch Fam Med*. 1999;8:257-263.

Tenover JL. *Endocrinol Metab Clin North Am*. 1998;27:969-987.

### T in Men and E2 in Women During the Middle Years



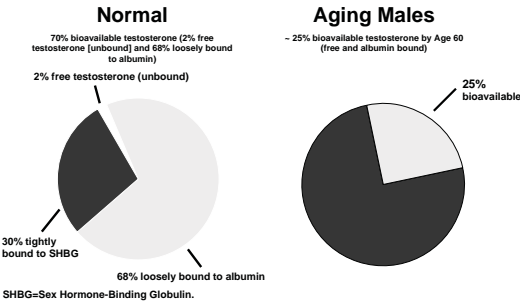
Massachusetts Women's Health Study (1981-1996) and Massachusetts Male Aging Study (1986-1989)

### Age-related Changes in Testosterone Level

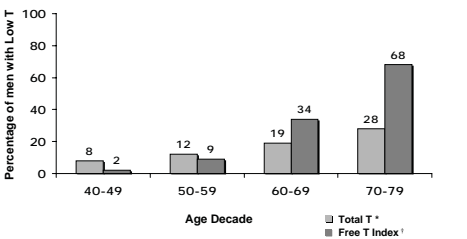
- New Mexico Aging Process Study
  - Men, 61-87 years old
  - Average rate of decrease in serum testosterone concentration is 110 ng/dL per decade

Morley JE, et al. *Metabolism*. 1997;46:410-413.

### Testosterone Levels in Aging Males

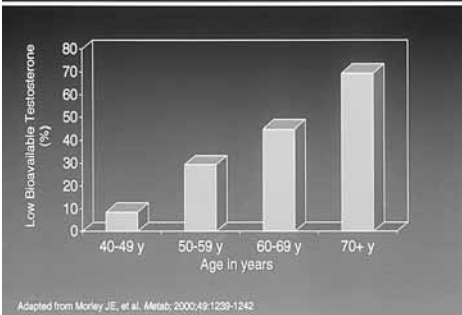


### Prevalence of Low T in Men

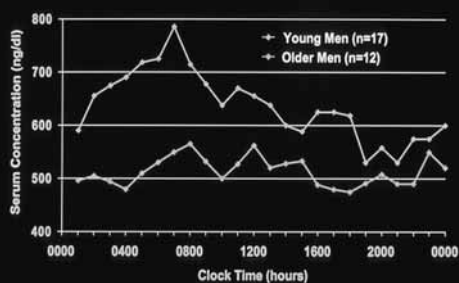


Harman SM, et al. *J Clin Endocrinol Metab*. 2001;86:724-731.

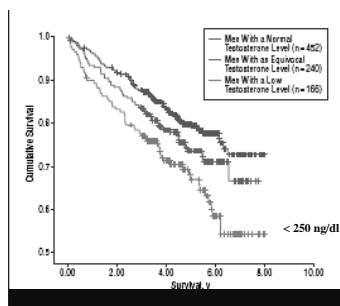
### Percent of Men With Bioavailable Testosterone Levels <70 ng/dL



### Hourly Serum Testosterone Profiles in Normal Young and Older Men



### LOW T & MORTALITY



### SERUM T & MORTALITY

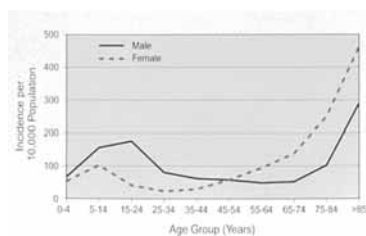
n = 794, AGE X = 73.6y, 11.8 y f/u, 538 deaths  
Rancho Bernardo, CA, pop based study

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





### 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<sub>x</sub> OLDER MEN

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

2. Lean Body Mass  8% over 3 yrs

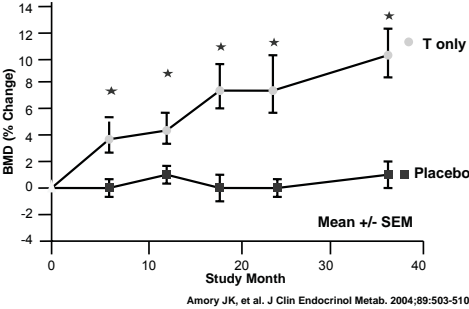
3. Body Fat  15% over 3 yrs

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

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

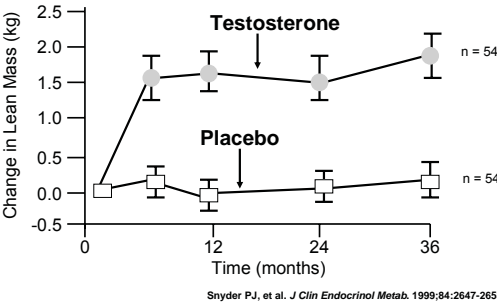
- 3 months
- 6 months
- 9 months
- 12 months.

LS Spine BMD with TRT Aging  
Men

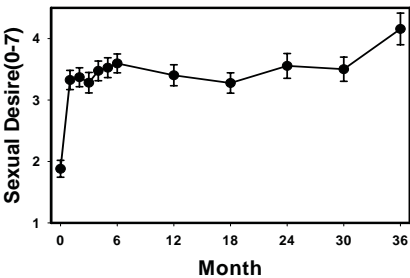


EFFECT OF T ON LEAN MASS

ELDERLY MEN (>65y)



EFFECT OF T ON LIBIDO  
Hypogonadal Men (19-68y)



Slide 30  
N21 Change Y axis to 1 to 5. Text from previous slide added to notes here. Previous slide deleted  
NSA 2/20/01, 6/3/2008

## 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

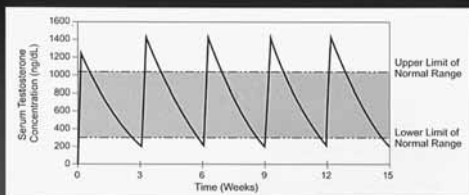
BUCCAL

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; 1998:329-348

## ANDROGEN PREPARATIONS

### TRANSDERMAL PATCH

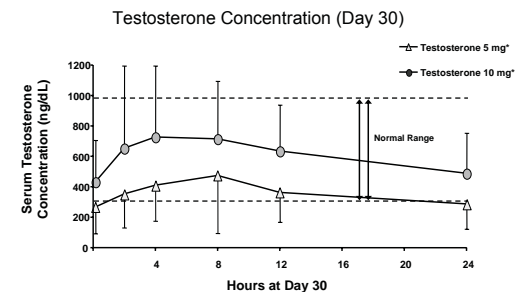
- Testoderm (scrotal) - Delivers 4-6 mg testosterone daily
- Testoderm TTS (arm/torso/thigh skin) Delivers 5 mg testosterone daily
- Androderm (arm/torso/thigh skin) Delivers 2.5-5 mg testosterone daily

ANDROGEN PREPARATIONS

TRANSDERMAL GEL

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

Testosterone 1% Gel



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

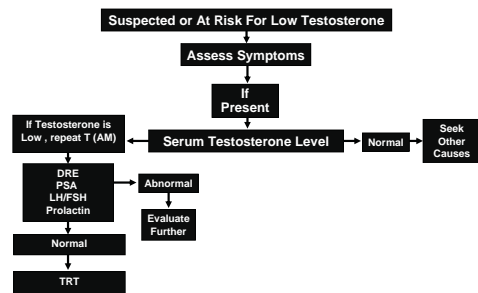
Rajfer J; Personal experience

TRT : NOT RECOMMENDED

hCG, DHEA, DHEAS, DHT

[http://www.uroweb.org/fileadmin/user\\_upload/Guidelines/14%20Hypogonadism.pdf](http://www.uroweb.org/fileadmin/user_upload/Guidelines/14%20Hypogonadism.pdf)

## Diagnosis and Treatment Algorithm for Testosterone Deficiency



DRE=Digital Rectal Exam, PSA=Prostate Specific Antigen, TRT=Testosterone Replacement Therapy, LH=Luteinizing Hormone, FSH=Follicle Stimulating Hormone.

## 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

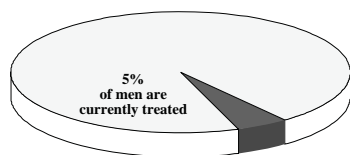
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- (2) Changes in **mood** with concomitant **decreases in intellectual activity, cognitive functions, spatial orientation ability, fatigue, depressed mood and irritability.**
- (3) **Sleep disturbances.**
- (4) **Decrease in lean body mass** with associated 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](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](http://www.fda.gov/fdac/departs/196_upd.html). Accessed January 19, 2004.

## LOH : why is it under tx?

FEAR OF ADVERSE EVENTS

1. PROSTATE CANCER
2. BPH / LUTS
3. SLEEP APNEA
4. C V EVENTS
5. NO DATA TO SUPPORT ↓ MORTALITY

ARE THESE FEARS APPROPRIATE?

The Effect of Castration, of Estrogen and of Androgen Injection  
on Serum Phosphatases in Metastatic Carcinoma of the  
Prostate

In men with metastatic prostate carcinoma to bone:

Acid phosphatase:

- Rose in 3 men after testosterone injection
- Decreased in 3 men after estrogen administration
- Decreased in 8 men after castration

Since low T causes prostate cancer to shrink, it has  
been assumed that higher T causes prostate cancer  
to grow. There are little data to support this.

REF: Huggins, Hodges. *Cancer Research* 1941; 1: 293-297.

Are Serum Hormones Associated With The Risk Of  
Prostate Cancer?  
Prospective Results From The Massachusetts Male  
Aging Study

- N = 1,576 men - Approximately 8 year follow-up
- 70 men (4%) developed prostate cancer
  - Correlated positively with PSA levels
- No correlation with:
  - Total testosterone
  - Free testosterone
  - SHBG
  - Androstenedione
  - Estradiol

Mohr, et al. *Urology* 2001; 57: 930-935

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

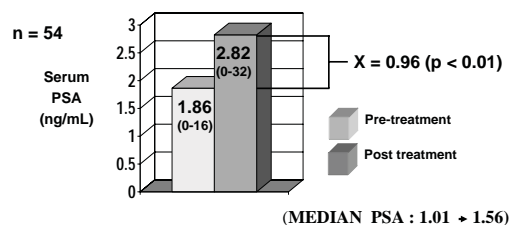
N = 33/35 men followed for 10-year minimum; 8/33 >50 y age

- 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.

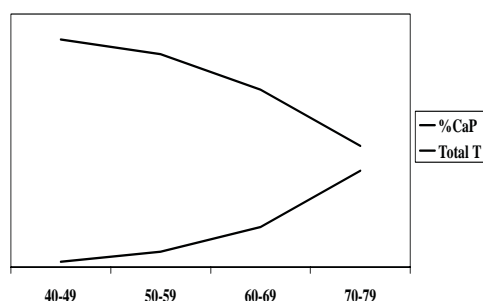
### Effect of Testosterone Supplementation on Serum PSA

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: 419-424

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

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

	With PIN	Without PIN
PSA		
Before TRT	1.49	1.53
After TRT	1.82	1.78

Biopsy for ↑ PSA	
Bx +	1
Bx -	2

0  
4

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

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

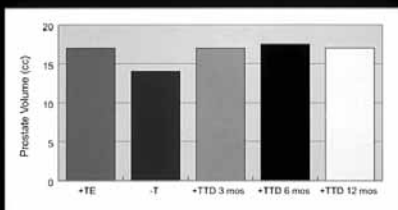
## EFFECTS OF TRT ON PROSTATE

- 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) <sup>10</sup>	24	—	—
Sih et al. (1997) <sup>9</sup>	12	0/15	0/17
Dobs et al. (1999) <sup>11</sup>	24	—	1/33
		—	0/33
Snyder et al. (1999) <sup>8</sup>	36	7/54	13/54
Snyder et al. (2000) <sup>6</sup>	36	—	—
Wang et al. (2000) <sup>20</sup>	6	—	0/76
		—	1/73
		—	4/78
Kenny et al. (2001) <sup>7</sup>	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*

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**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.

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**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

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**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

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

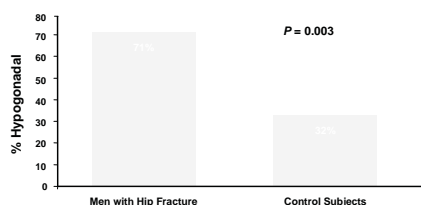
Hypoandrogenemia in men are associated with:  
Visceral obesity  
Insulin resistance  
Low HDL cholesterol  
Elevated: Triglycerides, LDL cholesterol

- 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
<b>North America</b>	<b>8.2</b>	<b>12.4</b>	<b>18.5</b>	<b>21.5</b>
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

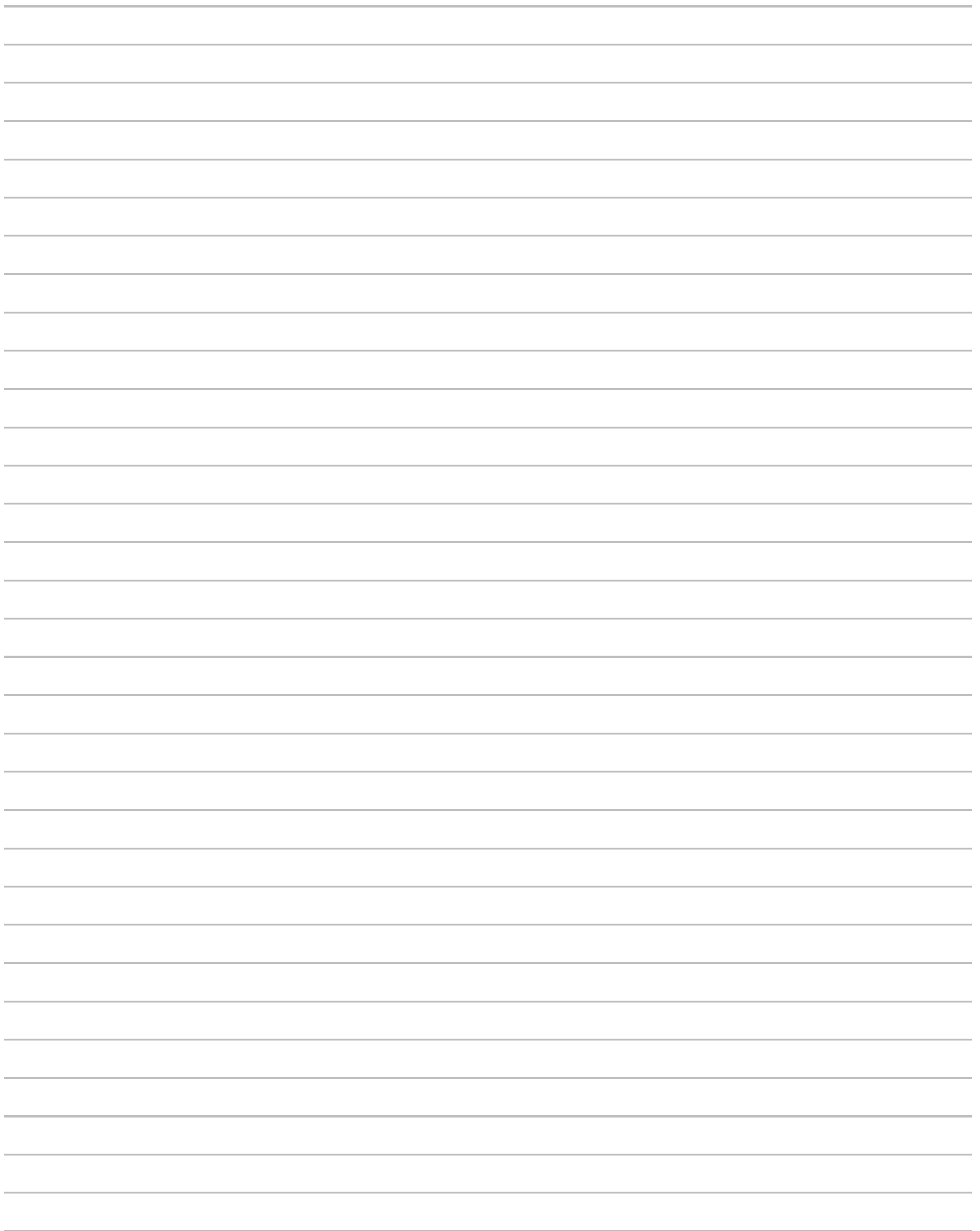
## Conclusions

### 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

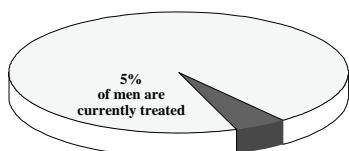
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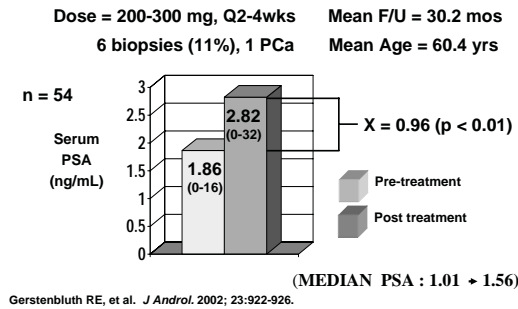
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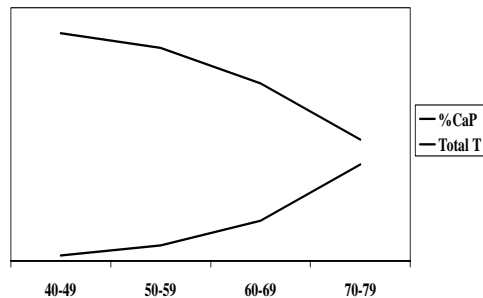
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### Effect of Testosterone Supplementation on Serum PSA



### 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

- 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?

## 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

	<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

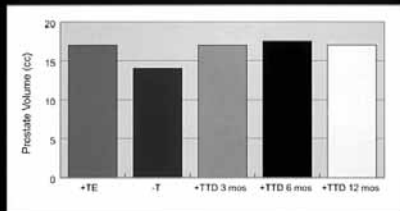
Rhoden et al. J Urol. 2003; 170: 2348-2351

- 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) <sup>10</sup>	24	—	—
Sih et al. (1997) <sup>9</sup>	12	0/15	0/17
Dobs et al. (1999) <sup>11</sup>	24	—	1/33
		—	0/33
Snyder et al. (1999) <sup>8</sup>	36	7/54	13/54
Snyder et al. (2000) <sup>6</sup>	36	—	—
Wang et al. (2000) <sup>20</sup>	6	—	0/76
		—	1/73
		—	4/78
Kenny et al. (2001) <sup>7</sup>	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: 163-217

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

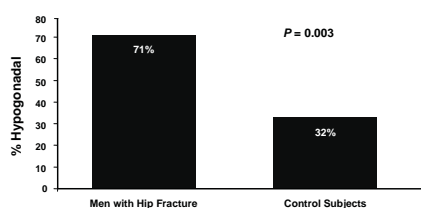
Hypoandrogenemia in men are associated with:  
Visceral obesity  
Insulin resistance  
Low HDL cholesterol  
Elevated: Triglycerides, LDL cholesterol

- 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
<b>North America</b>	<b>8.2</b>	<b>12.4</b>	<b>18.5</b>	<b>21.5</b>
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 ?



## Hypogonadism

sub-categories

Rx young males with Androgen  
deficiency with T

Rx Sexual disfunction with T

Older men with lower serum T

Chronic illness and lower serum T

Glucocorticosteroid treated men

## Hypogonadism

serum Testosterone

< 325 ng/dL

60's 20%

70's 30%

80's 50%

Baltimore Longitudinal Study of Aging 2001

## Hypogonadism

serum Testosterone

secondary; not primary

[role of obesity ?]

LH 9.4 to 13.8 15yrs

FSH 14.1 to 27.4

New Mexico Aging Process 1997

LH 0.9% / year

FSH 1.3% / year

Massachusetts Male Aging Study 2002

## Hypogonadism

serum Testosterone

total

free

bound to albumin

SHBG

bio-available free + albumin

Am Soc Repro Med, F&S 86, S236, 2006

**Hypogonadism**

benefits of therapy  
older men  
  
long term benefit in  
conditions of concern  
to patient and MD ?

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**Hypogonadism**

serum total Testosterone  
assay is widely available  
bio-available and free\* T levels  
are not widely available;  
  
\*free - challenged assay

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**Hypogonadism**

total Testosterone  
free Testosterone index\*  
total Testosterone / SHBG  
  
\* bio-available Testosterone

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**Hypogonadism**

consensus  
androgen replacement candidates  
hormonal criteria, No  
clinical criteria, No  
additional studies to elucidate  
patients who might benefit from  
androgen replacement

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## Hypogonadism

Endocrine Society

Testosterone total

< 200 ng / dL; treat

200 – 400 ; beneficial ??

> 400 ng / dL; unlikely to  
benefit

Bhasin JCE&M; 91: 1995, 2007

## Hypogonadism

Endocrine Society

measure LH when serum

Testosterone low, < 150 ng / dL

if LH normal or low

order Prolactin,  
pituitary MRI,

## Hypogonadism

candidates

clinical manifestations of ADAM

osteopenia,	low libido,
muscle mass	E quality,
strength down,	irritability,
stamina	impaired
energy down,	cognition,

## Androgen Deficiency suggestive

sexual development	infertility
libido and activity	height loss
decreased erections	muscle bulk/
breast discomfort	strength less
gynecomastia	hot flashes
loss of body hair	sweats
shrinking testes	



## Hypogonadism

**candidates**

**Testosterone concentration below which T administration improves outcome is unknown and may vary patient to patient and among target organs**

## Hypogonadism

**candidates**

**available evidence does not support the use of an arbitrary threshold for T below which clinical androgen deficiency occurs and that confirms the diagnosis of hypogonadism.**

## Hypogonadism

**candidates**

**threshold Testosterone level below which symptoms of androgen deficiency and adverse health outcomes occur is not known !**

## Hypogonadism

**consensus**

**androgen replacement candidates hormonal criteria, No clinical criteria, No additional studies to elucidate patients who might benefit from androgen replacement**



## Hypogonadism

initial evaluation

breast

heart

lungs

rectal

23,580 rectal tumors

CBC, PSA

## Hypogonadism

No evidence that clinical response depends on Testosterone form.

Benefits relate to level achieved !

endogenous / exogenous

goal – raise T over pretreatment

values but not exceeding levels of

normal young adult males

## Hypogonadism

normal range

Testosterone 300 ng / dL\*

free Testosterone 50 pg / dL

\* Use your reference laboratory

## Hypogonadism

lack on consensus on

1] case definition

2] extent to which androgen deficiency is an important health problem

3] lack of data on screening tools, population screening cannot be evaluated at present.



## Hypogonadism

monitoring  
 weight gain LUTs  
 peripheral edema sleep state  
 breast tenderness DRE  
 gynecomastia  
 measure T, Hgb, PSA  
 LFTs and lipids, No

## Hypogonadism

monitoring  
 examination @ 3 and 9 months  
 yearly thereafter  
 CBC, PSA\*, T  
 bone mineral density – at 2 years  
 \* Rapid PSA rise – unmasked Ca P

## Hypogonadism

therapy risks  
 fluid retention  
 erythrocytosis  
 sleep apnea worsened\*  
 benign\* or malignant\* prostate  
 problems \* YES \* No  
 cardiovascular disease risk

## Hypogonadism

contraindications  
 absolute relative  
 Ca prostate severe apnea  
 breast Ca LUTs  
 Hematocrit > 55% > 52%  
 sensitivity fluid retention

**Testosterone trials**

testosterone – young men  
Improvement in overall sexual activity, sexual thoughts and fantasies, attention to erotic stimuli, frequency and duration of nighttime erections, hair growth, increases in fat-free mass, muscle strength, decrease in fat mass.

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**Testosterone trials**

Bone mineral density increases but effect on fracture risk is unknown. T improves positive and reduces the negative aspects of mood, improves energy and sense of well-being, and some studies report improvement in visuospatial cognition and verbal memory.

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**Testosterone trials**

**recommendations**

The recommendations to treat young, healthy, hypo-gonadal men with T places a higher value on alleviating hypo-gonadal symptoms and other benefits , and lower value on avoiding burdens of T dosing, monitoring and cost with ? long-term safety.

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**Testosterone trials**

testosterone - older men  
There are no randomized, placebo- controlled trials of T therapy on depression, cognition, fracture fragility, quality of life and cardiovascular outcomes; libido improved but no significant improvement in self-reported erectile function.

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## Testosterone trials

bone mineral density [ BMD ]  
 Inconsistent and imprecise data  
 @ 1 year - insignificant  
 longer trials – 1 to 3 years  
 lumbar BMD 2% increase  
 femoral neck, No

## Testosterone trials

bone fracture  
 No trial reporting the effect of  
 Testosterone on bone fractures  
 was reported.

## Testosterone trials

body composition  
 Significantly greater increase  
 in LBM [ lean body mass ] and  
 reduction in fat mass.  
 Body weight change did not  
 differ significantly.

## Testosterone trials

muscle strength and physical  
 function  
 Greater improvement in grip,  
 lower extremity strength but  
 measures of physical function  
 were inconsistent .

**11 randomized clinical trials,  
474 men  
muscle strength  
larger effects for lower  
extremity muscle strength than  
upper extremity - injected >topical**  
Ottenbacher J Am Ger Soc 54: 1666, 2006

**sexual function**  
**Two placebo- controlled trials**  
**on overall sexual satisfaction**  
**yielded imprecise results.**

**sexual function**  
**17 trials - 862 men**  
**low T; moderate, non-significant**  
**and inconsistent effect of T on**  
**satisfaction with erectile function;**  
**large effect on libido**  
**none on sexual satisfaction**

**sexual function**  
**17 trials - 862 men**  
**low normal and normal T**  
**small satisfaction of EF effect**  
**moderate, non-significant libido**  
**no effect sexual satisfaction**  
 Boloqa Mayo CI Pro 82: 20, 2007

## Testosterone trials

quality of life

The results were imprecise and inconsistent across trials.

There was improvement in physical function domain.

## Testosterone trials

depression

Three randomized T trials for 3 months or longer showed no significant effects on depression. Inconsistent and imprecise results limit the inferential strength.

## Testosterone trials

cognition

Three placebo-controlled randomized trials, one which studied men with Alzheimer's Disease and low Testosterone, reported imprecise effects on several aspects of cognition; none of which were significant after pooling data.

## Testosterone trials

adverse outcomes

19 randomized trials

Prostate Events

Rates of prostate Ca, PSA > 4 ng and prostate biopsies were numerically higher but not significantly higher.



## Testosterone trials

adverse outcomes

Lipid profiles

5 trials reported insignificant  
changes in major lipid fractions.

Cholesterol - 4mg/dl

HDL - 6 mg/dl

triglycerides - 9 mg/dl

## Testosterone trials

HIV infected men

Low T yielded weight loss\*,  
lean body mass\*, AIDS wasting\*  
AIDS progression, depression\*  
and loss of muscle mass\*, mood\*\*  
exercise capacity, and QoL\*\*.

\* Improved      \*\* minimal to none

## Testosterone trials

gluco-corticoid- treated men

5 – 7.5 mg Prednisone or >

changes in muscle mass and BMD

bronchial asthma and COPD

greater gain in LBM and decrease

in fat mass; increase in lumbar,

+/- femoral BMD; no fracture data

## Testosterone trials

gluco-corticoid- treated men

higher value on potential

benefit and lower value of

avoiding adverse events,

burdens of T administration,

monitoring and cost and long

term safety

**summary – older men  
small sample size, healthy men,  
normal or low T, asymptomatic,  
Insufficient power to detect  
meaningful gains in outcomes or  
changes in cardiovascular or  
prostate event rates**

**recommendations**

**The recommendations not to treat older men with age-related decline in T place a lower value on unproven, beneficial events of T and higher value on avoiding burdens of T dosing, monitoring and cost with ? long-term safety.**

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## Testosterone trials

### recommendations

The recommendations not to treat older men with age-related decline in T place a lower value on unproven, beneficial events of T and higher value on avoiding burdens of T dosing, monitoring and cost with ? long-term safety.

## Testosterone trials

### recommendations

The recommendations not to treat older men with age-related decline in T place a lower value on unproven, beneficial events of T and higher value on avoiding burdens of T dosing, monitoring and cost with ? long-term safety.

## Testosterone trials

### recommendations

The recommendations not to treat older men with age-related decline in T place a lower value on unproven, beneficial events of T and higher value on avoiding burdens of T dosing, monitoring and cost with ? long-term safety.

## Prostate Biopsy

### transition zone biopsies

suspicious; PSA rise, velocity +,  
negative biopsies,  
negative repeat biopsies,  
negative 12 or + core biopsies,  
biopsy TZ and anterior, separate  
specimens from repeat PZ cores



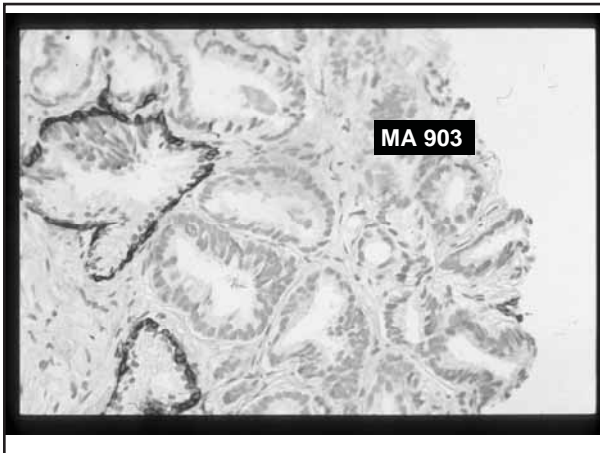
## Thompson

Google

Prostate Cancer Risk Calculator

risk 44%

high grade 14%



## Racemase and P<sup>63</sup> stains

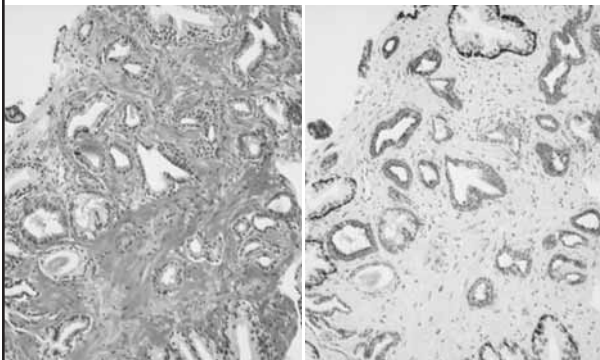
MA 903 - basal cell cytoplasm;  
benign, 2 layer prostate glands  
no basal layer = malignancy

Racemase – cytoplasmic epithelial  
cell; stains = malignancy

P<sup>63</sup> – basal cell nuclei, basal cells  
present, stain = benign gland

R +, P<sup>63</sup> - = Ca;

## AMACR + p63 in PCa



**1.5 positive 3.9**

**0 8 7**

**0 negative 7**

**0 negative 7**

## 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



**Testis Pain**

42 year old male,  
bilateral testicular pain,  
chronic, intermittent,  
No other GU or GI symptoms  
nor fever,  
left testis lower than right

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**Testis Pain**

no history of  
cryptorchidism,  
atrophy,  
trauma,  
surgery in groins,

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**Testis Pain**

history  
hypertension  
Rx Lisinopril  
left knee pain,  
arthrosocpy

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**Testis Pain**

physical examination  
scalenus anticus nodes normal  
no gynecomastia  
no upper abdominal mass  
no groin scars

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## Testis Pain

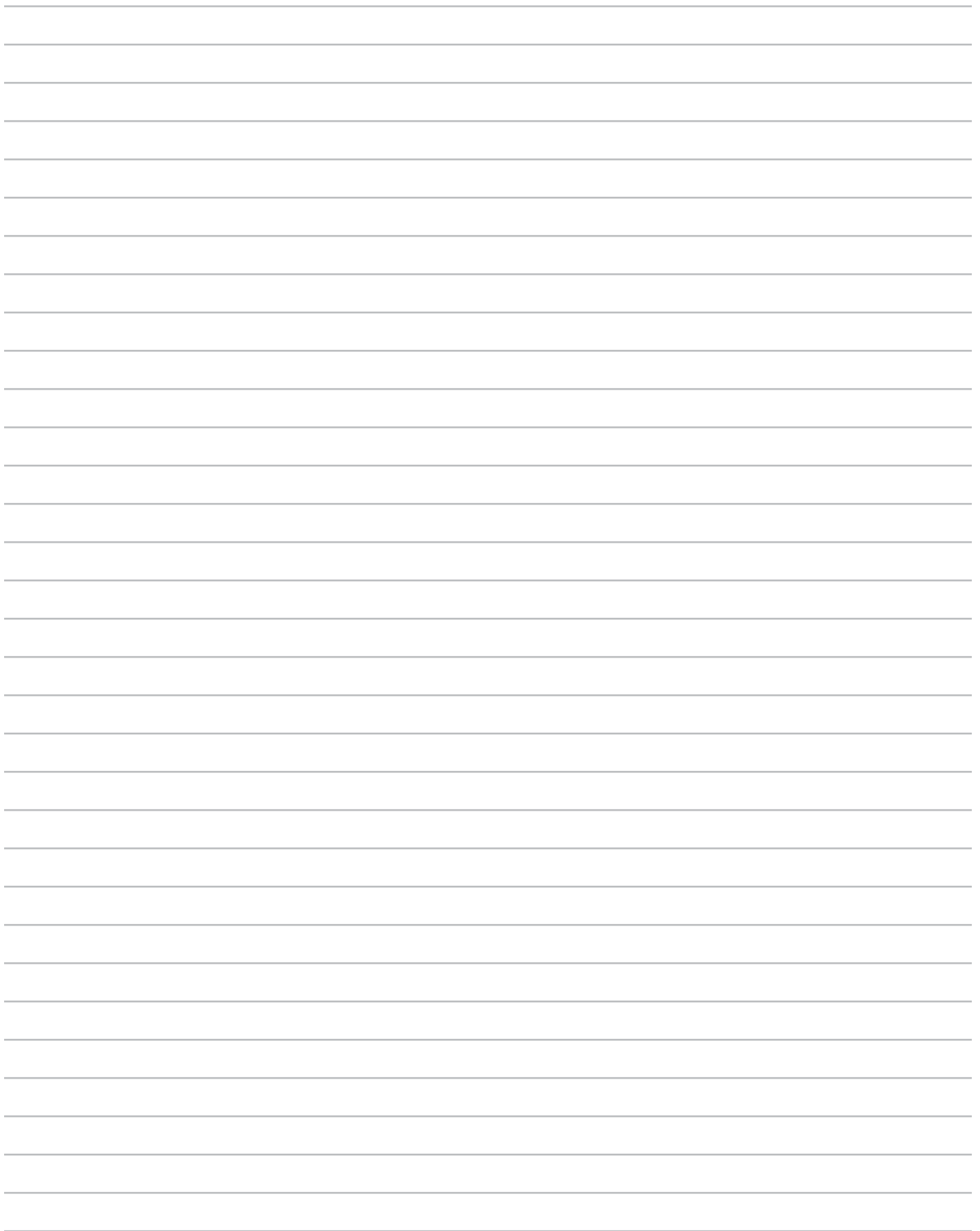
physical examination  
pubic hair pattern normal  
penis circumcised, normal  
left testis, epididymis, vas  
normal, varicocele

## Testis Pain

physical examination  
right testis located higher than  
normal in the scrotum,  
smaller than the left testis  
no mass palpable in testis,  
normal epididymis and vas

## Testis Pain

chest x-ray normal  
alpha fetoprotein 2.9  
beta HCG < 2



# Fad Diets and Dietary Supplements for Urology Patients: What Works and What's Worthless

~ Mark A. Moyad, MD, MPH

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## Diet & Dietary Supplements: What works & what is worthless from A to Z?!

Mark A. Moyad, MD, MPH  
Jenkins/Pokempner Director of Preventive/Alternative  
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University of Michigan Medical Center  
Dept of Urology  
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Hobbies: Telling you that less is More!



## Disclosure Statement

- I am a consultant for Abbott Labs Inc., NBTY, Embria, Farr Labs, FTC, & Guthy-Renker, Inc & may receive royalties for product invention from Guthy-Renker and on the speakers bureau for Abbott Labs, Inc. I will not be discussing drugs that are unlabeled or used for investigational purposes.



## Overview of the Talk

- Pre-Game Locker Room Speech
- A-Z=Lifestyle/Pill=Game time
- Post-Game Summary



**Dietary Supplements=Big Business  
(Where is the Objectivity?)**

Annual Sales of nutritional supplements in the  
U.S. (CDC/NIH)?

- A) 1 Billion
- B) 3 Billion
- C) 5 Billion

(Nahin RL, et al for the National Health Statistics Report  
2009;18, July 30, 1-14 )



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**Moyad Rule**

- “Approximately 2-3 weeks before any surgical or radiation  
procedure please stop the use of most OTC dietary  
supplements...”
- LESS IS MORE! (FDA/Canada & 2010 Maybe)
- Most natural products are not better for you...

Moyad MA. Promoting Wellness for Prostate Cancer Patients, 2006.



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**PRE-GAME-Probability Diet**

BOTTOM LINE=Heart Healthy=Bladder Healthy=Bone  
Healthy=Brain Healthy=Breast Healthy=Colon  
Healthy=Eye Healthy=Joint Healthy=Kidney  
Healthy=Prostate Healthy=Skin Healthy=Sexual  
Health=ALL HEALTHY!!!

(Vioxx vs. Vitamin E vs. Fish Oil...?)

Moyad MA. Promoting wellness for prostate cancer patients. JW Edwards Publishing, 2006.  
Moyad MA, Carroll PR. Urol Clin N Am 2004;31:289-300.



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**BUCKLE UP!-Last sec. Tips...**

- Nutrients can be added back to diet-unlike Rx  
(selenium, folic acid)=“Over-Anti-Oxidation Of  
Our Population!”
- LESS IS MORE...
- LESS IS MORE...
- LESS IS MORE...
- LESS IS MORE...

Moyad MA, Carroll PR. Urol Clin N Am 2004;31:289-300. & Moyad MA.  
AUA Update 37 & 38, 2008.



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## B=Belly Fat

Just Released!  
-EPIC Study!  
-9 countries

-360,000!!!  
-Most Accurate  
-10 years  
-15,000 deaths

-BMI=25-26 men

-BMI=24-25  
women



-BMI & WC=  
General +  
Abdominal  
Obesity

-CVD  
-Cancer  
-Overall Mortality

(Pischon T, et al. N Engl J Med 359:2105-2120, 2008).



## **B=BELLY FAT** (WC=Waist Circumference=Belly)

WC (U.S.)	WC (METRIC)	What this means?
Men-<35 inches	<89 cm	"Normal"
Men-35-39 inches	89-100 cm	"Overweight"
Men-≥40 inches	≥101 cm	"Obese"
Women-<32.5	<83 cm	"Normal"
Women-32.5-36	83-93 cm	"Overweight"
Women-≥37	≥94 cm	"Obese"

Moyad MA. Promoting Wellness, 2009 & No BS Health Advice, 2009.



## **B=BELLY FAT/FAT** (Moyad MA. ABCs Nutr, 2004) (HEART HEALTHY=ALL HEALTHY)

FAT TYPE	PRIMARY SOURCE	COMMENT
Monounsaturated (Oleic acid...)	Cooking oils + nuts..	GOOD
Polyunsaturated (Omega-3s)	Soy, Flax, Fish...	GOOD
Saturated (hydrogenated)	Dairy/non-game-meat...	BAD? Not Exactly!
Trans (partially hydrogenated)	Marg/shorten/deep fried/fast-food...	BAD



## **B=BELLY FAT (surgery)** (Saturated Fat=Higher Calories!)

TYPE OF MILK	SATURATED FAT (8 oz)	TOTAL CALORIES
Skim Milk	0 grams	80 Calories
1% Milk	1.5 grams	100 Calories
2% Milk	3 grams	120 Calories
Whole Milk	5 grams	150 Calories
Reindeer Milk	Does it matter?!	580 Calories

Moyad MA. No BS Health Advice, 2009. & Strom SS, et al. Int J Cancer 2008;122:2581-2585.



<b><u>SPECIAL DIET</u></b> <b>(1400 Calories) (n=811)</b>	<b><u>RESULTS</u></b> <b>(2-years)</b>
Fad Diet I	-9 lbs=4 kg, -2 inches=5 cm
Fad Diet II	SAME
Fad Diet III	SAME
Fad Diet IV	SAME

N Engl J Med, On-Line, March, 2009.



- n=48, 6-months, 37-39 yrs, BMI=27-28, 175-180 lbs

- Control=2 lbs
- CR (25%)=17-18 lbs
- CR (12.5%) + Exercise (12.5%)=17-18 lbs
- Severe CR (890 cal/day until 15% loss)=24-25 lbs
- Insulin reduced, core temp reduced, thyroid, DNA damage...

Heilbronn LK et al. JAMA 295(13):1539-1548. 2006.



- Rimonabant (Acomplia®)=No Chance!
- “ALLI” (\$2/day)=Not exciting!
- Meridia (Sibutramine)=Maybe!
- Green Tea=Why?
- FISH OIL & EXERCISE=Why not?
- Fiber (30gram/d)=Why not?

Movad MA, No BS Health Advice, 2009.



CALCIUM CARBONATE (40% elem)	Caltrate, Oscal...	- <u>W/Meals</u> -Colon? -PSA? (PCPT...)
CALCIUM CITRATE (21% elem)	Citracal...	- <u>W/or w/out meal</u> -Best for stone patients...
CALCIUM PHOSPHATE (39% elem)	Posture-D...	- <u>W/or w/out meal</u>

Moyad MA. Promoting Wellness for Prostate Cancer Patients. 2009. & Panju AH. et al BJU Int 2009;103:753-7.



## Would You Take This Pill If It was Free & Had No Side Effects?

### Physical health

- Premature death=30-50%
- Heart disease=40-50%
- Stroke=30-50%
- Type II diabetes=30-40%
- BREAST CANCER=20-30%
- Colon cancer...=30-50%
- Osteoporosis=40-50%
- Kidney stones, E.D., & FATAL P.C.!!!

(Manson J, Amend P. The 30-minute fitness solution, 2006.)

### Mental Health

- Depression



## E=Exercise/Fatigue... (Weight Lifting & Cancer Study)

2 sets  
8-12 repetitions  
3 times per week

- Calf raise
- Leg extension
- Leg curl
- Chest press
- Latissimus pull-down
- Overhead press
- Triceps extension
- Biceps curl
- Modified curl-up



Segal RJ, et al. J Clin Oncol. 2003; 21:1653-1659.

Just Released!

-Randomized  
Trial of  
Weight-Lifting  
In LHRH  
& Radiation.



-Univ of PA  
Lymphedema  
Study  
N Engl J Med  
(n=141, 2x/wk,  
1-year)

Segal RJ, et al. J Clin Oncol 2009;27:344-351. & Schmitz KH, et al. N Engl J Med 2009;361:664-673.



## E=Exercise/Wt Lifting (Bone Loss & LHRH?)

- Australia Study (10 men, age=70)
- 20 wk high-intensity resistance exercise (5 months)
- 5 men on acute & 5 on chronic ADT
- Increased Muscle Strength, No change in Fat Mass
- No bone loss at any site + No Hgb change!

Bottom Line=Rx-Exaggerated? Moyad Experience.

Galvao DA, et al. (Spry N, Newton R...). Pros Cancer Prostat Dis, 2006.



**E=Exercise**  
**Aerobic vs. Weight Lifting**

HEALTH AREA	AEROBIC	WT. LIFTING
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)

	<u>Placebo</u>	<u>Flaxseed</u>	<u>Low-Fat</u>	<u>Flax+LF</u>
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)

<u>GOOD NEWS</u>	<u>BAD NEWS</u>
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?

<u>BEVERAGE</u>	<u>CALORIES (8 oz)</u>
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!



## **H=HOT FLASHES** **(Treatments?)**

<b><u>HOT FLASH TREATMENTS</u></b>	<b><u>COMMENTS</u></b>
Lifestyle Changes/Diary Flax, Sesame, Mag, Acup	Mild to Moderate Hot Flashes
Estrogens (Topical?)	Clots, DVT, Stroke, CVD
Progesterone	HDL drop, wt gain, CVD
SSRI, SNRI	CVD, Bone Loss...
OTHER	Gabapentin...(side effects)

Moyad MA. Promoting Wellness. 2009.



A=ACUPUNCTURE



-N/V=Yes!  
-Pain=Yes!  
-Xerostomia=Yes!  
-Hot Flashes=?  
-Low Back Pain=?

(Johnstone PAS, et al.  
Cancer 2002;94:1151-56.,  
Moyad MA. Sem Prev Alt  
Med 2006.)



## **F=FOLIC ACID & Polyp Prevention Study Group (1mg/d)**

<b><u>SIDE EFFECT</u></b>	<b><u>FOLIC ACID (n=516)</u></b>	<b><u>PLACEBO (n=505)</u></b>	<b><u>RESULT</u></b>
Died	10 (2%)	19 (4%)	Non-sign (p=0.09)
Colon Cancer	3 (0.5%)	4 (1%)	No impact
Other Cancers	54 (10.5%) (24=p ca)	32 (6.3%) (9=p ca)	P=0.02!!! (BPH)

Cole BF, et al: JAMA 297:2351-2359, 2007.



## **M=Multivitamin-SU.VI.MAX- French Study**

- N=13,017 (5141 men, age=45-60)
- 120 mg vit C + 30 mg vit E + 6 mg beta-carot + 100 mcg selenium, + 20 mg zinc vs. placebo
- 7.5 years
- Men=31% reduction in cancer & 37% all-cause mortality! PCa=REDUCED 48%, but...!!!!

Hercberg S, et al. Arch Intern Med 164:2335-2342, Nov. 22, 2004 & 2005.



## MULTIVITAMINS (& Zinc) (LESS IS MORE!)

- 295,344 (NIH-AARP study) or WHI
- 10,241 cases
- Double the risk of fatal p. cancer or no impact

**Bottom Line** =Men Take Women's Multi OR  
KIDS MULTI! (Max 1 pill a day). Zinc=15-20  
mg/d---that is all (Zicam anyone?).

Lawson KA, et al. J Natl Cancer Inst 99:754-764, 2007.



## Ornish Trial?

- N=87 (Pca, PSA=4-10, Gleason<7)
- Combo lifestyle change + supplements???
- 1yr=Mean PSA decrease 3%
- Increase=7% w/control

**Bottom Line**=??? Catch \_\_\_\_\_???

Ornish D, et al. J Urol 174:1065-1070, 2005. & Ornish D, et al. AUA Annual Meeting 169:page 74  
(abstract #286), 2003.



## Ornish (1-yr)

(Ornish D, et al. J Urol 174:1065-1070, 2005)

-Vegan Diet (no animal products)
<b>-10% or less calories from fat</b>
-Soy products (1 serving tofu + 58g soy protein beverage)
-Fish Oil supplement (3g daily)
-Vitamin E supplement (400 IU/day)
-Selenium supplement (200 mcg/day)
-Vitamin C supplement (2000 mg/day)
<b>-Moderate exercise (walking-30 min/d/6 days-wk)</b>
-Stress reduction/mgmt (yoga, meditation..60-min/d)
-Support Group Meeting (1-hour wk)



## Ornish Plan-I

(Ornish D, et al. J Urol 174:1065-1070, 2005)

PARAMETER	LIFESTYLE(44)	CONTROL(49)
TC (mg/dL)*	-32	-2
LDL*	-30	-1
HDL*	-5	+1
TG	+5	+1
Testost (ng/dl)	+29	+48
Weight (lbs)*	-10	No change
PSA*	-0.25	+0.38

Quality of life? N=44 & 49, Age=66, Gleason=6 or less



## Gaziano JM, et al. PHS II. JAMA 2009;301:52-62



1 Death From Prostate Cancer...& \_\_\_\_\_ deaths from heart disease  
Lippman SM, et al. SELECT. JAMA 2009;301:39-51.



## Lippman SM, et al. SELECT. JAMA 2009;301:39-51



HOPE-TOO=Heart Outcomes Prevention Evaluation Study Extension  
Lonn E. et al. JAMA. 2005;293:1338-1347.



### Zinc & Cancer

- Zinc & BPH + immune-supp (1970s)
- HPFS (N=47,974 US men-14 yr follow-up)
- 2901 New cancers (434 advanced)
- >100 mg/d=RR=2.29
- 10 or more yrs=RR=2.37

Bottom Line=Stop high-dose zinc now!!!

Leitzmann MF, et al. JNCI 95:1004-1007, 2003.



### FOREST OVER THE TREE-52 COUNTRIES STUDY!!!

- 90-95% REDUCTION!
- 70% Chance of living to the age of 85 without mental or physical disability.

INTERHEART STUDY INVESTIGATORS. Lancet 364:937-952, Sept 11, 2004/2006 Update.



### FOREST OVER THE TREE-52 COUNTRIES STUDY!!!

- 1) Do you SMOKE?

INTERHEART STUDY INVESTIGATORS. Lancet 364:937-952, Sept 11, 2004/2006 Update.



### FOREST OVER THE TREE-52 COUNTRIES STUDY!!!

- 1) Do you SMOKE?
- 2) Low CHOLESTEROL (LDL<100, hs-CRP)

INTERHEART STUDY INVESTIGATORS. Lancet 364:937-952, Sept 11, 2004/2006 Update.





INTERHEART STUDY INVESTIGATORS. *Lancet* 364:937-952, Sept 11, 2004/2006 Update.



INTERHEART STUDY INVESTIGATORS. *Lancet* 364:937-952, Sept 11, 2004/2006 Update.

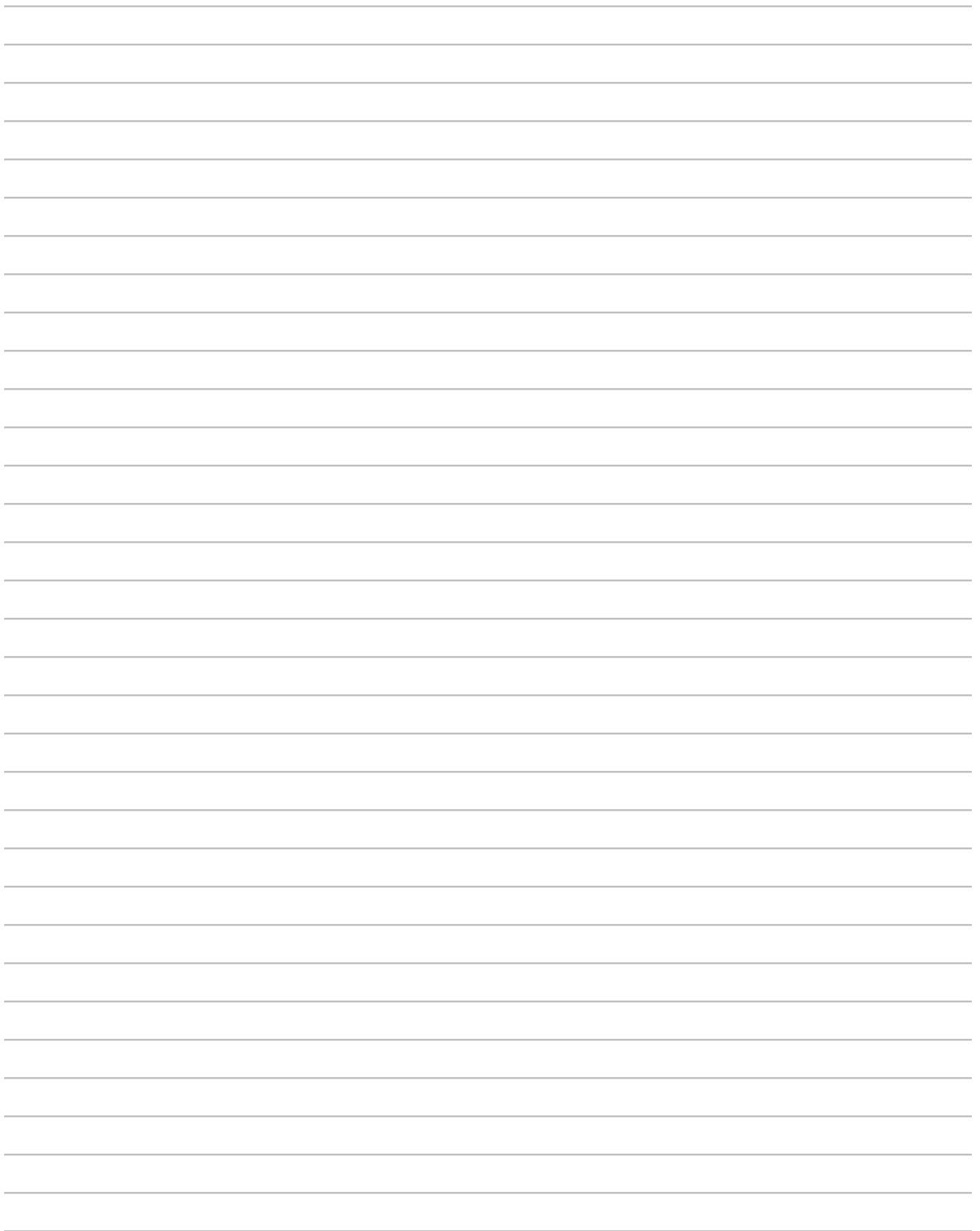


INTERHEART STUDY INVESTIGATORS. *Lancet* 364:937-952, Sept 11, 2004/2006 Update.



INTERHEART STUDY INVESTIGATORS. *Lancet* 364:937-952, Sept 11, 2004/2006 Update.





# Pills and Tests: What Should I (the urologist) Be Taking and Getting?

~ Mark A. Moyad, MD, MPH

## Pills & Tests: What should I (the urologist) be taking and getting?!

Mark A. Moyad, MD, MPH  
Jenkins/Pokempner Director of Preventive/Alternative  
Medicine  
University of Michigan Medical Center  
Dept of Urology  
Ann Arbor, MI  
moyad@umich.edu

Hobbies: Telling you that less is More!



## Lets Take a Doctor Moyad Quiz! Part I

- Angelina Jolie is married to \_\_\_\_ Pitt
- Oprah \_\_\_\_ has a good TV show!
- The actor that played Moses in the movie the Ten Commandments was \_\_\_\_ Heston.
- This actor (Sally \_\_\_\_ ) said "You like me...you really really like me" after winning her oscar!

Moyad MA. No BS Health Advice, Ann Arbor Media Group, 2009.



## Lets Take a Doctor Moyad Quiz! Part I

- A normal vitamin D blood level may reduce my risk of osteoporosis and may reduce my risk of certain autoimmune diseases, cancers, & heart disease. Anyhow, my last vitamin D blood test was \_\_\_\_ ng/ml and the number that is ideal for me \_\_\_\_ ng/ml.
- A normal hs-CRP test has been shown to reduce the risk of the number 1 cause of death in men & women, & my last test was \_\_\_\_ mg/L.
- My Framingham Risk Score or Reynolds Risk Score (paid for by the tax payers) that can determine my risk of the 1 cause of death in men & women is \_\_\_\_
- The Over the Counter product that costs pennies that works as well as the number 1 selling expensive medicine in the U.S. to fight cough and colds is known as \_\_\_\_

Moyad MA. No BS Health Advice, Ann Arbor Media Group, 2009.



COLONOSCOPY	Cure at biopsy?!
FLU VACCINE (& H1N1)	Right now! (other benefits--imm boost)
PNEUMONIA	Age 60-65 & over!
SHINGLES	APPROVED (Zostavax®)



1. CVD	426,772
2. Cancer	286,741
3. Accidents	67,923
4. Respiratory Diseases*	60,456
5. Diabetes*	35,217



1. CVD (since 1984)	483,842
2. Cancer	267,902
3. Respiratory Diseases*	65,672
4. Alzheimer's Disease	45,058
5. Diabetes*	35,748



**PRE-GAME-Probability Diet**

- #1 cause of death for 107 out of 108 years?
- #1 cause of death post-localized trt for ca (Moyad...)
- #1 in cancer prevention trials?

BOTTOM LINE=Heart Healthy=Bladder Healthy=Bone  
Healthy=Brain Healthy=Breast Healthy=Colon  
Healthy=Eye Healthy=Joint Healthy=Kidney  
Healthy=Prostate Healthy=Skin Healthy=Sexual  
Health=ALL HEALTHY!!!  
(Vioxx vs. Vitamin E vs. Fish Oil...?)

Moyad MA. Promoting wellness for prostate cancer patients. JW Edwards Publishing, 2006.  
Moyad MA, Carroll PR. Urol Clin N Am 2004;31:289-300.


**STATINS**  
**LDL CHOLESTEROL**

LDL (mg/dL)	LDL (mmol/L)	COMMENT
<70	<1.81	High-Risk
<100	<2.59	Optimal
100-129	2.59-3.34	Near optimal
130-159	3.37-4.12	Borderline High
160-189	4.14-4.90	High
≥190	≥4.92	Very High

NCEP Guidelines. JAMA 285:2486-2497, 2001.


**STATINS**  
**HDL CHOLESTEROL**

HDL (mg/dL)	HDL (mmol/L)	COMMENT
<40	<1.04	Low
40-59	1.04-1.53	Normal
≥60	≥1.55	IDEAL

NCEP Guidelines. JAMA 285:2486-2497, 2001.


**STATINS**  
**TRIGLYCERIDES**

TRIGLYCERIDE (mg/dL)	TRIGLYCERIDE (mmol/L)	COMMENT
<150	<1.70	Normal
150-199	1.70-2.25	Borderline High
200-499	2.26-5.64	High
≥500	≥5.65	High

NCEP Guidelines. JAMA 285:2486-2497, 2001.



High-sensitivity C-reactive protein	Number
< 1 mg/L	Low risk (normal)
1-3 mg/L	Moderate risk
> 3 mg/L	High risk

Ridker PM. *Circulation*. 2003;107:363-369.



NCEP Guidelines. JAMA 285:2486-2497, 2001.



NCEP Guidelines, JAMA 285:2486-2497, 2001.



NCEP Guidelines. JAMA 285:2486-2497, 2001.



### Framingham 10 yr-Risk: Step 4

HDL (mg/dl)	POINTS
≥60	-1
50-59	0 (Moyad)
40-49	1
<40	2

NCEP Guidelines. JAMA 285:2486-2497, 2001.



### Framingham 10-yr Risk: Step 5

Systolic Blood Pressure (mm Hg)	If Untreated	If Treated
<120	0 (Moyad)	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

NCEP Guidelines. JAMA 285:2486-2497, 2001.



NCEP Guidelines. JAMA 285:2486-2497, 2001.

### Framingham Risk-10 yr: Step 6

TOTAL POINTS	10-YR RISK (%)
<0	<1
0, 1, 2, 3, 4	1
5, 6	2
7	3
8	4
9	5
10	6
11	8
12	10



### Framingham Risk 10-yr: Step 6

TOTAL POINTS	10-YR RISK (%)
13	12
14	16
15	20
16	25
≥17	30
TOTAL SCORE	=??? (Moyad=0=1% risk)

NCEP Guidelines. JAMA 285:2486-2497, 2001.





## A=Alcohol

### MODERATION:

- HDL
- Heart health
- Estrogenic
- Bone health  
(not hard liq?)

### EXCESS:

- Increases triglycerides
- Calories
- Increases BP
- Immune-Suppressive
- Reduces folic acid/EFA..
- Oral/Esophageal cancer
- Breast/colon cancer...
- OSTEOPOROSIS
- CALORIES PER GRAM???

Moyad MA. Sem Prev Alt Med, Dec, 2007.



## A=Aspirin

- “Aspirin is a miracle drug for the people who NEED it (>10% Reynold’s Risk), but it is a potential disaster for the people that do not need it!”
- -New Meta-Analysis of 6 Studies
- Worried about Tylenol?! ASA is everywhere!

ATT Collaboration. Lancet 2009;373:1849-1860.



## A=Aspirin=WHS-39,876 Women

CONDITION	RISK REDUCTION-ASA
Heart Attack-age 65+	34% Reduction
Ischemic Stroke-age 65+	30% Reduction
Hemorrhagic Stroke	24% Increase
Major GI Bleed	40% Increase
Peptic Ulcer	32% Increase

Ridker PM, et al. N Engl J Med March 9, 2005;352



## Low-Dose ASA per 1000 treated for 5 years (meta=5 trials=>55,000)

CHD event risk/yr	CHD Events Avoided	Ischemic Strokes Avoided	Hem Strokes from ASA	Major Bleeds from ASA
Low=<10%	5	0	1	5
Moderate=10-20%	14	0	1	5
High=>20%	25-50	25-50	1	5

NCEP Guidelines. JAMA 285:2486-2497, 2001. ALL-CAUSE MORTALITY?



WHICH ONE  
IS BEST?

Depression, Weight loss...

Moyad MA: Sem in Urol Oncol 23:28-35 &amp; 36-48, Part I &amp; II, 20055

Autism-1.5 g/d

### -Hyperactivity



WHAT ABOUT COD LIVER OIL? (Consumer Reports, 2009.)



(Movad MA, et al, Urol August/Sept 2006)



Adjusting for PSA testing...=More Robust!!! Murtola TJ, et al. Nat Clin Prac Uro 2008;5(7):376-387

Red Yeast Rice (600 mg=1-2.5 mg).....VYTORIN (2011)

### C=CHOLESTEROL=Statins!

Atorvastatin=Lipitor®	?
Fluvastatin=Lescor®	?
Lovastatin=Mevacor®	Patent lost
Pravastatin=Pravachol®	Patent lost-06
Rosuvastatin=Crestor®	? (once a week?!)
Simvastatin=Zocor®	Patent lost-June 06

Moyad once a week solution???



### JUPITER SHOULD CHANGE YOUR LIFE (less is more)!

LDL "bad cholesterol"	hs-CRP	WHAT HAPPENED?
≥70	≥1 mg/L	-9% Reduction
≥70	≤1 mg/L	-35% Reduction
<70	≥1 mg/L	-50% Reduction
<70	≤1 mg/L	-79% Reduction!!!

Ridker PM, et al. Lancet 373:1175-1182, April 4, 2009. Justification for the Use of Statins in Prevention of DVT?



### Arthritis Pills (OA) (Summary)

- Pycnogenol (100 mg/d)
- Glucosamine...
- SAM-e
- Tylenol/Aleve
- Capsaicin?
- Hyaluronic Acid?
- Vitamin C?

Moyad MA et al: Sem Prev Alt Med-2007



### F=FOLIC ACID & Polyp Prevention Study Group (1mg/d)

SIDE EFFECT	FOLIC ACID (n=516)	PLACEBO (n=505)	RESULT
Died	10 (2%)	19 (4%)	Non-sign (p=0.09)
Colon Cancer	3 (0.5%)	4 (1%)	No impact
Other Cancers	54 (10.5%) (24=p ca)	32 (6.3%) (9=p ca)	P=0.02!!! (BPH)

Cole BF, et al: JAMA 297:2351-2359, 2007.





## 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

### Chemoprevention Prostate Cancer

E. David Crawford, MD

Professor of Surgery (Urology) and Radiation Oncology  
Head, Urologic Oncology

E. David Crawford Endowed Chair in Urologic Oncology  
University of Colorado Health Sciences Center  
Denver, Colorado



### "PSA Poster Boys"



### The Clinical and Economic Burden of Prostate Cancer

Expenditures

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

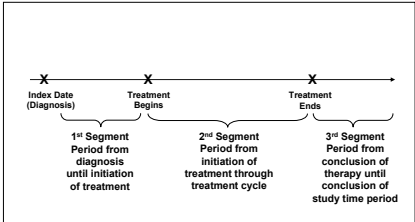
Presentation Outline

- Study Design
- Research Objectives
- Results
- Next Steps

Selection Criteria

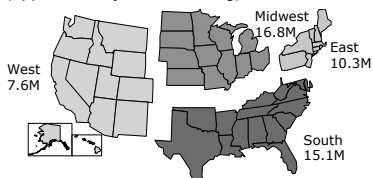
- **Inclusion Criteria**
  - Men ≥ 40 years of age
  - Index date occurs during the enrollment period
  - Continuously eligible for at least 18 months (6-month pre-period and a minimum 12-month post-period)
- **Exclusion Criteria**
  - Members with ICD-9 claims for any other cancer

Measurement Segments



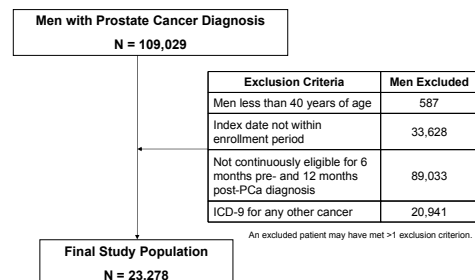
## Data Sources

- 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)



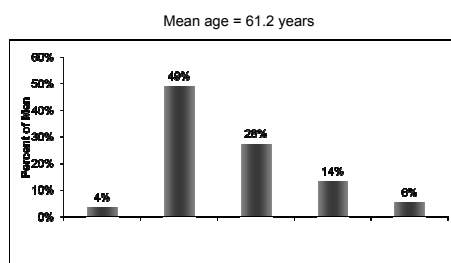
8

## Patient Selection



9

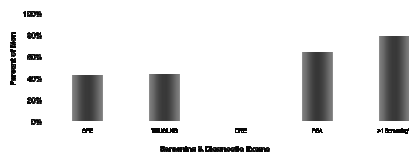
## Age



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.



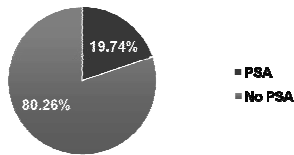
\*35% had 1, 16% had 2, and 30% had ≥3 screening or diagnostic exams

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.

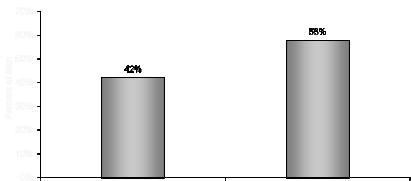


N=23,278  
PSA - Prostate Specific Antigen

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.

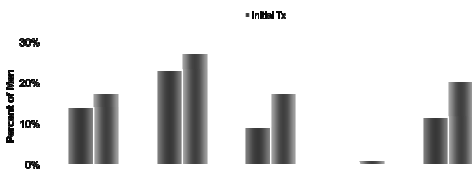


N=11,227  
WW - Watchful Waiting

13

Type of Treatment

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

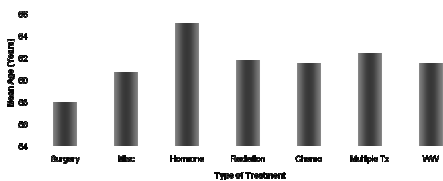


The percentages add to more than 100% as there were patients that received more than one treatment  
\*Misc=ketoconazole, aminoglutethimide, and any corticosteroid

14

Characteristics of Treatment Cohorts

Men receiving surgery as their initial treatment were younger.

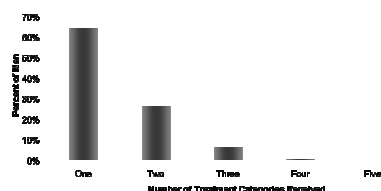


WW - Watchful Waiting

15

## Number of Treatments

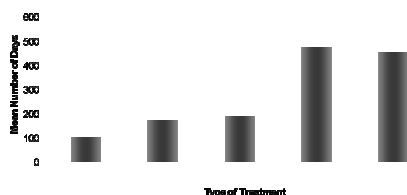
Of men that were treated, the majority received one type of treatment.



16

## Time to Treatment

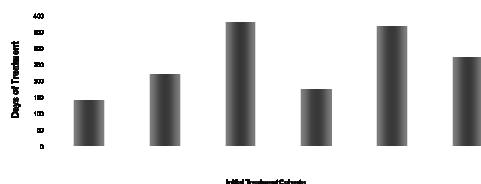
Of all men that received treatment, surgery occurred closest to diagnosis, and miscellaneous treatments occurred furthest from diagnosis (1.31 years).



17

## Average Duration of Treatment

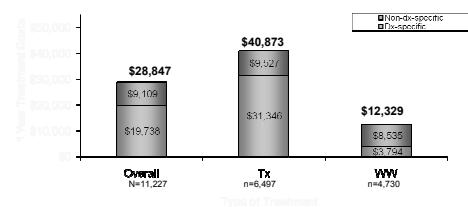
Mean days from first to last treatment ranged from 141 days for surgery cohort to 381 days for hormone therapy cohort.



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.

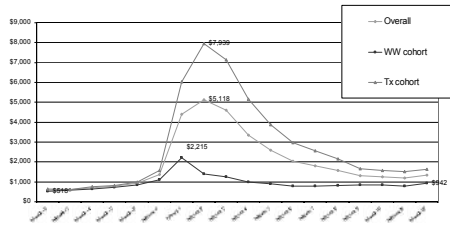


Costs were calculated from diagnosis through 1 year  
WW - Watchful Waiting

19

Average Total Monthly Medical Costs

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

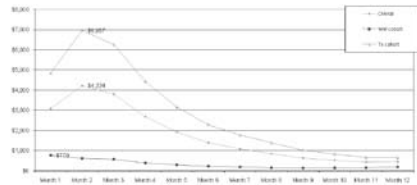


WW – Watchful Waiting

20

Average Prostate Cancer-specific Monthly Medical Costs

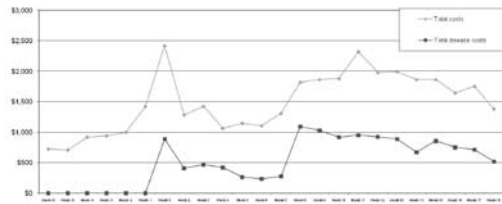
Disease-specific costs account for a high proportion of total costs



WW – Watchful Waiting

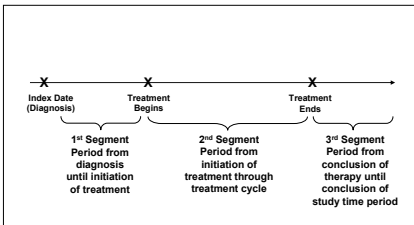
21

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



22

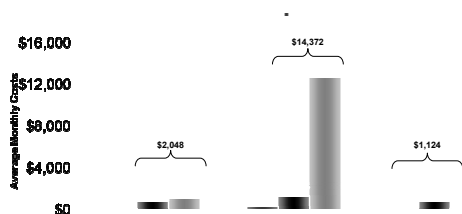
Measurement Segments



23

## Costs

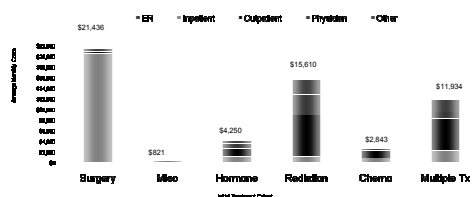
The majority of costs are accrued during treatment; almost all medical costs during treatment are related to prostate cancer.



24

## During-treatment Costs

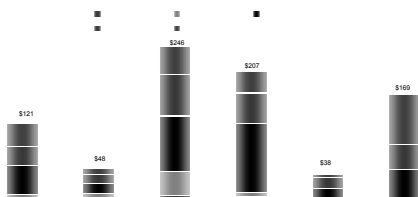
The surgery cohort had the highest during-treatment costs, driven by inpatient costs. Outpatient costs were the drivers in the radiation and multiple treatment cohorts.



25

## After-treatment Costs

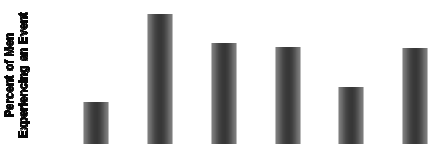
Prostate cancer-related medical costs were highest among the hormone and radiation cohorts. In most cohorts, outpatient costs were the highest.



26

## Clinical Events

Men who received treatment were more likely to experience an event than the watchful waiting cohort. Men who received surgery were the most likely to experience at least one event.



WW - Watchful Waiting

27

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.

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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

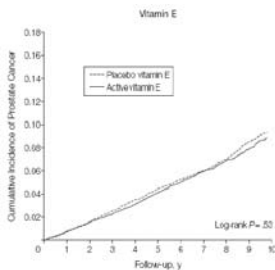
Prostate Cancer  
Diet & Exercise Risk Factors

- 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

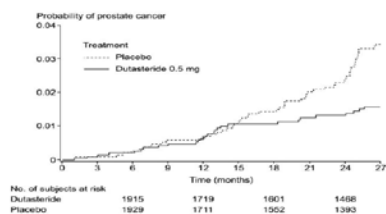
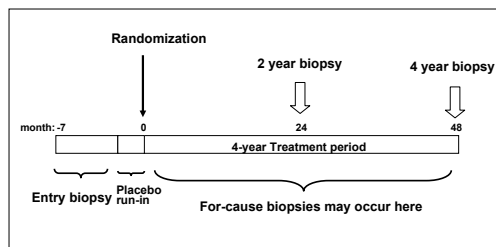


FIGURE 1. Kaplan-Meier estimates of proportion of subjects experiencing a prostate cancer adverse event with onset after randomization (study population).

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.

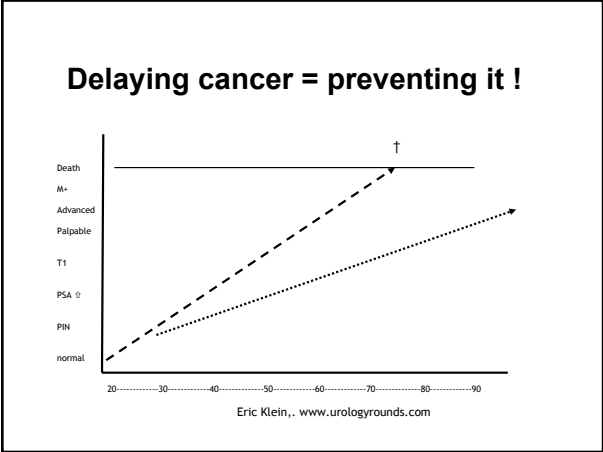
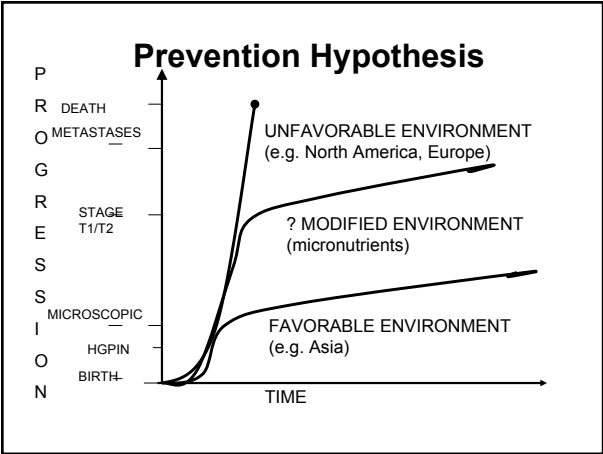
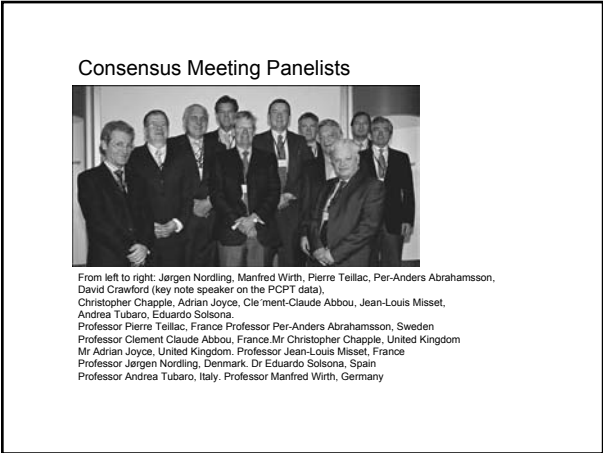
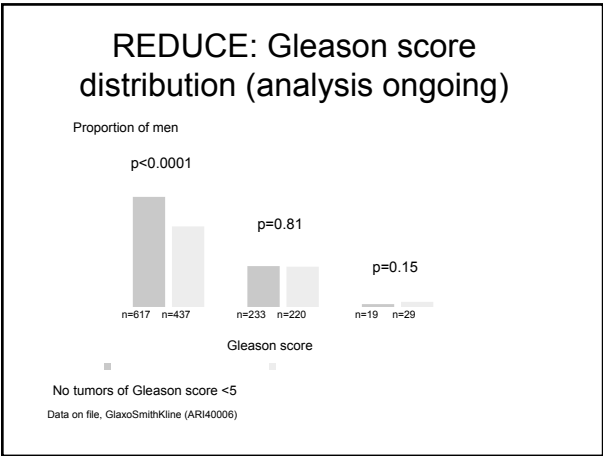
1. Thompson IM et al. NEJM 2003;349(3):215-224. 2. Andriole G et al for the REDUCE Study Group. J Urol 2004;172:1314-1317. 3. Goremlis LG. Curr Opin Urol 2005;15:2932. 4. Musquera M et al. Expert Reviews 2008;8(7):1079-1079.

## REDUCE: Primary endpoint (analysis ongoing)

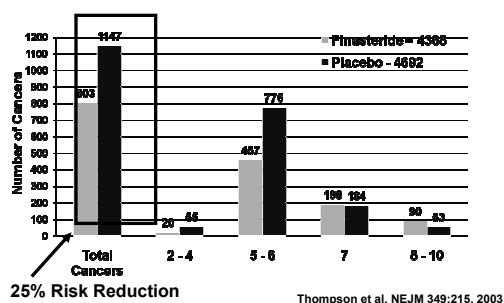
Dutasteride reduced the risk of prostate cancer over 4 years by  
**23%**  
**p<0.0001**  
(857 placebo vs 659 dutasteride)

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)



## Total Number of Cancers by Gleason Score



## 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

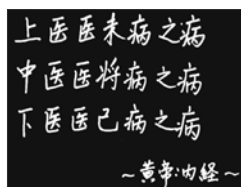
Health Professionals Follow-up Study, N = 34,989

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)

Hobbies: Forest over the tree & why there are no support groups for men that have...!

(Bonow RO. Circulation 2002;106:3140-3141)

(CDC 2006)

1. CVD	426,772
2. Cancer	286,741
3. Accidents	67,923
4. Respiratory Diseases*	60,456
5. Diabetes*	35,217

((Moyad MA. Sem Prev Alt Men, 2006))

1. CVD (since 1984)	483,842
2. Cancer	267,902
3. Respiratory Diseases*	65,672
4. Alzheimer's Disease	45,058
5. Diabetes*	35,748

## **predictor CVD/all-cause mortality!!**

- 3-largest prospective investigations
- Follow-up 16-34 years

(Stamler J, et al. JAMA 2000;284:311-318)



## **3. CVD is #1 cause of death in largest U.S./world Rx prev. trials!!!**

- P-1 tamoxifen trial
- PCPT (10 deaths vs. \_\_\_\_\_)

(Fisher B, et al. J Natl Cancer Inst 1998;90:1371-1388. & Thompson IM, et al. N Engl J Med 2003;349:215-224)



## **4. CVD= #1 cause of death in largest diet/supplement prev. trials!**

- ATBC
- Selenium supplement trial
- SELECT (1 death vs. \_\_\_\_\_)

(The ATBC Study Group. JAMA 2003;290:476-485. & Clark LC, et al. JAMA 1996;276:1957-1963.)



## **5. CVD= #1 cause of death in largest PSA screening trials!**

- PLCO????????????????????
- 1700 CHD vs. 174 Pca.
- 472 from "accidents"
- ERSPC? Where are they??? (appendix 8?)

(Andriole GL, Crawford D, et al. for PLCO Project team. N Engl J Med 2009;360:1310-1319.)



## (Eidelman RS, et al. Arch Intern Med 2004;164:1552-1556)

China (1993)	ATBC (1994)	CHAO (1996)	GISSI (1999)	HOPE (2000)	PPP (2001)	HPS (2002)
5 yrs -29500	6.1 yrs -29133	1.5 yrs -2002	3.5 yrs -11324	4.5 yrs -9541	3.6 yrs -4495	5 yrs -20536
30 mg	50 mg	800 to 400 mg (n)	300 mg	400 mg (n)	300 mg	600 mg



Bottom Line=Why?

Leitzmann MF, et al. JNCI 95:1004-1007, 2003.



- N=160, 3-yr randomized trial
- 800 IU vitamin E +
- 100 mcg selenium +
- 1000 mg vitamin C +
- 25 mg beta-carotene

Brown BG et al: N Engl J Med 345:1583-1592, 2001.



- Over 1000 men= 3 cities
- 8% abnormal PSA/DRE...
- 52% w/dyslipidemia!

Moyad MA, et al. ASCO 2005.



## 9. Majority of diet/lifestyle changes for prostate cancer=heart healthy?

- Exercise
- Fat in the diet
- Flaxseed, Fruits & veggies
- Lycopene-diet & CVD
- Soy
- Weight Control...

(Moyad MA. Urol Oncol 2004;22:466-471)



## 10. CVD=#1 cause of death in men post-dx & treatment!

- 14,000 men (307,931 records)
- 66% die from non-prostate causes!

Bottom Line=Heart healthy=Prostate Healthy!

Sun L, et al. AACR 43:page 932, abstract 4616, 2002



## Klotz-Canada WW

- “Most men with favorable risk prostate cancer will die of unrelated causes.”
- PSA<10, Gleason=6 or less, T2a or less
- N=299, mean age >70 yrs
- 8 yrs=overall survival=85%,
- Disease Specific Survival=99%...

Klotz L. J Urol 2004;172(5,pt 2 of 2):S48-S51.



## 11. Mechanisms increase risk of CVD=increase p.ca risk-MSR-1...

- Prospective study (Austria)=862 patients
- Group 1=P.cancer (n=291)
- Group 2=2 biopsies (no cancer) (n=340)
- Group 3=no prostate cancer (n=231)

Bottom Line=Signif. elevated cholesterol/HDL


Sonnleithner M, et al. AUA Annual Meeting J Urol 169: page 76-abstract #294, 2003.



### 12. Statins & laboratory data

- Cholesterol increased in solid tumors.
- Prostate synthesizes cholesterol at a rate=liver.
- Inhibits all cell lines=PC-3, LNCaP...
- Add LDL=increase tumor growth...
- SCID mice=increase cholesterol=HRPC


(Moyad MA. Urol Oncol 23:49-55, 2005)



### 13. Pleiotropic effects & secondary benefits?

- Alzheimer’s disease
- Mac. Degen.
- E.D./F.S.D.
- M.S.
- Osteoporosis
- R.A...

Moyad MA. Urol Oncol 2004;22:466-471, 472-477.




### Biologic Properties of Statins-Apart from Cholesterol Reduction?

- Inhibit thrombotic process
- Inhibit tumor cell proliferation
- Inhibit angiogenesis
- Modulate immune responses
- Reduce inflammation

- Improve vascular endothelium function
- Stimulate bone growth/prevent bone loss
- Reduce oxidative stress
- Modulate smooth muscle cell proliferation
- Stabilize plaques
- Enhance fibrinolysis


Stamm JA, Ornstein DL. Oncology 19(6):739-754, May, 2005.



### 14. P Ca. Effects (aka forest over the tree)?

Jacobs (2007)	N=55,454 (317 adv)	Followed=6-years	-40% Adv/Fatal P Ca.
Flick (2007)	69,047 (131)	14 years	-43%
Murtola (2007)	49,446 (3680)	8 years	-25% (CC)
Platz (2006)	34,989 (316)	13 years	-50%
Marcella (2009)	380 cases	10 years	-63% DEATHS!!

Adjusting for PSA testing...=More Robust!!! Murtola TJ, et al. Nat Clin Prac Uro 2008;5(7):376-387.



**15. Cost?**

Atorvastatin=Lipitor®	?
Fluvastatin=Lescol®	?
Lovastatin=Mevacor®	Patent lost
Pravastatin=Pravachol®	Patent lost-06
Rosuvastatin=Crestor®	? (once a week?!)
Simvastatin=Zocor®	Patent lost-June 06

Moyad once a week solution???

**death/clinical endpoints) Evidence Exists?**

<u>LDL</u> <u>"bad cholesterol"</u>	<u>hs-CRP</u>	<u>WHAT</u> <u>HAPPENED?</u>
≥70	≥1 mg/L	-9% Reduction
≥70	≤1 mg/L	-35% Reduction
<70	≥1 mg/L	-50% Reduction
<70	≤1 mg/L	-79% Reduction!!!

Ridker PM, et al. Lancet 373:1175-1182, April 4, 2009. Justification for the Use of Statins in Prevention  
-DVT?

**NUMBER 17=I am tired!  
Other promising agents?**

- COX-II inhibitors
- Finasteride
- Toremifene
- Vitamin E
- Selenium

Moyad MA. Urol Oncol 2004;22:466-471, 472-477.

