Current Diagnosis and Management of Prostate Cancer

Prostate Cancer

• Risk Factors
  – Age: median age of diagnosis is 72yo
  – Smoking
  – High Fat/ Western diet
  – Family History: 8-9% of all cancers due to inherited gene higher for younger men
• Incidence of prostate cancer increases with age so that up to 70-80% of men in their 80-90’s have autopsy evidence of prostate cancer

**Prostate Cancer**

• Most common non cutaneous malignancy in men
  – Second leading cancer killer of men

<table>
<thead>
<tr>
<th>Prostate</th>
<th>Breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>180,400 cases/yr</td>
<td>182,000 cases/yr</td>
</tr>
<tr>
<td>36% of new ca cases</td>
<td>32% of new ca cases</td>
</tr>
<tr>
<td>40,400 deaths</td>
<td>46,000 deaths</td>
</tr>
<tr>
<td>1/6 chance of dvlp.</td>
<td>1/8 chance of dvlp.</td>
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</table>
Hormone dependence

Prostate Cancer

- Prostate Cancer Development
  - Develops from the epithelium
- Possibly from the basal cell layer – Requires androgens to develop
- Patients castrated before puberty do not develop BPH or Prostate cancer
  - Increased cell proliferation and decreased apoptosis
  - BPH is not a risk factor
Prostate Cancer

- What’s in a name?
- PIN-prostatic intraepithelial neoplasia
  - May be a precursor lesion to prostate cancer
- Characterized by cytologically atypical cells with architecturally benign glands
• Approximately 20% of patients with PIN will go on to have a subsequently positive biopsy

• ASAP-atypical small acinar proliferation
  – Atypical glands and cells but can’t quite call it cancer
    • Up to 50% will have a future positive biopsy
Prostate Cancer

Uniform round glands
Single cell layer (loss of basal cells)
Some prominent nucleoli
Perineural invasion
Prostate Cancer

- Grading
  - Gleason grade 1-5
  - 2 most predominant patterns combined to give Gleason score
  - 2-4 well differentiated
  - 5-7 intermediate
  - 8-10 poorly differentiated
  - Gleason scores very predictive of metastases and outcome

- Remember high grade PCa may not make much PSA
Prostate Cancer

Zonal Anatomy of the Prostate
Prostate Cancer

- Develops in the peripheral zone of the prostate
  - 75% peripheral zone,
    15-20% transition zone,
    5%
    central zone, essentially none in AFMS
- Biopsies directed toward the peripheral zone

Prostate Cancer

- Screening
Prostate Cancer

- Diagnosis
  - Screening: Who should be screened?
• American Urological Association, American Cancer Society: recommend offering PSA and DRE to men at risk (ie, with a >10-year life expectancy)

• US Preventive Services Task Force: don’t even offer DRE or PSA

– Arguments against screening
  • Detection of clinically insignificant cancers
  • Expensive-Initial estimates of screening men aged 50 to 70 years for prostate cancer $25 billion during first year alone
  • Not effective in decreasing mortality from the disease
Prostate Cancer

- Screening
  - Prostate, Lung, Colorectal, Ovarian (PLCO) screening study in the US (148,000 men and women randomized to screening or community standard of follow-up)
  - Europe: Rotterdam screening trial
  - Results of both: 10 years from now
Prostate Cancer

• Screening
  – Evidence that screening works

• Fall in mortality now seen:
  – SEER*
  – Olmsted County, MN† – Canada/Quebec‡
  – US Department of Defense (DOD)
  – Tyrol, Austria
  – Mortality fall not seen (where PSA screening not performed) Mexico

SEER=Surveillance, Epidemiology and End Results
*Levy IG. *Cancer Prev Control*. 1998;2:159;
Prostate Cancer

• PSA
  – 25% positive predictive value to detect disease
  – predictive of tumor stage
  – Most predictive factor for biochemical recurrence
  – Excellent tumor marker for detecting recurrent disease

• Free PSA
  – Portion of PSA which is not complexed to alpha-1 antichymotrypsin
  – Measured as ratio of Free/Total PSA
  – Decreased by 50% in patients on Proscar

• Therefore ratio still remains useful
Prostate Cancer

• Advantages and Disadvantages of Using Molecular forms of PSA
  – Advantage: eliminates about 10%–20% of negative prostate biopsies in men with PSA of 4.0–10.0 ng/mL
  – Disadvantage: misses some (about 5%–10%) of cancers that would be detected with PSA alone

Prostate Cancer

• PSA velocity
  – Defined as > .75ng/ml year

• Age specific PSA

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Recommended Reference Range for Serum PSA (ng/mL)</th>
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</thead>
<tbody>
<tr>
<td>40–49</td>
<td>0.0–2.5</td>
</tr>
<tr>
<td>50–59</td>
<td>0.0–3.5 60–69 0.0–4.5</td>
</tr>
<tr>
<td>70–79</td>
<td>0.0–6.5</td>
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</table>

Prostate Cancer

• Screening
  – Digital Rectal Exam
    • DRE abnormal in 6%–15% of men
    • About 25% of cancers found with DRE alone • Still plays a role

Prostate Cancer

• Digital Rectal Exam and Screening
Annals of Urology

“When Australian rugby player John Hopoate resigned in disgrace after receiving a 12-match suspension for jabbing his fingers into opposing players’ anuses, the New Zealand Cancer Society used his photo to promote prostate cancer checks. The ad, features a close-up photo showing Hopoate inserting his index finger into another player’s anus and states the exam “won’t hurt a bit—promise” AP 4/15/01
Prostate Cancer

- **Diagnosis**
  - Transrectal ultrasound and Biopsy
  - Traditionally Sextant Biopsy Used
  - More recently 10-12 core biopsy advocated
  - Cores may be sent separately to help identify margin at risk

Detection Rates of Systematic Schemes

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Detection Rate</th>
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<tbody>
<tr>
<td>Top</td>
<td>80%</td>
</tr>
<tr>
<td>Middle</td>
<td>89%</td>
</tr>
<tr>
<td>Bottom</td>
<td>89%</td>
</tr>
<tr>
<td>Left</td>
<td>91%</td>
</tr>
<tr>
<td>Right</td>
<td>95%</td>
</tr>
<tr>
<td>Front</td>
<td>96%</td>
</tr>
</tbody>
</table>

Prostate Cancer

Staging

T1a-<5% on TURP
T1b>5% on TURP
T1c-non palpable diagnosed by PSA
T2a-palpable one lobe
T2b-both lobes
T3a-extraprostatic
T3b-seminal vesicle involvement
T4 adjacent structures
Prostate Cancer

- Diagnosis
  - Transrectal ultrasound and biopsy
Prostate Cancer

- Diagnosis - Other tools
  - Endorectal coil MRI
Prostate Cancer
Prostate Cancer

- Diagnosis - Other diagnostic tools
Bone Scans - limited usefulness with PSA < 20

Prostate Cancer

• Predictive Models
  – Preoperative Nomograms
    • Available at Nomograms.org
    • Available for pre treatment, post RRP, and radiation
    • PSA continues to be a driving variable

  – Partin tables
    • Recently updated, also useful for prediction of outcomes
Extra Credit
Prostate Cancer

• Treatments
  – Watchful Waiting
  – Hormone Therapy
  – Surgery
- Radiation
- Cryotherapy

**Prostate Cancer**

- **Watchful Waiting**
  - Waiting for what?
  - 70-80% of me in 80’s have prostate cancer not all men need to be treated
  - Look at PSA doubling times
  - Look at comorbid conditions
  - May rebiopsy in one year and follow PSA
Prostate Cancer

• Hormonal Therapy
  – LHRH agonists and antagonists
  – Block production of testosterone
  – Anti-androgens block the androgen receptor

Prostate Cancer

• Hormonal Therapy
Casodex Monotherapy-150mg per day

- Initial results seem to show equal efficacy to LHRH agonists (US data still pending)
- Side effects
  - Gynecomastia and nipple tenderness a significant problem causing high withdrawal from studies
  - Improvement in side effects of osteoporosis, hot flashes seen with LHRH agonists.

Prostate Cancer

- Hormone Therapy
  - Typically hormone deprivation will cause PSA to go very low and stay low for 18 months
– May add anti-androgen which may work for another 3-6 months
– Antiandrogen Withdrawal

**Prostate Cancer**

- Disadvantages of Hormone Therapy
- Side effects
  - Hot flushes – Helped with soy, depo-provera, megace
  - Osteoporosis-leading to pathologic fractures
    - Start patients on Vit D 400IU and Calcium(Citracal) 500mg per day when initiating treatment
    - Bisphosphonate is DEXA scan shows osteoporosis
      » Fosamax oral
» Zolendronic Acid-IV

• Other side effects: fatigue, impotence, anemia, etc..

**Prostate Cancer**

• Treatment-Surgical
  – Radical Retropubic Prostatectomy

• Complications associated with RRP continue to decline

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>18</td>
<td>90</td>
</tr>
</tbody>
</table>
- Treatment Surgical
  - Radical Prostatectomy

- Have come to realize the importance of surgical margins
TI-T2NxM0 tumors
Prostate Cancer

Radical Prostatectomy

- Used to hopefully help improve surgical margins by allowing wider dissection
- Restoration of erectile function in damaged nerves or resected nerves
- Uses the sural nerve most commonly, but genitofemoral or ilioinguinal can also be used
  - Sural Nerve Grafts
Prostate Cancer

• Surgical Treatment
  – Laparoscopic Prostatectomy

• Initial results from high volume centers look good
  – High learning curve
    » Results in up to 50% positive margins initially
  – Need longer follow-up
  – Erectile function and continence still need validation and longer follow-up
    – Sural nerve grafts can be done laparoscopically
      » Typically use fibrin glue for anastomoses

• Probably will be reserved for a few centers
Prostate Cancer

• Surgical Treatment
  – Perineal Prostatectomy
    • Renewed interest with decreased morbidity shown by laparoscopy
    • Good data to support oncologic efficacy
    • Nerve sparing possible, although no reports of sural nerve grafts
    • Decreased morbidity over RRP, mainly in blood loss and transfusion requirements
Prostate Cancer

• Cryotherapy
  – New generation of cyrotherapy units uses a template similar to brachytherapy
    • Allows for more accurate probe placement
Prostate Cancer

• Radiation Therapy
  – External beam radiotherapy
• Dose escalation studies now pushing doses up into the 80-90Gy range
• IMRT allows better targeting
• Side Effects
  – Incontinence-rare
  – Impotence-common
  – Rectal irritation
  – Hematuria, bladder/urethral irritation

Prostate Cancer
• Radiation
  – Brachytherapy-
• Outpatient, low morbidity
  – Incontinence rare
  – Impotence occurs over 2 year period
  – Urethral irritation, worsening of BPH symptom

• Best for low grade, low stage tumors in older patients

Prostate Cancer

• Biochemical Recurrence
• Approximately 30-40% of patients will experience a rising PSA after local therapy

• 180,400 patients diagnosed with prostate cancer in 2000

• 2/3 (119,064) of these patients receive definitive local therapy

• 30-40% (35,719-47,625) recur

  – Definition of biochemical recurrence varies
    • Best data from Amling paper >0.4ng/ml*

#Based on SEER statistics. 1998

Prostate Cancer

• Hormone Refractory Prostate Cancer
– Typically patients will remain hormone responsive for median of 18 months

• Hormone deprivation options include
  – LHRH agonists
  – Antiandrogens
  – Orchiectomy
  – Estrogens
  – On average from time of HRPC to death is median of 2 years