Prostate Cancer

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Objectives

- Understand the epidemiology, etiology and risk factors associated with prostate cancer
- Be able to explain the clinical presentation, diagnostic procedures, and staging of prostate cancer.
- Outline the drug and surgical therapies for prostate cancer, including their side-effects, advantages and disadvantages

Epidemiology

- Prostate Cancer
  - The most common cancer found in men (excluding skin cancers)
  - The second leading cause of cancer related death in men, exceeded only by lung cancer
  - 1/5 men will develop prostate cancer during their lifetime
  - In 2002, 189,000 new cases expected with an estimated 30,200 deaths.
Etiology/Risk Factors

- **Age**
  - mean incidence in men > 50 years old
- **Androgens**
  - necessary for neoplastic development
- **Genetics**
  - The hereditary prostate cancer (HPC) gene has been identified and linked to the development of prostate cancer in a small group of patients.

Etiology/Risk Factors

- **Diet**
  - The consumption of a diet high in animal fats, red meats and dairy products has been associated with increased risk of prostate cancer
- **Environment**
  - Workers exposed to cadmium, farmers and rubber tire workers have a higher rate of prostate cancer

Etiology/Risk Factors

- **Race**
  - African American males have the highest incidence of prostate cancer in the world nearly doubling that of white males. Japanese men have the lowest incidence.
Clinical Presentation

- Presenting signs and symptoms of prostate cancer are dependent on both the location and extent of the disease.
  - Prostate cancer limited to the prostate may cause no signs or symptoms OR may present similar to BPH (benign prostatic hypertrophy): urinary frequency, difficulty initiating a urinary stream, urgency and nocturia.

Clinical Presentation

- More advanced local prostate cancer can lead to bladder outlet obstruction and subsequent urinary retention, anuria and uremia.
- Advanced metastatic prostate cancer occurs more commonly in the bones adjacent to the prostate: lower spine, pelvis and femurs.
- Advanced prostate cancer that has spread beyond adjacent bones can present as anemia and weight loss.

Screening

- NCCN
  - Recommend men be tested for prostate cancer by PSA (prostate specific antigen) and DRE (digital rectal exam) annually beginning at the age of 50 in those men with life expectancies > 10 years.
Diagnosis

- Digital Rectal Exam (DRE)
  - sensitivity: 55-69%, safe, easy, cheap
  - Disadvantage: highly subjective, less sensitivity, not fun!

Screening

- NCCN
  - Recommend men be offered both the prostate specific antigen (PSA) and DRE exams. Men in high risk groups with 2 or more affected first-degree relatives or African Americans may begin testing at a younger age, usually 45 years.

PSA

Androgen-regulated protease, normally secreted into lumen; also a biomarker for PCa in serum.
- 25% of men who have prostate cancer will have a low/normal PSA. A DRE must be done concomitantly with the PSA blood test.
- Sensitivity: 70%, safe, easy to perform
- Disadvantages: low specificity
PSA

- Cutoff = 4 ng/mL.
- PSA Velocity = change in PSA values over time; >0.75 ng/mL/year = high likelihood; should be at least 3 measurements over 18 months.
- Patients receiving 5-α reductase inhibitors (e.g., finasteride, dutasteride (Avodart®)) should ~ double PSA value for more accurate interpretation.
- Saw Palmetto- contains phytoestrogens and may affect PSA levels
- Levels increase as part of aging

In blood, PSA highly protein-bound to endogenous protease inhibitors (e.g., α-1-antichymotrypsin).
- In normal prostate, PSA turnover (degradation) to inactive, unbound form.
- In Pca, fewer basal cells available to inactivate PSA.
- Less inactive PSA formed, meaning less unbound.
- < 25% unbound is cutoff for PCa detection.
- Used when PSA = 4-10 ng/mL and negative for DRE

Patients with PSA < 2 ng/mL, normal DRE, and no risk factors – Measure PSA every other year, yearly DRE if positive risk factors
- Patients with PSA = 2-4 ng/mL – Measure PSA yearly.
- Patients with PSA <4 ng/mL, who have PSA velocity > 0.75 ng/mL/yr, percent free <25%, and African American or men with positive family hx and PSA > 2.5 ng/mL suggests need for biopsy.
Diagnosis

- Transurethral Ultrasound (TRUS)
  - Usually done after an elevated PSA or abnormal DRE. It can visualize prostate size, configuration and gland consistency.
  - This procedure is also used to guide a biopsy needle for prostate tissue samples. Tissue sampling is imperative for staging.

AJCC Staging

- Primary tumor (T)
  - T0- no evidence of primary tumor
  - T1- clinically inapparent tumor not palpable or visible
  - T1a-Tumor histologic finding in 5% or less tissue
  - T1b- Tumor histologic finding in more than 5%
  - T1c-Tumor identified by needle biopsy

- T2-Tumor confined within prostate
  - T2a-Tumor involves half of 1 lobe
  - T2b-Tumor involves > half of 1 lobe
  - T2c- Tumor involves both lobes
  - T3-Tumor extends through the prostatic capsule
  - T3a-Extracapsular extension (unilateral)
  - T3b- Extracapsular extension (bilateral)
  - T3c-Tumor invades the seminal vesicle
  - T4-Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, pelvic wall
AJCC Staging

Regional Lymph Nodes (N)- MRI/CT Scan
- NX-regional lymph nodes cannot be assessed
- N0-No regional lymph nodes metastasis
- N1-Metastasis in regional lymph node(s) < 2 cm across largest dimension
- N2-Metastasis in regional node(s) 2<X<5 cm across largest dimension.
- N3- > 5 cm across largest dimension

Distant Metastasis (M)
- MX-presence of metastasis cannot be assessed
- M0-No distant metastasis
- M1-Distant metastasis
- M1a-Nonregional lymph nodes
- M1b-Bone(s) – bone scan
- M1c-Other site(s)

Histopathologic Grade (G)
- GX-Grade cannot be assessed
- G1-Well differentiated (slight anaplasia)
- G2-Moderately well differentiated (moderate anaplasia)
- G3-4-Poorly differentiated or undifferentiated (marked anaplasia)
Staging: Gleason Score

2-4 Well differentiated
5-6 Moderately differentiated
7 Moderately poorly differentiated
8-10 Poorly differentiated

Treatment

- Observation
  - If life expectancy is <5 years without symptoms
  - Advantages: Absence of side-effects and complications
  - Monitor the PSA, if it rapidly increases, more aggressive therapy may be necessary.

- Radiotherapy
  - A good alternative for patients who are not good surgical candidates
  - Done by external beam radiation or by implantation of radioisotope seeds (brachytherapy)
  - Advantages: less incontinence, impotence develops more slowly
  - Disadvantages: Overall survival less than surgery, healthy tissue can be exposed.
Treatment

- Surgical Approach
  - Radical prostatectomy
  - The surgical approach is the standard of treatment.*
  - Advantages: Fastest in decreasing levels of testosterone
  - Disadvantages: Impotence and incontinence
- Orchiectomy
  - Causes immediate drop in testosterone levels

Treatment

- Androgen Inhibition Therapy
  - Luteinizing hormone-releasing hormone (LHRH) Analogue:
    - Leuprolide (Lupron®): 1 mg SQ daily, Depot: 7.5 mg IM monthly, 22.5 mg IM q 3 months, or 30 mg IM q 4 months
    - Goserelin (Zoladex®): Implant, 3.6 mg SQ q month or 10.8 mg SQ q 3 months
    - Side-Effects: hot flashes, gynecomastia, N/V/D, depression, disease flare*

Treatment: Antiandrogens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Half-Life</th>
<th>Side-Effects</th>
<th>Baseline T levels 250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutamide</td>
<td>250 mg (2 caps) po tid</td>
<td>9.6 hours</td>
<td>12-26% diarrhea, hematuria, hepatotoxicity, rare methemoglobinemia</td>
<td></td>
</tr>
<tr>
<td>Bicalutamide</td>
<td>50 mg po qd</td>
<td>1 week</td>
<td>2-12% diarrhea, hematuria</td>
<td></td>
</tr>
</tbody>
</table>
Treatment: Antiandrogens

- Nilutamide (Nilandron)
  - Dose: 300 mg (6 tabs) po qd x 1 month then 150 mg po qd
  - Half-Life: 41-49 hours
  - Side-Effects: 2% diarrhea, 7% constipation, disulfiram-reaction, decreased visual accommodation, (13%), interstitial pneumonitis (2%)

Treatment

- **Antiandrogens**
  - Class side-effects: gynecomastia, N/V/D, increased LFT’s, loss of libido
- **Estrogens**
  - Diethylstilbestrol - WITHDRAWN
  - Ethyl Estradiol: side-effects include peripheral edema, gynecomastia, N/V/D, loss of libido

Treatment

- **Androgen Synthesis Inhibition**
  - Aminogluthethimide
  - Ketoconazole
  - Megestrol Acetate
Treatment

- Antiandrogens and LHRH analogues are often used together in what is called “CAB” therapy (combined androgen blockade).
  - It is most often used during the first 6-8 weeks to block the tumor flare that is associated with LHRH analogues.

Treatment

- HRPC (hormone-refractory prostate cancer) is defined as cancer that progresses despite hormonal intervention. Treatment involves different agents but if the patient fails CAB therapy (or orchiectomy) the best recommendation is to STOP the antiandrogen. It is believed that antiandrogens act as androgens after long term therapy or the androgen receptor mutates.

Treatment Based on Risk Group
(NCCN Guidelines)

<table>
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<tr>
<th>Risk Group Recurrence</th>
<th>Stage</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Very Low Risk</td>
<td>T1-2a, Gleason 2-6, PSA&lt;10, low tumor involvement (&lt;5%)</td>
<td>Life expectancy: &lt;10 yrs - observation, &gt;10 yrs - RT or prostatectomy</td>
</tr>
<tr>
<td>Low Risk</td>
<td>T1-2a, Gleason 2-6, PSA&lt;10, large tumor involvement (&gt;5%)</td>
<td>Life expectancy: &lt;10 yrs - observation, 10-20 yrs - observation, RT, or prostatectomy, &gt;20 yrs - RT or prostatectomy</td>
</tr>
</tbody>
</table>
### Treatment Based on Risk Group (NCCN Guidelines) - Cont’d

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<th>Risk Group Recurrence</th>
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<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Risk</td>
<td>T2b-c, Gleason 7, PSA 10-20 ng/ml</td>
<td>Life expectancy: &lt;10 yrs - observation, RT, or prostatectomy; &gt;10 yrs - RT or prostatectomy</td>
</tr>
<tr>
<td>High Risk</td>
<td>T3a-b, Gleason 8-10, PSA&gt;20 ng/ml</td>
<td>Life expectancy: &lt;5 yrs - observation or hormone therapy (HT); &gt;5 yrs - RT PLUS HT</td>
</tr>
<tr>
<td>Very High Risk</td>
<td>T3c &amp; T4, N1 or M1</td>
<td>Androgen ablation or RT plus androgen ablation</td>
</tr>
</tbody>
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### Treatment

- **Chemotherapy**
  - Reserved for patients with advanced prostate cancer who are symptomatic and have failed hormonal interventions.
  - No currently approved antineoplastic agent, alone or in combination, has been shown to prolong survival in prostate cancer patients.
  - Mitoxantrone + prednisone – FDA approved chemotherapy for androgen-independent disease.

- **Single agents which have shown modest activity include:**
  - Cyclophosphamide, Estramustine, 5-FU, Methotrexate, Dacarbazine, Mitoxantrone, Doxorubicin, and Cisplatin
Treatment

- The following combinations have been studied in patients with HRPC:
  - Estramustine + Vinblastine
  - Estramustine + Oral Etoposide
  - Estramustine + Paclitaxel
  - Doxorubicin + Ketoconazole
  - Doxorubicin + IV Cyclophosphamide
  - Docetaxel + estramustine

Treatment (continued)

- Oral Cyclophosphamide
- Oral Cyclophosphamide + oral Etoposide

Treatment - Bone Metastasis

- Strontium⁹⁰ or Samarium¹⁵³ lexidronam – myelosuppressive for up to 2 weeks; palliative effects expected to last ~ 6 weeks.
- Bisphosphonates
  - Zoledronic acid (Zometa®) at 4 mg every 3 weeks for 15 months reduced skeletal-related events (bone fractures, spinal cord compression, etc.) in patients with Pca. Patients also received 500 mg calcium supplements and 400-500 IU Vit. D QD. Saad F, et al. JNCI, 2002.
  - Pamidronate (Aredia®) – Much longer infusion time
Future Approaches to Prostate Cancer?

- Atrasentan (endothelin-A antagonist)
- Prinomastat (matrix metalloprotease inhibitor) also known as "AG-3340"
- Exisulind + docetaxel
- Calcitriol + docetaxel
- vaccines
- Thalidomide alone or with
  - Docetaxel
  - Ketoconazole

References

- NCCN Practice Guidelines for Prostate Cancer, 2002.