Prostate Cancer Surgery: Radical Prostatectomy?

Larry Goldenberg, CM, OBC, MD, FRCSC, FACS
The Prostate Gland

Understanding this anatomy is important if one is to understand the side effects and risks of various prostate cancer treatments.
What Does the Prostate Do ???

- A reproductive organ
- Contributor to urinary control
- Glandular secretions

Da Vinci
Management of Localized Prostate Cancer

Active Surveillance
Prostatectomy
Brachytherapy
External Beam Radiation
Other
Surgery
PROSTATECTOMY
(= Surgical removal of the prostate)

WHO IS THIS TREATMENT BEST FOR?

✓ Men with low to intermediate grade disease confined to the prostate and select men with higher grade disease.

✓ Fit for surgery

✓ No sign of cancer spread

✓ Patient’s choice
Prostate - Anatomic relationships
Radical Retropubic Prostatectomy - Surgical Approach
Radical Perineal Prostatectomy - Surgical Approach
Radical Prostatectomy - Surgical Approach
Prostate - Lymph Drainage
Prostate - Lymph Drainage
Priority #1: Remove the cancer
WHAT TO EXPECT:

• Preoperative consult with anesthesiologist
• Diet and bowel cleansing 1 day prior to treatment
• Antibiotics: Given prior to procedure
HOW IS THE SURGERY DONE?

1. Open surgery
2. Laparoscopic or Robotic surgery

✓ Common features:

- General anesthetic
- “Nerve sparing” surgery is possible if tumor is not too large or near the edges of the prostate.
PROSTATECTOMY

WHAT TO EXPECT:

✓ Hospital stay usually 1-2 days
✓ Minimal to moderate discomfort
✓ Catheter to drain urine: 1-2 weeks
✓ 3-6 weeks off work (depends on type of work you do)
PROSTATECTOMY

Advantages:

✓ Well tolerated
✓ Lymph nodes can be sampled to check for spread of the disease.
✓ Assessment by pathologist of prostate
✓ “Good or bad”, you know what you have
✓ Hence psychological relief
✓ Prevention of “aging” urinary problems
PROSTATECTOMY

Advantages:

✓ Excellent long term results (i.e., high cure rate).
✓ Low risk of life threatening complications.

However, there are risks of urinary leakage (incontinence) and erectile dysfunction.
Positive Margins
Robotic Prostatectomy

da Vinci® Surgical System

• State-of-the-art robotic technology

• 3-D Visualization

• Intuitive Movement
Surgeon directs the instrument movements using Console controls.
Robotic Prostatectomy
Why Perform RALP?

- Patients desire minimally invasive surgical approaches
- Reduced length of stay
- Patient related outcomes are at least equal to RRP in all measures and superior in some
  - Less intraop blood loss = less postop anemia
  - Transfusion in only a small proportion of patients
Wizard of Id
by Brant Parker

Someday, robots will do this job.

What will we do then?

Clean the robots.

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PROSTATECTOMY

Side Effects and Risks

- Erectile Dysfunction: 50-90/100 men—usually treatable, but may take >1 year to recover
- Incontinence (stress): 5-10/100 men—usually mild and tolerable
- Incontinence requiring surgery: 1-2/100 men
- Blood transfusion: 1-10/100 men
- Bladder neck scarring: 1-3/100 men
- Rectal/Bowel Injury: rare
Long-term issues after surgery

- Sexual Dysfunctions
- Urinary Incontinence
Post-Radical Prostatectomy Sexual Dysfunctions

- Erectile dysfunction (ED)
- Anejaculation
- Anorgasmia
- Dysorgasmia (painful ejaculation)
- Orgasm associated urine leak (climacturia)
- Penile length alterations
- Penile curvature
Risk Factors of Post-Prostatectomy ED: Patient Factors

- Age more than 60 years
- Vascular diseases
- Diabetes
- Dyslipidemia
- Smoking
- High stage of disease
- Non-motivated partner
- PDE$_5$-I user
- Obesity

Assessment of a patient’s preoperative erectile function is essential.

Using a validated questionnaire, e.g. International Index of Erectile Function (IIEF) may help diagnose and determine the severity of erectile dysfunction.
Potency Recovery after Surgery

Maximal recovery after bilateral NSRRP may take up to 4 years

Rabbani et al., AUA 2004
Recovery of Erections According to Preoperative Sexual Functioning

Penile Rehabilitation?

- After radical prostatectomy, there is neural and vascular damage
- Decreased oxygenation of the penis, loss of nighttime erections ....ischemia
- By using ED therapy, you stimulate circulation of blood
How common is incontinence post RP?

• **Large studies tell us:**
  – Risk of any urinary leakage = 30%
  – Risk of bothersome urinary leakage = 10%
  – Risk of serious leakage requiring surgery = 1-2%
Risk Factors: Incontinence

1. Overactive bladder
2. Increased Age
3. Prior Radiotherapy (57 – 64% incontinence)
4. Prior transurethral prostate surgery
5. Pre-operative continence status
6. Surgical expertise
Wait, Wait, Wait !!!

Eastham, Kattan, Rogers J Urol 1996
"MY INTEREST IS IN THE FUTURE BECAUSE I AM GOING TO SPEND THE REST OF MY LIFE THERE"

CHARLES KETTERING
Advances In Radiation Therapy for Prostate Cancer

Arthur Hung, M.D.
Concepts of Radiation
Topics

• Identify the basic radiation techniques for prostate cancer
  – 3-D conformal
  – IMRT
  – Proton therapy

• Learn the new options for shorter treatment courses
  – hypofractionation
  – stereotactic body radiation therapy (SBRT)

• Understand how radiation is added to surgery to improve outcomes for patients with advanced prostate cancer
  – adjuvant radiation
The Biological Effect of Radiation

- Radiation therapy uses high-energy electro-magnetic energy, like radiowaves, microwaves, & visible light
- Ionizing Radiation damages DNA in rapidly dividing cells
Radiation Damages DNA

Before:

After:

Incoming UV photon
Normal Tissue repairs DNA Damage

DNA Radiation

DNA is cut off by radiation

Repair protein accumulates around an injury

Repair protein is repairing the injury

Successful DNA restoration!
Goal of treatment is to deliver radiation to just the prostate

- focusing the radiation on only the tumor eliminating collateral damage to normal tissue
  - External beam radiation
    - Linear Accelerator
    - Proton Therapy
    - Stereotactic Body Radiation
  - Internal Radiation
    - Prostate Brachytherapy
    - HDR Brachytherapy
  - Intraoperative Radiation
External Beam Radiation
Modern Linear Accelerator
Traditional Radiation Therapy
Targeting Prostate Cancer with Radiation
Focusing the Radiation
CT-Guided Targeting
Intensity Modulated Radiation Therapy

IMRT

Normal Spray

Pulse Massage Spray

Soft/Champagne Spray

Combined Spray
Elekta Versa HD Accelerator
Radiation Beam Shaping
How we shape the radiation
Cyberknife
Brachytherapy
Prostate Brachytherapy
Prostate Brachytherapy
Brachytherapy

High dose rate brachytherapy

Using transrectal ultrasound and a template as a guide, metal needles are inserted into the prostate.

Template is sutured to the skin between the scrotum and the anus and metal needles are replaced with hollow plastic ones. Thin cable from HDR unit is passed through needles to deliver high-intensity radiation directly into the prostate.

High-intensity radiation delivered directly into the prostate.

© Western and Central Melbourne Integrated Cancer Service
Intraoperative Radiation
Intrabeam – Intraoperative Radiotherapy
Intraoperative Radiation

**STEP 1**
Remove tumor

**STEP 2**
Prepare breast

**STEP 3**
Visually position/place applicator

**STEP 4**
Deliver electron radiation to at risk tissue, short radiation time (~2 minutes)

**STEP 5**
Close incision
Mobile IOERT Solution

- Complete Treatment System
- **No room shielding**
- Mobile--use in multiple operating rooms
- **6 MeV - 12 MeV**
- **3 – 10 cm Field Size**
- **10 Gy/min dose rate**
Proton Therapy (External Beam Radiation)
Proton therapy centers

PROTON THERAPY CENTERS ◆ = In Operation  ◆◆ = Under Construction or in Development  ◆◆◆ = Expanding
Proton Therapy

- a form of external beam radiation
- protons are charged particles and deposit energy in tissue
- as they slow down, they deposit all their energy and then stop: Bragg Peak
Proton Therapy Center

- synchrotron
- switchyard
- treatment rooms
- 45 tonne gantry
A 21,000 lb. magnet guides the beam to the patient through a nozzle.

**Gantry**
The gantry can rotate 360° around the patient and position the nozzle in the correct angle to the tumor.
Proton therapy
X-rays go through the nidus.

Proton beams stop at the nidus.
Targeting Prostate Cancer with Protons
Proton Therapy pros & cons

• PROS
  – external beam radiation
  – no exit dose!
  – less total energy used

• CONS
  – limited beam shaping
    • (only 2 beams vs. 9+ vs. 360°)
  – limited accuracy at stopping
  – no beam modulation
  – limited access
  – expensive!
Proton Therapy vs. IMRT
A Prospective Comparative Study of Outcomes with Proton and Photon Radiation in Prostate Cancer


- **Outcomes**: A goal of the proposed study is to answer the following patient-centered questions:
  - How likely am I to experience different quality-of-life issues with proton therapy versus IMRT?
  - How likely am I to experience different side effects with proton therapy versus IMRT?
  - Given my prostate cancer, will proton therapy or IMRT result in a better cure rate?
  - If I choose proton therapy, is shorter treatment as safe and effective as longer treatment?
# Proton Therapy vs. IMRT

## Project Details

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<tr>
<th>Principal Investigator</th>
<th>Other Principal Investigator</th>
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<tbody>
<tr>
<td>Nancy Mendenhall, MD</td>
<td>Ronald Chen, MD, MPH</td>
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<th>Project Status</th>
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<td>Research Project</td>
<td>Pragmatic Clinical Studies to Evaluate Patient-Centered Outcomes</td>
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<td>Perinatal Health - Other, Urinary Disorders</td>
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Image Guidance
Daily Image Guidance

• Linear accelerator with CT capability

• Daily CT imaging allows
  – reduce the volume of tissue irradiated
    ✓ targeting only tumor
    ✓ sparing surrounding normal tissue
  – reducing irradiated normal tissue
    ✓ reduces toxicity
    ✓ improves quality of life
  – delivering higher radiation doses
    ✓ improving local tumor control
Daily Image Guidance

summary

• CT Imaging ensures daily accuracy of the target
  – treatment margins can be smaller
  – avoidance of normal organs is improved

• Daily Image Guidance reduces side effects
  – reducing the normal tissue treated – reduces toxicity
  – improves quality of life

• Daily Image Guidance involves a snapshot
  – prior to treatment
  – cannot track the target during the treatment
Calypso® 4D Localization System
Calypso — GPS for the Body®

Wireless miniature Beacon® Electromagnetic Transponders

Accurate, objective guidance for target localization and continuous, real-time tracking

Actual size: ~8.5 mm
Electromagnetics Locate and Track Continuously

GPS for the Body®

Step 1

Step 2
Transponder Signals

- Transponders excited sequentially at each of three unique resonant frequencies.
- Each transponder subsequently responds with a decaying magnetic field.
- Process of excitation and sensing is repeated several hundred times to improve signal/noise for each transponder localization.

![Excitation Waveform](image)

- **Excitation Waveform**
  - Source Coil Current

![Response Waveform](image)

- **Response Waveform**
  - Resonator Current
  - Excitation Phase
  - Ring Down Phase

**Beacon® Electromagnetic Transponder**

Actual size: ~ 8.5mm
Unique Frequencies Identify Location
Calypso Overview

Optical System

4D Electromagnetic Array™

4D Localization System™

4D Tracking Station™

4D Console™

Implanted Beacon® Electromagnetic Transponders

Optical Targets

Infrared Cameras
Image Guidance

summary

• Daily Image Guidance is Identifying the Internal Target on a daily basis

• Calypso technology further ensures only the target is being treated
  – treatment margins are at biological limits (4 mm)
    • smaller margins would potentially miss extracapsular extension
  – real-time tracking ensures accurate treatment 100% of the time
    • eliminating the potential of the target moving out of the treatment field, also simultaneously reduces other tissue moving in
    • reducing toxicity and side effects while improving control
Radiation Dose Escalation

• Technology enables
  – reducing the margins needed to treat
  – increasing radiation dose to the target

• Does increasing radiation dose improve control?
Background:
Higher doses to the prostate result in more cures

Memorial Sloan Kettering Experience with High Risk Pts (Gleason ≥ 7 and PSA > 10)
Leibel, et al., The Cancer Journal 8:164-176, 2002
Hypofractionation

• Radiation has traditionally been delivered to the prostate over 8 or 9 weeks
  – 78 Gy / 39 fractions
  – 81 Gy / 45 fractions

• Technical improvements (IMRT and Image Guidance) allow safe delivery of larger doses per day

• Biological argument that larger doses per day may be more effective
  – 70 Gy / 28 fractions (5 ½ weeks)
Randomized Trial of Hypofractionation

- 303 men assigned radiation to
  - 76 Gy over 38 fractions (7 ½ weeks of treatment) vs.
  - 70.2 Gy over 26 fractions (5 weeks of treatment)

- After 68.4 months (5 ½ years), no differences
  - prostate cancer survival
  - toxicity
  - biochemical control
Randomized Trial of Hypofractionation

CIMRT – Conventional
HIMRT – Hypofractionated
Randomized Trial of Hypofractionation

GU Toxicity  CIMRT – Conventional
HIMRT – Hypofractionated

D

Cumulative Incidence

\( P = 0.669 \)

Time (years)

No. at risk

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<th>CIMRT</th>
<th>HIMRT</th>
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<td>151</td>
<td>149</td>
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<td>2 years</td>
<td>122</td>
<td>120</td>
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<td>3 years</td>
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<td>4 years</td>
<td>96</td>
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<td>5 years</td>
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<td>6 years</td>
<td>57</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>17</td>
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</tbody>
</table>
Randomized Trial of Hypofractionation

GI Toxicity
CIMRT – Conventional
HIMRT – Hypofractionated

![Graph showing cumulative incidence over time]

Time (years)

No. at risk
CIMRT 151 147 139 121 105 85 85 38
HIMRT 149 142 132 111 98 68 35

P = .916
Stereotactic Body Radiation Therapy for Prostate Cancer / EXTREME hypofractionation

• With the technical ability to deliver radiation with high levels of accuracy, how few treatments are possible?

• SBRT is 5 treatments
  – to 36 – 50 Gy

• Early data
  – median f/u of 12 – 60 months (as of 2018)
  – for robust prostate studies, median f/u > 10 years
Hypofractionation - Conclusions

• Shorter treatment courses
  – 4 to 5 ½ weeks vs. 8 - 9 weeks

• No difference in toxicity

• No difference in disease control

• Less time for patients, cheaper, same side effects!

• SBRT is on the horizon. Promising early data
technology has significantly improved radiation delivery

CHANGING HOW WE USE RADIATION
Surgery vs. Radiation for Prostate Cancer

• The power of AND. Adjuvant and Salvage RT.
• Combining Radiation and Surgery
Radiation Therapy (according to Urologists)
Radiation AND (after) Surgery

• 3 Randomized Controlled Trials
  – SWOG 87-94 (473 pts)
  – EORTC 22911 (1005 pts)
  – ARO 96-02 (388 pts)

• Adding radiation to surgery reduces by 50% the chance the cancer returns
Advances in Radiation Technology

• Targeted Therapy with Radiation =
  – Reduced Toxicity
  – Better Tumor Control

Our Goal is to preserve Quality of Life while eradicating the cancer.
How to Manage PSA Recurrence + Active Surveillance

Julie N. Graff, MD
Chief of Hematology/Oncology
VA Portland Health Care System
Associate Professor of Medicine
Knight Cancer Institute, Oregon Health & Science University
Example

 71 yo man diagnosed with prostate cancer in 2013. He underwent a radical prostatectomy that revealed Gleason 4+4 disease and no lymph nodes involved. After the surgery, his PSA was undetectable.

 In January 2016, his PSA became 0.1 ng/ml.

 Repeat in March 2016 was 0.35 ng/ml.

 What does this mean?
Scope of this discussion

- Definition of “PSA Recurrence” and other commonly used terms
- Natural History of PSA Recurrence (without intervention)
- Using the PSA to predict prostate-specific mortality
- Androgen Deprivation Therapy (ADT) in patients with PSA Recurrence
- Toxicities of ADT
- Predicting life span by response to ADT
- Active Surveillance
What is a PSA recurrence?

No evidence of disease:
Nothing on imaging
PSA undetectable

PSA Recurrence:
Nothing on imaging
PSA detectable

Metastatic Cancer:
Spread on imaging
PSA detectable

What is the definition of PSA recurrence*

◊ After radical prostatectomy, 0.2 ng/ml

◊ After radiation, three consecutive rises with the time of failure being the midpoint between the PSA nadir and the first rise.

*Some disagreement
This study included 1997 men who had a radical prostatectomy at Johns Hopkins between 1982 and 1997. They were followed for a mean of 5.3 years (range of 0.5-15 years).

Of the 1997 men, 315 (15%) had a biochemical recurrence, defined as a PSA ≥ 0.2 mg/ml. Eleven of them received early hormonal therapy and were not included in this analysis.
- The median time to developing metastases was **8 years**.
- In this analysis, 103 (34%) did develop metastases.

Subgroup Analysis

Figure 3. Actuarial Likelihood of Metastasis-Free Survival in 304 Men With Prostate-Specific (PSA) Antigen Elevation After Radical Prostatectomy

A. Based on Gleason scores in the radical prostatectomy specimen (P<.001). B, Based on years until initial biochemical recurrence (P<.001). C, Based on prostate-specific antigen doubling time (PSADT) (P<.001).

Treating the rising PSA

- Options:
  - Some may be candidates for salvage curative therapies (surgery or radiation)
  - Some may choose to watch the PSA
  - Others start androgen suppression therapy

There may not be an obvious choice. Personal preference is important.
Salvage Radiation Therapy

- Statistics
- Some may not do well
  - Gleason 8, 9, 10
  - Pre-treatment PSA > 2.0 ng/ml
  - Negative margins
  - PSA doubling time ≤ 10 months
  - Seminal vesicle invasion

*Figure 1. Kaplan-Meier Estimate of Progression-Free Probability After Salvage Radiotherapy*

Error bars indicate 95% confidence intervals.

*JAMA. 2004;291:1325-1332*
Bicalutamide with Salvage RT

Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer

Patients and Treatment

- Men who had undergone radical prostatectomy (surgery) with lymph node dissection and then had biochemical recurrence.
- Stage T2 (confined to the prostate but also with a positive surgical margin) or T3 (with histologic extension of the tumor beyond the prostatic capsule) without nodal involvement.
- Detectable PSA at least 8 weeks after surgery that was 0.2 to 0.4 ng/ml.
- Received radiation plus either bicalutamide 150 mg daily or placebo for 2 years.
Outcomes

- 840 patients were randomized from 1998-2003
- 760 patients participated (384 in the bicalutamide group, 376 in the placebo group)
- There was more breast enlargement and tenderness in the bicalutamide group.
Table 2. Antitumor Efficacy with Respect to Key Secondary End Points at 12 Years.

<table>
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<tr>
<th>End Point and Subgroup</th>
<th>Bicalutamide Group</th>
<th>Placebo Group</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td></td>
<td>Patients at Risk</td>
<td>Rate of End Point</td>
<td>Patients at Risk</td>
<td>Rate of End Point</td>
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<tr>
<td></td>
<td>no.</td>
<td>%</td>
<td>no.</td>
<td>%</td>
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<tr>
<td>Metastatic prostate cancer</td>
<td>384</td>
<td>14.5</td>
<td>376</td>
<td>23.0</td>
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<tr>
<td>All patients</td>
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<td>Gleason score</td>
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<td>2–6</td>
<td>111</td>
<td>7.8</td>
<td>103</td>
<td>16.5</td>
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<td>7</td>
<td>205</td>
<td>15.4</td>
<td>208</td>
<td>19.8</td>
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<td>8–10</td>
<td>67</td>
<td>21.2</td>
<td>64</td>
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<td>PSA level at trial entry</td>
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<td>&lt;0.7 ng/ml</td>
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<td>13.4</td>
<td>195</td>
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<td>0.7–1.5 ng/ml</td>
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<td>17.4</td>
<td>118</td>
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<td>&gt;1.5 ng/ml</td>
<td>55</td>
<td>13.1</td>
<td>63</td>
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<td>Positive surgical margin</td>
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<td>Yes</td>
<td>288</td>
<td>11.8</td>
<td>281</td>
<td>20.3</td>
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<td>384</td>
<td>5.8</td>
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<td>384</td>
<td>17.9</td>
<td>376</td>
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* Death from prostate cancer included all deaths from prostate cancer or treatment complications as well as death from an unknown process in patients with active prostate cancer on the basis of central review.
What Happens When The Shots Stop Working?
Two New Options as of 2018

- **Enzalutamide** (=Xtandi) or **Apalutamide** (=Erleada)
- Both block interactions with the Androgen Receptor
- Both delay the time to metastatic disease
- Both decrease the PSA
- Both add toxicity
- So far, we do not know if they help men live longer
# Toxicities from Androgen Deprivation Therapy (ADT)

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<th>Those you can feel</th>
<th>Other</th>
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<td>Weight gain</td>
<td>Hot flashes</td>
<td>Bone density loss</td>
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<tr>
<td>Muscle loss</td>
<td>Fatigue</td>
<td>Lipid changes</td>
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<tr>
<td>Hair pattern changes</td>
<td>Depression</td>
<td>Decreased insulin sensitivity</td>
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<tr>
<td>Fat redistribution</td>
<td>Mental slowing</td>
<td>Heart disease (?)</td>
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<td>Testicle/penis size decrease</td>
<td>Anemia</td>
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Changes in Body Habitus

- More abdominal fat
- 10-15 pound weight gain
- Loss of height if you develop compression fractures related to osteoporosis
Hot flashes

- Affect 55-80% of men receiving ADT
- Range from mild to severe
- Therapies can decrease the number and intensity of hot flashes
  - Megestrol (Megace) 40 mg/day, but may lead to increased appetite and weight gain, increased risk of blood clots and possibly raise the PSA
  - Venlafaxine (Effexor) 75-150 mg/day, but can cause mood or behavior changes
- Other: acupuncture has been tried with variable response; soy; estrogens
Central Nervous System Effects

- Depression - medication or counseling may be helpful
- Emotional lability
- Mental sluggishness - usually not profound but may be very concerning
  - One study suggested a connection between ADT and Alzheimers. Another did not.
What can you do to stay healthy?

- Talk to your urologist or oncologist about all of your concerns.
- Exercise - weight bearing is best for the bones, but it is not always possible.
- Take supplemental calcium and vitamin D to protect your bones.
- Eat healthy foods - beware of weight gain.
- Continue to be seen by your primary care physician so that you can optimize your cardiovascular risk factors (blood pressure, cholesterol, smoking cessation, etc).
Active Surveillance
(Watchful Waiting)
Competing Risk Analysis
SEER Connecticut Registry

767 men diagnosed with localized disease.
138/767 (18%) Grade I (GS 2-4)
549/767 (72%) Grade II (GS 5-7)
138/767 (10%) Grade III (GS 8-10)

Mean age - 68 years, WW or delayed ADT

Analyzed cohort for cumulative mortality from prostate cancer and other causes.

Albertsen, P. C. et al. JAMA 2005;293:2095-2101
Active Surveillance

Active Surveillance

- Patient selection: low PSA, low Gleason, low stage T1c-T2a
- PSA, DRE q 3 months x 1 years, then q 6 months
- Repeat biopsy at years 1, 3, 6, 9, 12....
- Treatment if PSA increasing rapidly or biopsy shows more aggressive cancer.
  - Radical Prostatectomy
  - Radiation Therapy
# Inclusion Criteria AS Protocols

<table>
<thead>
<tr>
<th>AS protocol</th>
<th>Clinical stage</th>
<th>PSA</th>
<th>Gleason</th>
<th>Positive cores</th>
<th>Core positivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tosoian et al. (Johns Hopkins)</td>
<td>&lt;T2a</td>
<td>–</td>
<td>≤3 + 3</td>
<td>≤2</td>
<td>≤50</td>
</tr>
<tr>
<td>Klotz et al. (University of Toronto)</td>
<td>≤10*</td>
<td>≤3 + 3*</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Bul et al. (PRIAS)</td>
<td>≤T2</td>
<td>≤10</td>
<td>≤3 + 3</td>
<td>≤2</td>
<td>≤50</td>
</tr>
<tr>
<td>Dall'Era et al. (UCSF)</td>
<td>≤T2a</td>
<td>≤10</td>
<td>≤3 + 3</td>
<td>≤33%</td>
<td>≤50</td>
</tr>
<tr>
<td>Berglund et al. (MSKCC)</td>
<td>≤T2a</td>
<td>≤10</td>
<td>≤3 + 3</td>
<td>≤3</td>
<td>≤50</td>
</tr>
<tr>
<td>Van As et al. (Royal Marsden)</td>
<td>≤T2a</td>
<td>≤15</td>
<td>≤3 + 3</td>
<td>≤50%</td>
<td>–</td>
</tr>
<tr>
<td>Soloway et al. (Miami)</td>
<td>≤T2a</td>
<td>≤10</td>
<td>≤3 + 3</td>
<td>≤2</td>
<td>≤20</td>
</tr>
</tbody>
</table>

*Until 1999, PSA ≤15 and Gleason ≤3+4 were used.*
## Follow-up for AS Protocols

<table>
<thead>
<tr>
<th>Protocol</th>
<th>DRE</th>
<th>PSA</th>
<th>Biopsy</th>
<th>Imaging techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tosoian et al. (Johns Hopkins)</td>
<td>6 months</td>
<td>6 months</td>
<td>Annual</td>
<td></td>
</tr>
<tr>
<td>Klotz et al. (University of Toronto)</td>
<td>3 months (2 years)</td>
<td>3 months (2 years)</td>
<td>Confirmation: 6–12 months</td>
<td>MRI optional</td>
</tr>
<tr>
<td></td>
<td>6 months if PSA stable</td>
<td>6 months if stable</td>
<td>Repetition: 2 years (to age 80 years)</td>
<td></td>
</tr>
<tr>
<td>Bul et al. (PRIAS)</td>
<td>3 months (2 years)</td>
<td></td>
<td>1, 4, and 7 years</td>
<td>TRUS 6–12 months</td>
</tr>
<tr>
<td></td>
<td>6 months (after)</td>
<td></td>
<td>If PSADT = 3–10, repeat biopsy</td>
<td></td>
</tr>
<tr>
<td>Dall'Era et al. (UCSF)</td>
<td>3 months</td>
<td>3 months</td>
<td>1–2 years (since 2003)</td>
<td></td>
</tr>
<tr>
<td>Berglund et al. (MSKCC)</td>
<td></td>
<td></td>
<td>Confirmation: 3 months</td>
<td>MRI prior to confirmation biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Repetition: annual</td>
<td></td>
</tr>
<tr>
<td>Soloway et al. (Miami)</td>
<td>3 months (2 years)</td>
<td>3 months (2 years)</td>
<td>Confirmation: 9–12 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 months if PSA stable</td>
<td>6 months if stable</td>
<td>Repetition: annual</td>
<td></td>
</tr>
<tr>
<td>Carter et al. (Johns Hopkins)</td>
<td>6 months</td>
<td>6 months</td>
<td>Annual</td>
<td></td>
</tr>
</tbody>
</table>

# Criteria for Progression

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Gleason</th>
<th>Positive cores</th>
<th>Percentage of core affected</th>
<th>PSADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tosoian et al. (Johns Hopkins)</td>
<td>&gt;6</td>
<td>&gt;2</td>
<td>&gt;50</td>
<td>–</td>
</tr>
<tr>
<td>Klotz et al. (University of Toronto)</td>
<td>4 + 3</td>
<td>–</td>
<td>–</td>
<td>&lt;3 yrs</td>
</tr>
<tr>
<td>Dall'Era et al. (UCSF)</td>
<td>Increase</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Soloway et al. (Miami)</td>
<td>&gt;3 + 3</td>
<td>&gt;2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Thomsen et al. (University of Copenhagen)</td>
<td>≥4 + 3</td>
<td>&gt;3</td>
<td>–</td>
<td>≤3/5 yrs</td>
</tr>
</tbody>
</table>

Long-term Follow-up of AS Cohort University of Toronto (Sunnybrook)

- N=993 (220 followed ≥10 yrs, 50 more than 15 yrs)
- Median follow-up: 6.4 years
- Mets in 2.8% at median 7.3 yrs (from dx)
- 15 deaths (1.5%) from prostate cancer
- Cumulative hazard non-prostate to prostate cancer mortality: 9.2:1
Thank you!
Multidisciplinary Care for High Risk Newly Diagnosed Prostate Cancer

Mark Garzotto, MD
Professor of Urology and Radiation Medicine
Portland VAMC
Trends in Death Rates Among Males for Selected Cancers

PCA Mortality has dropped 40% since introduction of PSA Test

CA CANCER J CLIN 2012;62:10–29
### Estimated Cancer Deaths in the US in 2015

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>312,150</td>
<td>277,280</td>
</tr>
<tr>
<td>Prostate</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Key Point: Prostate Cancer is the second most lethal cancer in men in West
Demographic Factors for High-risk Disease

• Age
• Race
• Obesity
• Diet
• Family history
• Environmental exposures
Prostate Cancer Heterogeneity: Not One Disease

http://prostate-cancer.org/the-gleason-score-a-significant-biologic-manifestation-of-prostate-cancer-aggressiveness-on-biopsy/

What is the Natural History of Prostate Cancer

16-fold increase in death by grade

JAMA. 2005 May 4;293(17):2095-101
## NCCN Guidelines Version 4.2018
### Prostate Cancer

#### Risk Stratification and Staging Workup

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very low</strong></td>
<td>• T1c AND</td>
<td>Not Indicated</td>
<td>Not Indicated</td>
<td>Consider if strong family history[^2]</td>
<td>See PROS-4</td>
</tr>
<tr>
<td></td>
<td>• Gleason score 6/grade group 1 AND</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PSA &lt;10 ng/mL AND</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Fewer than 3 prostate biopsy fragments/cores positive, &gt;50% cancer in each fragment/cores AND</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PSA density &lt;0.15 ng/mL/g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>• T1-T2a AND</td>
<td>Not Indicated</td>
<td>Not Indicated</td>
<td>Consider if life expectancy ≤10y[^2]</td>
<td>See PROS-3</td>
</tr>
<tr>
<td></td>
<td>• Gleason score 6/grade group 1 AND</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PSA &lt;10 ng/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Favorable intermediate</strong></td>
<td>• T2b-T2c OR, Gleason score 3+4/7/grade group 2 OR AND</td>
<td>Bone imaging[^4]: not recommended for staging</td>
<td>Consider if life expectancy ≤10y[^2]</td>
<td>Consider if strong family history[^2]</td>
<td>See PROS-6</td>
</tr>
<tr>
<td></td>
<td>• PSA 10-20 ng/mL AND</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Percentage of positive biopsy cores &lt;50%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unfavorable intermediate</strong></td>
<td>• T2b-T2c OR, Gleason score 3+4/7/grade group 2 OR AND</td>
<td>Bone imaging[^4]: recommended if T2 and PSA &gt;10 ng/mL</td>
<td>Not routinely recommended</td>
<td>Consider if strong family history[^2]</td>
<td>See PROS-7</td>
</tr>
<tr>
<td></td>
<td>• PSA 10-20 ng/mL AND</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Gleason score 3+4/7/grade group 2 or Gleason score 4+5/7/grade group 3 OR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>• T2a OR</td>
<td>Bone imaging[^4]: recommended</td>
<td>Not routinely recommended</td>
<td>Consider[^5]</td>
<td>See PROS-8[^6]</td>
</tr>
<tr>
<td></td>
<td>• Gleason score 3/grade group 4 or Gleason score 4+5/7/grade group 5 OR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PSA ≥20 ng/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Very high</strong></td>
<td>• T3a-T4 OR</td>
<td>Bone imaging[^4]: recommended</td>
<td>Not routinely recommended</td>
<td>Consider[^5]</td>
<td>See PROS-8[^6]</td>
</tr>
<tr>
<td></td>
<td>• Primary Gleason pattern 5 OR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ≥4 cores with Gleason score 8–10/ grade group 4 or 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[^1]: Imaging includes bone imaging and pelvic or abdominal imaging.
[^2]: Consider if strong family history.
[^3]: See PROS-4, PROS-3, PROS-6, PROS-7, PROS-8.
[^4]: Bone imaging is not recommended for staging.
[^5]: Pelvic and abdominal imaging is recommended if nomogram predicts >10% probability of pelvic lymph node involvement.
[^6]: Pelvic and abdominal imaging is recommended if nomogram predicts >10% probability of pelvic lymph node involvement.
### Nomograms/Prognostic Tools

<table>
<thead>
<tr>
<th>Definitive Therapy</th>
<th>Prognostic Tool/Nomogram</th>
<th>Predicted Outcome</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-RP</td>
<td>Partin(^1)</td>
<td>Pathological stage</td>
<td>OC = 0.77</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EPE = 0.70</td>
</tr>
<tr>
<td></td>
<td>Kattan(^2)</td>
<td>Low Pathological stage</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>Stephenson(^3)</td>
<td>10-year disease recurrence</td>
<td>0.79</td>
</tr>
<tr>
<td>3D-CRT</td>
<td>Kattan(^4)</td>
<td>BCR</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-year Mets free survival</td>
<td>0.81</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>Kattan(^5)</td>
<td>5-year biochemical risk recurrence without neoadjuvant hormonal therapy</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Eur Urol editorial 2006 (Frohner):
“The course of early prostate cancer remains difficult to predict despite the multitude of available nomograms.”

Decipher Post Prostatectomy Test

- Test: 22 gene RNA assay on archived tissue.
- Output = Genomic Classifier (GC).
- FDA approved: No
- Cost: $4000.
- CMS Covered in Palmetto GBA (high-risk)
- Data: retrospective
- Indication: High-risk PCA
## Decipher: Clinical Data

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Samples</th>
<th>Outcome</th>
<th>Predictors</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnes</td>
<td>N= 219 Retrospective RP cohort Very High Risk</td>
<td>RP Specimens</td>
<td>Time to- Mets</td>
<td>Prognostic: GC Score Superior to: Gleason PSA LN+ ECE SM</td>
<td>No validation set No Clinical Utility shown HR=1.5/10% increase AUC = 0.79 Compared to Stephenson nomogram (NS)</td>
</tr>
<tr>
<td>Cooperberg</td>
<td>N=185 Retrospective RP cohort Very High Risk</td>
<td>RP Specimens</td>
<td>PCA mortality</td>
<td>Prognostic (MVA): GC Score CAPRA-S</td>
<td>No validation set No Clinical Utility shown HR = 1.7/unit (CI:1.3 to 2.3) GC vs. CAPRA: AUC = 0.75 vs. 0.78 (NS) GC+CAPRA = 0.78 (NS)</td>
</tr>
</tbody>
</table>

Cooperberg Eur Urol 2014
Probability of Mets Stratified by Decipherer GC Score
How is High-risk Localized Prostate Cancer Treated?
**High or Very High Risk Group**

**Expected Patient Survival**

- **EBRT\(^e\) + ADT\(^f\) (2–3 y; category 1)\(^{aa}\)**

- **EBRT\(^e\) + brachytherapy\(^e\) + ADT\(^f\) (1–3 y; category 1)**

- **>5 y**

  - Adverse feature(s) and no lymph node metastases:\(^{ul}\)
    - EBRT\(^e\)
    - Observation\(^l\)

  - **No adverse features or lymph node metastases**
    - **RP\(^s\) + PLND\(^bb\)**
    - **Lymph node metastasis:**
      - ADT\(^f\) (category 1) ± EBRT\(^e\) (category 2B)
      - Observation\(^l\)

- **Undetectable PSA after RP or PSA nadir\(^w\) after RT**

**See Monitoring for Initial Definitive Therapy (PROS-10)**

**See Radical Prostatectomy PSA Persistence/Recurrence (PROS-11)**

**See Radiation Therapy Recurrence (PROS-12)**
Treatment patterns by risk level.

Cooperberg M R et al. JCO 2010;28:1117-1123
What is the effect of treatment on PCA outcomes?
SPCG-4: Surgery Results in Improved Cancer Survival and Reduction in Systemic Spread

- 38% decrease in cancer death
- 41% reduction in metastatic disease

Bill-Axelson et al. NEJM 364:18, 2011
PIVOT: Prostate cancer mortality: PSA >10 ng/mL

PIVOT: Prostate cancer mortality: high-risk disease

Improvement in clinical outcome in patients treated with surgery

Key Point: If aggressive prostate cancer is detected it can be cured

<table>
<thead>
<tr>
<th></th>
<th>SPCG-4</th>
<th></th>
<th>PIVOT study</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td></td>
<td>PSA &lt; 10 ng/ml</td>
<td>PSA ≥ 10 ng/ml</td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>25%</td>
<td>ns</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Prostate cancer survival</td>
<td>38%</td>
<td>ns</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>Metastases-free survival</td>
<td>41%</td>
<td>ns</td>
<td>72%</td>
<td></td>
</tr>
<tr>
<td>Local control</td>
<td>67%</td>
<td>ns</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: SPCG = Swedish Prostate Cancer Group, PIVOT = Prostate Cancer Intervention Versus Observation Trial, ns = non-significant, NA = not available. All numerical outcomes statistically significant (P<0.05).*

Garzotto, Hung Surg Onc Clinics NA, 2013
EORTC 22863
Radiotherapy + Adjuvant ADT vs Radiotherapy Alone
Study Design

T1-2 WHO 3 or T3-4, N0-1

Randomized (n=415)

Radiotherapy + adjuvant goserelin 3.6 mg (n=207)

Radiotherapy Alone (n=208)

Hormonal Therapy at progression

Median follow-up at 45 months and 66 months

EORTC = European Organization for Research and Treatment of Cancer
Radiation: 50 Gy over 5 weeks + 20 Gy over 2 weeks
ZOLADEX 3.6 mg sc every 4 weeks starting day 1 of radiation and continuing for 3 years
Cyproterone acetate: 150 mg po qd for 1 month starting 1 week prior to ZOLADEX

Bolla M et al. NEJM 1997; 337(5)295-300; Bolla M et al. Lancet. 2002;360:103-108,
EORTC 22863:
Overall Survival 66-Month Follow-up

Log-rank test  \( p < .0001 \)
Hazard ratio 0.51
(95% CI: 0.36-0.73)

# RTOG Studies of AS with RT

<table>
<thead>
<tr>
<th>RTOG Study</th>
<th>Arms</th>
<th>Winner</th>
</tr>
</thead>
<tbody>
<tr>
<td>86-10</td>
<td>RT vs 3 mo. neo. ADT+RT</td>
<td>Neo. ADT+RT</td>
</tr>
<tr>
<td>85-31</td>
<td>RT vs. adj. ADT+RT</td>
<td>adj. ADT+RT</td>
</tr>
<tr>
<td>92-02</td>
<td>ST vs. LT ADT +RT</td>
<td>LT ADT +RT</td>
</tr>
<tr>
<td>94-13</td>
<td>Prostate vs. WP/Prostate Neo/adj. Vs. adj. ADT</td>
<td>WP/prostate Neo/adj. ADT</td>
</tr>
</tbody>
</table>

Abbreviations: RT: radiation therapy, ADT= androgen deprivation, LT= long-term, ST = short-term, WP= whole prostate, adj = adjuvant
Further Advances Will Require Multimodal Therapy

• OHSU Studies
Phase I/II Trial of Pre-operative Chemotherapy Prior to Prostatectomy for High-risk Prostate Cancer

Mark Garzotto, Cathy A. O’Brien, Celestia (Tia) Higano, Emily M. Wersinger, Christopher L. Corless, Paul H. Lange, Chris W. Ryan, Larry D. True, Pete Nelson, Tomasz M. Beer

Division of Urology & Renal Transplantation, Division of Hematology and Medical Oncology; Department of Pathology, Oregon Health & Science University and Portland VA Medical Center, Department of Urology; Division of Oncology; Department of Pathology, University of Washington
Neoadjuvant Mitoxantrone Plus Docetaxel: Initial Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA decline after chemotherapy*</td>
<td>88%</td>
</tr>
<tr>
<td>Median PSA change after chemotherapy</td>
<td>-42%</td>
</tr>
<tr>
<td>Negative surgical margins</td>
<td>68.8%</td>
</tr>
<tr>
<td>Post-operative serum PSA &lt; 0.2 ng/ml</td>
<td>83.3%</td>
</tr>
<tr>
<td>Nodal metastases present</td>
<td>18.8%</td>
</tr>
</tbody>
</table>

*testosterone unchanged
**PHASE I/II STUDY OF PREOPERATIVE RADIATION AND DOCETAXEL ACTIVITY IN HIGH-RISK LOCALIZED PROSTATE CANCER**

---

### Table #1: Patient Characteristics (n = 25)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Median</th>
<th>Range 48 - 76</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Cooperative Oncology Group</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PSA at Entry</td>
<td>Median</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>2.2 - 37.9</td>
</tr>
<tr>
<td>Clinical Stage (2002 Criteria)</td>
<td>T1c</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>T2a</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>T2c</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>T3a</td>
<td>6</td>
</tr>
<tr>
<td>Biopsy Gleason Score</td>
<td>3+4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>4+3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

### Table #3: Pathologic Outcome (n = 25)

<table>
<thead>
<tr>
<th>Pathologic Stage</th>
<th>T2a</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2c</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>pCR =0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node Positive (%)</td>
<td>6 (24%)</td>
<td></td>
</tr>
<tr>
<td>Surgical Gleason Score</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3+4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>4+3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Negative Margin (%)</td>
<td>22 (88%)</td>
<td></td>
</tr>
<tr>
<td>Post-op PSA &lt;0.1 ng/ml</td>
<td>24 (96%)</td>
<td></td>
</tr>
</tbody>
</table>

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Post-treatment effects of chemoradiation on prostate adenocarcinoma.
A) Atrophy of tumor glands with mucin accumulation;
B) Malignant glands being replaced by marked inflammation and fibrosis;
C & D) Marked nuclear atypia in benign and malignant glands.
Further Advances Will Require Multimodal Therapy

- Novel Therapeutics
  - Anti-androgens
  - Small Molecule Inhibitors
  - Immunotherapy
  - Chemotherapy

- Advanced Imaging

- Pathology

- Genomics
Map of Genetic Aberrations in PCA

Key Point: Genetically, PCA is a very heterogeneous disease.

Figure 6. Recurrent alterations in primary prostate cancer. The spectrum and type of recurrent alterations and genes (mutations, fusions, deletions, and overexpression) in the cohort are shown (left to right) grouped by main molecular subtypes. On the right, the statistical significance of individual mutant genes is shown. Mutations in IDH1, PIK3CA, RB1, KMT2D, CHD1, BRCA2, and CDX12 are also shown, despite their not being statistically significant. SPINK1 overexpression is shown for reference. (From Cancer Genome Atlas Research Network 2015; reprinted, with permission from Elsevier 2015.)

Rubin et al. Cold Spring Harb Perspect Med, 2018
PCA is heterogeneous but has a low mutational burden

For Prostate CA (TCGA cases): 13 ±18 mutations/case (mean ±SD)
Mutation rate 8.3E-7 ± 8.7E-7

Lawrence et al. Nature 2013
OHSU Advanced Imaging Research Center

- Director: Charles Springer, PhD
- Bruker 12T MRI
- Siemens 7T MRI
- Siemens 3T

Future Current Directions

Knight Cancer Research Building

- 320,000 sq feet
- Houses 600 researchers
- Biostatistics
- Home of Cancer Early Detection Advanced Research Center (CEDAR)

[Link](https://news.ohsu.edu/2016/06/16/ohsu-breaks-new-ground-in-cancer-research)
CEDAR Focus Areas

https://www.ohsu.edu/xd/health/services/cancer/research-training/research-programs/cedar/research/focus.cfm