6th Annual Prostate Cancer Forum
Thursday, September 19, 2019

5:00 P.M. | Reception

6:00 P.M. | Welcome
Randall Holcombe, MD, MBA
Director
UH Cancer Center

6:05 P.M. | Introduction
Charles Kim, MD
Urologist
Pali Momi Medical Center

6:10 P.M. | Prostate Cancer – To treat or not to treat
David Wei, MD, FACS
Urologist
Kaiser Permanente

6:25 P.M. | New Imaging Agent to Evaluate Early Prostate Cancer Recurrence
Marc Coel, MD, FACR
Nuclear Medicine, Diagnostic Radiologist
The Queen’s Medical Center

6:40 P.M. | Advances in Prostate Radiation Oncology
Richard Lee, MD, PhD
Radiation Oncologist
The Cancer Center of Hawai’i

6:55 P.M. | Treatment Options for Advanced Prostate Cancer
Ian Okazaki, MD
Medical Oncologist
Straub Medical Center

7:10 P.M. – 8:00 P.M. | Open forum, Q & A
Prostate Cancer
Radiation Therapy Past, Present, and Future

Richard Y. Lee, MD PhD

September 19, 2019
Prostate Cancer

- 2nd most frequently diagnosed cancers (19% of all male cancers)
- 2nd leading cause of cancer death in men (lung cancer first) in the US
- 6th leading cause of cancer death in men, worldwide

Risk Factors
- Age, Obesity, family history
- Average time of diagnosis is 70 years old
- Higher rates in developed countries
# Workup

## NCCN Guidelines Version 4.2019
**Prostate Cancer**

### Initial Risk Stratification and Staging Workup for Clinically Localized Disease

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Clinical/Pathologic Features</th>
<th>Imaging[^1]</th>
<th>Germline Testing</th>
<th>Molecular and Biomarker Analysis of Tumor[^1]</th>
<th>Initial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>T1c AND Grade Group 1 AND PSA &lt;10 ng/mL AND Fewer than 3 prostate biopsy fragments/cores positive, &lt;50% cancer in each fragment/core AND PSA density &lt; 0.15 ng/mL/l</td>
<td>Not indicated</td>
<td>Recommended if family history positive or intraductal histology [See PROS-1]</td>
<td>Not indicated</td>
<td>See PROS-4</td>
</tr>
<tr>
<td>Low</td>
<td>T1-T2a AND Grade Group 1 AND PSA &lt;10 ng/mL</td>
<td>Not indicated</td>
<td>Recommended if family history positive or intraductal histology [See PROS-1]</td>
<td>Consider if life expectancy ≥10y[^2]</td>
<td>See PROS-5</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Has no high- or very-high-risk features and has one or more intermediate risk factors (IRFs): T2b-T2c, Grade Group 2 or 3, PSA 10–20 ng/mL</td>
<td>Favorable Intermediate</td>
<td>Bone imaging[^1]: not recommended for staging pelvic ± abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</td>
<td>Recommended if family history positive or intraductal histology [See PROS-1]</td>
<td>Consider if life expectancy ≥10y[^2]</td>
</tr>
<tr>
<td></td>
<td>Unfavorable Intermediate</td>
<td>2 or 3 IRFs and/or Grade Group 3 and/or &gt;50% biopsy cores positive[^9]</td>
<td>Bone imaging[^1]: recommended if T2 and PSA &gt;10 ng/mL pelvic ± abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</td>
<td>Recommended if family history positive or intraductal histology [See PROS-1]</td>
<td>Not routinely recommended</td>
</tr>
<tr>
<td>High</td>
<td>T3a OR Grade Group 4 or Grade Group 5 OR PSA &gt;20 ng/mL</td>
<td></td>
<td>Bone imaging[^1]: recommended pelvic ± abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</td>
<td>Recommended[^2]</td>
<td>Not routinely recommended</td>
</tr>
<tr>
<td>Very High</td>
<td>T3b-T4 OR Primary Gleason pattern 5 OR &gt;4 cores with Grade Group 4 or 5</td>
<td></td>
<td>Bone imaging[^1]: recommended pelvic ± abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</td>
<td>Recommended[^2]</td>
<td>Not routinely recommended</td>
</tr>
</tbody>
</table>
Treatment Options

HIGH OR VERY HIGH RISK GROUP

EXPECTED PATIENT SURVIVAL

>5 y or symptomatic

≥5 y and asymptomatic

INITIAL THERAPY

ADJUVANT THERAPY

EBRTq + ADTu (1.5–3 y; category 1 for ADT)

EBRTq + brachytherapyq + ADTu (1–3 y; category 1 for ADT)

Adverse feature(s) and no lymph node metastases:
EBRTq ± ADTu (6 mo) or Observation

No adverse features or lymph node metastases

Lymph node metastasis:
ADTu (category 1) ± EBRTq (category 2B) or Observation

Undetectable PSA after RP or PSA nadirx after RT

PSA persistence/recurrence

See Monitoring for Initial Definitive Therapy (PROS-11)

See Radical Prostatectomy PSA Persistence/Recurrence (PROS-12)

See Radiation Therapy Recurrence (PROS-13)
The Physics of Radiation Oncology

- What is radiation?
  - “the complete process by which energy is emitted by one body, transmitted through an intervening medium or space, and absorbed by another body.”
- Gray (Gy) -- amount of energy absorbed in tissue
Bragg’s Peak

Particles and photons
The electromagnetic spectrum
How are x rays generated?
The linear accelerator

- High energy photons and electrons
- Uniform beam characteristics
- Precise field shaping
- Precise delivery
  - The gantry rotates
  - The couch rotates
  - The patient is immobilized
The 4 “R”s of fractionated radiation

- **Repair**
  - Healthy cells repair DNA damage (so do tumor cells unfortunately)

- **Reassortment (redistribution)**
  - Radiation causes cells to accumulate in certain phases of the cell cycle

- **Reoxygenation**
  - Tumors reoxygenate after radiation

- **Repopulation**
  - Tumor and normal cells repopulate between doses of radiation
DNA is the primary target of radiation

- Indirect
- Direct
- SSB are repaired
- DSB are key

Cells that correct DNA dsb go on to divide another day…..REPAIR
Outline

Redistribution

Ionizing Radiation

- Rb-dependent G1 Arrest
- Cdk2 phosphorylation
- Atm phosphorylation of Serine-15
- CDKs down regulation
- c-Abl binding
- dephosphorylation of Serine-376
- phosphorylations
- p53 binding
- 14-3-3 binding
- Increased sequence-specific DNA binding
- Transcriptional Transactivation
- Cell Cycle Arrest
- Apoptosis

Accumulation in G1 & G2

Figure 2. Cell Replication Cycle Showing Checkpoints Influenced by Intact p53 and p21 Genes.

G2 Checkpoint
- Mitosis
- G2 Phase
- DNA Synthesis
- G1 Phase
- G0 Resting Phase
- G1 Checkpoint

Radiation induces cell cycle arrest to repair DNA Damage….. REDISTRIBUTION
M > G2 > ES > LS Redistribution into a sensitive phase can matter!
Reoxygenation

Following radiation, tumors reoxygenate rapidly…...REOXYGENATION
Repopulation – Minimize treatment breaks

- Cell population also grows during radiotherapy
- For tumour cells, this repopulation partially counteracts the cell killing effect of radiotherapy
- The potential doubling time of tumours, $T_p$ (e.g. in head and neck tumours or cervix cancer) can be short as 2 days – therefore one loses up to 1 Gy worth of cell killing when prolonging the course of radiotherapy
Shaping Advancements of EBRT Delivery

- 2-Dimensional planning (using x-rays films)
- 3-dimensional planning (Using CT Scans)
- IMRT (Intensity Modulating Radiation Therapy)
- VMAT (Volume Modulated Arc Therapy)
3 D Conformal (Conventional) RT

CONVENTIONAL EBRT PORTALS

- Field Borders
  - Superior border: L5-S1
  - Inferior border: 1.5-2 cm distal to junction of prostatic and membranous urethra (lower border of ischial tuberosity)
  - Lateral border: 1.5-2 cm lateral to bony pelvis
- Common iliac LN treated by extending field 3 cm superiorly

Lateral Borders

- Anterior margin: Anterior to pubic symphysis
- Posterior margin: S2-3 interspace to include the upper presacral LN

Boost field

- Prostate+ SV
  - Superior border extends to the top of the acetabulum - 3-5 cm above pubis
  - Inferior border: ischial tuberosity
  - Laterally to include 2/3 of the obturator foramen
  - Anterior border: 1.5 cm posterior to ant. margin of pubic symphysis
  - Posterior border: 2 cm behind the rectal marker
• Intensity Modulated Radiation Therapy
  ▪ Inverse planning is the key
  ❖ The radiation oncologist selects the volume to be irradiated and the volumes to be spared. The computer then selects the optimal way to deliver dose
• VMAT: Volumetric Modulated Arc Therapy
  ▪ This is a newer form of delivering IMRT
    ▪ The gantry is constantly moving in an arc
    ▪ In the older version of IMRT delivery, called fixed angle, the gantry stops at certain points and delivers the dose
Advancements of Brachytherapy

- Low Dose Rate (< 2 Gy / hour)
  - $^{125}$I (half-life 59.4 days)
  - Pd$^{103}$ (half-life 17 days)
  - Cs$^{131}$ (half life 9.7 days)
- High Dose Rate (> 12 Gy / hour)
  - Ir$^{192}$ (half life 74 days)
LDR Brachytherapy
HDR Brachytherapy
Dose Volume Histogram

Prostate:1 - Treatment Approved - Dose Volume Histogram

Outline
# Radiation Toxicities

<table>
<thead>
<tr>
<th>Immediate Reactions</th>
<th>Long Term Reactions</th>
</tr>
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<tbody>
<tr>
<td><strong>Common:</strong></td>
<td><strong>Common:</strong></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Loss of sexual function</td>
</tr>
<tr>
<td>Increased urinary frequency and/or urgency</td>
<td>Sterility</td>
</tr>
<tr>
<td>Burning or discomfort on urination</td>
<td><strong>Uncommon:</strong></td>
</tr>
<tr>
<td>Rectal irritation; increased frequency of bowel movement or change in stool consistency; straining/discomfort with bowel movement</td>
<td>Rectal bleeding</td>
</tr>
<tr>
<td>Skin reddening and irritation</td>
<td>Chronic mild diarrhea</td>
</tr>
<tr>
<td>Hair loss in the treated area</td>
<td><strong>Rare:</strong></td>
</tr>
<tr>
<td>If present, hemorrhoidal irritation</td>
<td>Chronic severe diarrhea</td>
</tr>
<tr>
<td><strong>Uncommon:</strong></td>
<td>Decreased bladder capacity</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Difficulty passing urine</td>
</tr>
<tr>
<td>Rectal bleeding or blood in the urine</td>
<td>Blood in urine</td>
</tr>
<tr>
<td><strong>Rare:</strong></td>
<td>Rectal or urinary bleeding or ulceration requiring transfusion</td>
</tr>
<tr>
<td>Urinary obstruction</td>
<td>Extremely Rare:</td>
</tr>
<tr>
<td><strong>Extremely Rare:</strong></td>
<td>Rectal or urinary bleeding, ulceration requiring surgery, rectal damage requiring permanent colostomy</td>
</tr>
<tr>
<td>Decreased blood cell count</td>
<td>Leg or scrotal swelling in patients who underwent a nodal dissection</td>
</tr>
<tr>
<td></td>
<td>Tumors caused by radiation</td>
</tr>
</tbody>
</table>

NOTE: The risk of complications may be increased if a TURP is required in the future
Imaging

- Standard (Portal Image with MV x-rays)
IGRT

• Image Guided Radiation Therapy
  ▪ Uses daily imaging (X-ray, US, CT, MRI, etc) to limit the effect of ITV
IGRT (CBCT)
Outline

SpaceOARs
Phase 3 Clinical trial: SpaceOARs

Grade 1: Mild; intervention not indicated
Grade 2: Moderate symptoms; medical intervention or minor cauterization indicated

Hamstra et al. IJROBP 97 (5), 2017
Thank you.
Treatment Options for Advanced Prostate Cancer

Ian Okazaki, MD
Chief, Oncology/Hematology
Objectives

- Intensification of androgen deprivation.
- Combination therapy for castrate-sensitive and castrate-resistant prostate cancer.
- Bone protecting agents for skeletal metastases.
Definitions

• Androgen deprivation therapy (ADT).
  – Depleting testosterone to treat advanced prostate cancer.
  – Leuprolide, degarelix.

• Castrate-sensitive prostate cancer.
  – Prostate cancer (PSA) remains suppressed with a ADT.

• Castrate resistant prostate cancer.
  – Prostate cancer (PSA) progression in spite of ADT.
ADT: Androgen Deprivation Therapy

Intensification of ADT

Crona, DJ et al. Cancers 2017, 9(6), 67
Intensification of ADT with Docetaxel

- ADT vs. ADT + docetaxel (6 cycles) for metastatic hormone insensitive prostate cancer (ECOG-ACRIN E3805, CHAARTED).
- 790 patients from July 2006 through December 2012.
- Primary objective: Overall survival.
- Secondary objective: PSA, side effects.
Adding docetaxel to ADT improves survival in men with metastatic castration-sensitive prostate cancer

**Primary endpoint: Overall survival**

- HR = 0.61 (0.47-0.80), p = 0.0003
- Median OS:
  - ADT + D: 57.6 months
  - ADT alone: 44.0 months

Presented by Christopher J. Sweeney, MBBS

Presented By Christopher Sweeney at 2014 ASCO Annual Meeting
CREATING A HEALTHIER HAWAIʻI

CHAARTED

Christopher Sweeney et al NEJM 2015
Intensification of ADT with Abiraterone

- ADT vs. ADT plus abiraterone/prednisone for metastatic hormone-sensitive prostate cancer (LATITUDE).
- 1199 patients with median follow-up of 30.4 months.
- Primary endpoints:
  - Overall survival.
  - Radiographic progression-free survival.
- Secondary end points:
  - Time to the next skeletal-related event.
  - Time to PSA progression.
  - Time to pain progression.

Overall survival and a graphic progression-free survival.

The median rate of overall survival was not reached in the abiraterone group and was 34.7 months in the placebo group.

The medians for progression-free survival were 33.0 months and 14.8 months.
Abiraterone Adverse Effects

- Common: Sweating, hot flashes, weakness, joint swelling or pain, cough, vomiting, diarrhea, swelling in the legs or feet.
- Less common: Swelling of the hands/feet, muscle aches/discomfort, decreased levels of potassium.
Intensification of ADT with Enzalutamide

• ADT plus nonsteroidal antiandrogen (bicalutamide) vs. ADT plus enzalutamide for metastatic castrate-sensitive prostate cancer (ENZAMET).

• 1125 patients with median follow-up of 33 months.
  – High versus low volume of metastases.
  – Early docetaxel versus no docetaxel.

• Primary endpoints:
  – Overall survival.

• Secondary endpoints:
  – PSA progression free survival.
  – Clinical progression survival.
  – Adverse effects.

Overall Survival, PSA Progression-free and Clinical Progression-free Survival

Ezalutamide Adverse Effects

- **Common:** Fatigue, weakness, decreased appetite, weight loss, hot flashes, joint pain, headache, dizziness, vertigo, high blood pressure,
- **Less common:** Allergic reactions, coronary artery disease, seizure, falls and fractures, posterior reversible encephalopathy syndrome (PRES).
Intensification of ADT with Apalutamide

- ADT vs. ADT plus apalutamide for metastatic castrate sensitive prostate cancer (TITAN).
- Primary endpoints:
  - Overall survival.
  - Radiographic progression-free survival.
- Secondary end points:
  - Time to chemotherapy.
  - Time to pain progression.

ADT with Apalutamide

Intensification of ADT with Apalutamide

• Apalutamide improved overall survival with a 33% reduction in risk of death.
  – Median overall survival was not reached in the apalutamide or placebo groups.
  – Time to initiation of cytotoxic chemotherapy was significantly improved with apalutamide.

• Apalutamide improved radiographic progression-free survival with a 52% reduction in risk of death or radiographic progression.
  – The median radiographic progression-free survival was not reached in the apalutamide group and was 22.1 months in the placebo group.

Apalutamide Adverse Effects

• Common (≥10%): Fatigue, hot flush, decreased appetite, weight loss, rash, nausea, diarrhea, arthralgia, fall, fracture, peripheral edema, and hypertension.

• Less common: Seizures and falls.
Intensification of ADT in Metastatic Castrate-sensitive Prostate Cancer.

• ADT plus abiraterone increased overall survival and radiographic progression-free survival.
  – There was a slightly increased risk of hypertension and potassium with the addition of abiraterone,

• ADT plus enzalutamide improved overall survival and progression-free survival.
  – There was a higher incidence of seizures and falls in the enzalutamide group, and other toxic effects among those treated with early docetaxel chemotherapy.

• ADT plus apalutamide improved overall survival and radiographic progression-free survival.
  – Apalutamide is also effective for castrate-resistant prostate cancer without radiographic evidence of metastases.
Metastatic Castrate-resistant Prostate Cancer

- ADT plus apalutamide is effective for castrate-resistant prostate cancer without radiographic evidence of metastases.
- The addition of abiraterone or enzalutamide to ADT improves progression free survival and progression of skeletal events for metastatic castrate-resistant prostate cancer.
- Is combined antiandrogen therapy any better than one agent at a time?
Metastatic Castrate-resistant Prostate Cancer

- ADT and enzalutamide plus placebo vs. enzalutamide plus abiraterone for metastatic castrate-resistant prostate cancer (PLATO).
- 509 patients treated with enzalutamide (period 1) then 251 randomized to enzalutamide plus placebo or enzalutamide plus abiraterone if there is no PSA progression at 13 and 21 weeks (period 2).

Primary endpoints:
- Progression-free survival.

Secondary end points:
- PSA progression.
- Pain progression.

Abiraterone With or Without Enzalutamide in Metastatic Castrate-resistant Prostate Cancer

Fig 1. (A) Scientific hypotheses underlying PLATO trial and (B) PLATO trial design. Actual patient numbers at each trial milestone are included on the bottom row of panel B, and target numbers are included in brackets. More details on period one patient disposition are provided in the Data Supplement. AR, androgen receptor; PFS, progression-free survival; PSA, prostate-specific antigen. (*) Random assignment was stratified by confirmed PSA response at week 13 in period one (i.e. 0% to < 30% v
Abiraterone With or Without Enzalutamide in Metastatic Castrate-resistant Prostate Cancer


HR, 0.83; 95% CI, 0.61 to 1.12; P = .22

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Control group</th>
<th>Combination group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>125</td>
<td>126</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td>85</td>
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<tr>
<td>6</td>
<td>46</td>
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<td>10</td>
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<tr>
<td>18</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No. at risk:
Metastatic Castrate-resistant Prostate Cancer

• Abiraterone and enzalutamide (or other second-generation antiandrogen) should not be combined in the metastatic CRPC setting.
• No difference in progression free survival for PSA progression.
• More patients in the combination group stopped therapy because of the adverse events.
• Sequential therapy in addition to ADT is the standard of care, although there is suspected cross-resistance with sequential agents to intensify androgen deprivation.
Metastatic Castrate-resistant Prostate Cancer

• Sipuleucel T-cell immunotherapy for castration-resistant prostate cancer.
  – Sipuleucel-T (341 patients) vs. placebo (171 patients) administered intravenously every 2 weeks, for a total of three infusions.

• Primary endpoint:
  – Overall survival.

• Secondary endpoint:
  – Time to objective disease progression.

Sipuleucel-T: Activated Dendritic Cells Stimulate Cytotoxic T Cells

Handy, CE et al. FUTURE ONCOLOGY 2017;14(10):
Sipuleucel-T prolonged survival among men with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. However, no significant effect on the time to objective disease progression was observed.


The median survival was 4.1 months longer in the sipuleucel-T group (25.8 months) than in the placebo group (21.7 months)
Skeletal-related Events in Prostate Cancer
Bone-protecting Agents: Denosumab or Zoledronic Acid

Boyle, WJ et al. Nature 2003; 423:337-342
Bone Protecting Agents

• ERA223 trial randomized 806 patients with chemotherapy-naïve, mCRPC with bone metastasis to radium-223 vs. placebo, in addition to abiraterone acetate.

• Fractures were more common among patients receiving radium-223 plus abiraterone acetate (29%) than those receiving abiraterone acetate plus placebo (11%). Subsequently, the FDA advised against this combination.

• Only 40% of patients in this trial received bone protective agents. In post-hoc analysis, bone protective agents significantly reduced the rate of fracture 37% vs 15% in the abiraterone-radium 223 arm with and without bone protective agents, respectively.

Smith, M et al. Lancet Oncol 2019, MAR 1: 20(3); 408-419
Bone Protecting Agents

- EORTC 1333/PEACE III trial randomized patients to enzalutamide vs. enzalutamide plus radium-223 in asymptomatic or mildly symptomatic mCRPC patients.
- There is a 13% risk of fracture with enzalutamide in asymptomatic mCRPC, and the risk is significantly increased to 33% when radium-223 is added to enzalutamide.
- The risk is almost abolished by mandatory continuous administration of bone protective agents starting at least 6 weeks before the first injection of radium-223.
Bone Protecting Agents

• Decreased fracture rate by mandating bone-protecting agents for mCRPC.
• Bone protecting agent is standard of care and should be initiated 6 weeks prior to radium-223.
• Combination of radiation 223 and additional agent is not recommended outside of a clinical trial.
Summary

- ADT plus docetaxel or androgen receptor targeted therapy (abiraterone, enzalutamide, apalutamide) is effective therapy for metastatic castrate-sensitive prostate cancer.
  - Docetaxel may be preferred for high volume metastatic disease.

- Abiraterone or enzalutamide is effective when added to ongoing ADT for metastatic castrate-resistant prostate cancer.
  - Abiraterone and enzalutamide (or other second-generation antiandrogen) should not be combined in the metastatic castrate-resistant prostate cancer setting.

- Sipuleucel-T prolonged survival among men with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer.
  - However, no significant effect on the time to objective disease progression was observed.

- Bone protecting agent is the standard of care for metastatic castrate-resistant prostate cancer and should be administered at least 6 weeks prior to radium-223 therapy.
  - Combination of radiation 223 and additional agent should be avoided except in a clinical trial setting.
Thank you!

I am not Superman but I'm fighting prostate cancer so close enough.
Prostate Cancer:
To Treat or Not To Treat

David C. Wei, MD FACS
Assistant Clinical Professor, UH School of Medicine
Kaiser Moanaula Medical Center Urology Service
Prostate Cancer

• The most common cancer in American males
  • 174,650 men will be diagnosed in 2019.
  • 1 in 7 men will be diagnosed in lifetime

• Third highest cancer death in the United States.
  • 1 out of 41 men will eventually die from prostate cancer.
  • Until recently, it was the second leading cause of cancer death.
  • Reduced by 51% from the peak, “possibly” due to early detection and improved treatment.

• Why the controversy – to treat or not to treat?
Why the Controversy?

• Prostate cancer can be an indolent disease
  • 174,650 men will be diagnosed to have prostate cancer in 2019.
  • 31,620 men will die from prostate cancer in 2019

• Prostate cancer can be over diagnosed and over treated
  • If a patient is unlikely to die from prostate cancer, why the diagnosis or treatment?
  • Infection or sepsis from prostate biopsy. Impotence and urinary problems from treatment

• False positive screening tests, such as PSA (prostate specific antigen), cause unnecessary worries
  • The feared C word
  • What is my PSA level this time – PSA anxiety
PSA (prostate specific antigen)

• Good
  • Excellent screening tool
    • Provide lead time of prostate cancer diagnosis by 12.3 years in 55-year-olds
  • A simple test
    • Blood test
  • Relatively inexpensive
    • Covered by insurances for most patients
  • End result
    • 51% reduction in prostate cancer between 1993 and 2016 in what is generally considered to be the PSA era

• Bad
  • Results are easily influenced by
    • Medications, instrumentation, infection, trauma or ejaculation.
  • Low sensitivity and predictive values
    • 18%-25% for PSA between 4-10 ng/mL
  • Not a cancer-specific marker
    • 25% of patients has normal PSA level on repeat study after initial high PSA blood test.
Studies about the PSA Screening Efficacy

• PLCO (prostate, lung, colorectal and ovarian) Trial
  • 76,685 men
  • 13 and 15 years follow-up
  • Control vs. screening groups – no significant changes in the disease-specific survival.
  • Flawed study
    • Low biopsy rate
    • PSA screening in control group (2.7 tests per person)
    • Not reflective of general population make up (<5% African American).

• ERSPC (European Randomized Study for Screening Prostate Cancer)
  • 182,000 men in 8 European countries
  • 11 years median follow-up - 21% reduction in death with screening
  • 13 years median follow-up - 27% reduction in death with screening
  • 11 years median follow-up - Need to screen 1055 men and to treat 37 men in order to avoid one death
  • 16 years follow-up – Need to screen 570 men and to treat additional 18 patients to avoid one death
US Preventive Services Task Force

• The U.S. Preventive Services Task Force is an independent, volunteer panel of national experts in disease prevention and evidence-based medicine. The Task Force works to improve the health of all Americans by making evidence-based recommendations about clinical preventive services

• 2012 USPSTF gave recommendation letter grade D for PSA screening

• 2018, the final recommendation was changed to letter grade C for PSA screening
After USPSTF Recommendation

- After recommendation was released in 2012
  - Decline in the PSA screening
  - Decline in the prostate biopsy
  - Decline in the diagnosis of localized prostate cancer
  - Decline in the surgery for prostate cancer
  - Increase in metastatic disease
USPSTF Current Recommendation

- New 2018 recommendation
  - PSA screening is an individual decision — **not a population-based exam.** Discussed with your health provider.
  - PSA screening only between age 55 to 69.
  - PSA screening not advised for patient over age 70.
<table>
<thead>
<tr>
<th>Other Guidelines</th>
</tr>
</thead>
</table>
| **AUA (American Urological Association)**  
Early Detection of Prostate Cancer Guidelines 2018 |
| - No screening before age 40 |
| - No ROUTINE screening between age 40 and 54 except for patients with family history and African Americans |
| - Routine screening between age 55 and 69 should be an individual decision |
| - Routine screening every 2 years or more is preferred. |
| - PSA screening NOT recommended for age 70+ or life expectancy <10 years. |

| **American Cancer Society Early Prostate Cancer Detection Guidelines** |
| - A personal but shared decision with one’s health provider |
| - PSA screening and DRE on patients |
|   - Age 50 or older with average risks |
|   - Age 45 or older with high risks – African Americans, family history |
|   - Age 40 or older with even higher risks – more than one family members with prostate cancer diagnosed at early age. |
| - PSA screening is done annually if PSA is >2.5 ng/mL |
| - No PSA screening in patients who have less than 10 years of life expectancy. |
Diagnosing Prostate Cancer

• Start with
  • PSA screening
  • DRE
    • PPV – 4% to 21%
    • SEER 2003-2007 – 0.4% high grade prostate cancer
  • mpMRI (mutiparametric MRI)
    • More sensitive but less specific
    • Reduce biopsy 27% to 36%
    • Missed significant tumor 6-7%
• Biomarkers
  • Free PSA
  • Prostate Health Index (PHI)
  • 4K Score,
  • EPI (ExoDx Prostate IntelliScore) in patient with PSA >3 ng/mL and without prior biopsy

• Need tissue diagnosis by prostate biopsy
  • Transrectal US guided biopsy
    • Standard 12 cores
    • 2-4% infection/sepsis
  • mpMRI/transrectal US image fusion targeted biopsy
    • Identified more clinically significant prostate cancer
    • Current recommendation – combined approach of systematic and targeted biopsies
  • Saturation/template transperineal prostate biopsy
    • Much less chance of infection
    • For high risk patient with prior negative prostate biopsies.
Prostate Biopsy Results

• BPH (benign prostate hyperplasia)
  • Low 20-year cumulative risks for cancer-specific mortality – 0.7% for PSA < 10 ng/mL. 3.6% for PSA >10 but < 20 ng/mL. 17.6% for PSA >20 ng/mL.

• PIN (prostatic intraepithelial neoplasia) high grade
  • Focal – followed as BPH patients
  • Multifocal – followed as atypia suspicious for cancer

• Atypia suspicious for cancer
  • Repeat biopsy at the suspicious site
  • Consider use of biomarkers or mpMRI to identify the suspicious lesions

• Prostate cancer
  • Gleason score = predominate Gleason grade (3, 4 or 5) + secondary Gleason grade (3, 4 or 5)
  • New grouping system in 2014
    • Group 1: Gleason 3+3
    • Group 2: Gleason 3+4
    • Group 3: Gleason 4+3
    • Group 4: Gleason 4+4, Gleason 3+5, Gleason 5+3
    • Group 5: Gleason 4+5, Gleason 5+5
“Standard” Treatment for Prostate Cancer

• Reflex reaction – cancer needs to be treated, eradicated or controlled.

• Surgery – Better cancer control but with possible side effects
  • 12% cancer-specific mortality in 15-year follow-up (5% for low risk patients), N=12,677
  • 13.5% (surgery) vs 19.5% (watchful waiting) cancer-specific mortality in 10.8-year follow-up, N=695, Randomized study in Scandinavia. 8 men to be treated to avoid 1 death
  • Da Vinci robotic prostatectomy – comparable cancer control results as open surgeries

• Radiation treatment – non- or minimally- invasive.
  • External beam radiation – IMRT, proton beam radiation, SBRT
  • Brachytherapy – LDR (radiation seeds) or HDR (temporary catheter placement)

• Androgen deprivation– started by Dr. Charles Huggins in 1941
  • He was awarded Nobel prize in 1966
  • Excellent for initial control of prostate cancer progression
Reasons for Not Treating Prostate Cancer

• Treatment side effects, impacting quality of life
  • Surgery
    • Impotence – common in patients with pre-existing erectile function, non-nerve sparing
    • Incontinence – stress incontinence improves over time
    • Side effects minimized with robotic DaVinci prostatectomy and patient selection
  • Radiation
    • GI symptoms, radiation proctitis
    • Radiation cystitis, rectourethral fistula
    • Impotence
    • Incidence is reduced with use of conformal radiation beam and use of spacer between prostate and rectum
  • Androgen deprivation
    • Hot flushes, depression, osteoporosis, cardiovascular disease, diabetes, fatigue
    • Intermittent treatment (drug holiday) can lessen the side effects.
Reasons for Not Treating Prostate Cancer

• Big gap between prostate cancer incidence and death
  • 2019 estimated new cases: 174,650 men
  • 2019 estimated deaths from prostate cancer: 31,620
  • Need to treat 37 diagnosed patients to avoid one death
  • Or need to treat 100 low risk prostate cancer to avoid one death

• Localized prostate cancer treatment outcomes are equivalent amongst three groups – surgery, radiation or surveillance, after 10 years in a randomized trial.
  • 545 (surveillance), 553 (surgery), 545 (radiation)
  • Death from prostate cancer in 10 years: 8 (surveillance), 5 (surgery), 4 (radiation)
  • Higher rate of disease progression in surveillance patients (112) vs surgery (42) or radiation (42)
Reasons for Not Treating Prostate Cancer

• Cost of treatment
  • Surgery - $14,000 to $25,000
  • Radiation treatment
    • IMRT - $11,000 to $25,000
    • Proton Beam - $35,000
    • Freestanding clinic costs $11,000 more than hospital-affiliated facility
      • August 11 in the Journal of Oncology Practice.

• Androgen deprivation
  • Leuprolide injection -$680-$3000 every 3-4 months.
Reasons for Not Treating Prostate Cancer

• Slippery slope if there are significant side effects
  • Diminished quality of life
  • Cost for care of side effects from treatment
    • Incontinence – diaper, additional surgery for pelvic sling or artificial sphincter
    • Impotence – prescription of Viagra, Cialis or Levitra, prescription of Trimix injection, surgery for penile prosthesis implant.
    • Radiation cystitis – hyperbaric treatment, hospitalization for treatment of acute bleeding, surgery
    • Radiation proctitis – hyperbaric treatment, hospitalization for treatment of acute bleeding, blood transfusion, surgery
    • Cardiovascular or diabetes or osteoporosis side effects from androgen deprivation – hospitalization, medications
Reasons for Treating Prostate Cancer

• Low grade prostate cancer on biopsy may not be what it seems to be
  • Upgrading can be as high as 40% of the time
• Some low grade and intermediate grade prostate cancer will progress and ultimately required treatment
• Data from Active Surveillance series:
  • John Hopkins – N=1298, 50% converted to treatment (10 years)
  • UCSF – N=810, 40% converted to treatment (5 years)
  • Toronto – N=993, 36.5% converted to treatment
  • Trigger point for treatments – Gleason grade change, PSA increase, personal choice (cancer anxiety)
Reasons for Treating Prostate Cancer

• If high risk cancer is not treated timely and becomes metastatic
  • It is not curable
  • Require androgen deprivation for life
  • Eventually will develop castration resistant prostate cancer
  • Will need newer medication such as abiraterone, enzalutamide or apalutamide
    • Cost about $8,000 to $10,000 per month
    • 60,000 Americans are prescribed enzalutamide
  • Sipuleucel-T (Provenge) vaccine
    • $150,000 for the course of three harvesting and infusion. On average, extending life by 6 months.
  • Chemotherapeutic agents – Docetaxel, cabazitaxel etc.
Other than Surgery, Radiation or Hormonal Therapy

- **Observation**
  - Best for maintaining existing quality of life
  - Palliative treatment with androgen deprivation when symptoms develop
  - May develop urinary retention, bone fracture, significant rise of PSA level
  - For patients with limited life expectancy

- **Active surveillance**
  - Formerly known as deferred treatment, expectant management, watchful waiting
  - **Intent to treat**
  - In one study – 64% patients (N=11,726) did not need treatment for 5 years
  - Another study – 55% patients (N=993) did not need treatment for 15 years.
  - For patients who required treatment eventually, all showed delayed in treatment do not impact survival
Actuarial Life Table from Social Security Administration 2016

Figure 2a—Life Expectancy at age 0 by Sex and Calendar Year (Based on Period Tables)

Figure 2b—Life Expectancy at age 65 by Sex and Calendar Year (Based on Period Tables)
Active Surveillance

• Patient selection for active surveillance based on the risk groups
  • Very low risk group – T1c, Gleason Group 1, PSA <10 ng/mL, few than 3 positive cores, low PSA density
  • Low risk group – T1c or T2a, Gleason Group 1, PSA <10 ng/mL
  • Intermediate favorable risk group – T1c or T2, Gleason Group 1 or 2, PSA 10-20 ng/mL, <50% biopsied cores are positive

• When place a patient on surveillance, it is better to use molecular markers to predict the prognosis of the likelihood of success with conservative management
  • Decipher – Predict clinical metastasis and cancer-specific mortality by testing the expression of 22 selected RNA markers (from a total of over 1.4 million)
  • Oncotype DX Prostate – Predict the possibility of metastasis and mortality by examining 17 genes that are associated with growth and survival of tumor cells.
  • Polaris – Predict the cancer aggressiveness by measuring the expression of cell cycle progression genes in the tumor, in conjunction with PSA level and Gleason score
  • ProMark -Predict cancer aggressiveness in patients with biopsy Gleason Scores of 3+3 and 3+4 based on the signatures of 8 proteins.
Conclusion

• PSA screening for early detection of prostate cancer is a personal but shared decision with your health care providers.

• To avoid over diagnosis, over treatment and side effects associated with treatment, PSA screening should be limited to certain age groups and to people who have at least 10 more years of life expectancy.

• Active surveillance is the preferred treatment for patients with very low risk, low risk and intermediate favorable risks of prostate cancer.

• Definitive treatment for intermediate unfavorable risks and high risks should be based on the guidelines from NCCN.

• Goal of prostate cancer management in the future – early detection of high-risk patients without unnecessarily involving the low-risk patients.