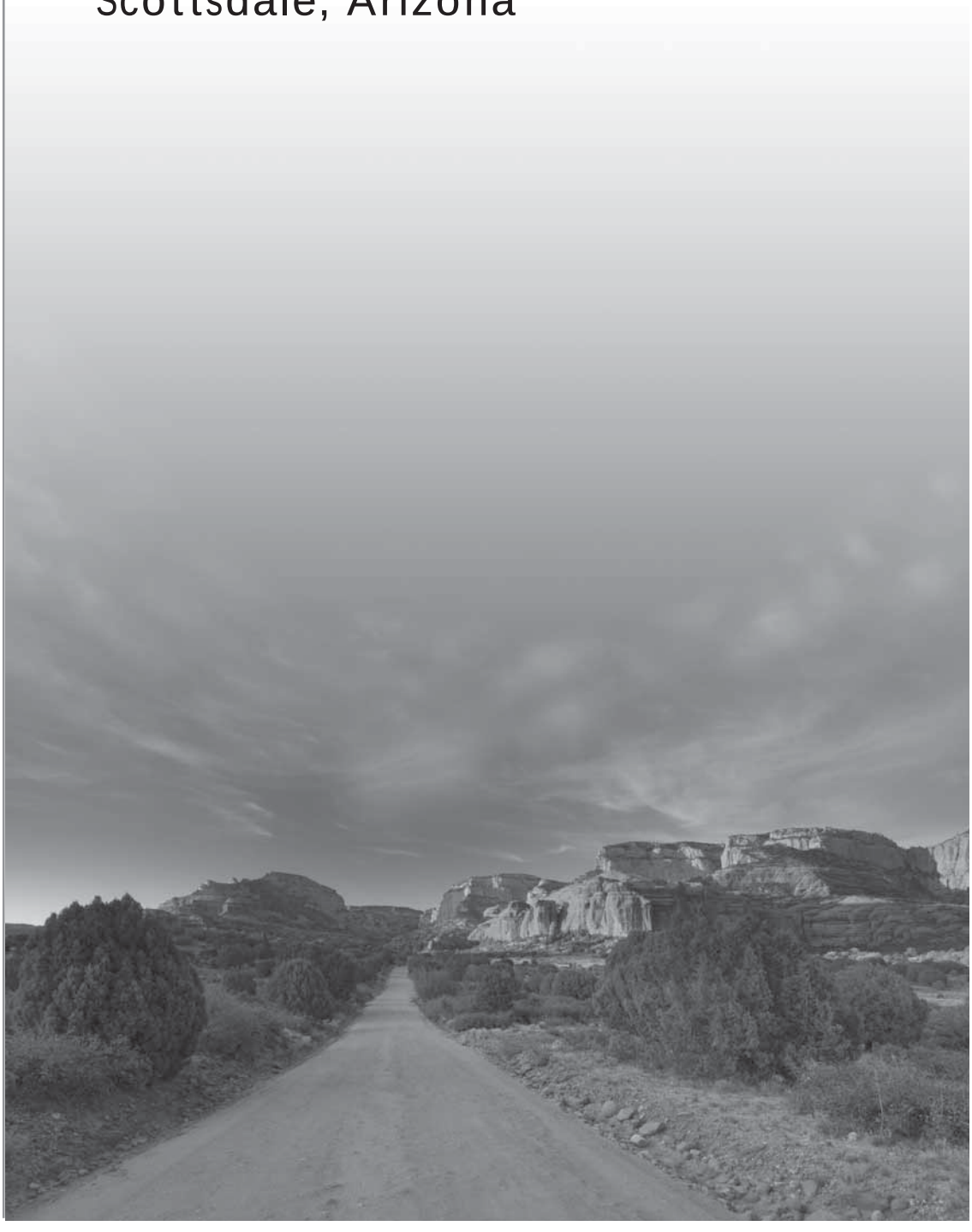
18th Annual

PERSPECTIVES IN UROLOGY

POINT COUNTERPOINT2009

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 *~ 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	
Female Urology, Part II		
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	
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 *~ David C. Beyer, MD*	11.1
1:20 – 1:50 pm	Clinical and Pathologic Characteristics of Prostate Cancer (including new markers such as PCA3) *~ M. Scott Lucia, MD*	12.1
1:50 – 2:10 pm	Chemoprevention Strategies *~ M. Scott Lucia, MD*	13.1
2:10 – 2:40 pm	Point-Counterpoint:	14.1
	Early Detection of Prostate Cancer Is Not Valuable In a Lot of Men *~ E. David Crawford, MD*	*14.1*
	We Can't Go Backwards – Of Course Screening Has Saved Lives *~ Robert E. Donohue, MD*	*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)? *~ Matthew Rettig, MD*	15.1
3:20 – 3:50 pm	An Update on Radiation Therapy for Prostate Cancer *~ David C. Beyer, MD*	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

TCC Cases

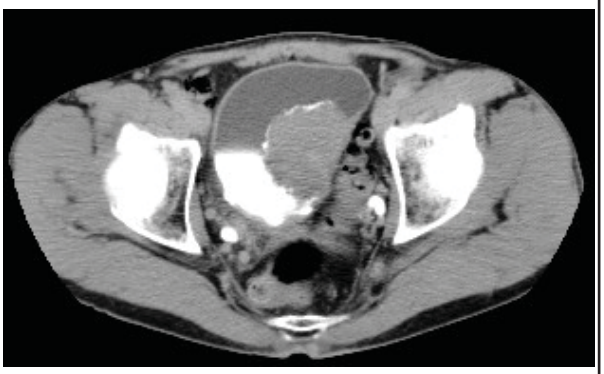
Robert E. Donohue M.D.
Denver VAMC
University of Colorado

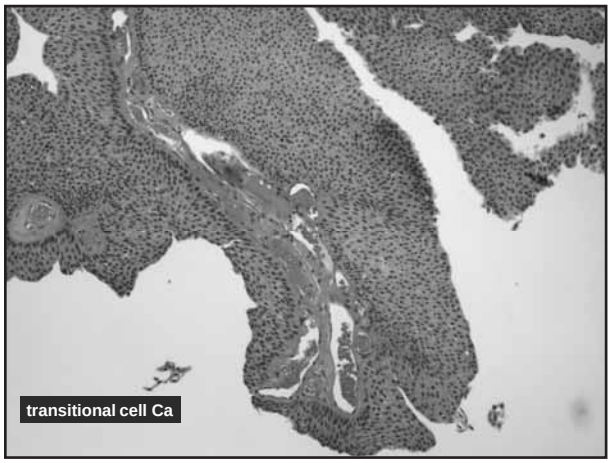
Bladder cases

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-adjivant Ch Rx + cystecytomy

Bladder cases #1

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





Bladder cases #1

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

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

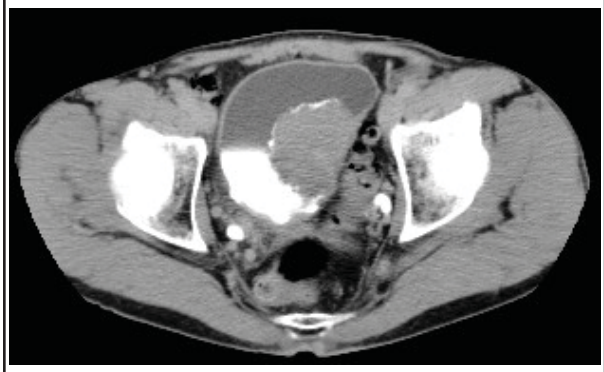
HARRY W. HERR
From the Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York

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)



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

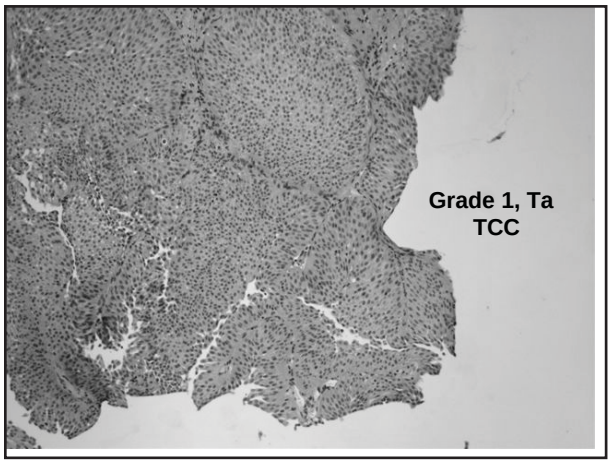
JU 178: 1201, 2007

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

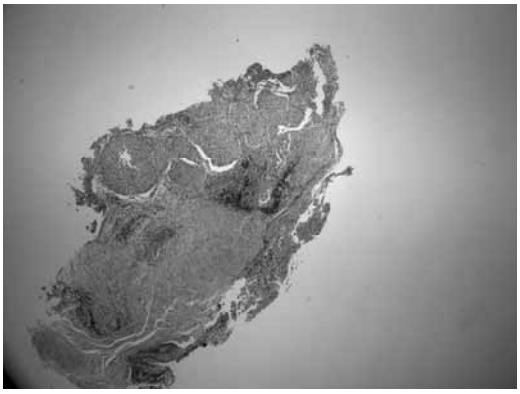
64 – microscopic hematuria
3 or 6 months of anti-tuberculous therapy ?
restart BCG, normal dose ?
1/100 dose ?
switch to alpha-Interferon ?
switch to BCG + alpha-Interferon ?
Mitomycin C ?
Gemcitabine ?

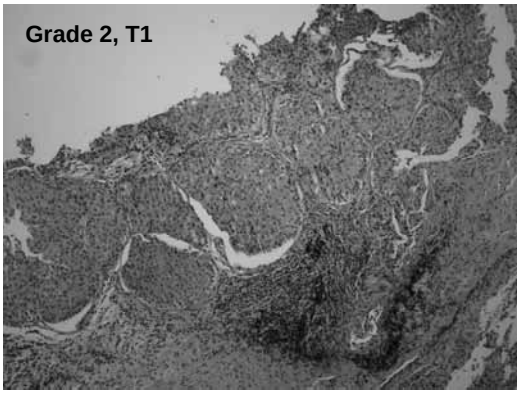
Bladder cases #4

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

Bladder cases #4

75 - 2005
recurrent tumor, 1 / Ta
LFTs are normal, NED surgery
78 - 2008
recurrent tumor, 2 / T1



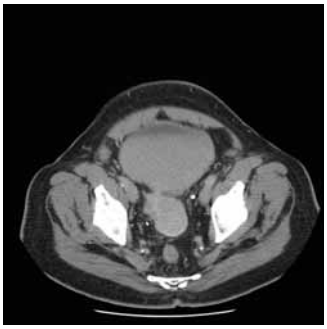


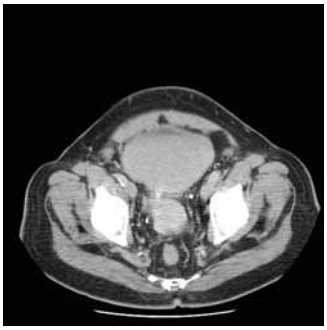
Bladder cases #4

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



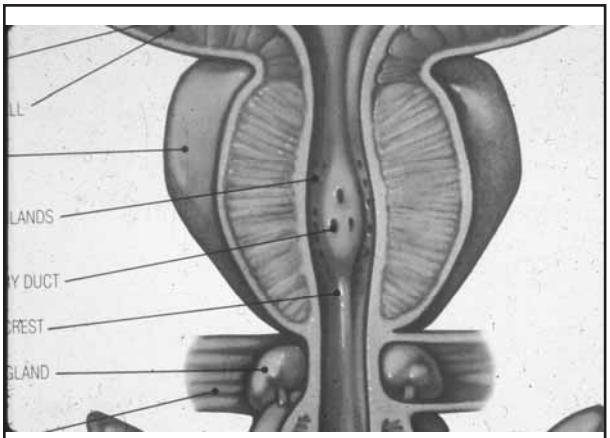


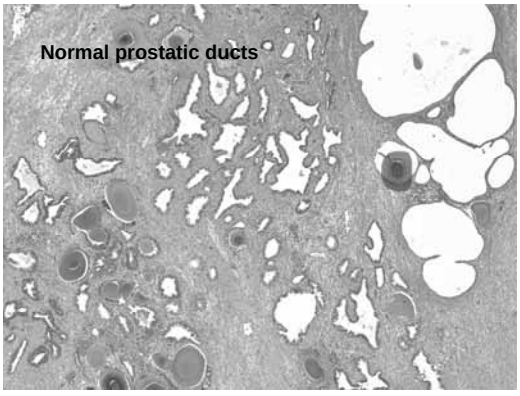
Bladder cases #5

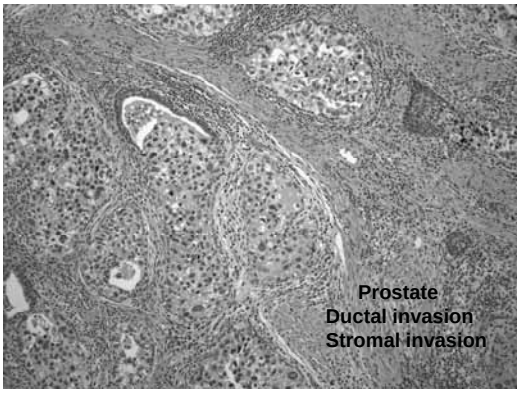
bladder mapping negative
Where do we take biopsies ?
How many ? Technique ?
what about prostatic urethra ?
WHERE ?

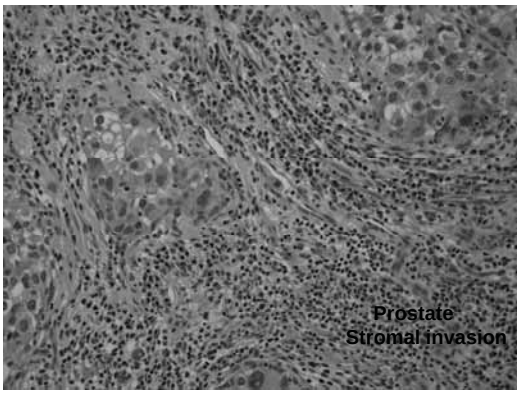
Bladder cases #5

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



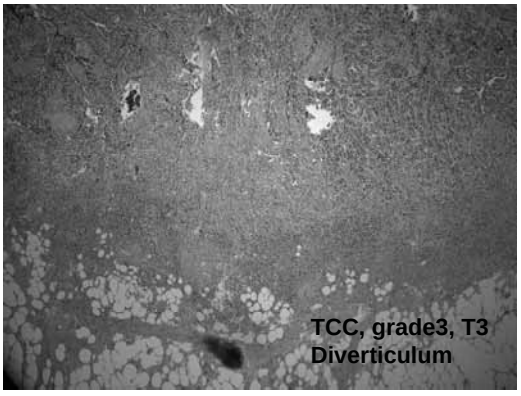






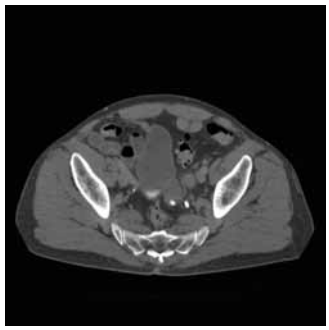
Bladder cases #5

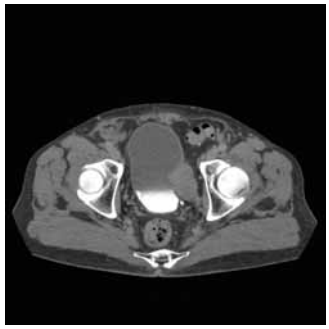
options
- **cystectomy vs partial cystectomy**
  - **nodes to be done,**
  - **tumor is on one side, extent LN**
- **requirements for partial**
  - **first tumor**
  - **cystoscopy, bladder negative**
    - **bladder mapping negative**

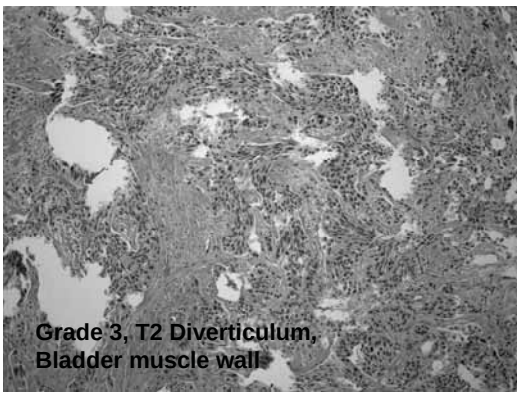


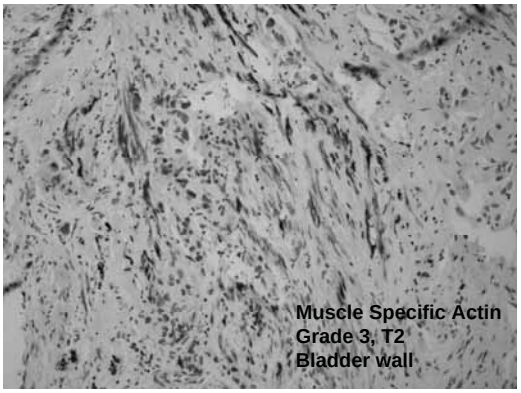
Bladder cases #6

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

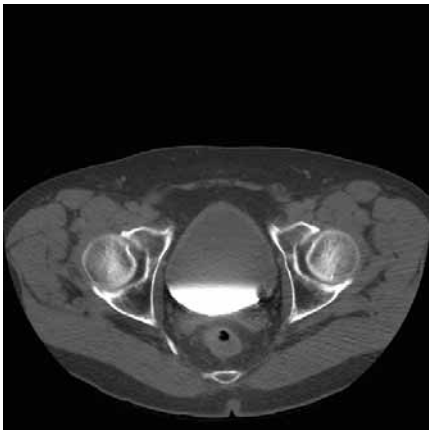
62 gross hematuria for 4 months
2 diverticula
tumor into the bladder; 2 / T2
not a candidate for partial cyst
lymph node dissection extent ?

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



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 ?**

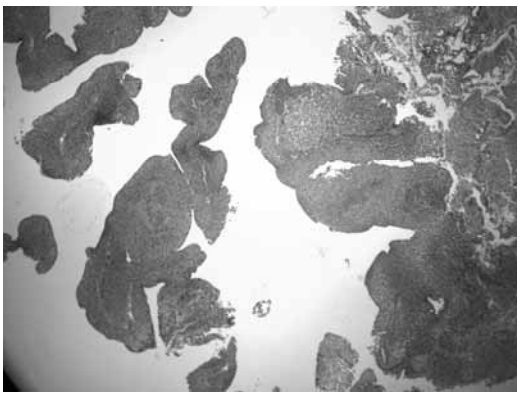
at 1 month, 3 months, 8 months ?

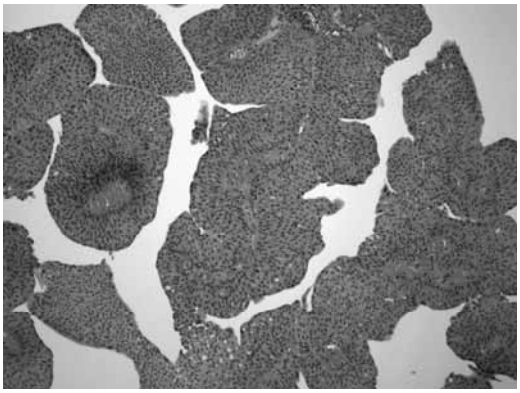
Bladder cases #7

What to do ?
- **waited for year**
- **uneventful TURBT**

vs

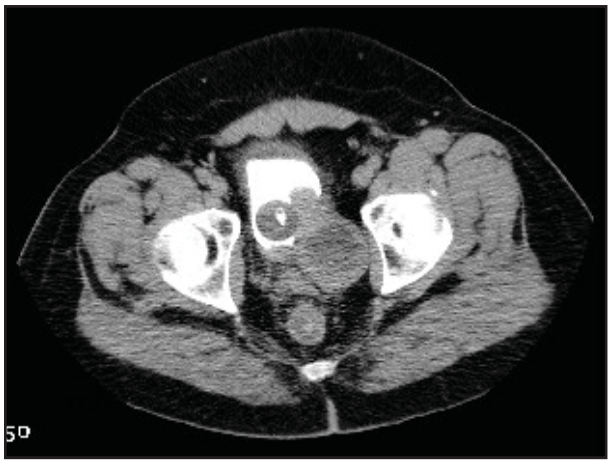
TURBT within year; 40% mortality as months progress from DES placerment, mortality from coronary thrombosis lessens.

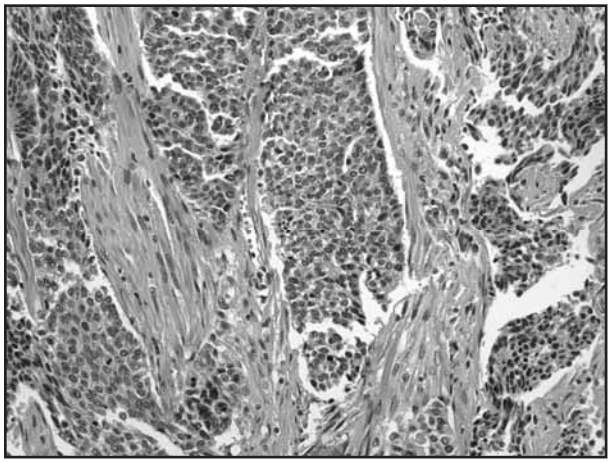




Bladder cases #8

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 ?

Bladder cases #8

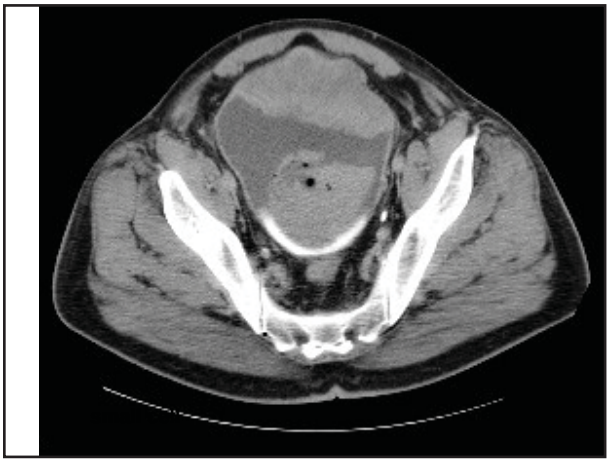
lymph node dissection extent ?
obturator, hypogastric, external iliac and 2 cm common iliac nodes
pre-sacral nodes
inter aortic bifurcation nodes
nodes pre and para aorta and vena cava to level of Inferior Mesenteric Artery
separate node samples Yes, No

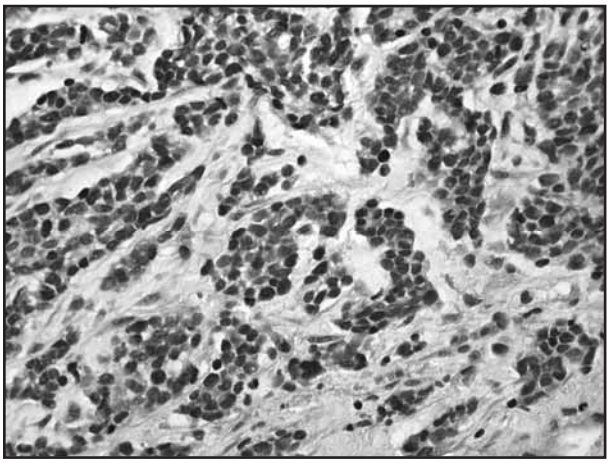
Bladder cases #8

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

Bladder cases #9

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





Bladder cases #9

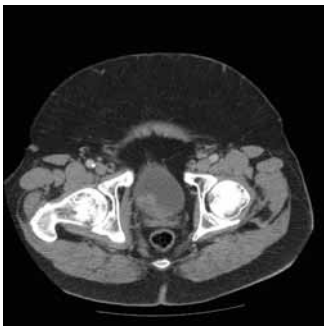
55, bartender
extensive tumor
TURBT
small cell carcinoma
neo-adjuvant ChRx
What therapy ?
transitional cell therapy or
small cell therapy ?

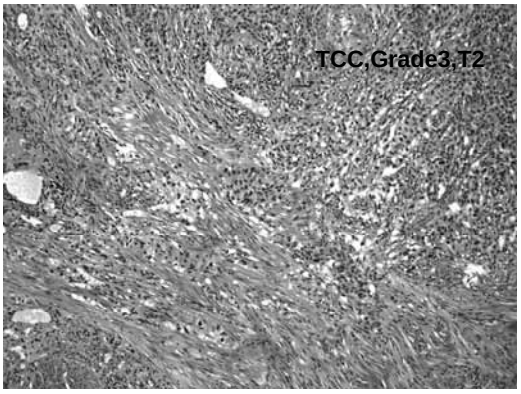
Bladder cases #9

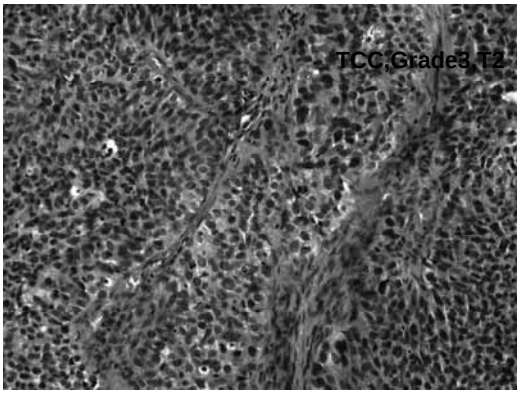
55, bartender
neo-adjuvant small cell ChRx
cis-platinum and VP 16
complete response
radical cystectomy, ileal conduit
pathology pTo ;
follow-up ?

Bladder cases #10

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

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

Definitions

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

Treatment by Risk Category

- 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

Diet and Lifestyle BT Prevention

- 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 insectacides.
- 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 signficantly 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.

Oral Allium sativum (AS) or BCG in Murine TCC: Incidence, Growth & Survival

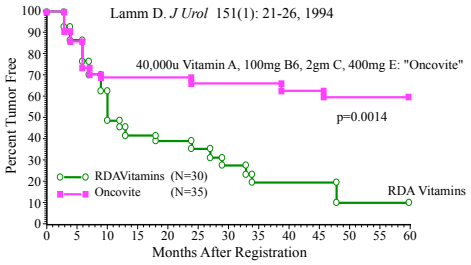
Group	Inc d2	Vol d35	Survival d50
Saline:	18 (90%)	4047	4 (20%)
BCG:	3 (15%)***	390***	15 (75%)***
AS5mg:	17 (85%)	4670	3 (15%)
AS50mg:	14 (70%)	2563**	8 (40%)
AS 500mg: *	12 (60%)	1644***	10 (50%)*

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

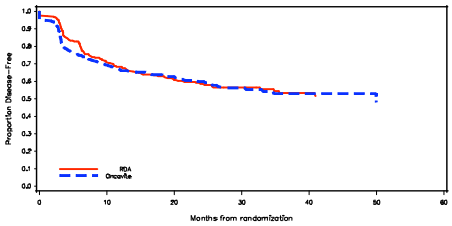
Lamm DL: J Nutr. 2001,131:1067S

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



9

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)

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)

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

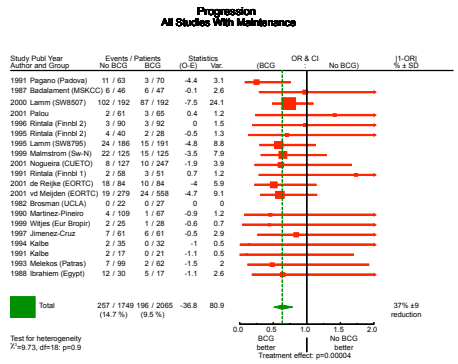
Treatment		Progression
• No BCG		304/2205 (13.8%)
• BCG		260/2658 (9.8%)
Difference		4.0%
Odds ratio (OR)	0.73	
Odds reduction		27% (95% CI: 11%–40%)
P Value		0.001

Progression: Maintenance BCG

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

Test for heterogeneity: P = 0.008

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



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

[a]Department of Urology/Surgery, Bristol Royal Infirmary & Bristol Urological Institute, Bristol, United Kingdom
[b]Department of Surgery, University of Arizona; BCG Oncology, Phoenix, Arizona, USA
[c]Department of Urology, AUSL Modena Estense and B Ramazzini Hospitals, Modena, Italy
[d]Department of Urology, University of Miami School of Medicine, Miami, Florida, USA
[e]Department of Urology, Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain
[f]Department of Urology, HELIOS Agnes Karll Hospital, Bad Schwartau, Germany
[g]Department of Urology, Claude Bernard University, Hôpital Edouard Herriot, Lyon, France
[h]Department of Urology, University of Tsukuba, Tsukuba, Japan
[i]Department of Urology, North York General Hospital, Toronto, Ontario, Canada
[j]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**
EAU	G1-2Ta Low risk of tumour recurrence and progression (EORTC recurrence score = 0; progression score = 0)	Multifocal G2Ta, G1T1, solitary G2T1 Intermediate- or high-risk of recurrence and intermediate risk of progression (EORTC recurrence scores ranging from 1–9; progression scores ranging from 1–6)	Multifocal G2T1, G3Ta-T1, CIS High-risk of progression (EORTC progression scores ranging from 7–23)
FICBT	Low-grade Ta	Low-grade Ta with high-risk factors for recurrence or recurrent low-grade Ta tumors	High-grade Ta, all T1, CIS
NCCN	G1-2Ta	G3Ta, solitary G1-2T1	Multifocal T1, G3T1 (CIS listed separately)
AUA	Small volume, low-grade Ta	Multifocal and/or large volume low -grade Ta High risk of recurrence, low risk of progression	High-grade Ta, all T1, CIS

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

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

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

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

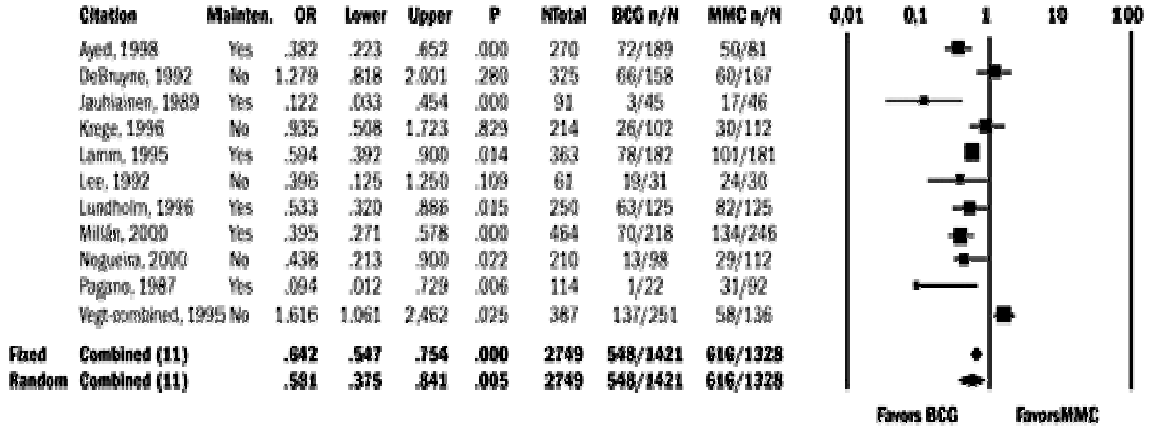
maintenance schedule versus induction Epirubicin. In that study of 957 intermediate risk patients followed for 9.2 years time to first recurrence ($p<0.0001$), time to distant metastases ($p=0.03$), and overall ($p=0.02$) and disease-specific survival ($p=0.03$) were all significantly prolonged with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

Guideline	Definition of Intermediate Risk	Recommendations
EAU	Multifocal G2Ta, G1T1, solitary G2T1 Intermediate- or high-risk of recurrence and intermediate risk of progression (EORTC recurrence scores ranging from 1–9; progression scores ranging from 2–6)	• 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 • Further adjuvant intravesical therapy: – First-line: intravesical chemotherapy < 6 months (grade B) – Second-line: BCG (grade A)
	Recurrent low-grade Ta	• Office fulguration only in select patients with < 5 small (< 0.5 cm) low-grade recurrent tumours and negative cytology (grade C) • Formal TURBT if clinical doubt that tumour is low-grade, cytology positive, or change in tumour appearance has occurred (grade C) • Adjuvant intravesical therapy (see above)
NCCN	G3Ta, solitary G1-2T1	• 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 High risk of recurrence, low risk of progression	• TURBT • Intravesical BCG or mitomycin C (recommendation) • Maintenance BCG or mitomycin (option)

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

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

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



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

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

Guidelines	Definition	Recommendations
EAU	Multiple G2T1, G3Ta-T1 High-risk of progression (EORTC progression scores ranging from 7–23)	• 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)
FICBT	High-grade Ta	• Second-look TURBT and bladder mapping biopsies 2-4 weeks after initial resection (grade B) • If residual tumour is found: – Re-resection and one immediate instillation of chemotherapy – Followed 2-3 weeks later by 6-week BCG induction and 1-3 years of BCG maintenance (grade A)
	T1	• Repeat TURBT (grade B) • Initial intravesical BCG for patients with completely resected primary and recurrent T1 tumours (based on a negative repeat resection) (grade C)
	CIS	• Intravesical BCG for 6 weeks (grade A) • Maintenance BCG for ≥ 1 year (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	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)

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

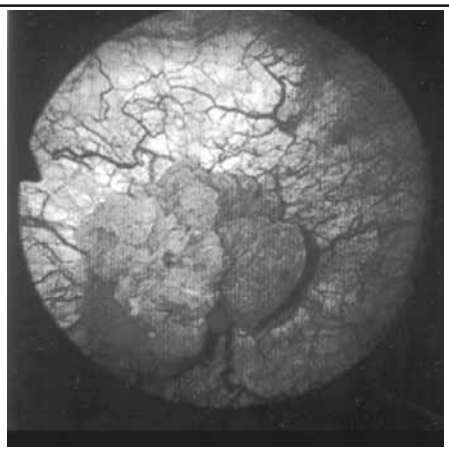
Radiation Plays a Major Role in Certain Stages of Bladder Cancer
~ David C. Beyer, MD

Radiation Therapy; no role in management of bladder cancer

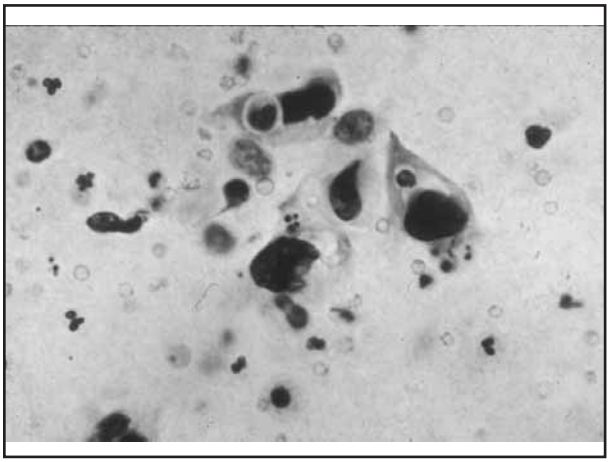
Robert E. Donohue M.D.
Denver VAMC
University of Colorado

TURBT classic

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



~ *Robert E. Donohue, MD*



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. prorpria
resection of deeper tissue [muscle?]
bladder mapping, carcinoma-in-situ

~ *Robert E. Donohue, MD*

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

~ *Robert E. Donohue, MD*

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%]

~ *Robert E. Donohue, MD*

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

~ *Robert E. Donohue, MD*

Maintenance BCG

maintenance BCG

weekly for 3 weeks, every 6 months for 3 years

weekly for 3 weeks, every 12 months for 2 years

weekly for 3 weeks, every 24 months for 2 years

Maintenance BCG

induction and maintenance therapy, if initially successful

7 year plan

cytology q 3 months

cystoscopy q 3 months

tumor marker[s] q 3 months

Maintenance BCG

induction and maintenance therapy,

c-i-s	**84% CR**	**68%**
papillary	**87% 2y**	**57%**
c-i-s +		
papillary	**77 mth**	**36 mth**
		Lamm JU

16% all courses; 25% toxicity

TURBT

induction and maintenance

urgency / frequency

Pyridium

Ditropan

other anti-cholinergics

Librium / Valium

Quinolone

~ *Robert E. Donohue, MD*

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. boivs, 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

~ *Robert E. Donohue, MD*

Muscle Invasive TCC

historically
neo-adjuvant radiation
Whitmore 4,000 r – 4 weeks
2,000 r – 1 week
6,000 r – 6 weeks
Skinner 1,500 r – 3 days
Wallace 4,000 r –
cystoscopy – no Tumor, 6,000 r
tumor - cystectomy

Muscle Invasive TCC

historically
pelvic node dissection,
radical cystectomy,
ileal conduit diversion,
mortality 5- 12%
morbidity 50%
survival – roughly 50%

Muscle Invasive TCC

historically
pelvic node dissection,
standard – obturator, hypogastric,
external and common iliac nodes
extensive – Inferior Mesenteric A
radical cystectomy,
ileal condiut,
ileo-cecal pouch
ileal, colonic neo-bladder

Muscle Invasive TCC

currently
pelvic node dissection,
standard – common iliac
extensive – IM artery
radical cystectomy,
ileal condiut,
ileo-cecal pouch
ileal, colonic neo-bladder

~ *Robert E. Donohue, MD*

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 presservation
  - 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

~ *Robert E. Donohue, MD*

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

~ *Robert E. Donohue, MD*

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

~ *Robert E. Donohue, MD*

Bladder Preservation

190 patients, T2,T3,T4
TURBT
CMV – 2 courses
external beam 40Gy + CDDP

	DSS	DSS [b]
41 cystectomy	63%	59%
149 study	46%	45%

Shipley 2002

Bladder Preservation

3 single institution
2 RTOG pilot studies

pTo preservation 49% 5 years
38 – 43% intact bladder

pT+ cystectomy 63% 5 years

Shipley 1999

Bladder Preservation

complete response
3 single institutions
2 RTOG pilot studies

TURBT, ChRx and CRT 65 --70%
survival 50 – 60%
intact bladder survival 35 – 40%

Shipley 1999

Bladder Preservation

CRT without Ch Rx
RTOG 89-03
2 cycles of cis-platinum
T2,T3,T4

	survival	bladder
CMV + ChXRT	49%	36%
ChXRT	49%	40%

now, 100 mg/M2 q 3 weeks

~ *Robert E. Donohue, MD*

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

~ *Robert E. Donohue, MD*

Bladder Preservation

RTOG 99-06
greater GI 3-4 toxicity from 15%
70% Rx completion [RTOG 90%]
RTOG 97-06
no Paclitaxel 4% Zeitman 2003
RTOG 02-33
5 FU in place of Paclitaxel Rodel

Radiation Therapy

conclusions
no large role in bladder cancer
single therapy, No
neo-adjuvant, No
bladder preservation studies
response to neo-adjuvant ChRT
decides +/- XRT
If no tumor, Why give the XRT ?
If tumor present, cystectomy !

Radiation Therapy

conclusions
occasional studies show an early benefit ; multi-institutional, bladder functional reports, Uro-dynamics, careful toxicity studies, Grades 3, 4 and 5 and quality of life issues must be described in detail and considered by the M.D. and patient.

Bladder Cancer
Role of Radiation in Bladder Sparing

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

Primary Radiation for Bladder Cancer

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

Some Seminal Studies

- 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

Chemotherapy Alone is Inadequate

- 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

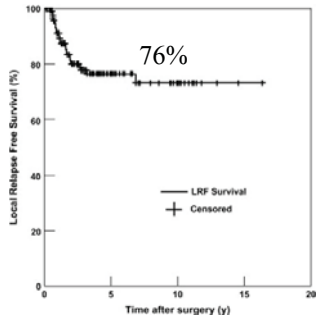
XRT + Brachytherapy for Bladder Cancer <5cm

- 122 patients
  - 94 men
  - 81 pT2
  - 103 Grade 3

  - 10.5-40 Gy XRT with Cystotomy 10 days later
  - 20-70 Gy Brachytherapy

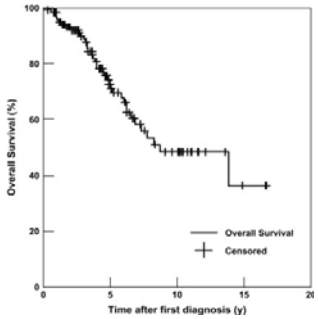
Blank et al; IJROBP 2007, 69(2):454-458

Local Relapse Free Survival



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

Overall Survival



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

Principles for RT

- XRT rarely for superficial tumors or diffuse CIS
- Precede XRT by maximal TUR of tumor
- Concurrent chemotherapy with XRT
- Simulate and treat with empty bladder
- Multiple fields
- High energy
- 40-55Gy Bladder; boost 64-66Gy total

Montie et al, JNCCN 3(1):4-34, Jan 2005

T1 Bladder Cancer

- Treated with TURBT + BCG
- Decrease recurrence by 30%
  - Still face 20-40% recurrence
- Pilot study XRT for high risk T1 bladder cancer
  - Progression 15-20%
  - Bladder preservation >80%

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

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

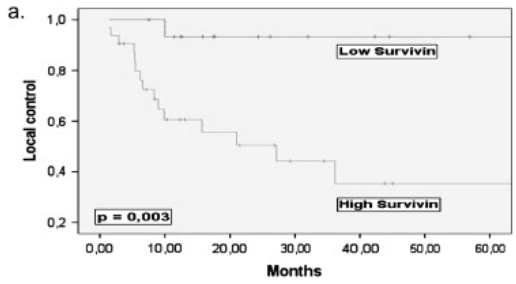
Weiss, C. et al. J Clin Oncol 24:2318-2324, 2009

Survivin in Bladder Cancer

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

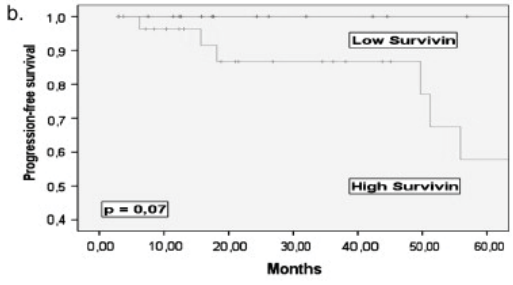
Weiss, C. et al. IJROBP V74(5): 1455-1460, 2009

Survivin Over-Expression Predicts XRT Bladder Tumor Control



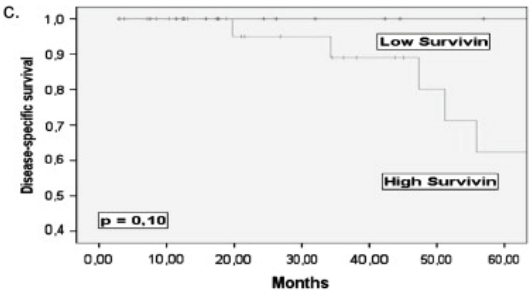
Weiss, C. et al. IJROBP V74(5): 1455-1460, 2009

Progression-free Survival



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

Disease-Specific Survival Rates



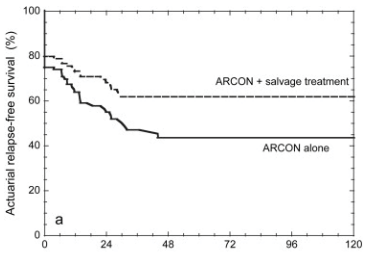
Weiss, C. et al. IJROBP V74(5): 1455-1460, 2009

"Although radical cystectomy is still considered by many to be the gold standard treatment, there is strong evidence to support the use of radical radiotherapy as an alternative."

- Accelerated Radiotherapy, Carbogen and Nicotinamide
  - (ARCON)
- 105 patients T1G3 or ≥T2
- 55 Gy / 20 Fx's / 4 weeks

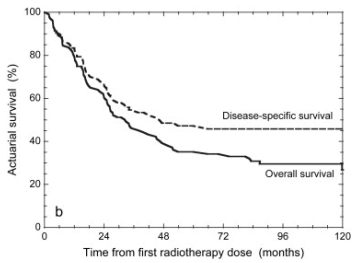
Hoskin, P. et al. IJROBP. V73(5): 1425-1431, 2009.

Bladder Cancer Relapse-free Survival after ARCON or ARCON + Salvage



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

Bladder Cancer Overall Survival & Disease-specific Survival



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% ≥ cT3
- Median survival 13.3 mos.
- Acute toxicity
  - GI 52%
  - GU 36%
  - Hematologic 36%

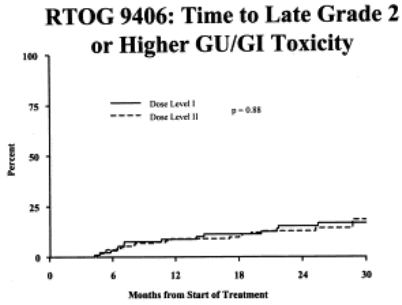
Ash, Welch, Winquist, Bauman; IJROBP 2007 69(3):S340

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)



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

Ongoing Studies
RTOG 0233

- Candidates for surgery
- Phase II
- TURBT
- XRT 64.3Gy
  - 44.8Gy to nodes
  - 1.6Gy bid
- + Cisplatinum
  - 5FU or paclitaxel
- + Adjuvant emcitabine/paclitaxel/cisplatinum

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

Ongoing Studies
RTOG 0524

- Phase I/II
- Non cystectomy candidates with muscle invasive disease
- XRT 64.8Gy
  - 1.8Gy/day
  - Reduction at 39.6Gy
  - Weekly Paclitaxel
- +/- Trastuxumab
  - Statified by her2/neu overexpression
  - Evaluate role of EGFR

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

Bladder Cancer
Role of Radiation in Bladder Sparing

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

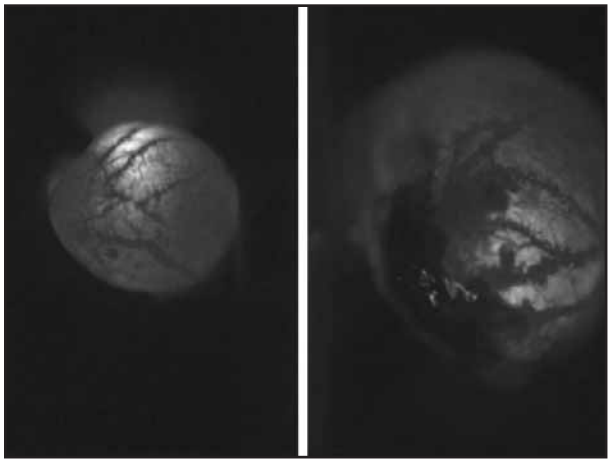
What the Community Urologist Needs to Know About BCG

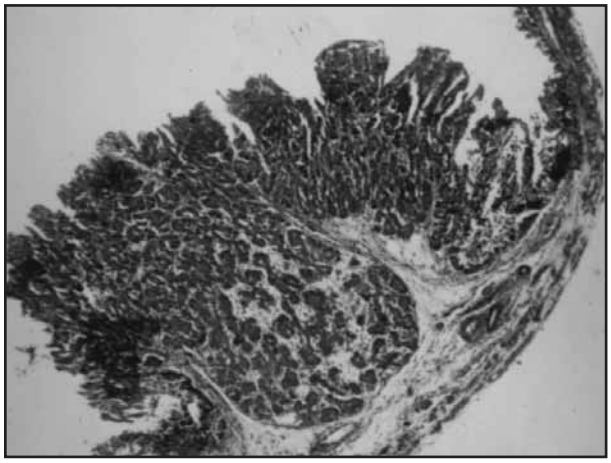
~ Donald L. Lamm, MD

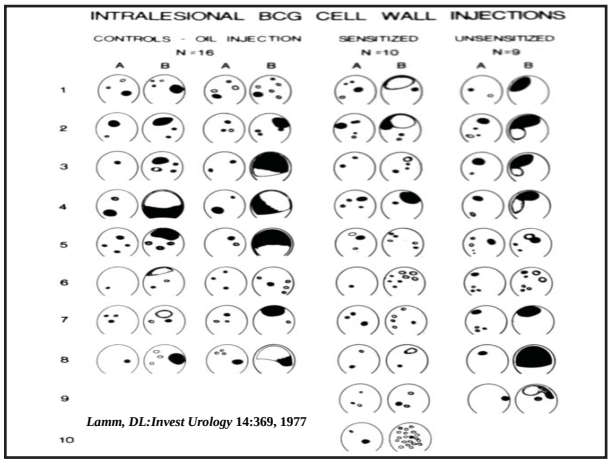
Optimal Bladder Cancer Management:
What Private Urologists Need to Know About BCG

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

BCGOncology.com

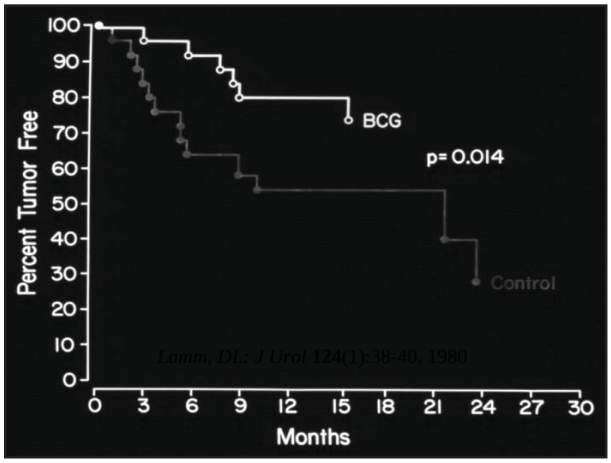


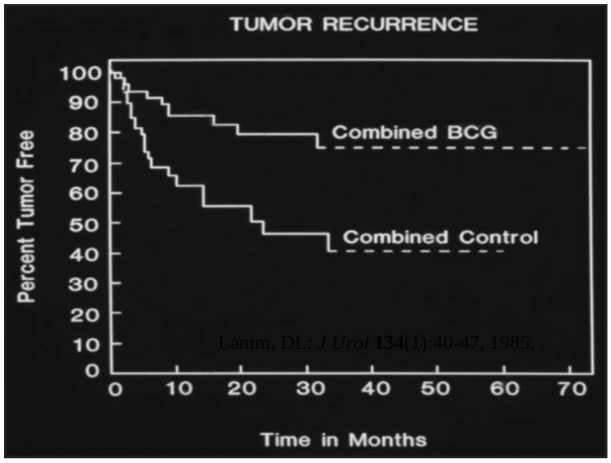




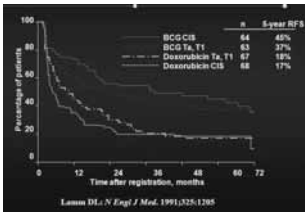
BCG in Bladder Cancer

- 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

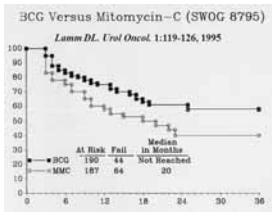




BCG vs Chemotherapy



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



BCG reduces recurrence by 11% vs Mitomycin C

BCG Present

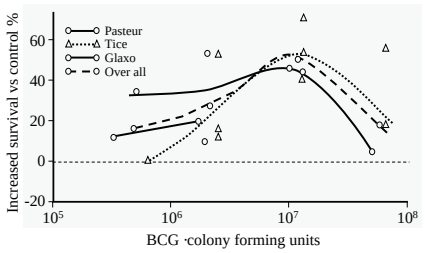
- BCG efficacy established as superior to chemotherapy
- Risk versus benefit and optimal schedule- questions remain
- Benefit in reducing progression and mortality questioned

What is the best BCG regimen?

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

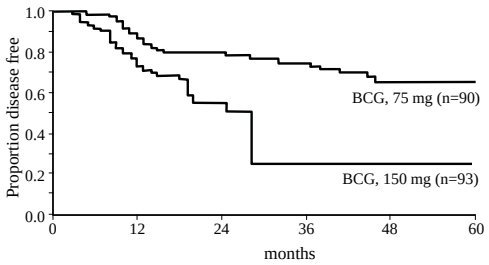
BCG Dose-Response in Murine TCC

Too little or too much BCG reduces effect



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

Low-Dose Versus High-Dose BCG



40% reduction in recurrence with 50% Pasteur BCG

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

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

6+6 versus other schedules

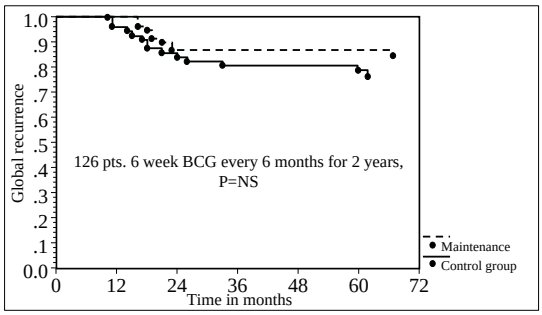
- 64% NED 2 years, no better than 6 week induction or monthly maintenance.
- Immune stimulation peaks at 6 weeks during the initial course and at 3 weeks with subsequent courses.
- The 4th, 5th and 6th instillation of a second course can suppress the immune response.

DeBoer EC, 1994

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

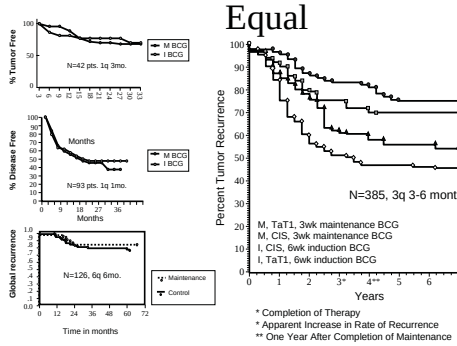


Second Induction Course of BCG

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

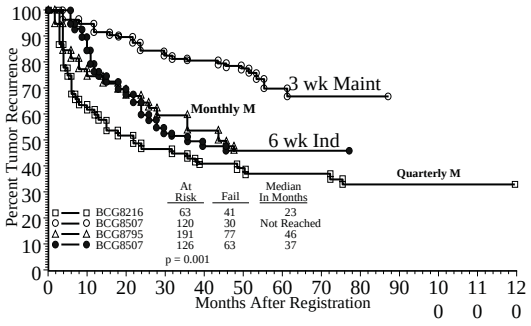
*BCG plus interferon: 53% recurrence free 26 m.

BCG Maintenance: Not Created Equal



SWOG BCG Arms

Papillary Patients Only



3 Week Maintenance BCG

p < 0.0001 **p = 0.04** **p = 0.08**

Lamm DL et al, J Urol 163, 1124, 2000

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

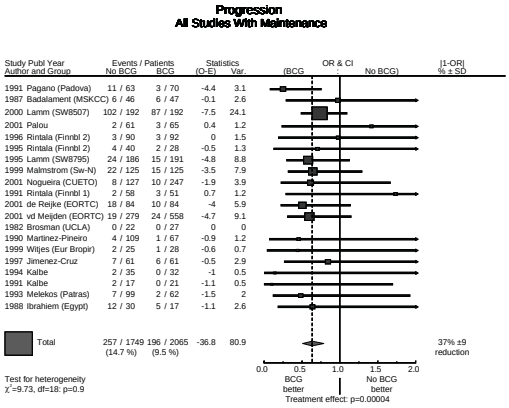
Although their prognosis is different, the size of the treatment effect was similar in papillary tumors and CIS

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

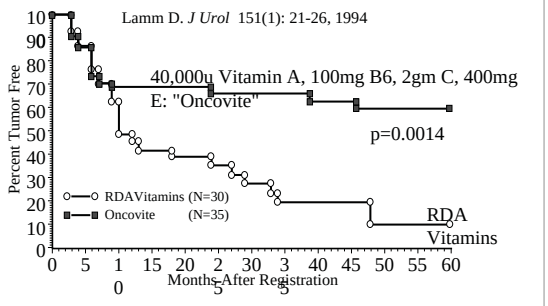
BCG Future

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

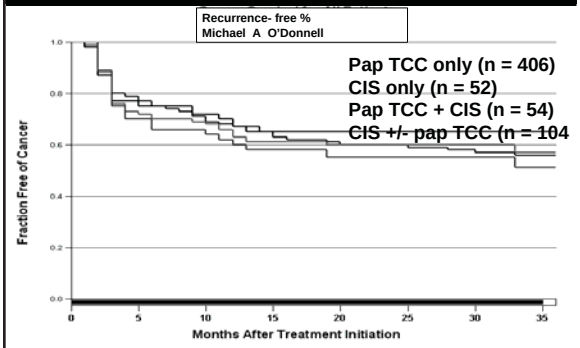
Kaplan Meier Estimate of 5 Year Tumor Free Rate

In Patients Receiving Vitamin Supplement and BCG Therapy For Bladder Carcinoma

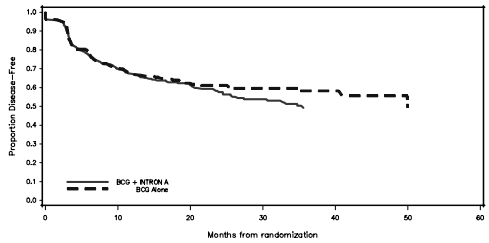
Lamm D. *J Urol* 151(1): 21-26, 1994



BCG Intron A in BCG Naive

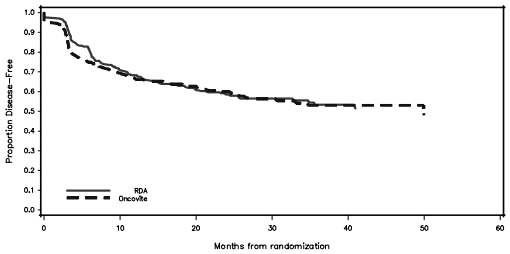


Efficacy Results – Disease Free Interval BCG + Intron A vs BCG alone



31

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



32

What about **percutaneous** BCG?

BCG, Scar Formation and Mortality

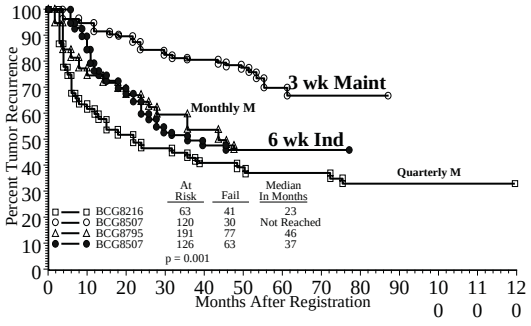
- Several studies show a positive correlation between BCG vaccination in childhood and a reduction in mortality.
- Hazard ratio for death in those with a BCG scar is 0.55(0.32-0.96), and is lowest in girls: 0.31 (0.11-0.88)

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

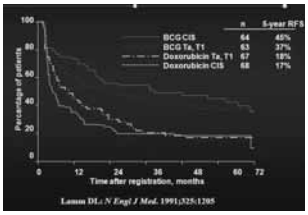
How long should 3 week maintenance BCG be continued?

SWOG BCG Arms

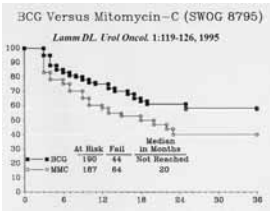
Papillary Patients Only



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
BCG X6																			
BCG x3	x	x	x		x		x		x		x	x	x	x	x		x		x

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
- Niether 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
- Niether 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

Conclusions

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

Conclusions

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

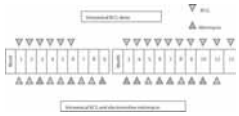
Conclusions

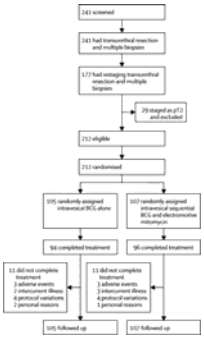
- High dose vitamins A, B6, C and E appear to further reduce recurrence in BCG treated patients
- Combination BCG plus interferon alfa may be superior to BCG alone, and rescues 60% of BCG failures
- Recombinant BCG may be superior
- BCG should be evaluated in other malignancies

What's New?

What's Needed?

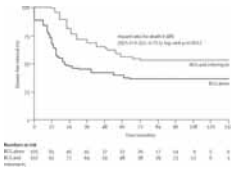
BCG & Electromotive Mitomycin



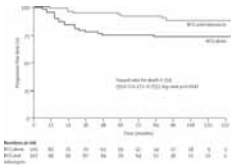


Di Stasi SM, et al. *Lancet Oncol.* 2006;7:43-51.

BCG & Electromotive Mitomycin



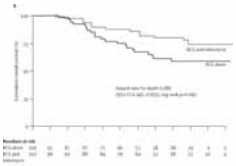
Disease-free Survival



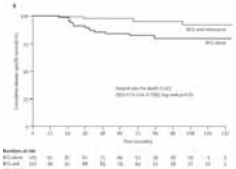
Progression-free Survival

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

BCG & Electromotive Mitomycin



Overall Survival

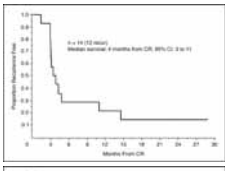


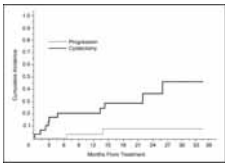
Disease-specific Survival

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

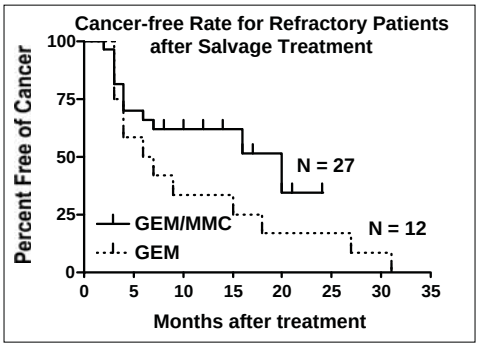
Vesicant Profile of Chemotherapeutic Agents

Vesicants
Platinums✓
Alkylating agents
Mitomycin ✓
Anthracyclines
Adriamycin ✓
Epirubicin ✓
Valrubicin ✓
Vinca Alkaloids
Taxanes
Paclitaxel (vesicant)
Docetaxel (irritant) *→

Non-Vesicants
Gemcitabine*
5-FU*
Cytarabine *
Methotrexate*
Pemetrexed (Alimta)
Bleomycin*
Thiotepa * ✓

✓ 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

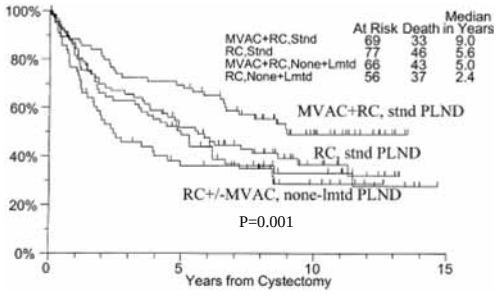
Mike O'Donnell, 2006, MD Anderson Bladder Cancer Meeting

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

Grossman HB:MVAC Neoadjuvant Chemotherapy
NEJM. 2003;349:859

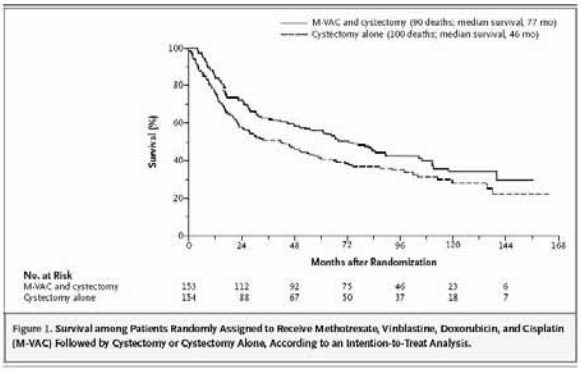
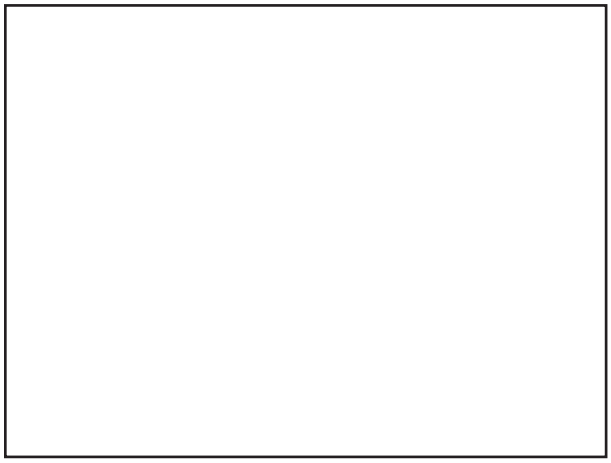
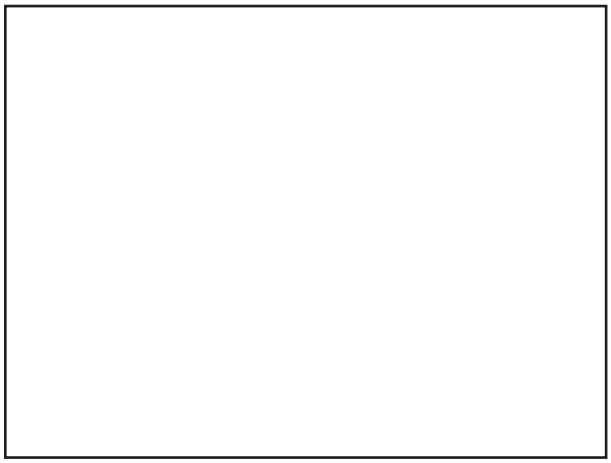
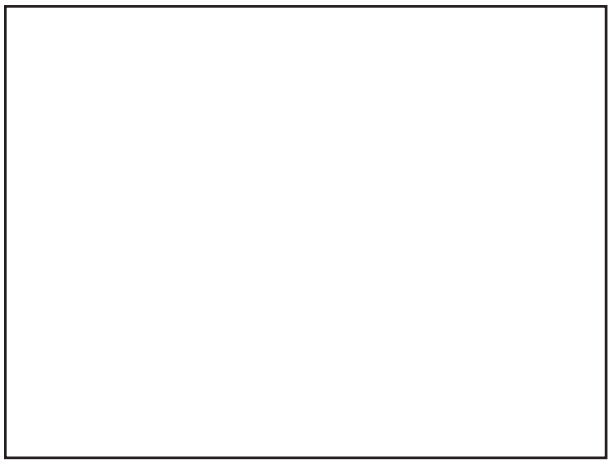
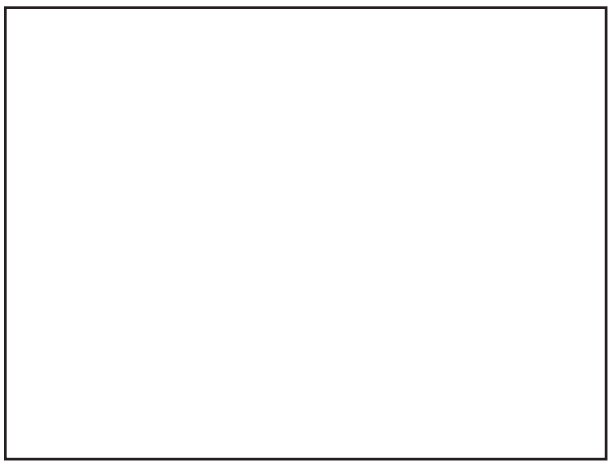


Figure 1. **Survival among Patients Randomly Assigned to Receive Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (M-VAC) Followed by Cystectomy or Cystectomy Alone, According to an Intention-to-Treat Analysis.**









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 Urogynecolgy, 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

Spectrum of SUI Surgery
Pubovaginal Sling Trends

Out	Trends	In
• Proximal urethra • Tension • Biological materials • Gortex, marlex	⇨	• Mid-urethra • Transobturator • Tension-free systems • Polpropylene 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

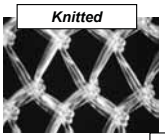
Mid-urethral Tapes ('kits')
Timeline

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'

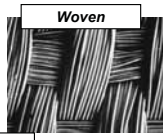
Perspectives in Urology 2009

Midurethral Tapes
Are they all the Same?

Knitted



Woven

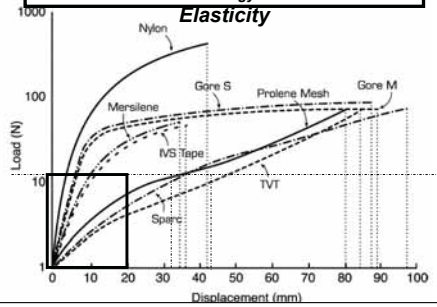


Non Knitted, Non Woven

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

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

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

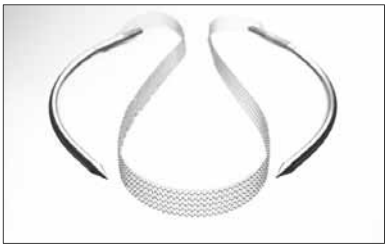
"Serious Complications with Mesh Use in PFR and SUI Repair"[1]

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

Retropubic Tapes
First Generation TVT

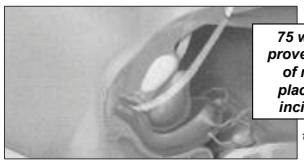
Perspectives in Urology 2009

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



Perspectives in Urology 2009

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



** Gynecare Inc., Summerville, NJ*

75 women with urodynamically proven SUI had a ribbon-like strip of mesh tape (polypropylene) placed through a small vaginal incision under the mid-urethra

† Ulmsten, U, et al: Int Urogynecol 1996

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

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

Tension-Free Vaginal Tape
Multicenter Scandinavian Trial *

"In order to find out how easy, effective and safe the procedure could be in ordinary gynecologic units."

131 patients with GSUI prospectively underwent primary TVT in six Scandinavian community hospitals

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

* *Ulmsten, U, Falconer, C, Johnson, P, et al: Int Urogynecol 1998*

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

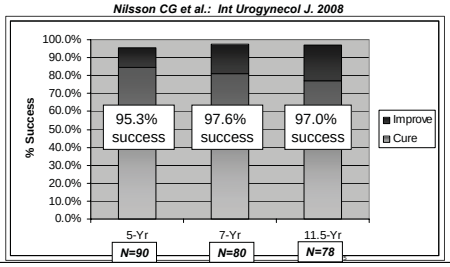
Retropubic Devices	GYNECARE TVT™ Retropubic	SPARC™	Advantage®	Advantage Fit®
Total RCTs	32	7	0	0
Longest Follow-Up in Any Published Study	11.5 years[5]	3 years[9]	N/A	N/A

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

Tension-Free Vaginal Tape
11-year Data

90 patients with GSUI prospectively underwent TVT in three centers

Nilsson CG et al.: Int Urogynecol J. 2008



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

Tension-Free Vaginal Tape
"SUI and ISD"

49 women with SUI and ISD underwent TVT *

161 with SUI underwent TVT †*
- *Recurrent SUI 28%*
- *Mixed UI 37%*
- *ISD 11%*

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*

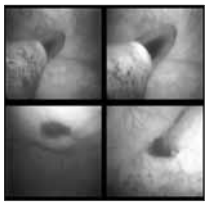
Perspectives in Urology 2009

*Trademark

TVT Complication
Polypropylene Bladder Erosion: Retropubic Approach

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

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

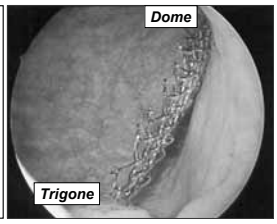


** Minaglia S, Klutke C, Klutke, J: Urol 2004*
† Azam J, et al: J Urol 2001

Perspectives in Urology 2009

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

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



McLennan and Melick Obstet Gynecol 2005

Perspectives in Urology 2009

Question

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

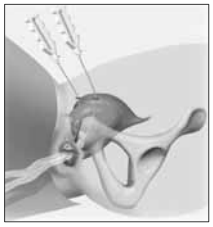
A. *Yes, I have had one personally*
B. *Yes, one of my partners*
C. *Yes, the other group*
D. *Yes, the other specialty*
E. *No*

Perspectives in Urology 2009

Complications
SPARC™ Sling System *

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 retropubic 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 contalateral leg, not straight out
- 70 degree scope mandatory with full bladder

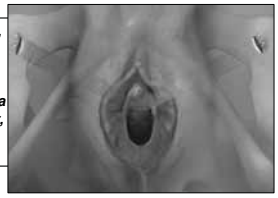
Perspectives in Urology 2009

Transobturator Tapes
Second Generation TVT

Perspectives in Urology 2009

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 42º and postoperative was 32º*
- *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, at al: Urol 2000*

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

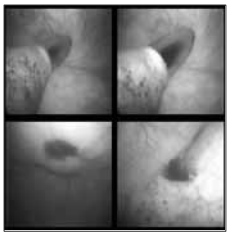
† Atherton, MJ and Stanton, SL: Neurourol Urodyn 1999

Perspectives in Urology 2009

Transobturator Tape
Proposed Advantages

Avoidance of retropubic space

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



Perspectives in Urology 2009

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

Flynn BJ: SC AUA 2008

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

- *64 (53%) patients had prior surgery*
- *Mean follow-up 29.4, 12-46 months*
- *OR time, 26 minutes (range 14-38)*
- *Cured 111 (92%), failed 10 (8%)*

- *Complication (6)*
  - *Bladder perforation (0)*
  - *Mean EBL 33 ml*
  - *De novo urgency (1)*
  - *Urinary retention (3)*
  - *Vaginal erosion (2)*
  - *Urethral injury (1)*

Perspectives in Urology 2009

TVT-Obturator
'Inside-Out'

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

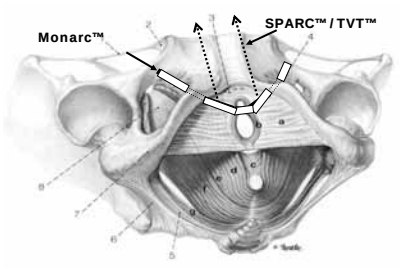
- *17 patients had prior surgery*
- *1-year minimum follow-up*
- *Mean OR time, 14 minutes (range 7-20)*
- *Cured 91%, improved 9%*

- *Complication (6)*
  - *Bladder perforation (0)*
  - *Hematoma (0)*
  - *De novo urgency (2)*
  - *Urinary retention (3)*
  - *Vaginal erosion (1)*
  - *Urethral erosion (0)*

** De Leval, J: Eur Urol 2004*

Perspectives in Urology 2009

Monarc® Mesh Position



Perspectives in Urology 2009

Reiffenstuhl ,Platzer & Knapstein

Transobturator Tape
Overview of "Level I Evidence"

Transobturator Devices	GYNECARE TVT™ Obturator	Monarc™	Obtryx®	Align TO®
Total RCTs	9	4	0	0
Longest Follow-Up in Any Published Study	3 years[18]	2 years[19]	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

*Desarai® 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

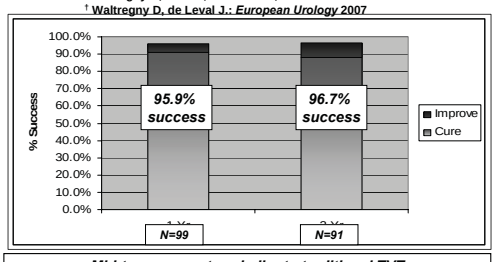
	Liapis (12 mo)[20]		But (4 mos)[21]	
	GYNECARE TVT[a] Obturator System	AMS Monarc[a]	GYNECARE TVT™ Obturator	AMS Monarc™
Obj Cure	**95%***	94%*	**98%**	97%
Sub Cure	**80%**	77%	N/A	N/A
Erosion	N/A	N/A	0%	0%
Bladder Perf	0%	0%	N/A	N/A
Urethral Perf	**0%**	2%	N/A	N/A
Pt Satisf VAS	N/A	N/A	**91%**	89%

Perspectives in Urology 2009

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

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

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

Single-Incision Slings or 'Mini-Sling'

Third Generation TVT

Spectrum of SUI Surgery
What we Need in a 3rd Generation Sling

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*

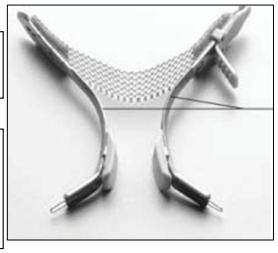
Perspectives in Urology 2009

Tension-Free Vaginal Tape Secur (TVT-S™)
Proposed Advantages

Simple, outpatient procedure done under local anesthesia

Sling Design

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

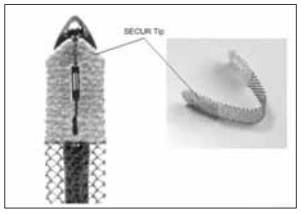


Procedure Advantages

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

Perspectives in Urology 2009

Tension-Free Vaginal Tape Secur (TVT-S™)
Absorbable Fixation Tips



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 (polydioannone)*

Perspectives in Urology 2009

Tension-Free Vaginal Tape Secur (TVT-S™)
Tape Location

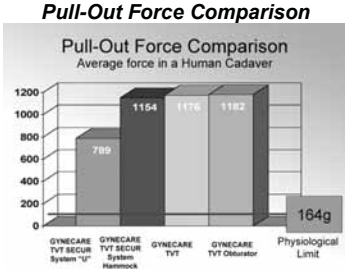

Hammock position


U position

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

Perspectives in Urology 2009

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



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

Perspectives in Urology 2009

AUA 2008 Abstract 1566: UNFAVORABLE IMMEDIATE OUTCOME OF THE TVT SECUR SLING IN TWENTY CONSECUTIVE WOMEN WITH SUI
Fabio Baracat, et al Sao Paulo, Brazil*

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

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

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

Perspectives in Urology 2009

2009 AUGS Abstract: Efficacy and complications of TVT-Secur in the management of stress urinary incontinence
Terlecki RP and Flynn BJ et al, Denver, CO

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

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

Flynn BJ et al: AUGS 2009

Perspectives in Urology 2009

2009 AUGS Abstract: Efficacy and complications of TVT-Secur in the management of stress urinary incontinence
Terlecki RP and Flynn BJ et al, Denver, CO

Anesthesia

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

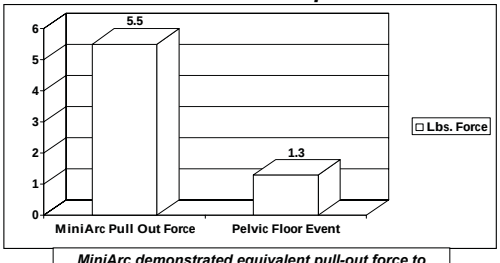
- *dimensions 8.5 cm x 1.1 cm*
- *slim Needle Design*
  - *2.3mm diameter*
- *ergonomic Handle*
- *blunt, bladeless tip*

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/m²***
  - ***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***

Perspectives in Urology 2009

ICS 2009: MiniArc Multicenter Prospective Single-Arm Trial
Michael Kennelly, Dirk DeRidder and Steve Siegel, ICS 2008

6 Week Follow-up Results

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%***

6 month Efficacy

- ***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)***

Perspectives in Urology 2009

Single-Incision (Mini) Sling Tensioning Recommendations

- ***mini-sling tensioning is <u>tighter</u> 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***
- ***<u>MinArc</u>***
  - ***<u>only push forward</u> 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[32]	6 months[33]	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/1 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 (29-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 <u>tighter</u> 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

"…Transobturator 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

- 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

Laurikainen et al; Ob Gyn 2007

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

- 273 women with ISD
  - VLPP < 60 cm H2O or
  - MUCP <20 cm H20
- Follow up at 24 months
- Cure = subjective absence of sx & -CST
  - PVS= 87%
  - TVT=87%
  - TOT= 35%

Jeon et al AJOG 2008

- N=164, 2 hospitals
- Cure = absence of SUI on UDS
- Secondary outcomes
  - Sx stress
  - Surgical complications
  - QOL questionnaires
- Urodynamic testing at 6 months
  - TVT-21% leakage (79% cure)
  - TOT-45% leakage (55% cure)

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)

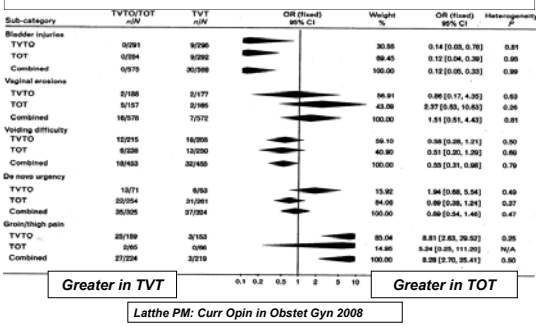
- *Baseline characteristics were similar*
- *Relative risk of postoperative SUI 3 months after surgery was 2.85 in all patients when Monarc was compared to TVT*
- *RR was 0.56 if MUCP > 42 cm H2O*
- *RR was 5.89 if MUCP < 42 Cm H20*

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



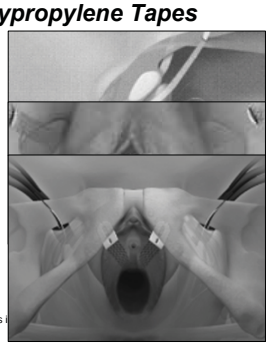
Latthe PM: Curr Opin in Obstet Gyn 2008

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

↓

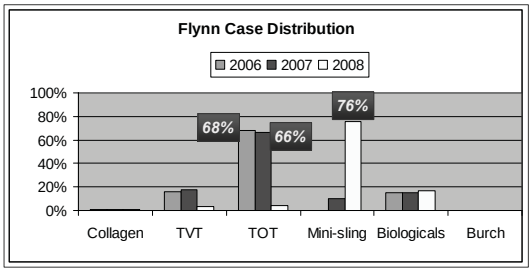
Transobturator Tape 2004

↓

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

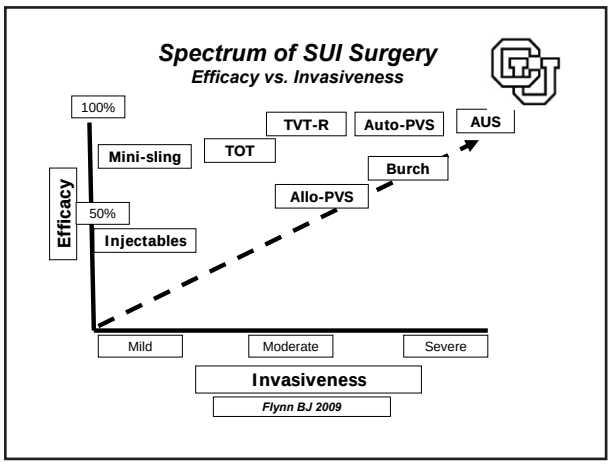
Flynn BJ et al, Denver, CO

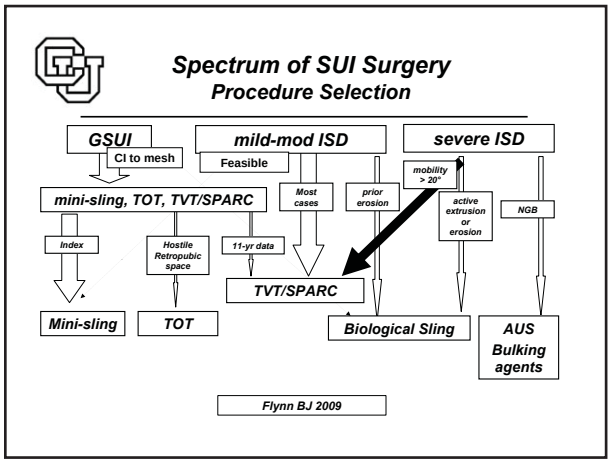
Retrospective review in 82 patients that underwent explantation of an eroded device due to recurrent vaginal wall extrusions and/or urinary tract erosions

- 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

~ Brian J. Flynn, MD





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, FACR, 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

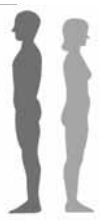
Prostate	234,460	33%
Lung	92,700	13%
Colon & Rectum	72,800	10%
Bladder	44,690	6%
Melanoma	34,260	5%
All Sites	720,280	

Breast	212,920	31%
Lung	81,770	12%
Colon & Rectum	75,810	11%
Uterine	41,200	6%
Non-Hodgkin Lymphoma	28,190	4%
All Sites	679,510	

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

Cancer Deaths

Lung	90,330	31%
Colon & Rectum	27,870	10%
Prostate	27,350	9%
Pancreas	16,090	6%
Leukemia	12,470	4%
All Sites	291,270	



Lung	72,130	26%
Breast	40,970	15%
Colon & Rectum	27,300	10%
Pancreas	16,210	6%
Ovary	15,310	6%
All Sites	273,560	

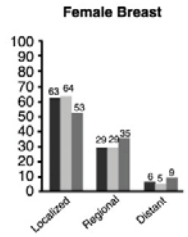
Jemal, A. et al. CA Cancer J Clin 2006;56:106-130

Probability of Developing Invasive Cancers 2000 to 2002

		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

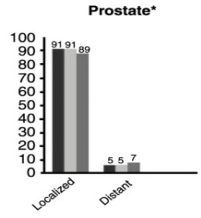
DevCan Software, Probability of Developing or Dying of Cancer Software, Version 6.0. Statistical Research and Applications Branch, National Cancer Institute, 2005. hhtp//srab.cancer.gov/devcan.

Breast Cancer at Diagnosis



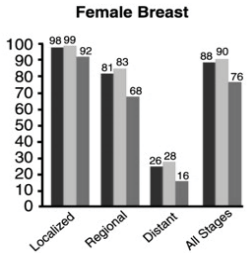
Ries LAG, Eisner MP, Kosary CL. et al. http://seer.cancer.gov/csr/1975_2002/.

Prostate Cancer at Diagnosis



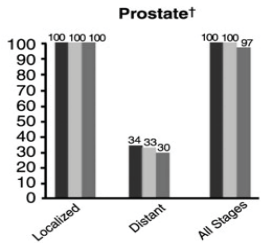
Ries LAG, Eisner MP, Kosary CL. et al. http://seer.cancer.gov/csr/1975_2002/.

Five-year Survival by Stage: Breast



Ries LAG, Eisner MP, Kosary CL. et al.
http://seer.cancer.gov/csr/1975_2002/.

Five-year Survival: Prostate



Ries LAG, Eisner MP, Kosary CL. et al.
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

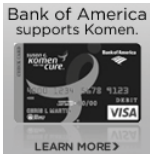
One Day on Google

- **Breast cancer:** **7,700,000 hits**
- **Prostate cancer:** **12,000,000 hits**

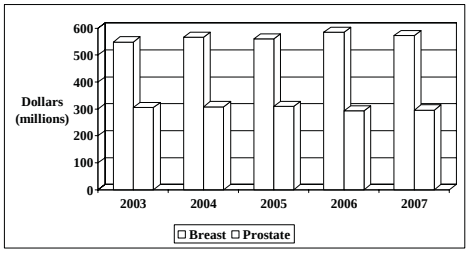
- **Komen:** **42,800,000 hits**
- **Us Too International:** **204,000,000 hits**

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, John's Hopkins Hosp Bull, 1895 4:297
Fisher, Breast Cancer Res Treat 1981; 1:17

Treatment Issues

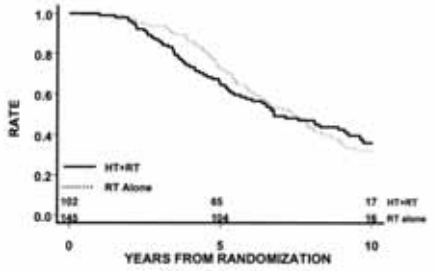
- **Breast**
- **ER/PR receptor assay**
- **Level I evidence**
- **Prostate**
- **Presumed sensitivity**
- **Level I evidence**

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%

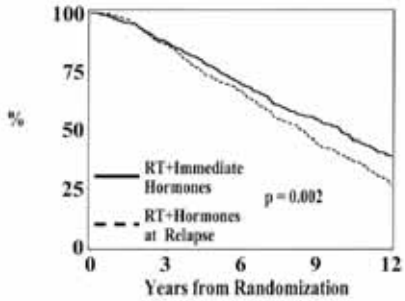
Does Early HT Compromise Late Salvage HT?

Overall Survival RTOG 86-10



Shipley et al, IJROBP, 2002, 54(5):1302-1310

RTOG 85-31
Reduction in Mortality



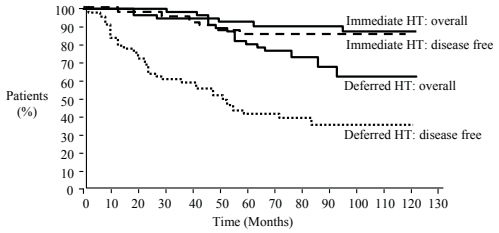
Pilepich et al, IJROBP 61(5) 1285-1290, 2005

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

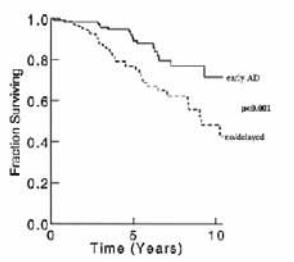
ECOG 7887: Disease-Free and Overall Survival

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



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

CSS from PSA Failure: Benefit to Early Hormone Therapy



313 Patients

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

RTOG 92-02

	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, IJROBP 2000 ASTRO

10 Year Update on RTOG 92-02

	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, IJROBP, 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}I 110 Gy (or ^{103}Pd 100Gy)
- **+/- 6 months TAB**
- **1520 patients**

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

Available Hormone Options

- **Tamoxifen**
- **Fareston**
- **Arimidex**
- **Aromasin**
- **Femara**
- **Megestrol**
- **Halotestin**
- **Bicalutamide**
- **Leuprolide**
- **Surgical castration**
- **DES**
- **Bicalutamide**
- **Flutamide**
- **Nilandrone**
- **Leuprolide**
- **Goserelin**
- **Degarelix**
- **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**
- **ER/PR receptor assay**
- **Level I evidence**
- **Hormones**
- **AI's**
- **Prostate**
- **Presumed sensitivity**
- **Level I evidence**
- **LHRH / Antiandrogen**

~ David C. Beyer, MD

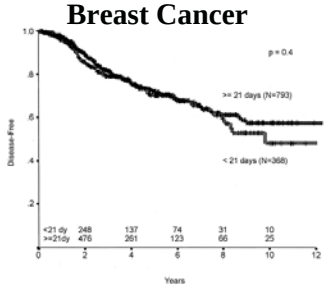
Treatment Issues

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

Adjuvant Chemotherapy: Breast

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

Timing of Chemotherapy: Breast Cancer



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

Sequencing Chemo/Radiation in Breast Conserving Therapy

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

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

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 ≥ 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 ≥ 7 and PSA nadir >0.2 ng/ml
  - Gleason ≥ 8 and Stage ≥ T3a (any PSA nadir)
- **Accrual 76 patients**
- **TAB 6 months**
- **XRT 66.6 Gy (at 8 weeks)**
- **Docetaxel 75mg/m^2 q21days x 6 cycles**

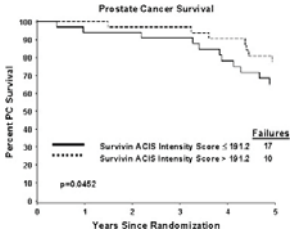
Treatment Issues

- **Breast**
- **ER/PR receptor assay**
- **Level I evidence**
- **Hormones**
- **AI's**
- **Chemotherapy**
- **No blood marker**
- **Genetic markers predict sensitivity**

- **Prostate**
- **Presumed sensitivity**
- **Level I evidence**
- **LHRH / Antiandrogen**
- **Chemotherapy (?)**
- **PSA**
- **Limited markers**

~ David C. Beyer, MD

Advanced Prostate Cancer Survival by Nuclear Survivin Intensity Score RTOG 8610



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

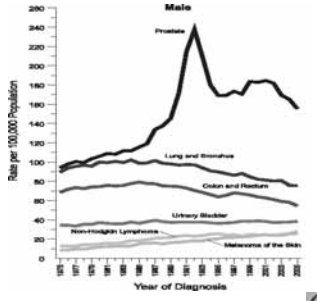
M. Scott Lucia, MD
Associate Professor
Chief of Genitourinary and Renal Pathology
Director, Prostate Diagnostic Laboratory
Dept. of Pathology
University of Colorado Denver SOM

Prostatic Carcinoma - 2009[1]

- >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

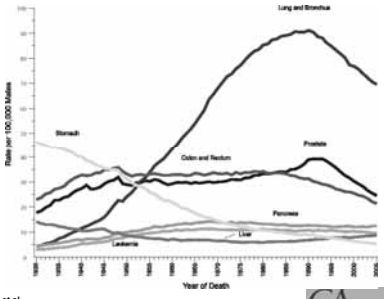
1. Jemal A. et al. Cancer Statistics 2009. *CA Cancer J Clin* 2009;59:225-48.

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.

FIGURE 4 Annual Age-adjusted Cancer Death Rates among Males for Selected Cancers, United States, 1930-2005

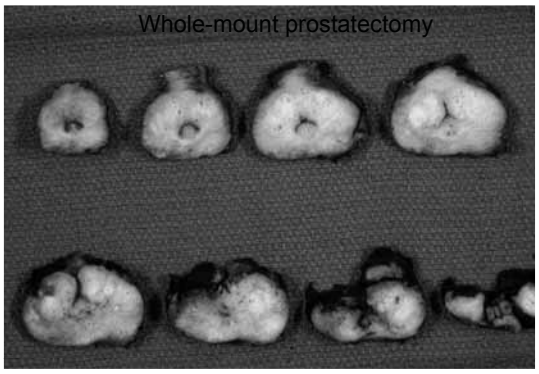


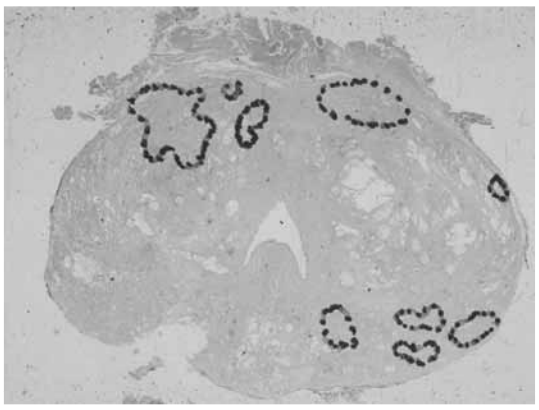
From Jemal, A. et al.
CA Cancer J Clin 2009;59:225-249.

CA
A Cancer Journal for Clinicians

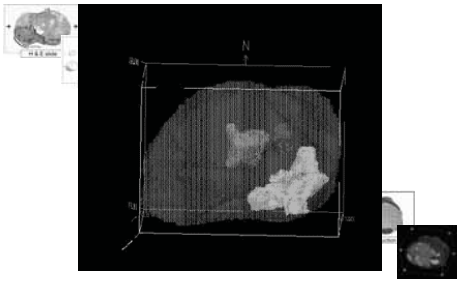
Prostate Cancer: The Landscape has Changed

- 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

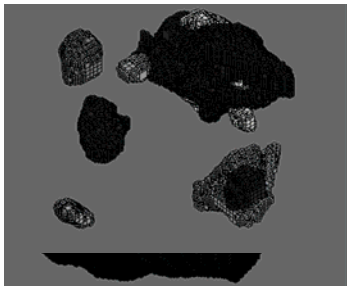




3-Dimensional Reconstruction of Whole-Mounted Prostatectomy Specimens



3-Dimensional Reconstruction of Prostatectomy: Tumor Multifocality and Heterogeneity



Multifocality of 293 carcinomas from 151 prostates (< 1994)

Miller GJ, *J Urol* 152:1709, 1994

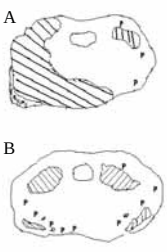
Tumors/Pt.	No. Pts. (%)	No. Tumors	Mean Tumor Vol. (cc)
1	66 (**43.7**)	66	**6.52**
2	47 (31.1)	94	1.48
3	25 (16.6)	75	1.01
4	8 (5.3)	32	0.59
5	4 (2.6)	20	0.40
6	1 (0.7)	6	0.22
Totals	151 (100)	293	

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

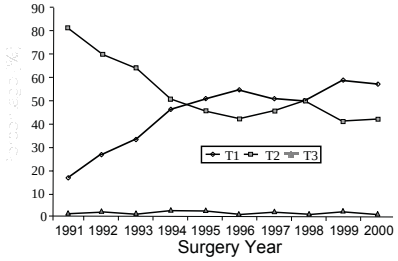
Lucia MS, *Unpub*

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

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



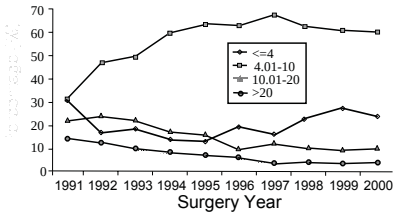
DoD CPDR National Database: Clinical T stage at diagnosis for patients who underwent prostatectomy



DoD = Department of Defense
CPDR = Center for Prostate Disease Research

Moul JW, et al. Surgery 2002;132:213-9

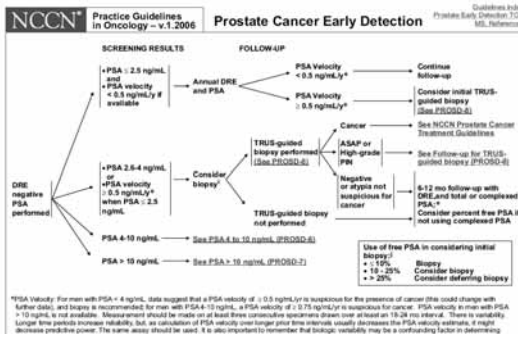
DoD CPDR National Database: PSA level at diagnosis for patients who underwent prostatectomy



DoD = Department of Defense
CPDR = Center for Prostate Disease Research

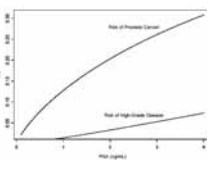
Moul JW, et al. Surgery 2002;132:213-9

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)



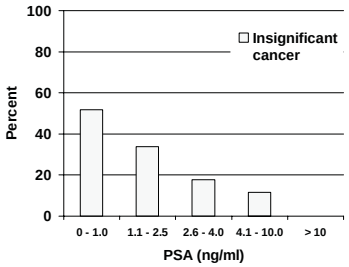
Thompson *et al*. JAMA 2005; 294: 66–70

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

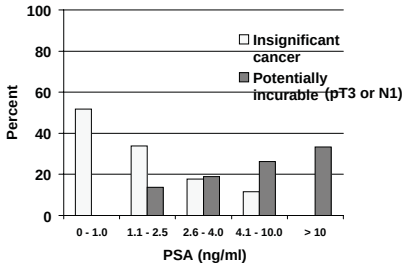
PCPT: PSA and Insignificant Cancer*



* 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

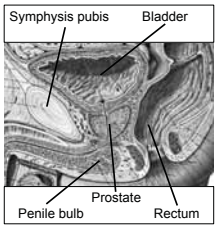
Lucia MS, et al. *Cancer Prev Res* 2008;1:167-73.

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 Cancer: Diagnostic Considerations

- 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, 2nd Ed., Urban & Schwarzenberg, Baltimore, 1981.

Prostate Cancer Detection by Needle Biopsy: Implications

- Cancer sampling is a function of tumor volume: prostate volume
- Negative biopsy ≠ 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

Comparison of needle biopsy with prostatectomy grades in PCPT (placebo group)

Gleason Score on Biopsy	Gleason Score at Radical Prostatectomy (RP) N = 272			
	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

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
- *Need new approaches to assess tumor aggressiveness*

Ideal Biomarker for Prostate Cancer

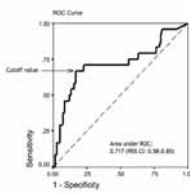
- Sensitive and specific for aggressive cancer
- When modulated, correlates with disease outcome
- Reproducible
- Quick and easy to assay
- Low cost
- Minimal invasiveness

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

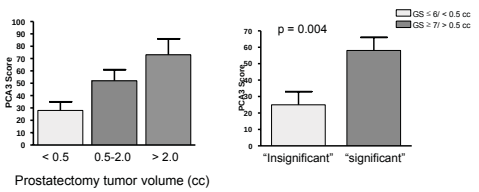
Hessels *et al.*, Eur Urol 2003;44:8-16

Validation Studies - PCA3

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

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

PCA3 score as a function of tumor volume and Gleason score

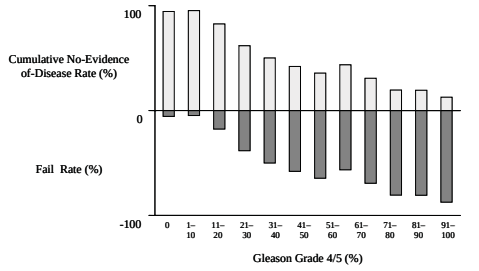


Nakanishi, H et al. J Urol 2008;179:1804-9. Used with permission

Pathology of Prostate Cancer: Assessing Aggressiveness

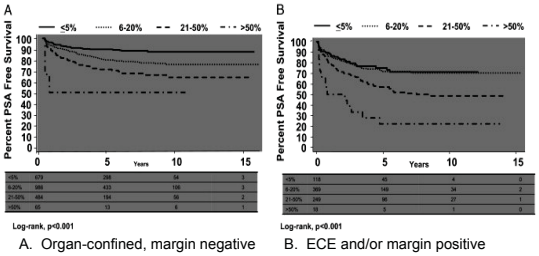
- Histologic type and grade
- Pathologic stage
- Margin status
- Tumor volume
- Biomarkers/molecular determinants?
  - Systems pathology – can we improve on traditional pathology?

Failure Rates as a Function of Percent GS 4/5 Cancer



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

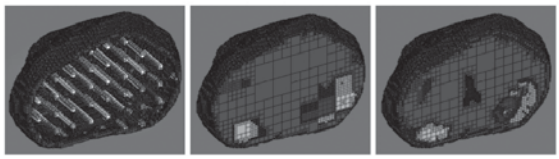
Actuarial 15-year Estimates of Biochemical Progession Rates Segregated by Percent Tumor Involvement



A. Organ-confined, margin negative B. ECE and/or margin positive

Rampersaud EN, et al. J Urol 2008;180:571-76

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

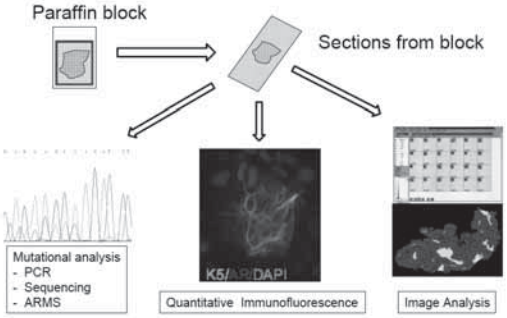


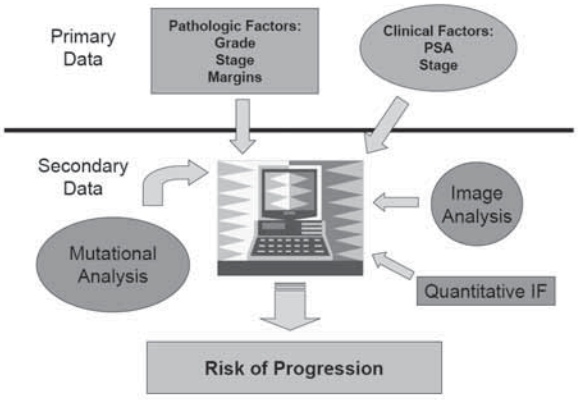
- Saturation grid-biopsy data (left)
- Reverse-reconstruction model (center)
- Actual RRP specimen (right)
- Model error: -15% for Gleason 3+4 tumor (right, 5.1cc)
  +15% for Gleason 3+3 tumor (left, 0.093cc)

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

Systems Pathology

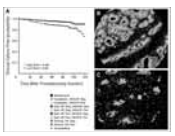
Definition: *Analyzing the interrelationships of multiple elements (molecular and pathological) in a system rather than each one at a time*





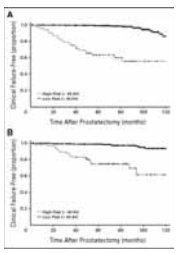
Systems Analysis Approach for the Prediction of Prostate Cancer Progression After Radical Prostatectomy*

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



↑ Analysis of AR and AMACR

CI=0.84



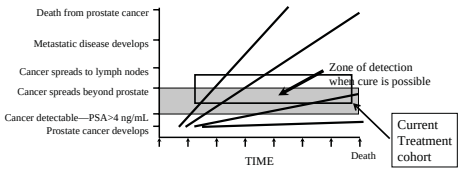
Kaplan-Meier curve demonstrating the classification of patients from the (A) training cohort and (B) validation cohort as being at low risk (blue line) or high risk (yellow line) for experiencing clinical failure (CF)

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

JOURNAL OF CLINICAL ONCOLOGY

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

~ M. Scott Lucia, MD



Metastatic Potential = ***p*** X ***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

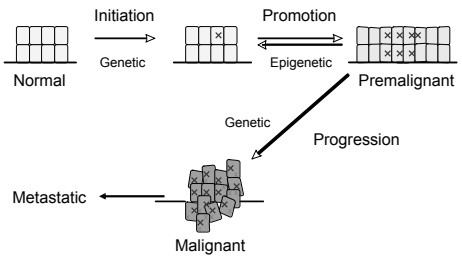
M. Scott Lucia, MD
Associate Professor
Chief of Genitourinary and Renal Pathology
Director, Prostate Diagnostic Laboratory
Dept. of Pathology
University of Colorado Denver SOM

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

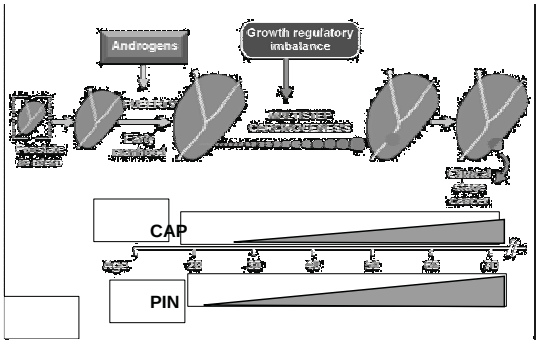


Characteristics of Prostate Cancer that support a role for chemoprevention

- Disease of aging (oxidative stress? Inflammation? epigenetic events)
- Long latency
- Putative precursor lesion
- Early dependence on androgen
- Susceptability to oxidative damage:
  - High prevalence of GSTP1 hypermethylation[1]
  - Overexpression of COX-2[2]
- 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

Early Events in Prostatic Carcinogenesis



Prostate Cancer – Risk Factors

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

Candidate Chemopreventive Agents for PCa

- Hormonal agents
  - 5α-reductase inhibitors (eg. Finasteride, Dutasteride)
  - Antiandrogens/ LHRH antagonists (eg. Flutamide, leuprolide)
  - SERM's (eg. Tamoxifen, raloxifene, toremifene, SERM-3)
- Phytoestrogens and Protein Kinase Inhibitors
  - Isoflavanoids (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)

Candidate Chemopreventive Agents for PCa

- Hormonal agents
  - 5α-reductase inhibitors (eg. Finasteride, Dutasteride)
  - Antiandrogens/ LHRH antagonists (eg. Flutamide, leuprolide)
  - SERM's (eg. Tamoxifen, raloxifene, toremifene, SERM-3)
- Phytoestrogens and Protein Kinase Inhibitors
  - Isoflavanoids (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)

Hormonal Agents
Antiandrogens/ 5α-reductase inhibitors

<u>Rationale</u>

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

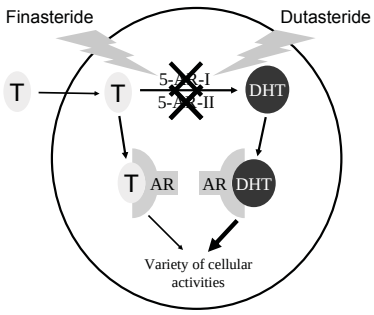
1. Moore RA. Surgery 1944.
2. Imperato-McGinley J et al. Science 1974.
3. Ross RK et al. Cancer Res 1998.

Hormonal Agents for Prostate Cancer Chemoprevention

<u>Limitations</u>

- 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
- 5α-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.

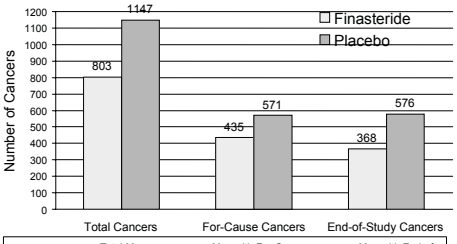
REduction by DUtasteride of prostate Cancer Events (REDUCE)

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

Design comparison between PCPT and REDUCE

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

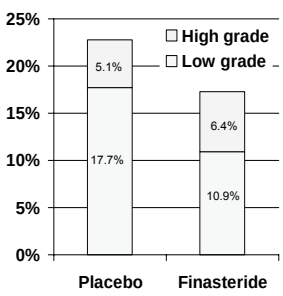
Prostate Cancer Prevention Trial



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

Thompson IM, et al. *NEJM* 2003.

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

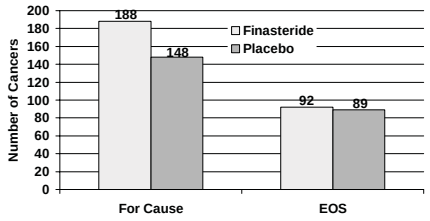


Cancer
RR=0.75 (0.60, 0.99)
p < .001

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

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

Grade 7-10 Cancers diagnosed in PCPT



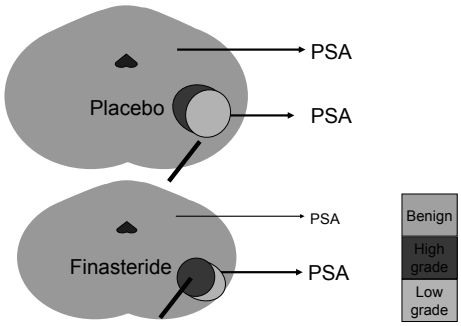
"For cause" = biopsy for ↑PSA and/or abnormal DRE
"EOS" = end-of-study biopsy

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

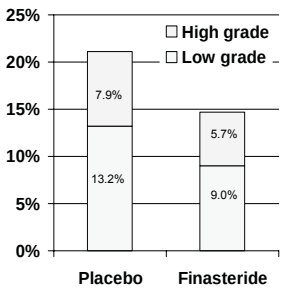
- Finasteride improved performance of PSA for cancer and high-grade cancer[1]
- Finasteride increased sensitivity of DRE[2]
- Finasteride increased sensitivity of prostate biopsy for detection of high grade cancer by reducing prostate volume[3]

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



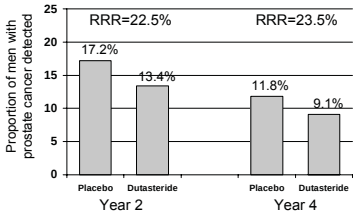
Cancer
RR=0.70 (0.64, 0.76)
p < .0001

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

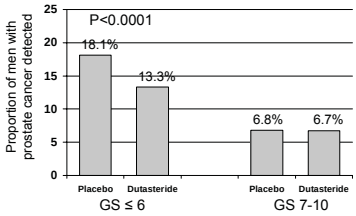
REDUCE Primary Results



Gleason 7-10: Placebo = 6.8%
Dutasteride = 6.7%

Andriole G. AUA 2009
Used with permission

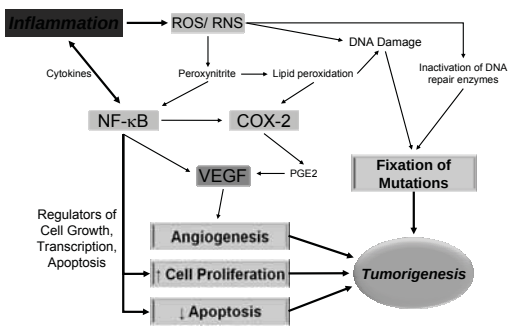
Gleason score (GS) distribution by treatment group in REDUCE



Andriole G. AUA 2009
Used with permission

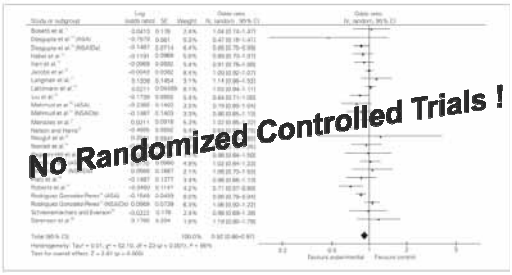
Future Directions for Prostate Cancer Chemoprevention: What next?

- 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



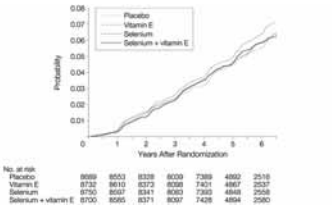
ROS=reactive oxygen species RNS=reactive nitrogen species
COX-2-cyclooxygenase-2 VEGF-vascular endothelial growth factor

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.

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



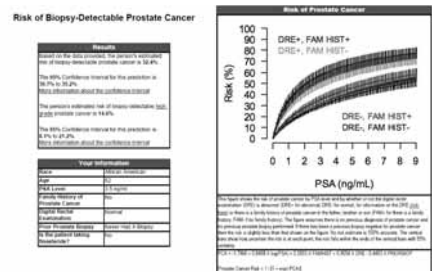
Lippman, S. M. et al. JAMA 2009;301:39-51.

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?

Prostate Cancer Risk Calculator based upon data from the placebo arm of the PCPT



http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp

Chemoprevention of Prostate Cancer
Challenges

- Candidates for chemoprevention
- Optimal dosages/ combinations
- Impact on lifestyle
- Surrogate biomarkers
- Design of trials

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

PLCO

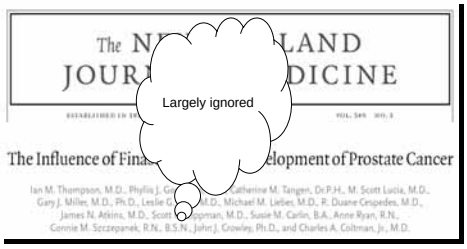
University of Colorado School of Medicine — Far Beyond The Ordinary

1989

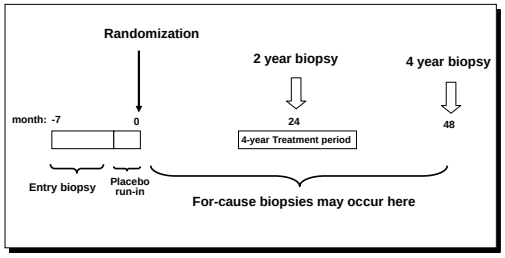
- Prostate cancer became the most common cancer in American Males
- And the second leading cause of death
- Options:
  - Do nothing
  - Prevention
  - Early detection
  - Improve outcome for advanced disease

1989-Fast forward, what happened?

Prevention: PCPT 25% reduction



REDUCE Schema to be presented



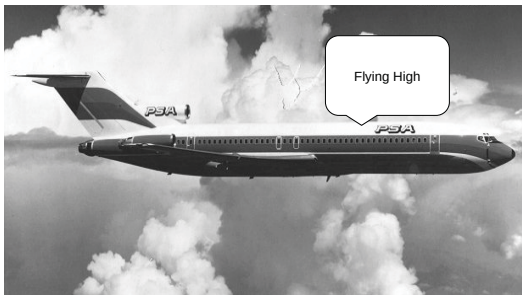
Andriole et al, J Urol 172:1314, 2004

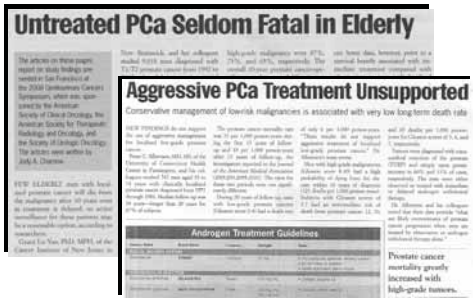
Optimism that Screening Is Associated with a Fall in Mortality

- Fall in mortality now seen
  - SEER
  - Olmsted County
  - Canada/Quebec
  - Denmark
  - Tyrol, Austria
- Mortality fall *not seen* where PSA screening not performed
  - Mexico—where little to no PSA screening is performed

Evidence is conflicting, not strong enough to support public policy

PSA

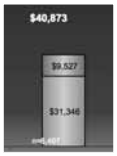




Renal and Urology News June 2005, April 2008

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	Recommendation
American Urological Association (AUA)	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.)
American Cancer Society (ACS)	[illegible] life expectancy of [illegible]
Centers for Disease Control and Prevention (CDC)	Considers evidence "insufficient to determine whether the benefits outweigh the harms".
U.S. Preventive Services Task Force (USPSTF)	Do not screen men [illegible] probably live 10 years or fewer. For men under 75, the evidence insufficient to determine whether the benefits outweigh the [illegible]
American College of Preventive Medicine (ACPM)	Discuss 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

NATIONAL CANCER INSTITUTE
PLCO
Prostate, Lung, Colorectal & Ovarian CANCER SCREENING TRIAL

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

Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb, III, M.D., Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, 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

The NEW ENGLAND JOURNAL of MEDICINE

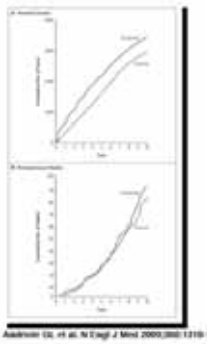
Characteristics of the Subjects at Baseline

The NEW ENGLAND JOURNAL of MEDICINE

Point-Counterpoint: Early Detection of Prostate Cancer Is Not Valuable In a Lot of Men

~ E. David Crawford, MD

Number of Diagnoses of All Prostate Cancers (Panel A) and Number of Prostate-Cancer Deaths (Panel B)



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

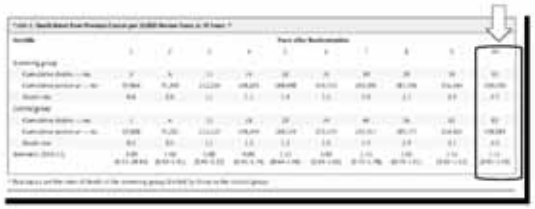
The NEW ENGLAND JOURNAL of MEDICINE

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

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

The NEW ENGLAND JOURNAL of MEDICINE

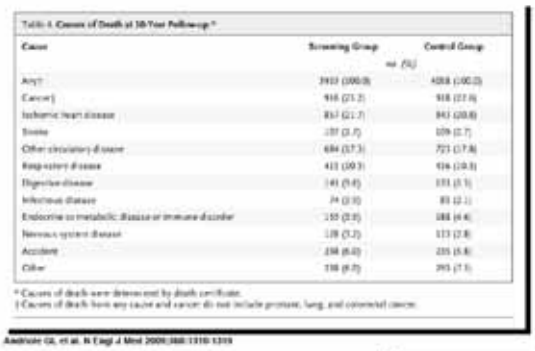
Death Rates from Prostate Cancer per 10,000 Person-Years at 10 Years



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

The NEW ENGLAND JOURNAL of MEDICINE

Causes of Death at 10-Year Follow-up



Cause	Screening Group	Control Group
	no. (%)	
Any†	3933 (100.0)	4238 (100.0)
Cancer‡	916 (23.3)	918 (27.9)
Ischemic heart disease	857 (21.7)	843 (20.0)
Stroke	107 (2.7)	109 (2.7)
Other circulatory disease	684 (17.5)	721 (17.0)
Respiratory disease	413 (10.5)	436 (10.3)
Digestive disease	141 (3.6)	151 (3.5)
Infectious disease	74 (1.9)	83 (2.1)
Endocrine or metabolic disease or immune disorder	155 (3.9)	188 (4.4)
Nervous system disease	128 (3.2)	123 (2.9)
Accident	238 (6.0)	255 (5.8)
Other	198 (5.0)	293 (7.1)

* Causes of death were determined by death certificate.
† Causes of death from any cause and cancer do not include prostate, lung, and colorectal cancer.

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

The NEW ENGLAND JOURNAL of MEDICINE

PLCO Trial Conclusions:

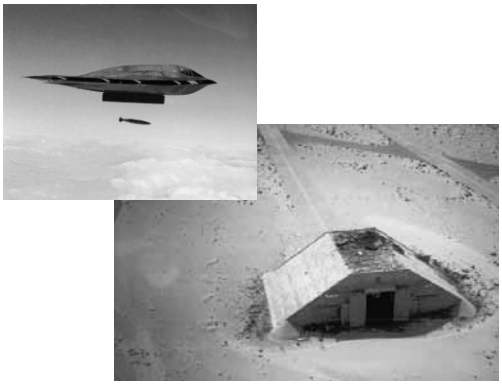
- 7-10 years, no difference in mortality
- Few CaP related deaths in either group- 92 screening and 82 control at 10 years
- Balance of benefits and harms unfavorable and does not support routine screening, at this time
- Even if mortality is shown to decrease, still significant harm to many men

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.



There are a lot of exciting things happening in the PLCO Trial

Biorepository: More than 2.7 million specimens

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

PLCO Prostate Subcommittee

Thanks to participants

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

Westat
D. Carrick

B. O'Brien
L. Ragard
T. Riley

IMS
J. Ciapp
B. Lake
J. Mabie
B. Wilcox

NCI
C. Berg
R. Hayes
G. Izmerlian
B. Kramer
D. Levin
A. Miller
P. Pinksy
P. Prorok

Others
D. Chia
T. Church
D. Reding

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 Biopsy

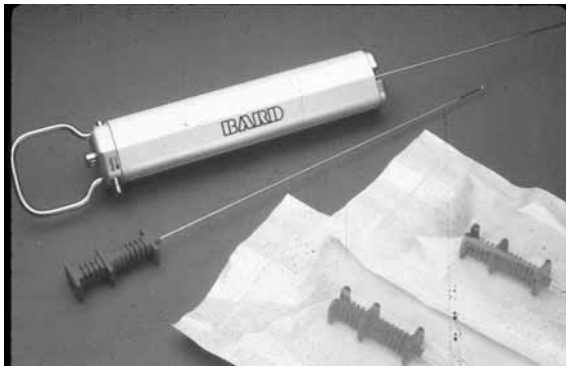
A prostate biopsy needle device in the hands of a Urologist !

Willet F. Whitmore Jr.

Prostate Biopsy

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

Willet F. Whitmore Jr.



Prostate Cancer

prevalence
- **disease in a population**

incidence
- **disease diagnosed in a population**

Prostate Cancer Prevalence

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

Prostate Cancer Prevalence

violent death series

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

Prostate Cancer Prevalence

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

Thompson NEJM 350:2239, 2004

Screening

AIMs

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

Screening

???? rectal exam
1936 acid phosphatase
1941 DRE + acid p'tase
1966 human semino-protein
1979 Prostate Specific Antigen
1930s perineal; 1937 rectal bx

Screening

prostate specific antigen
Free / Total PSA; cPSA [2-6]
PSA velocity
PSA density
PSA age specific
PSA doubling time

PSA – Age specific

40 – 44 1.8 ng/ml
45 – 49 2.0 ng/ml
50 – 54 2.6 ng/ml
55 – 59 3.6 ng/ml
60 - 64 4.3 ng/ml
65 – 69 5.0 ng/ml
70 – 75 5.5 ng/ml

Crawford PCAW

PSA – Age specific

40 – 44	**1.8 ng/ml**	**Cau**	**AA**
45 – 49	**2.0 ng/ml**	**2.5**	**2.0**
50 – 54	**2.6 ng/ml**		
55 – 59	**3.6 ng/ml**	**3.5**	**4.0**
60 - 64	**4.3 ng/ml**		
65 – 69	**5.0 ng/ml**	**3.5**	**4.5**
70 – 75	**5.5 ng/ml**	**3.5**	**5.5**

Crawford PCAW **Moul JAMA**

Prostate Cancer

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

Tumors 2009

incidence	mortality

Tumors 2009

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

Tumors 2009

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

Tumors 2009

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

Prostate Biopsy

indications

80% PSA
20% abnormal digital rectal exam

Prostate Biopsy

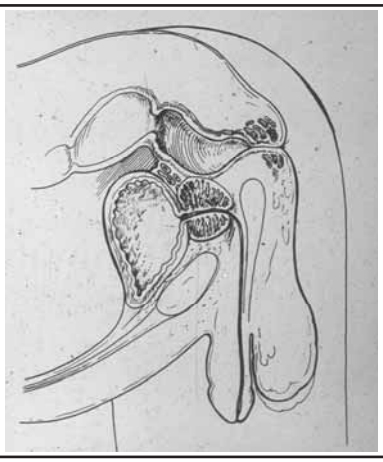
indications
181 patients

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

Prostate Biopsy

indications
181 patients

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



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

ERSPC and PLCO studies
no significant benefit
to screening
in lessening mortality

Schroeder NEJM 360: 1320, 2009
Andriole NEJM 360: 1310, 2009

Screening 2009

ERSPC
182,160 men screened,
PSA q 4 years, [2.5 to 4.0]
3 ng/ml
+/-DRE
+/-TRUS
+/-free PSA

Screening 2009

ERSPC
162,243 men between 55 and 69
9 years
mortality 20% lower in screened,
no biopsies in control group,
1410 men screened; 1 cancer death
screened 8.2%; control 4.8%
48 diagnosed; 1 cancer death

Screening 2009

ERSPC
large number screened,
less contamination,
20% fall in mortality,
better impact,
better patient control,
1068 screened, 48 Rx – 1 death,
27 Rx - 1 patient with mets

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

Screening 2009

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

Screening 2009

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

Screening 2009

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%

Screening 2009

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

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

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

Treatments

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

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

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!!!

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

Screening

One shoe does not fit all !!!

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

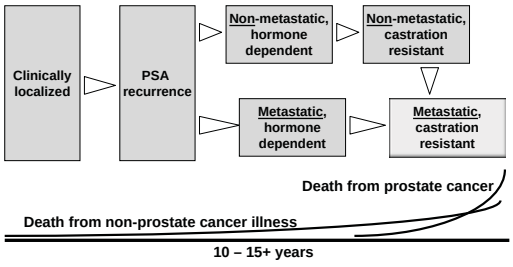
What's New in Advanced Disease (castration resistant prostate cancer = CRPC)?

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*

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.

Huggins and Hormone Therapy

CHARLES HUGGINS

Endocrine-induced regression of cancers

Nobel Lecture, December 13, 1966

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

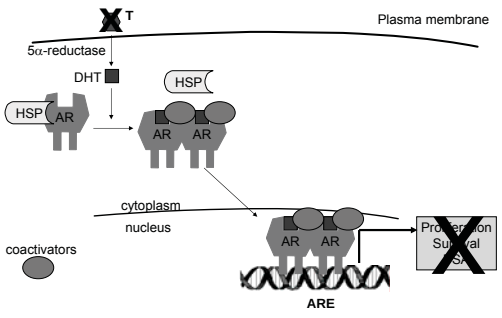
"We wanted to see if hormone therapy would do for elderly gentlemen what it would do for their best friends, elderly male dogs."

The first series of patients with prostatic cancer treated by orchiectomy[15] 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.

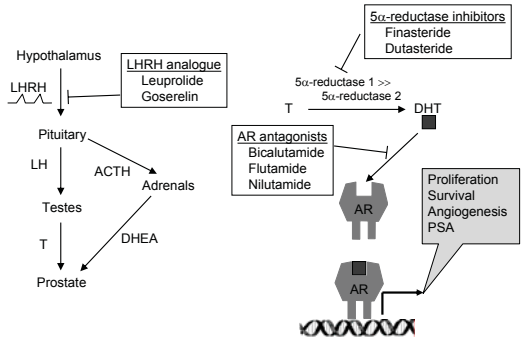
↓

First recognition of CRPC.

AR Working Mechanism



~ Matthew Rettig, MD



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 ⇒ 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

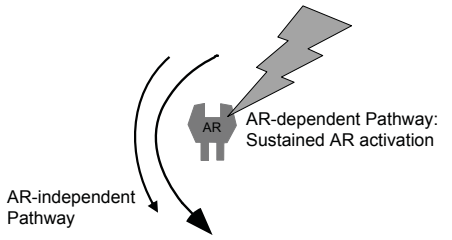
- Docetaxel-based chemotherapy is the only treatment that has been established to extend life expectancy in patients with *metastatic* CRPC.
  - extends median survival by 2-3 months.[1,2]
  - Well-tolerated and can be given irrespective of age.

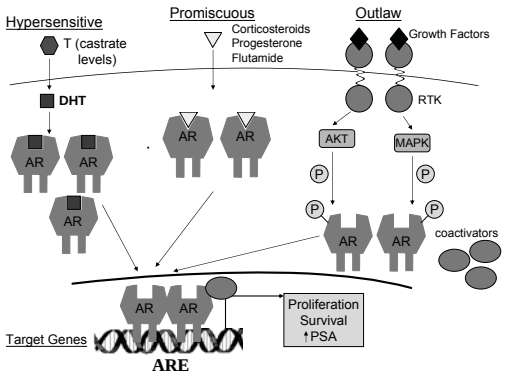
[1] NEJM 351:1502, 2004
[2] NEJM 351:1513, 2004

Mechanisms of Castration Resistance

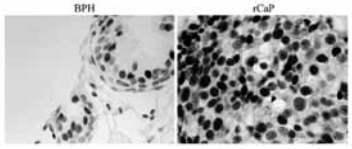
1. AR-dependent
2. AR-independent

Mechanisms Giving Rise to CRPC



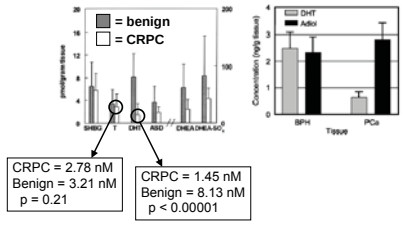


AR Expression in CRPC



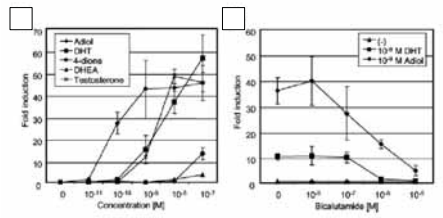
Clin Can Res 10:440, 2004

Intracellular Androgen Levels in CRPC



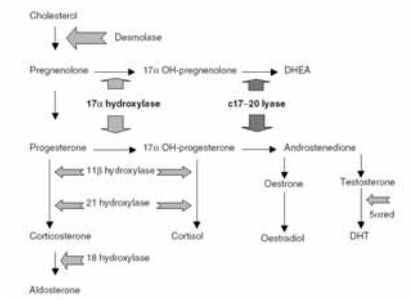
Clin Can Res 10:440, 2004.
Can Res 64:765, 2004.

Activation of AR transcriptional activity by androgens

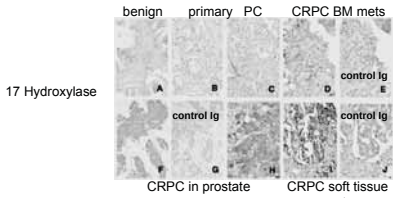


Can Res 64:765, 2004.

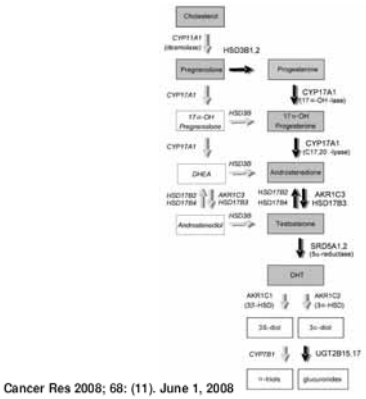
Biosynthesis of Androgens



CRPC cells activate the androgen synthesis enzymatic pathway.

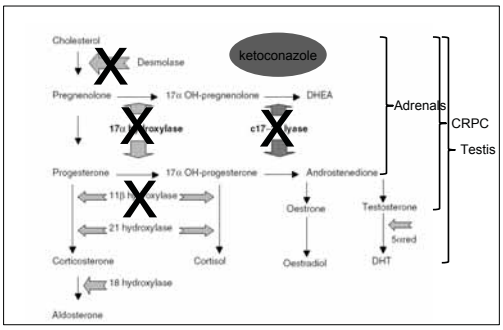


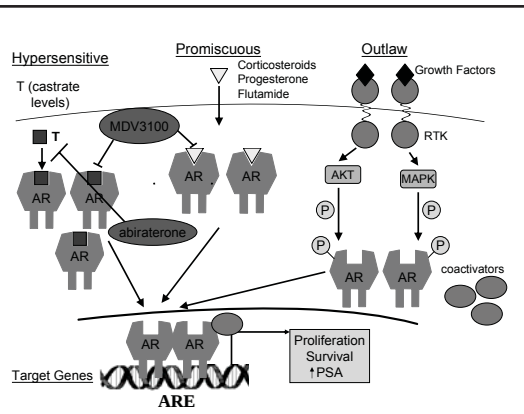
Cancer Res 66:2815, 2006.



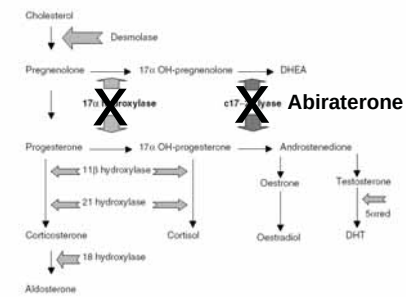
Cancer Res 2008; 68: (11). June 1, 2008

Biosynthesis of Androgens





Inhibition Androgen Production



Abiraterone Phase 2 CRPC: Chemo-Naive

- 27/44 (61%) have durable PSA declines ≥ 50%.
- 11/44 (25%) had ≥ 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 ≥ 50% PSA decline.
  - Median time to PSA progession ~ 6 months.
- 4/18 pts with measurable disease had PR.

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

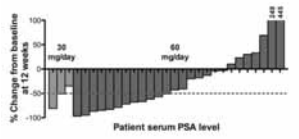
- Multinational, phase 3, placebo-controlled, double-blind study in patients with metastatic CRPC with progression after docetaxel-based chemotherapy.
  - 175 centers, 1158 patients.
- Randomization allocation 2:1. (abiraterone:placebo).
  - All patients receive prednisone 5 mg po bid.
- Primary endpoint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

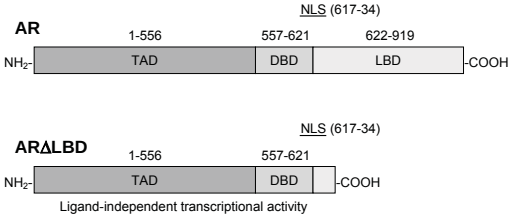
- 22/30 have PSA response, 12 of which were > 50% decline.



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

Science 324:787, 2009.

A Cautionary Note



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

Conclusions, Take Home Messages, and Other Comments

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

An Update on Radiation Therapy for Prostate Cancer

~ David C. Beyer, MD

An Update on Radiation Therapy for Prostate Cancer

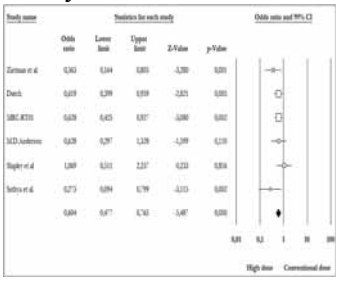
David C. Beyer, MD, FACR, FACRO, FASTRO
Arizona Oncology Services
Phoenix, Arizona

Objectives

- Review significant new data
- Identify leading trends in PCa

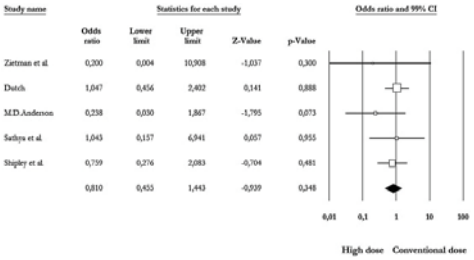
- 2009 Issues for:
  - Dose and Fractionation
  - Post-operative radiation
  - Role of hormones

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



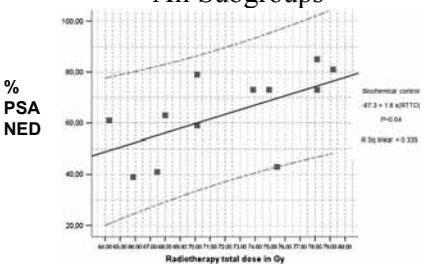
Viani, G. et al. IJROBP V74(5):1405-1418, 2009

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



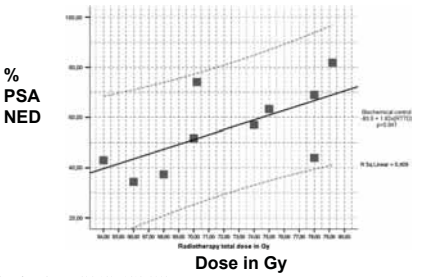
Viani, G. et al. IJROBP V74(5):1405-1418, 2009

Regression Analysis
All Subgroups



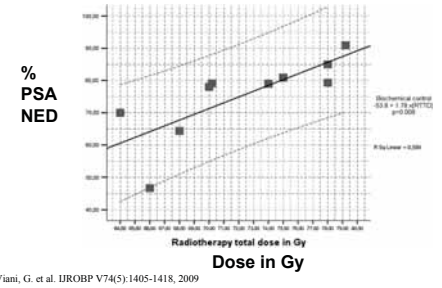
Viani, G. et al. IJROBP V74(5):1405-1418, 2009

Meta-regression Analysis
High-Risk Group



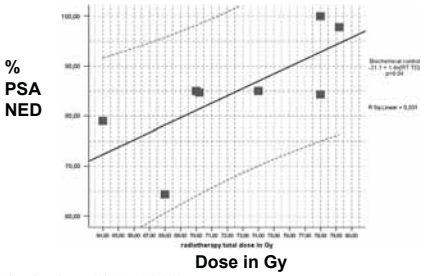
Viani, et al. IJROBP V74(5):1405-1418, 2009

Meta-regression Analysis
Intermediate-Risk Group



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"

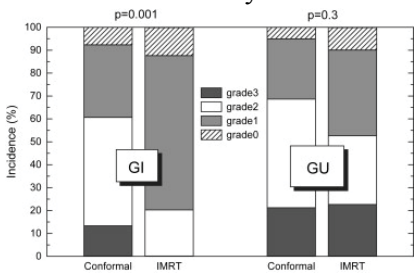
Low Risk	86.5 Gy
Intermediate Risk	90.4 Gy
High Risk	95.5 Gy

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

Improvements in Technology

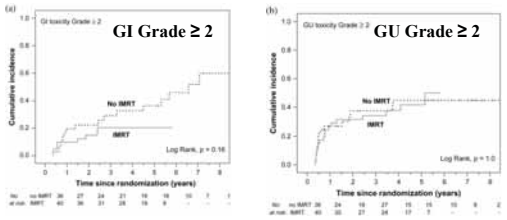
- IMRT allows greater precision in radiation delivery
  - Spare tissues adjacent to target
- IGRT allows greater accuracy in radiation delivery
  - "Hit" the target with each fraction
- Taken together should yield better cure and lower toxicity

IMRT *DOES* Reduce Acute GI & GU Toxicity



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

IMRT Reduces Late GI Toxicity



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

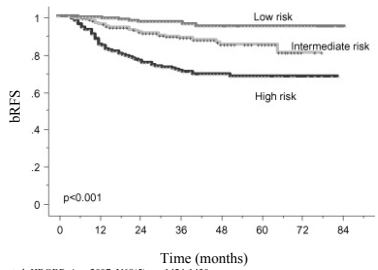
Fractionation = Daily Radiation

- Based on radiobiology principles
  - ✓α/β ratio determines optimal daily dose
  - ✓α/β ratio not precisely known for PCA nor for OAR
- Conventional wisdom
  - ✓Prostate cancer α/β ~ 10
  - ✓For any biologically effective does, 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 α/β 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. IJROBP. 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. IJROBP 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. IJROBP 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. IJROBP 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, IJROBP 75(3):S79, October 2009

Hypofractionation 3 Year Results

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

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

Stereotactic Body Radiation Therapy SBRT for Prostate Cancer

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

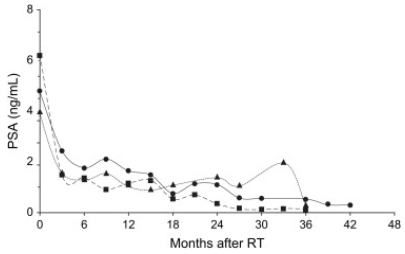
Stereotactic Body Radiation Therapy SBRT

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

SBRT Prostate Early "Phase II" Results

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

PSA Bounce following SBRT



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

Late Urinary & Rectal Toxicity on MDA dose escalation trial

	RTOG grade				
	0	I	II	III	IV
Urinary, late toxicity % (no. patients)	76%	14%	7%	7%	-
Rectal, late toxicity % (no. patients)	47%	28%	19%	19%	-

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

Comparison of QD vs QOD for SBRT

	QD	QOD	p=
GU QOL 4-6	19%	5%	0.34
Rectal (6mos), Any score 4-5	38%	0%	0.0035
Rectal QOL 4-5	24%	0%	0.048

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

Phase I Dose Escalation SBRT

- Low to intermediate risk prostate cancer
- 5 fractions
- 2 weeks
- 45 Gy -- 47.5 Gy – 50 Gy
- With 12 month follow-up
  - 100% PSA control
  - No dose limiting toxicity

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

Post-Operative Radiation Spectrum

- Immediate adjuvant
  - High risk
  - No gross residual / PSA
- Immediate salvage
  - Gross residual / PSA
- Late salvage
  - PSA failure
  - Documented recurrence
  - Hormone refractory

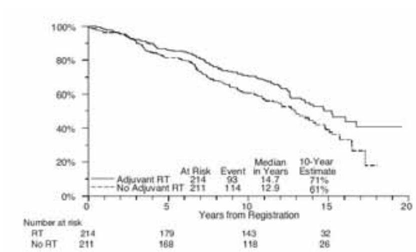
Phase III Trials: Adjuvant RT after RRP

	EORTC 22911		SWOG 8794		ARO 9602	
	RT	Observation	RT	Observation	RT	Observation
Eligibility	PT2-3N0 with PT3a, PT3b, or positive surgical margin		PT3N0		PT3N0 with undetectable postoperative PSA	
Stratification factors	Institution, PT3a, PT3b, margin status		PT3b, margin status, Prior hormone therapy		PT stage, margin status, Gleason score, Prior hormone therapy	
Number	502	503	214	211	108	153
Age (median)	65	65	64.1	65.8	N/A	N/A
Pre-op PSA	Median: 12.3	Median: 12.4	< 10: 51% ≥ 10: 49%	< 10: 53% ≥ 10: 47%	N/A	N/A
Postop PSA (<0.2)	89.8%	87.5%	45%	49%	100%	100%
Median follow-up	5 yrs	5 yrs	10.2 yrs	10 yrs	3.3 yrs	3.2 yrs
PSA prog free survival	74%* at 5 years	52.6%* at 5 years	71%*5 yr 52%*10 yr	44%* 5 yr 26%*10 yr	81%* at 4 years	60%* at 4 years
Clin prog free survival	85%* 5 yr	77.5%* 5 yr	84%* 5yr 68%*10 yr	69%* 5 yr 49%*10 yr	N/A	N/A
Metastasis-free survival	93.9%* at 5 years	93.7%* at 5 years	86% 5 yrs, 71%*10 yr	84% 5yrs, 63%*10 yr	N/A	N/A
Freedom from ADT	N/A	N/A	91%* 5 yrs	80%* at 5 yrs	N/A	N/A
Overall survival	92.3% 5yr	93.1% 5 yrs	90% 5 yrs, 74%* 10yr	89% 5yrs, 66%*10 yr	N/A	N/A

* statistically significant

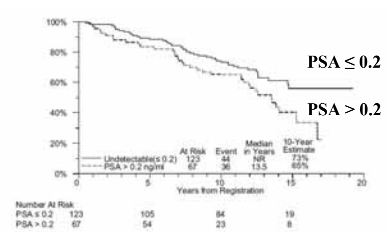
Bolla, M. et al, I.J. Rad Onc Biology Physics V60, N1 S180,
Pacholke, H et all, J. Urology, 2004, 06, 020: 982-986

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

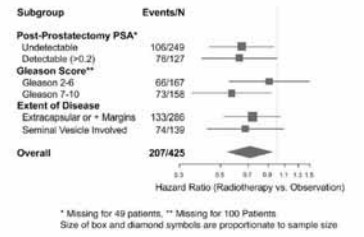


Thompson, I. et al. The Journal of Urology. 2009. V 181: 956-962

SWOG 8794 Overall Survival

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

Adjuvant Radiotherapy T3N0M0 Metastasis-free Survival HR



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

Hormone Therapy for Prostate Cancer

Hormones with Prostate Cancer

- In general
  - Improved outcomes with ADT
  - Long term better than short term
- Possible mechanism?
  - Eradicate subclinical microscopic disease
  - Synergy with XRT
    - ✓Enhanced response to dose of XRT
  - Compensate for suboptimal local therapy
    - ✓(65-70 Gy)

10 Year Results "Bolla" Study

- 415 patients treated EORTC 1987-1995
- XRT (pelvis + prostate) +/- 3 years Goserelin (concomitant and adjuvant)
- Median F/U 9.1 years

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

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

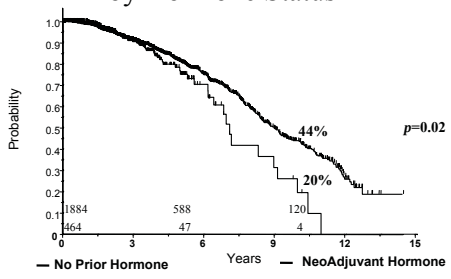
Impact of NHT on Mortality

- 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 ≥ 7	1.2	0.05

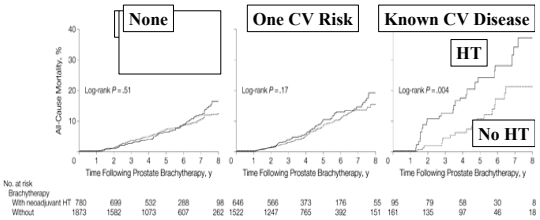
Dosoretz et al, IJROBP 72(1): s39, 2008 and USA Today 9/24/2008

Overall Survival by Hormone Status



Beyer et al, IJROBP 61(5):1299-1305, 2005

Impact of Hormones and Comorbidity on All Cause Mortality Following Brachytherapy



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

Value of Hormones with Dose Escalated XRT RTOG 0815

- Intermediate risk factors
  - Gleason 7
  - PSA 10-20
  - T2b-T2c
- Stratify for number of risk factors
  - Exclude if all 3 and >50% cores involved
- Endpoints
  - Survival
  - PSA
  - HRQOL
  - QALY

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

RTOG 0815

- XRT 79.2 Gy
  - @ 1.8/day
  - 3D or IMRT
- XRT 45 Gy + LDR implant
  - 110 Gy ^{125}I
  - 100 Gy ^{103}Pd
- XRT 45 Gy + HDR implant
  - 10.5 Gy x 2 fractions
  - ≥ 6 hour interval

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