Prostate Cancer

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Scope of Urologic Oncology

- Prostate Cancer
- Germ cell tumor
- Bladder cancer
- Renal cell carcinoma
- Penile cancer
- Adrenal gland tumor
Prostate cancer

- Important concepts

- Issues on screening

- Systemic therapy
  - Localized disease
  - Metastatic disease
Important concepts

- Demographic
- Gleason score
- Androgen-driven disease
  - benefit of chemotherapy is limited
Demographics

- Much more prevalent in western world

- Picking up in China
  10/100,000 -> 30/100,000; PSA screening
Gleason score

- Dr. Donald Gleason
  - 1960s

- Intratumoral heterogeneity
  - Scores of two predominant patterns
  - Add up of the two scores

- Most important prognostic factor
Androgen-driven disease

- **Castration**
  - Testosterone level < 50
  - Surgical vs. Medical (LHRH)

- **Castration-naïve**
  - 18-24 months

- **Castration-resistant (CRPC)**
  - Misnomer: hormone-refractory
  - Hormone hypersensitive
Androgen production $\rightarrow$ CRPC
Mechanisms of resistance

AR-dependent

STATE 1
Endocrine androgen dependent and AR dependent
Prostate cancer cells

STATE 2
Intracrine androgen dependent and AR dependent

STATE 3
Androgen (ligand) independent and AR dependent

STATE 4
Androgen (ligand) independent and AR independent

Clinical scenario

- 45 year-old male
  - Family history of prostate cancer
  - No medical comorbidities

- PSA screening?
Issues on screening

Pros and Cons

Pros: Early detection
Cons: Overdiagnosis and overtreatment
Repeat biopsy ➔ prostatitis, impotence

Important studies
- PLCO
- ERSPC
Clinical trials

- **Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial**
  - Incidence of death: 2.0 vs. 1.7; RR, 1.13
  - Control arm heavily contaminated 90%

- **ERSPC Trial**
  - Incidence 8.2% vs 4.8%
  - RR for death 0.80 --> reduce by 20%
  - 1410 to screen, 48 to be treated to prevent one death.

Current recommendations

- No, but discuss
  - U.S. Preventive Services Task Force (USPSTF)
  - American Urological Association (AUA)
  - American Cancer Society (ACS)
  - European Society for Medical Oncology (ESMO)

- Yes, but discuss
  - National Comprehensive Cancer Network (NCCN)
    Men 45-75 years old
  - EAU/ESTRO/SIOG
    Men > age 50 ; > age 45 with family history/African-American
    PSA > 1 ng/mL at age 40, > 2 ng/mL at age 60
The Consensus

- Shared decision making
- High risk factors
  - Family history
  - BRCA mutations
  - African American
- $4 \text{ ng/mL} \Rightarrow \text{consider biopsy}$
- Free PSA, PSA velocity
Clinical scenario

- 45 year-old male
  - Family history of prostate cancer
  - No medical comorbidities

- PSA: 16.1 ng/mL, DRE: no nodule
Clinical scenario (cont’d)

▶ Biopsy
  - Gleason 4+3 adenocarcinoma
  - 8/12 cores

▶ What is stage?

▶ Management?
Management of localized disease

▶ Staging/risk stratification

Tumor, PSA, and Gleason

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Pathologic (pT)³</th>
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<tbody>
<tr>
<td>CLINICAL</td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>pT2 Organ confined</td>
</tr>
<tr>
<td>T0</td>
<td>pT2a Unilateral, one-half of one side or less</td>
</tr>
<tr>
<td>T1</td>
<td>pT2b Unilateral, involving more than one-half of side but not both sides</td>
</tr>
<tr>
<td>T1a</td>
<td>pT2c Bilateral disease</td>
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<tr>
<td>T1b</td>
<td>pT3 Extraprostatic extension</td>
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<tr>
<td>T1c</td>
<td>pT3a Extraprostatic extension or microscopic invasion of bladder neck*</td>
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<tr>
<td></td>
<td>pT3b Seminal vesicle invasion</td>
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<tr>
<td></td>
<td>pT4 Invasion of rectum, levator muscles, and/or pelvic wall</td>
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<table>
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<tr>
<th>Regional Lymph Nodes (N)</th>
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<tr>
<td>CLINICAL</td>
</tr>
<tr>
<td>N0</td>
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<tr>
<td>N1</td>
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<th>Distant Metastasis (M)³</th>
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<tr>
<td>M0 No distant metastasis</td>
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*If the PSA or Gleason is not available, determine the stage by T stage and/or either PSA or Gleason, as available.
Clinical scenario (cont’d)

- Biopsy
  - Gleason 4+3 adenocarcinoma
  - 8/12 cores

- What is stage?
  Stage IIIB, pT2c, cT1c
  Intermediate risk: PSA 16.1
  Gleason 7
Management of localized disease

- **Surgery**
  - No established role of neo/adjuvant therapy
  - Either hormone (ADT) or chemo (docetaxel)

- **Definitive XRT**
  - Neo/concurrent/adjuvant ADT
  - Intermediate risk: 4-6 month
  - High risk: 2 years
Clinical course (cont’d)

- Radical prostatectomy
  - Pathology: T3, N0
  - PSA undetectable 6 weeks after surgery

- What is the next?
Management of high risk disease

- Indications for adjuvant radiotherapy
  - T3: extraprostatic extension
  - Seminal vesical invasion
  - Positive margin
  - SWOG 8794, EORTC 22911 and ARO 96-02

- No established role of neo/adjuvant therapy
Clinical course (cont’d)

- Elected not to have adjuvant radiation.
  - 1 year later, PSA 0.05

- How to manage?
Salvage radiotherapy

- The earlier, the better.

- Concurrent/Adjuvant ADT
  - RTOG: bicalutamide, 150mg x2 yrs
    N Engl J Med 2017; 376
  - GETUG-16: LHRH x6mon
    Lancet Oncol 2016;17:747
Clinical course (cont’d)

- Salvage radiotherapy without ADT.
  - 8 month later, PSA undetectable
  - Lost to follow up after 2 years
Clinical course (cont’d)

- 8 years later (54 yo), weakness and bone pain
  - Pancytopenia: Hgb 6.8, plt 78, WBC 3.6
  - Coagulopathy: PTT 42, PT 16.8, fibrinogen 106
  - Liver failure: AST 854, ALT 768 Tbili 2.8
  - Diffuse mixed sclerotic/lytic bone lesions
  - PSA 256

- How to manage?
  - ? biopsy, ?LHRH, ? androgen blockade
Natural history of prostate cancer

- Typical patient presentation as they move through different stages

Regulation of androgen synthesis

- GnRH-agonists: Leuprolide, GnRH-antagonists: Degarelix
  - 1985
  - 2008
- Estrogens, Progestins, Glucocorticoids
- CRH
- Hypothalamus
- Pituitary
- Adrenal
- Testis
  - CYP17A1 inhibitors: Ketoconazole
  - Abiraterone 4/2011
  - Huggins 1941
- DHEAS → DHT
- Androgen receptor antagonists: Bicalutamide, Nilutamide, Flutamide
- Prostate Cancer Cell

Enzalutamide 8/2012

Management of metastatic disease

Recent Evidence

- **ADT/ADT+ DOCETAXEL**
- **ADT+ ABIRATERONE**
- **Abiraterone**
  - Enzalutamide
  - Sipuleucel-T
  - Clinical trials
- **Docetaxel/Radium-223**
  - Clinical trials
- **Abiraterone**
  - Enzalutamide
  - Cabazitaxel
  - Clinical trials
- **Clinical Trials vs Best supportive care**

Treatment
- Naïve metastatic Prostate cancer

Castration Resistant
- with minimal symptoms

Castration Resistant disease
- with significant symptoms

Castration Resistant End stage disease
Clinical course (cont’d)

❖ **How to manage?**

- Ketoconazole 800mg, tid → ? Contraindicated for hepatic function
- Degarelix (antagonist)
- No need biopsy: osteoblastic lesions, high PSA

❖ **New concepts**

- Combined chemo/LHRH
- Combined Abiraterone/LHRH
Agents available in China

- **Chemotherapy**
  - Docetaxel (1st line)

- **Immunotherapy**
  - Sipuleucel-T

- **Hormonal manipulation**
  - Casodex, Ketoconazole
Ketoconazole 800mg tid x2 week (?why)->LHRH
-6 weeks later, he feels good, walking eating fine.
-PSA 176, Hgb 12.8, plt 178, WBC 5.6
-liver function normalized

What is the next?
Management of metastatic disease

**Recent Evidence**

1. **ADT/ADT+ DOCETAXEL**
   - Treatment Naïve metastatic Prostate cancer

2. **Abiraterone Enzalutamide Sipuleucel-T Clinical trials**
   - Castration Resistant with minimal symptoms

3. **Docetaxel/Radium-223 Clinical trials**
   - Castration Resistant disease with significant symptoms

4. **Abiraterone Enzalutamide Cabazitaxel Clinical trials**

5. **Clinical Trials vs Best supportive care**
   - Castration Resistant End stage disease
Clinical course (cont’d)

- Ketoconazole 800mg tid x2 week (why)->LHRH
  - 6 weeks later, he feels good, walking eating fine.
  - PSA 176, Hgb 12.8, plt 178, WBC 5.6
  - liver function normalized

- What is the next?
  - Continue LHRH vs. surgical castration
  - Docetaxel 75mg/m2 x 6 cycles

STAMPEDE-The Lancet 2016
OS: 57 vs. 43 months
Clinical course (cont’d)

18 month later, PSA 256 → 0.01

- PSA 0.06---→0.8---→5.2
- He feels fine

What is the next?
Management of metastatic disease

Recent Evidence

ADT/ADT+ DOCEXAXEL
ADT+ ABIRATERONE

Abiraterone Enzalutamide Sipuleucel-T Clinical trials

Docetaxel/Radium-223 Clinical trials

Abiraterone Enzalutamide Cabazitaxel Clinical trials

Clinical Trials vs Best supportive care

Treatment Naïve metastatic Prostate cancer

Castration Resistant with minimal symptoms

Castration Resistant disease with significant symptoms

Castration Resistant End stage disease
Clinical course (cont’d)

- 18 month later, PSA 256 $\rightarrow$ 0.01
  - PSA 0.06 $\rightarrow$ 0.8 $\rightarrow$ 5.2
  - He feels fine

- What is the next?
  - Sipuleucel-T

  N Engl J Med 2010
Issues with Sipuleucel-T

▶ **Provenge (普罗文奇)**
  
  - Dendritic cell-based therapy, Startup from Stanford
  
  -$100,000 for 3 treatment; OS 4.2 month
  
  -No PSA response, no radiographic response
  
  -2014, bankrupt ➔ Valeant (Canadian) ➔ 三胞集团, 8.19 亿美元, 2017

▶ **Who can benefit?**

  - PSA <20, Gleason 7, minimally symptomatic
Clinical course (cont’d)

- **Sipuleucel-T x 3**
  - PSA 5.2 ---> 22 ---> 48
  - He feels fine

- **What is the next?**
  - Ketoconazole, RR ~25%
  - Bicalutamide (康氏德), RR~20%
    - antiandrogen withdrawal, ~10%
Management of metastatic disease

Recent Evidence

ADT/ADT+ DOCETAXEL
ADT+ ABIRATERONE

Abiraterone
Enzalutamide
Sipuleucel-T
Clinical trials

Docetaxel/
Radium-223
Clinical trials

Abiraterone
Enzalutamide
Cabazitaxel
Clinical trials

Clinical Trials vs
Best supportive care

Treatment
Naïve metastatic
Prostate cancer

Castration
Resistant with
minimal symptoms

Castration Resistant disease
with significant symptoms

Castration Resistant End stage
disease
Ketoconazole, 12 month, PSA 48-->0.6
-PSA 0.56-->3.2-->6.4
-Bicalutamide added, PSA 6.4-->18-->46
-He is loosing weight, fatigued, bone pain

What is the next?
Management of metastatic disease

Recent Evidence

ADT/ADT+ **DOCETAXEL**
ADT+ **ABIRATERONE**

- Treatment Naïve metastatic Prostate cancer
- Castration Resistant with minimal symptoms
- Castration Resistant disease with significant symptoms
- Clinical Trials vs Best supportive care
- End stage disease
Clinical course (cont’d)

- **Ketoconazole**, 12 month, PSA 48---&gt; 0.6
  - PSA 0.56--&gt;3.2-&gt; 6.4
  - Bicalutamide added, PSA 6.4 --&gt;18--&gt;46
  - He is loosing weight, fatigued, bone pain

- **What is the next?**
  - **Docetaxel**
Docetaxel- 多西他赛/紫杉醇

- Prostate cancer is chemo-resistant before 2004
  Tannock IF N Engl J Med 2004
  Petrylak DP N Engl J Med 2004

- Dose: 75mg/m², q3w
  -40mg/m² weekly, only palliation

- OS benefit: ~2.5 month

- AEs: neutropenia, fluid retention, neuropathy
Clinical course (cont’d)

- 6 cycles of docetaxel, PSA 46→1.5
  - He is gaining weight, pain free, less fatigued

- What is the next?
  - Treat to tolerance?
  - Treat to progression?
Docetaxel- 多西他赛/紫杉醇

- Prostate cancer is chemo-resistant before 2004
  - Tannock IF N Engl J Med 2004
  - Petrylak DP N Engl J Med 2004

- Dose: 75mg/m2, q3w, 8-11 cycles in trials

- OS benefit: ~2.5 month
Principles of palliative chemotherapy

- **Palliative intent**
  
  Therapy should not be worse than disease

- **OS benefit:** \(~2.5\) month

- **Never 生命不息，化疗不止**

- **PRINCE Study**

  JCO 2016, intermittent vs. continuous
  Non-inferior, poor accrual
Clinical course (cont’d)

- 6 cycles of docetaxel, PSA 46 → 1.5
  - 4 month of break, PSA 40, symptomatic
- 6 cycles of docetaxel, PSA 40 → 5.6
  - 3 month of break, PSA 36

What is the next?
Management of metastatic disease

Recent Evidence

ADT/ADT+ DOCETAXEL
ADT+ ABIRATERONE

Abiraterone
Enzalutamide
Sipuleucel-T
Clinical trials

Docetaxel/
Radium-223
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Abiraterone
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Clinical trials

Clinical
Trials vs
Best supportive
care

Treatment Naïve metastatic Prostate cancer

Castration Resistant with minimal symptoms

Castration Resistant disease with significant symptoms

Castration Resistant End stage disease
Clinical course (cont’d)

- 6 cycles of docetaxel, PSA 46 $\rightarrow$ 1.5
  - 4 month of break, PSA 40, symptomatic
  - 6 cycles of docetaxel, PSA 40 $\rightarrow$ 5.6
  - 3 month of break, PSA 36

- What is the next?
  - Antiandrogen: ODM 201, ARN 509,
  - 17/21 lyase inhibitor: Galeterone
  - BRACA mutations: platinum, PARP inhibitor
  - PD-1 inhibitors
Take home message

- Androgen-driven disease
- Surgery
  - No adjuvant therapy yet
- Radiotherapy, cross talk with ADT
- Castration-resistance ≠ hormone refractory
Scope of Urologic Oncology

- Prostate Cancer
- Germ cell tumor
- Bladder cancer
- Renal cell carcinoma
- Penile cancer
- Adrenal gland tumor
Clinical scenario

- 22 year-old male
  - Right scrotum pain, no relief after a course of antibiotics
  - US revealed a testicular mass
  - AFP 15, HCG 200, LDH 156

- Next step?
  - ? biopsy, ? CT
Stage I Germ cell tumor

➤ Seminoma vs. Non-seminoma
  - AFP ➔ Non-sem
  - Non-sem, may need surgery.

➤ Orchiectomy ➔ inguinal approach
  Observation; RPLND; chemo; radiation

➤ Cure rate 99%
Clinical scenario

22 year-old male
- Right scrotum pain, no relief after a course of antibiotics
- US revealed a testicular mass
- AFP 15, HCG 200, LDH 156

Next step?
- Inguinal orchietomy → CT abd/pelvis, follow markers
- No transscrotal biopsy
Clinical scenario

45 year-old male

- Respiratory distress, intubated
- Multiple lung mass, RP nodes, liver mets
- AFP 1600, HCG 12,346, LDH 567

Prognosis?
Stage III Germ cell tumor

- Non-seminoma
  - Cisplatin based chemotherapy → surgery

- Cure rate
  - ~50% for poor risk disease
  - ~80% for good risk disease

- Lawrence Einhorn
Thanks!