

Update in the Diagnosis and Treatment (and Prevention) of Prostate Cancer

William Waller

Prostate cancer Update 2008

Practical points for Dx and Tx

- Will not be discussing new treatments for hormone refractory CaP or new treatments for recurrence after radiation failure

Prostate Cancer Update

Prostate Cancer Overview

- Single most common form of non-skin cancer in men in the united states
- An estimated 220,900 men will be diagnosed with prostate cancer, and some 28,900 will die of the disease

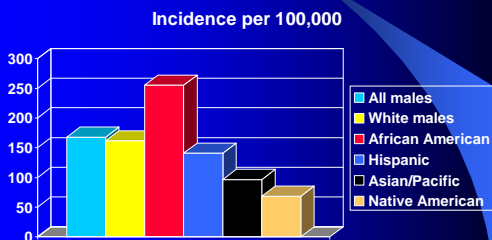
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Conundrum

- One of the problems facing prostate cancer patients is the uncertainty of many issues surrounding the management of the disease. It is not known, for instance, if the potential benefits of prostate cancer screening outweigh the risks, if surgery is better than radiation, or if treatment is better than no treatment in some cases.

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Incidence of CaP



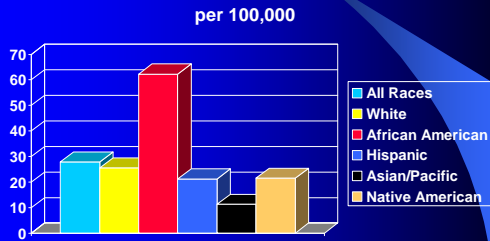
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Are we making a difference?

SEER Data from NCI

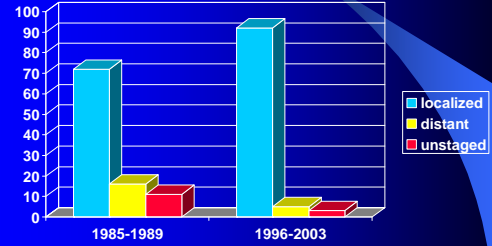
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Mortality from CaP



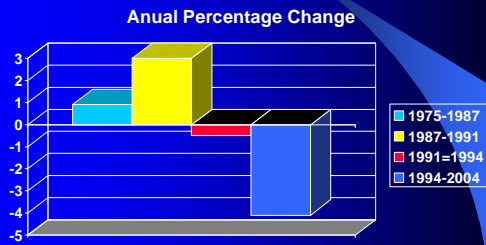
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SEER stage Distribution



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Trends in Mortality



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How do I use PSA?

- What is normal?
- What should be my threshold for referring to urologist?
- What PSA velocity should I worry about?
- What, besides CaP, can cause elevations in PSA?

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PSA

- Limitations
- Low sensitivity for acceptable false positive rates

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PSA

- More accurate in winter months
- 8000 men followed <one year
- 23% higher between June and august

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PSA

- None of the PSA derivations or isoforms such as PSA density, velocity, or free PSA improve operating characteristics enough to replace PSA
- University of Texas San Antonio and NCI review study

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New Markers

- Prostate stem cell antigen
- Alpha-methyl coenzyme-a racemase
- Pca3
- Early prostate cancer antigen
- Human kallikrein 2
- Hepsin

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Benign Factors than can elevate PSA

- Prostatitis
- BPH

There is no evidence that prostatitis or BPH causes cancer, but it is possible for a man to have one or both of these conditions and to develop prostate cancer as well.

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PSA Velocity

- PSA velocity threshold of 0.75 ng/ml per year has commonly been used to distinguish men with CaP vs benign conditions
- Mostly done in men with PSA >4
- Loeb and Catalona evaluated 22,019 with a PSA <4
- 0.4ng/ml was the threshold for recommending bx
- 2% men with PSA velocity <0.4ng/ml had CaP
- 13% men with PSA velocity >0.4ng/ml had CaP

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PSA Velocity and CaP Death

- Carter et al investigated PSA velocity with respect to cancer death
- PSA velocity measured 10–15 years before diagnosis (when most men had PSA levels below 4.0 ng/mL) was associated with **cancer-specific** survival 25 years later; survival was 92% among men with PSA velocity of 0.35 ng/mL per year or less and 54% among men with PSA velocity above 0.35 ng/mL per year ($P < .001$). Furthermore, men with PSA velocity above 0.35 ng/mL per year had a higher relative risk of **prostate cancer death** than men with PSA velocity of 0.35 ng/mL per year or less

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Obesity and PSA

- Study from Seoul, Korea found decrease in PSA and PSA velocity based on body mass index

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Risk Factors for CaP

- Age
- Family Hx
- Race
- Diet
- Body Habitus
- Activity level

Begins to look like risk factors for CAD!

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Prostate cancer and coronary heart disease: correlation or coincidence?

- Review article in Urologic Clinics of North America by Dr. Mark Moyad
- Take home: Heart healthy diet is probably prostate cancer healthy diet

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Diet Factors

- New study in Japan suggests green tea prevents advanced ca P
- Men who drank 5 or more cups a day had a 48% lower risk than men who drank less than one cup a day
- There was no association between green tea and localized ca P

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SELECT

- Selenium and Vitamin E Cancer Prevention Trial
- The Nutritional Prevention of Cancer Trial, published in 1996, included 1,312 men and women who had skin cancer. Men who took selenium to prevent nonmelanoma skin cancer received no benefit from selenium in preventing skin cancer. However, *men who had taken selenium for 6½ years had approximately 60 percent fewer new cases of prostate cancer than men who took the placebo (2).*

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SELECT

- Vitamin E
- Antioxidant like Selenium
- In a 1998 study of 29,133 male smokers in Finland, *men who took vitamin E to prevent lung cancer had 32 percent fewer new cases of prostate cancer than men who took the placebo.*

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Prostate Cancer Prevention Trial

- Determine the efficacy (i.e., decrease in tumor initiation, promotion, or progression rate) of long-term (7-year) treatment with finasteride (Proscar, MK-906) in reducing the incidence of prostate cancer in men aged 55 and older

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PCPT

- In June 2003, the PCPT was stopped early because of a clear finding that finasteride reduced the incidence of prostate cancer. However, those trial participants who did develop prostate cancer while taking finasteride experienced a slightly higher incidence of high-grade tumors.

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5 Alpha Reductase Inhibitors

- Blocks conversion of testosterone to dihydro-testosterone used for nuclear reproduction in prostate cells
- Originally used in early 90s for BPH
- Finasteride found to control symptoms of BPH only in men with prostate glands >40grams
- Finasteride and Avodart similar but Avodart blocks two pathways

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Avodart (dutasteride)

- Inhibits BPH and causes prostate atrophy
- Some long term efficacy shown for preventing AUR and subsequent TURP
- Probably inhibits low grade cancers
- Is being used off label for prostate cancer prevention in some offices
- **Caveat: DO a DRE and PSA q 6 months and ANY rise in PSA while on daily Avodart should be investigated**

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Lifestyle related factors CaP

- Positive correlation with adiposity and cap progression
- A study in Finland found that Vit E supplementations reduced deaths by CaP by 32% out of a pool of 29,000 men
- High cholesterol related to cap
- Heart healthy diet is preventative in CaP

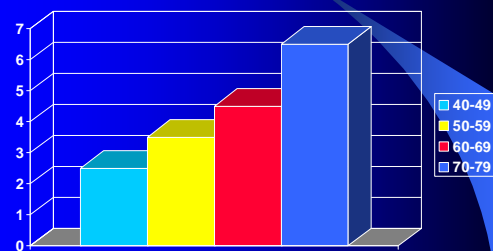
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Age Specific PSA

Good idea or bad?

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Osterling Age Specific PSA



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Expectant Management of CaP

- 407 men median age 65.7 yrs with stage T1c or T2a followed prospectively
- Recommended for intervention if follow up bx showed Gleason pattern 4 or 5, >2 bx cores with cancer, >50% of any core with cancer

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Unnecessary Intervention?

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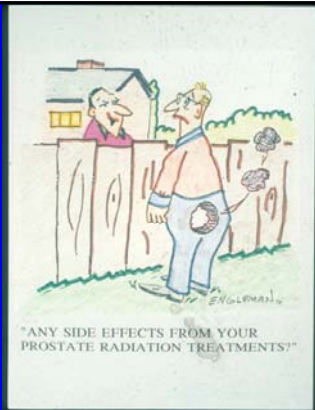
Expectant management of CaP

- 59% remained on active surveillance at median F/U of 3.4yrs
- 25% underwent curative intervention at a median of 2.2yrs after dx
- 16% either lost to F/U, withdrew from study, or died of other causes
- Older age at dx and earlier date of dx were significantly associated with curative intervention

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Surgery vs Radiation

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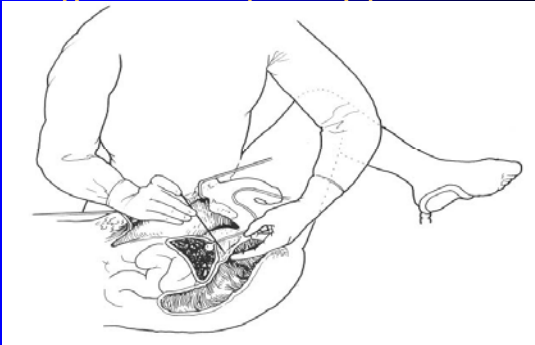
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Radiation Therapy for CaP

- EBRT (conformal)
- Brachytherapy
- HDR temporary brachytherapy
- IMRT
- Image based IMRT (CT tomotherapy)

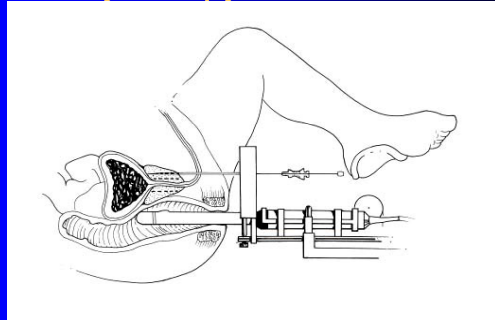
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Original Brachytherapy Seeds



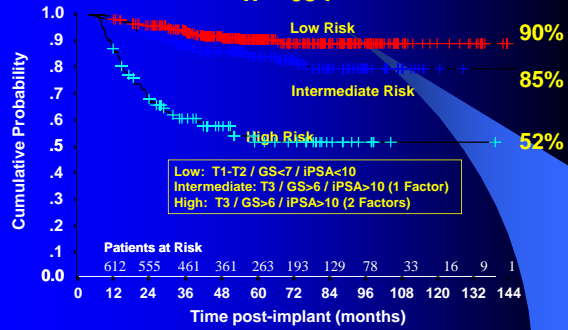
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Ultrasound Guided Brachytherapy



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^{125}I / ^{103}Pd Implant \pm EBRT BRFS by Risk Group n = 634



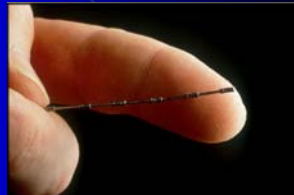
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Temporary Seed Brachytherapy

- Synonymous names –high dose rate (HDR)
- Implant procedure is similar to permanent seeds
- Outcome similar to permanent seeds
- Main difference
 - radiation is temporary
 - an HDR afterloader machine is needed

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HDR Afterloader Delivers The Temporary Seed – Ir^{192}



Ir^{192} seed strength – 5,000 mCi
 ^{125}I " " – 0.5


$\text{Ir}^{192} \times \text{Short Time} = ^{125}\text{I} \times \text{Long Time}$

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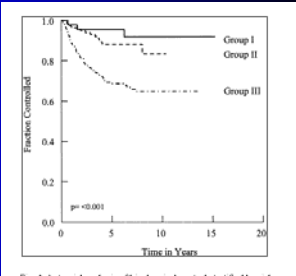
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Treatment



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Galalae et al:
 Long-term outcome using HDR brachytherapy for localized prostate cancer for 611 patients
 Int. J. Radiation Oncology Biol. Phys. 58: 1048-1055, 2004

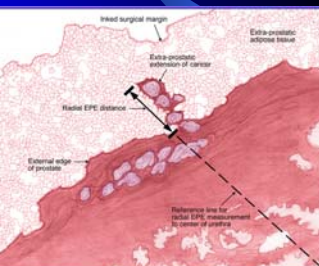


•Group I (favorable): $\leq T2a, GG \leq 6, PSA \leq 10$
 •Group II (intermediate): $\geq T2b, GG \geq 7, PSA \geq 10$ any 1 of these
 •Group III (unfavorable): $\geq T2b, GG \geq 7, PSA \geq 10$ any 2 or 3 of these

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Why does brachytherapy outperform surgery in intermediate to high risk patients?

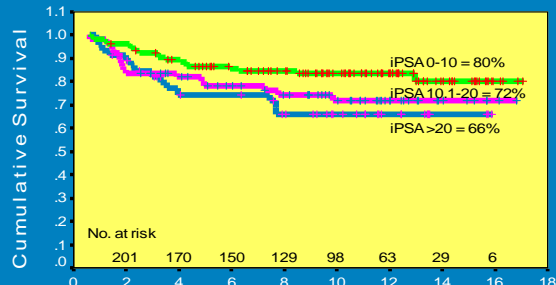
- Margins
 - Brachy margins 5-8 mm
 - EBRT + Brachy > 1 cm



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EBRT + Seed Implant (n=223)

BRFS by initial PSA value group



BRFS years post implant (log rank test=5.11, p=.078)


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Current Seattle Patient Selection Criteria

<p>Low risk $T1-T2b, GI \leq 6, PSA < 10$</p> <p>Intermediate risk $\geq T2c, GI \geq 7, PSA > 10$ One factor only</p> <p>High risk $\geq T2c, GI \geq 7, PSA > 10$ Two or more factors</p>	<p>→ <u>Seeds alone</u></p> <p>↙ $\leq 34\% + \text{cores: } \underline{\text{Seeds alone}}$</p> <p>↘ $> 34\% + \text{cores: } \underline{\text{Seeds+EBRT}}$</p> <p>→ <u>Seeds + EBRT (+ Hormones?)</u></p>
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Side Effects



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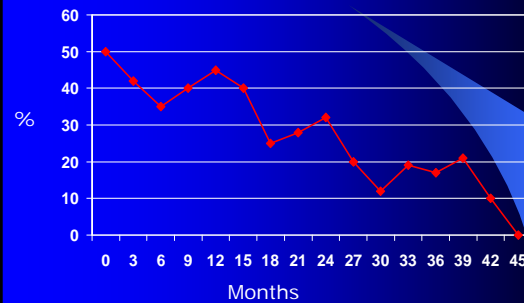
LUTS

- Lower Urinary Tract Symptoms

- Frequency
- Urgency or Urge Incontinence
- Dysuria
- Hesitancy
- Nocturia

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Dysuria



Merrick, Wallner, 2003
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Urinary Retention

- Reported Rates of 1%-20%
- Prospective Data
 - Han et al 32% at 1 year
 - 91% with retention resolved in month 1
 - Bucci et al 15% at 1 year
 - Locke et al 62 patients
 - 34% 1 Week
 - 10% 6 months
 - All patients eventually resolved

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Urinary Retention

- Associated With
 - High IPSS score
 - Large prostate volume
 - ADT
- Long Term Catheterization
 - 1-2%

Terk et al J Urol 1998; 160:1379
Bucci et al Int J Radiat Oncol Biol Physics 2002; 53:91

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Urethral Stricture

- Occurs in 8-14%
- Radiation injury to bladder outlet and proximal urethra
- Higher risk in pts with previous TURP, urethral surgery
- Modern Techniques
 - Improved radiographic guidance
 - Visualize and avoid the urethra

Ragde et al Cancer 1997; 80:442/
Zelevsky et al Int J Radiat Oncol Biol Physics 2000; 47:1261
Benoit et al Urology 2000; 55:91

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Proctitis / Rectal Irritation

- Mild to moderate symptoms (5-25%)
- Self-limited (6-24 months)
- Tx - stool softeners, anti-diarrheals, analgesics, steroid suppositories
- GI CONSULTATION! Do not let them Biopsy or Fulgurate the Rectum!!!

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ED Following Brachytherapy

- Acute- <12 months
 - Stock, et al Physician 15% (65)
 - Al-brooz et al Physician 32% (35)
 - Wei et al Patient-Validated 57% (21)
- Chronic- >12 Months
 - Zeitlin et al Physician 38% (212)
 - Benoit et al Unknown 8.4% (2124)
 - Potters et al Physician 47% (482)
 - Stock et al Physician 41% (313)
 - Merrick et al Patient-Validated 39% (181)

AUA Update Series , Lesson 2, Vol 23

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Symptoms after Primary Prostate Cancer Treatment Comparison of: RP, Seed Implant and EBRT

- Talcott JA et al: JCO Vol 21:3979-3986, Nov 2003

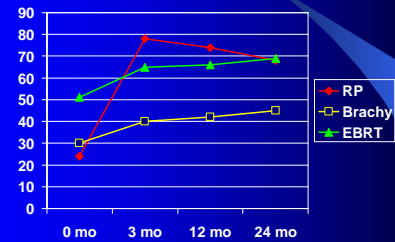
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Study

- Prospective study at MGH, Dana Farber and The Joint Center of Radiation Therapy
- Questionnaire prior, 3, 12, 24, 36 mo. post
- Short Form Health Survey (SF-36)
- 522 pts: 429 completed 24 mo. questionnaire
- 182 EBRT, (65 had HT) 129 had RP and 80 pts had Seeds.
- Average age: 65 RP pts were younger than Seed pts by 4 years, who were younger than EBRT by 5 years
- RP and Seed pts were better fit medically

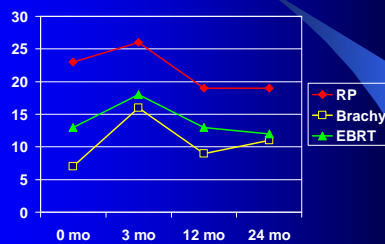
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Sexual Dysfunction



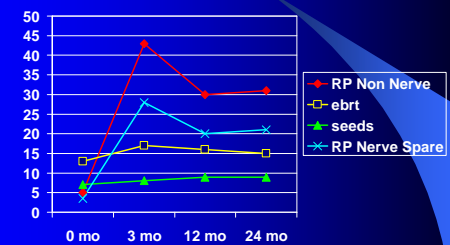
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Obstruction/Irritation



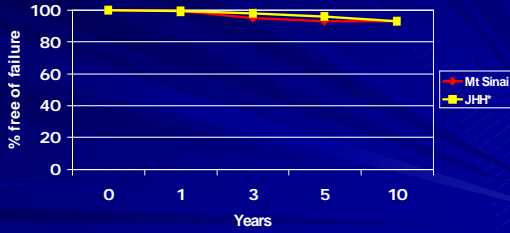
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Incontinence



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Biochemical freedom from failure Brachytherapy vs Radical Prostatectomy in low risk patients



*J Urol 169, 2003

Outcome	Radical Prostatectomy*	Radiation**
Survival duration compared to conservative disease management ¹	8.6 years	4.6 years
15-year prostate cancer survival rate ²	92%	87%
Survival rate for high-grade cancer patients ³	45% increase in overall survival rate vs. radiotherapy	-
Risk of cancer-specific death for high-grade cancer patients ⁴	49% less risk vs. radiotherapy	-
Cancer recurrence ⁵	Easy to detect	Difficult to detect
Risk of rectal cancer (Within 10 year follow-up) ⁶	5.1 out of 1000	10.0 out of 1000
Risk of bladder cancer ⁷	0.8% developed bladder cancer	1.3% developed bladder cancer
Bowel function impairment ⁸	-	Significantly greater vs. surgery
Disease-specific long-term quality of life ⁹	Stable	Unstable
Painful urination (at 18 month follow-up) ¹⁰	1% of patients	30% of patients
Long-term erectile dysfunction ¹¹	Lower risk	Higher risk

Da Vinci Vs Open Radical Vs LRP

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Outcome	dVP	Open	Lap
Cancer control			
T2 margin status	4.5 ¹	5.9 ²	7.7 ³
Complications			
Estimated blood loss (EBL)	109 ml ⁴	1355 ml ⁵	380 ml ⁶
Length of stay (LOS)	1.2 days ⁵	3 days ⁵	2.5 days ¹³
Major	1.7% ⁴	6.7% ⁵	3.7% ⁶
Minor	3.7% ⁴	12.6% ⁵	14.6% ⁶
Urinary function			
3 month	92.9% ⁷	54% ⁸	62% ⁹
6 month	94.9% ⁷	80% ⁸	77% ⁹
12 month	97.4% ⁷	93% ⁸	83% ⁹
Sexual function			
12 month	86% ¹⁰	71% ¹¹	76% ¹²

RALP Vs Open RRP?

- 1238 RALP, 509 RRP at Vanderbilt
- Statistically lower positive margin rate for patients undergoing RALP
- >250 cases required before surgeon is as competent in RALP as in RRP
- Average urologist does 12 to 18 radical surgeries a year
- Being driven in the private sector by industry

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RALP vs RRP?

- RALP did not provide a clinically meaningful decrease in pain compared with RRP
- Approximately \$2000 more expensive for RALP over RRP
- Much longer operative time with RALP
- Less blood loss with RALP

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Focal Therapy for CaP ?

- Incidence of focal cancers is 13% to 38%
- Staging accuracy is very limited
- Unpredictable aggressiveness of secondary foci
- Technology for focal ablation?

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Focal Therapy for Cap?

- HIFU
- Cryotherapy
- Radio frequency ablation
- Photodynamic ablation

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HIFU

- High intensity focused ultrasound
- Used in Europe and Canada
- One US based study showed 5% rectal fistula, 20% incontinence, and only 20% of the patients were cancer free by bx after first treatment
- Small study at Indiana university

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When Should We Biopsy?

- 1992 study showed with a PSA velocity of 0.75/yr in men with PSA 4-10 was significant for finding CaP
- New Study from Johns Hopkins showed PSA velocity of >0.4/yr predicted CaP in patients with PSA <4 (13% vs 2%)

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Saturation Bx Vs Standard Bx

- SBx >24 cores
- No better at detecting CaP than standard bx as primary Bx
- As second bx, SBx doubled the detection rate as compared to standard bx
- Pepe and Aragona, Italy

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Risk Factors for CaP

- Relative risk twofold in patients with first degree relative with CaP
- 4x greater if CaP dx'd age less than 65 or more than one relative
- Higher level of education was risk factor
- Low physical activity
- Italian study

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Rectal exams with PSA <4?

- Substantial portion of cancers detected by DRE at PSA<4ng/ml have features associated with clinically aggressive tumors
- 10 yr progression free, cancer-specific, and overall survival rates after radical prostatectomy were 83%, 99%, and 86%
- Men with CaP detected because of abnormalities in DRE and PSA level had substantially less favorable outcomes
- Dr. Catalona, Northwestern University
- DO A RECTAL EXAM!

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CaP in the general population

- Yin at University of Pittsburgh
- 340 prostates harvested from organ donors who died suddenly from 1994-2007
- 1 in 3 chance of having CaP in 60-69 yr olds
- 46% in 70-81 yr olds
- Confirmed military studies done in the 60s

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Take Home

- PSA and AGE should be considered when evaluating patient
- Always do a rectal exam on initial exam, even if PSA normal
- Even though we are possibly detecting a number of “insignificant” cancers, we ARE positively impacting survival
- Do NOT let GI docs bx or fulgerate rectum in patients who have had RT for CaP!
- Any rise in PSA in Patient on Avodart should be investigated

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