PROSTATE CANCER

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Learning Objectives

- Discuss the cancer diagnosis and screening, including the role of Prostate Specific Antigen (PSA).
- Review the basics of treatment of prostate cancer.
- Explain the benefits and risks of the latest oral therapies for prostate cancer.

Question

- Which of the following has NOT been shown to increase the risk of prostate cancer?

A) Male Gender
B) African-American Race
C) 5-alpha-reductase polymorphism (SRD5A2)
D) Benign Prostatic Hyperplasia (BPH)
E) Age

Background of Prostate Cancer

- Most common (non-dermatologic) cancer among men
- 2nd leading cause of cancer-related death in men
- Hormone-dependent

Risk Factors for Prostate Ca

- Race/Ethnicity Effects on Risk Factor
  - Scandinavian countries & US = highest reported rates
    - African American = highest overall incidence & death rates
      - Testosterone levels are 15% higher
      - More activation of testosterone receptor
  - Japan & Asian countries report lowest rates
    - May be due to low activity of 5-alpha-reductase
      - Converts testosterone to more active dihydrotestosterone (DHT)
    - Also have a diet relatively high in phytoestrogens which may be chemoprotectants

Risk Factors for Prostate Ca

- Family history
  - Can increase risk 2 – 3x
- Genetic Links
  - Lower number of CAG repeats in the androgen receptor
    - Higher activation of the receptor & thus cancer
  - Variant SRD5A2 of the 5-alpha-reductase enzyme
    - Increases risk of prostate cancer by increasing activity of that enzyme

Risk Factors for Prostate Ca

- Environmental Factors
  - Smoking & Alcohol
    - NOT associated!
  - UV exposure
    - More cases further away from the equator?
  - Obesity
  - Diet
    - May be associated
      - Increased fat and/or meat intake
    - Supplementation does not decrease risk
      - Vitamin E/Selenium (SELECT Trial)

Mythbustin' in Prostate Cancer

- No link between prostate cancer and:
  - BPH
    - Can complicate diagnosis
  - Sexual activity
  - Vasectomy
- Serum testosterone or DHT not always correlated with Prostate CA
  - Indicates Multifactorial Cause

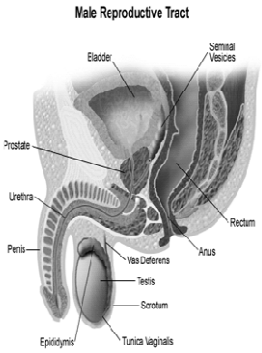
Prevention of Prostate Cancer

- Prostate Cancer Prevention Trial (PCPT)
  - Over 18,000 men with PSA <3 ng/dL
  - Finasteride 5mg po daily x7 years
  - Treatment group:
    - 30% reduction in prostate Ca (NNT=41)
    - Higher Gleason Score in those that developed cancer
  - Unknown survival benefit

Question

- What class of medications has been recently suggested to decrease risk of prostate cancer?
  - A) Calcium-channel Blockers
  - B) Beta-Blockers
  - C) Quinolone antibiotics
  - D) Statins
  - E) Prostablationers

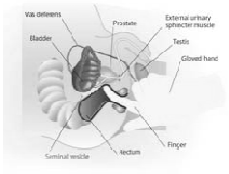
Prostate Physiology



- Aids in seminal fluid production and control of urination
- Prostate Specific Antigen (PSA)
  - Produced by prostate cells
  - Role in prostate growth
  - Increased in:
    - Damage to the prostate
    - Prostatitis
    - Benign Prostatic Hyperplasia (BPH)
    - Ejaculation

Prostate Cancer Detection

- Prostate Specific Antigen (PSA)
  - Cut-off is approximately 4ng/ml
    - Positive Predictive Value = 30%
- Digital Rectal Exam (DRE)
  - Detects nodules, induration & asymmetry
  - High interrater variability
  - Value of the Test
    - Positive Predictive Value = 5-30%



Brawer et al. 1999 & Meigs et al. 1996

Screening Controversy

- Observational Studies
- PLCO Study
  - Showed no mortality benefit in PSA screening
  - May not have enough power
- ERSPC Study
  - 20% relative risk reduction in death rate
  - More variability in screening methods
  - 1410 screenings & 48 treatments needed to prevent one death in 10 years
- Meta-analyses
  - 2010 & 2011
    - Screening does NOT reduce death, but does increase cancer diagnosis

Screening Controversy

- American Cancer Society
  - Age >50
- American Urologic Society
  - Ages 55 – 69
- US Preventative Services Task Force
  - No routine screening
- March 2014 – "Radical Prostatectomy is better than watchful waiting"

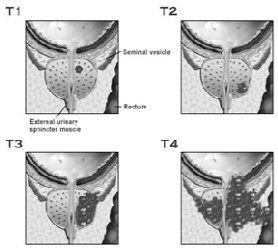
Diagnosing Prostate Cancer

- Biopsy Recommendations
  - Highly recommended in PSA >10ng/mL
    - Greater than 50% will have positive biopsies
  - Recommended in PSA 4-10ng/mL
    - About 20% will have positive biopsies
  - 20-40% will have cancer despite PSA <4ng/mL
- Transrectal prostate biopsy is the gold standard of diagnosis
  - 6-12 samples taken, give 90% detection

Presti et al. 2000

Prostate Cancer Staging

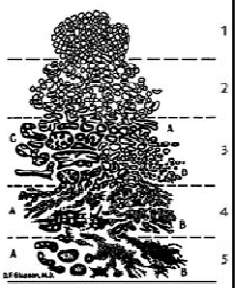
- Stage I – Stage II
  - Confined to prostate
- Stage III
  - Extending outside the capsule
- Stage IV
  - Metastatic disease
  - Lymph nodes → blood stream → bones → liver & lung



Gleason Score

- Reports primary & secondary
- Helps account for inherent heterogeneity of the prostate
- Summate scores to get total Gleason Score

Histologic Grade	Meaning
Gx	Cannot be assessed
G1	Well differentiated (Gleason 2-4)
G2	Mod differentiated (Gleason 5-6)
G3-4	Poorly or Undiff (Gleason 7-10)



Appearance of cancer cells, ranked according to the Gleason Grade.

Treatment Goals

- Overall goal is to minimize overall morbidity & mortality
- Stage I – III (Stage A – C)
  - Active surveillance is appropriate tx
    - <10% death over 20 years from low-risk, low-grade tumors
  - Goal = Symptom Relief (low risk) vs Cure (high risk)
- Stage IV (Stage D)
  - Not curable
  - Goal = symptom relief, extend life

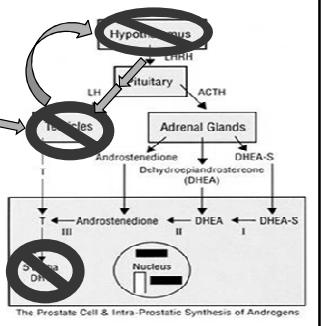
Prostate Cancer Treatment, Stage I - III

- Surgery
  - Radical Prostatectomy
    - 85% cure rate
    - Impotence 37%, Incontinence 17%, Mortality 0.3%
- Radiation Therapy
  - Brachytherapy
    - Insertion of radioactive beads into prostate
    - Fast, outpatient procedure
  - External Beam Radiation Therapy (EBRT)
    - 7 – 8 weeks of treatment
    - 50% incontinence, 30% ED
    - Combined with hormones in high risk patients

Prostate Cancer Treatment, Stage IV

- Goal: Shut off testosterone
  - Bilateral orchiectomy

    vs
  - Medical castration
    - LHRH Agonists
    - Non-steroidal Antiandrogens



LHRH Agonists

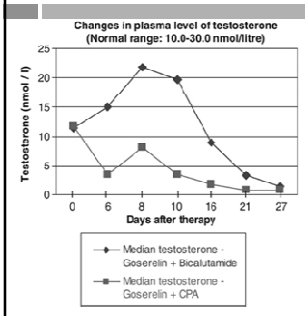
- Leuprolide Depot (Lupron®)
  - 7.5mg IM QMonth
  - 22.5mg IM Q3Months
  - 30mg IM Q4Months
- Leuprolide Suspension (Eligard®)
  - 7.5mg SQ QMonth
  - 22.5mg SQ Q3Months
  - 30mg SQ Q4Months
  - 45mg SQ Q6Months
- Goserelin implant (Zoladex®)
  - 3.6mg SQ qmonth
  - 10.8mg SQ q3months
  - Given in upper abdominal wall

Eligard®
(leuprolide acetate for injectable suspension)

LHRH Agonists

- Reversible method of androgen ablation as effective as orchiectomy
- Agents:
  - Leuprolide
  - Goserelin
- Response rate of up to 80%
- AE: disease flare at first week of therapy (bone pain or LUTS) that usually resolves after 2 weeks

LHRH Flare



- Can be fatal in patients with extensive mets
- Antiandrogens used for prevention
- NCCN guidelines recommend use in those patients who are at risk of metastatic symptomatic flare
- Antiandrogens should be used for at least two weeks surrounding LHRH Dose

Non-steroidal Antiandrogens

- Monotherapy shown to be less effective than LH-RH alone
- Response rate 50-87% reported
- Objective responses seen as decreased bone pain, decreased prostate size, decreased PSA and/or improved functional status
- Agents:
  - Bicalutamide
  - Flutamide
  - Nilutamide

Complete Androgen Blockade

- Combination of Antiandrogen & LHRH agonist
  - Good for creating a state of maximal androgen deprivation to avoid other mechanisms of hormonal stimulation of the prostate
  - Response rate >90% in untreated patients (<35% in previous tx)
  - Improved survival, but may have more AE

Efficacy of ADT

- Early vs Deferred Therapy
  - 17% decrease in relative risk for prostate cancer specific mortality
  - No decrease in overall mortality
- Intermittent ADT
  - Shown to be better tolerated
  - Insufficient data- need more clinical trials

Loblaw DA, et al. *J Clin Oncol*. 2007;25:1596-605

Benefits of ADT

Advanced Disease

Decrease In:	*Control*	*ADT*	*P Value*
Cord Compression	4.9	1.9	<0.025
Ureteral Obstruction	11.8	7.0	<0.025
Metastases	11.8	7.9	<0.05
Pathologic Fracture	7.9	2.3	NS

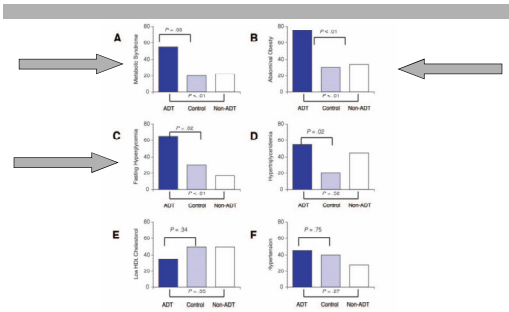
Sharifi N, et al. *JAMA*. 2005;294:238-44

Question

- What are the potential adverse effects of complete androgen blockade?

A) Fatigue
B) Bone Loss
C) Breast Changes
D) Hot Flashes
E) All of the above

Other ADT ADRs



Braga-Basaria M, et al. *J Clin Oncol.* 2006;24:3979-83

Castrate-Resistant Prostate Cancer (CRPC)

- Criteria:
  - Testosterone <30ng/dL
  - Prostate cancer growing, spreading despite this
- Treatment Options:

Prior to 2004

- Docetaxel + Prednisone
- Androgen withdrawal – no survival benefit
- Ketoconazole + Hydrocortisone – no survival benefit

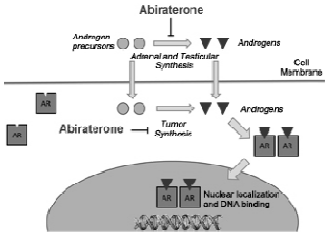
Today

- Docetaxel + Prednisone
- Abiraterone + Prednisone
- Sipuleucel-T

Docetaxel

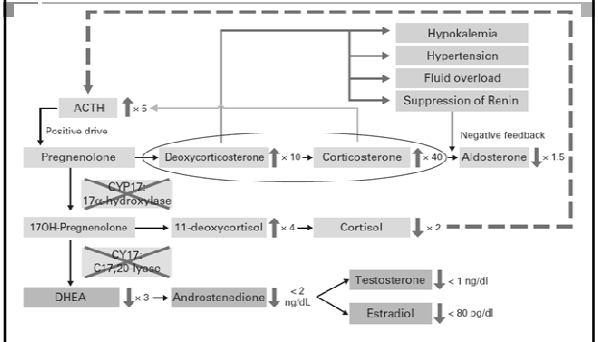
- Classical chemotherapeutic agent
- 75mg/m2 given every 21 days
- Significant ADRs
  - Full-body hair loss
  - Neuropathy
  - Hypersensitivity Reaction
    - Manifests acutely during treatment
    - 2/2 Diluent

Abiraterone (Zytiga)



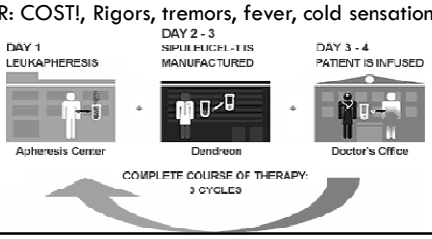
- CYP 17 Inhibitor (17 alpha-hydroxylase)
- Blocks formation of testosterone within tumor cells
- Oral agent
  - 4 tabs (1000mg) q day
- Used in combination with prednisone 5mg po bid
- 4 month survival benefit vs placebo

Abiraterone ADRs



Sipuleucel-T

- Autologous cells fused with PA2024 gene
  - (PAP linked to GMCSF)
- 4 month increase in median survival (vs active controls)
- ADR: COST!, Rigors, tremors, fever, cold sensation



Post-Docetaxel Treatment

- Enzalutamide (Xtandi)
  - Small molecule inhibiting overexpression of androgen receptor
    - Blocks translocation of the receptor to cell surface
    - Binds DNA
  - Oral agent
    - 4 tabs q day (160mg)
  - 5 month survival benefit (vs placebo)

Goodin S. *The Oncology Pharmacist.* 2009;2(3):10-3

Bone Health in Prostate Cancer

- Preventative
  - Androgen Deprivation Therapy
    - Annual BMD loss of ~5%/year
    - Greatest loss in the first year
  - Other risk factors: white, BMI <25, length of ADT
  - Treatment:
    - Calcium + Vitamin D
    - Exercise
    - Smoking Cessation
    - IV or PO bisphosphonates

Bone Health in Prostate Cancer

- Palliative
  - Metastatic/Lytic bone disease common in CRPC
- Treatment
  - Zoledronic Acid 4mg q3 – 4 weeks
  - Denosumab 120mg SQ q4 weeks
  - Pamidronate and PO bisphosphonates NOT shown to have benefit in this population
    - Except clodronate, not FDA approved

Investigational Therapies

- Prostate Cancer Vaccines
- Cabozantinib

Conclusions

- PSA Screening no longer recommended for all
- Hormonal Therapies:
  - LHRH Agonists
  - Antiandrogens
- Medications for CRPC:
  - Abiraterone
  - Enzalutamide
  - Docetaxel
- Coming Soon:
  - Vaccines??!!