Treatment of Advanced Prostate Cancer

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Advanced Prostate Cancer

- Rising PSA
- Metastatic Cancer
- Locally Advanced Prostate Cancer
Rising PSA after radical prostatectomy and radiation therapy
Rising PSA after radical prostatectomy and radiation therapy

A.

B.

C.

Rising PSA after radical prostatectomy and radiation therapy

A.

B.

C.
PSA doubling time or PSA slope

\[ DT = -\frac{\lambda + \sqrt{\lambda^2 + 4\gamma \ln 2}}{2\gamma} \]

http://www.mskcc.org/applications/nomograms/prostate/PsaDoublingTime.aspx
Rising PSA after radical prostatectomy and radiation therapy

Treatment Options

- Radiation therapy to prostate bed
- Dietary changes
- Hormone therapy
- Experimental therapy
  - Immunotherapy
  - Vaccines
  - Differentiation therapies
  - Novel Anti-androgens
  - Cytotoxic chemotherapy
Rising PSA and Risk of Developing Metastatic Disease after Surgery

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>$&gt; 7$</th>
<th>$\leq 7$</th>
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<tbody>
<tr>
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<tr>
<td><strong>Time to PSA relapse</strong></td>
<td>$\leq 3$ yrs</td>
<td>$&gt; 3$ yrs</td>
</tr>
<tr>
<td><strong>PSADT (month)</strong></td>
<td>$&lt; 3$</td>
<td>3 to 9</td>
</tr>
<tr>
<td><strong>Time to Mets (years)</strong></td>
<td>1</td>
<td>2</td>
</tr>
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Antonarakis et al.; ASCO 2009: Abstract #5008
Eating at least two servings a week of tomato sauce can significantly decrease the risk of developing prostate cancer.


Eating at least five servings a week of cruciferous vegetables can significantly decrease the risk of developing prostate cancer.


Eating red meat high in ALA can increase the risk of developing advanced prostate cancer, but eating fish high in EPA and DHA can decrease the risk.

Dietary Intervention After Radical Prostatectomy
Recommendations for observation and dietary intervention

- Good for Low risk patients
- Healthy lifestyle
- Need to be cautious not to overdue supplements
- Good source of Dietary information:
  http://www.prostatecancerfoundation.org/
- Change strategy if PSA DT increases

| Staying within the recommended ranges for vitamin and mineral intake is a smart choice |
|-----------------------------------------------|------------------|------------------|
| **Recommended Intake** | **Upper Intake Level** |
| Vitamin A | 3,000 IU/day | 10,000 IU/day |
| Vitamin B6 | 1.7 mg/day | 100 mg/day |
| Vitamin C | 90 mg/day | 1,800 mg/day |
| Vitamin D | 400 IU/day | 2,000 IU/day |
| Vitamin E | 22.5 IU/day | 1,500 IU/day |
| Calcium | 1,200 mg/day | 2,500 mg/day |
| Selenium | 55 μg/day | 400 μg/day |
| Zinc | 11 mg/day | 40 mg/day |

Values are for healthy males aged 19-70.
*Recommended dietary allowances or adequate intakes to be used as goals for individual intake.
†The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects; represents total intake from food, water, and supplements.
Phase II study of Pomegranate juice for men with rising PSA following surgery or radiation therapy

12% decrease in cell proliferation (p=0.0048)

17% decrease in apoptosis (p=0.0004)

Phase II Study of Pomegranate Juice for Men with Rising Prostate-Specific Antigen following Surgery or Radiation for Prostate Cancer
Systemic Treatment Options for Patients with PSA failure

• Observation with dietary modifications
• Investigational therapies
  – Vaccines

• Hormone Therapy (decrease male hormone testosterone)
  – LHRH analogs (Luprolide, Goserlin acetate)
  – Combined Androgen Blockade
  – Intermittent therapy
  – Potency spearing therapy
Hormone Therapy in Men with Prostate Cancer
“Response” Following Hormonal Therapy

1. Symptoms: Palliation

2. PSA: 61-74% normalize (<4 ng/ml)

3. Measurable disease: 30-50% regress, most stable

4. Bone Scan: Only 30-50% improve

Hormonal Therapy typically lasts an average of 12-24 months but may work for over 10 years in some patients.
Hormonal Therapy:
Side Effects

- Impotency
- Anemia
- Muscle wasting
- Weight gain
- Osteoporosis
- Increased lipids
- Increased cardiac disease
Bone Loss- Osteopenia or Osteoporosis with hormone therapy

**Prevention:**
- Calcium + Vitamin D
- Avoid Alcohol
- Avoid Smoking
- Exercise (weight bearing)
- Medications
  - Pamidronate
  - Zolendronic Acid
Intermittent Hormone Therapy
Intermittent Androgen Deprivation Therapy
S9346 (INT-0162) study schema

S9346 induction registrations
Men with newly diagnosed stage D2 prostate cancer and PSA ≥ 5 ng/mL

Late induction registrations started ADT ≤ 6 months prior to registration

Early induction registration (to start ADT after registration)

ADT = goserelin and bicalutamide × 7 months

Men treated with ADT for 7 months who achieve a PSA ≤ 4 ng/mL

If PSA > 4 ng/mL, off protocol

Random assignment

Continuous ADT

Intermittent ADT

Overall survival by prostate-specific antigen (PSA, ng/mL) status at end of induction

Biology of AIPC (HRPC)

Development of Androgen Independence

Cell numbers vs. Time

Deprive androgen → Androgen-independent cells take over

Responsive
Dependent
Independent

ADT 12-24 months

Second-Line Hormonal Therapies

- Anti-androgen withdrawal
- Bicalutamide
- Flutamide
- Nilutamide
- DES
- Ketoconazole
Chemotherapy in Prostate Cancer: Historical Perspective

- Pre-1990’s
  - clinical trials between 1960-1985
  - low response proportion (< 10%)
  - no impact on survival
  - does chemotherapy have a role?
Docetaxel Chemotherapy: Microtubules Dynamics as a Target of Cancer Therapy

Vinblastine
Docetaxel
Paclitaxel
Clinically localized

Relapsed and newly diagnosed M+

Hormone refractory

Local treatment

Endocrine

Docetaxel-based regimens

Improves survival

Prostate Cancer Treatment Paradigms: Chemotherapy Works!!
Expanding the Role of Chemotherapy in the Treatment of Prostate Cancer

Prostate Cancer Treatment Continuum

- Neoadjuvant
- PSA relapse
- HRPC, nonmetastatic
- HRPC, metastatic, first line
- Second-line options

Currently used
Trials ongoing

Endpoint selection: survival, time to progression vs palliative
# Novel Agents in CRPC

## Class of agent

<table>
<thead>
<tr>
<th>Agent</th>
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<tbody>
<tr>
<td>17α hydrolase/17, 20 lyase inhibitor</td>
<td>Abiraterone</td>
</tr>
<tr>
<td>Anti-angiogenic/immunomodulatory</td>
<td>CC4047, Lenalidomide, thalidomide</td>
</tr>
<tr>
<td>Anti-CTLA4 antibody</td>
<td>Ipilimumab</td>
</tr>
<tr>
<td>Anti-II-6 antibody</td>
<td>CNTO 95</td>
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<tr>
<td>Anti-insulin-like GFR antibody</td>
<td>IMC-A12</td>
</tr>
<tr>
<td>Anti-integrin anti-body</td>
<td>CNTO 95</td>
</tr>
<tr>
<td>Anti-PSMA immunoconjugate</td>
<td>MLN2704, 177 Lu-J591</td>
</tr>
<tr>
<td>Anti-prostate stem cell antibody</td>
<td>AGS-PSCA</td>
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<tr>
<td>Anti-VEGF</td>
<td>Bevacizumab</td>
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<tr>
<td>Cytotoxic agent</td>
<td>ABT-751, abraxane, E7389, GMO-paclitaxel, Irofulven, Paclitaxel poliglumex, Pemtrexed, Trabectin, Vinfluvine, Epothilones, Satraplatin</td>
</tr>
<tr>
<td>EGFR antibodies\TKI</td>
<td>Pertuzumab, Cetuximab, Erlotinib, Gefitinib, Lapatinib</td>
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<tr>
<td>GMP phosphodiesterase inhibitor</td>
<td>Exisulind</td>
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<tr>
<td>HSP-90 inhibitor</td>
<td>17-AAG</td>
</tr>
<tr>
<td>HDACi</td>
<td>LBH589, Romidepsin, Valproic acid, Vorinostat, Belinostat</td>
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<tr>
<td>Integrin receptor antagonist</td>
<td>Cilengitide</td>
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<tr>
<td>M-TOR inhibitor</td>
<td>RAD-001</td>
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<tr>
<td>Multi-targeted TKI</td>
<td>Sunitinib, Sorafenib, CEP 701</td>
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<tr>
<td>Pro-apoptotic agent</td>
<td>AT-101</td>
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<tr>
<td>Proteosome Inhibitor</td>
<td>Bortezomib</td>
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<tr>
<td>Signal Transduction inhibitor</td>
<td>PCK-3145</td>
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<tr>
<td>Survivin suppressant</td>
<td>YM155</td>
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</tbody>
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Thank You
Prostate Cancer: Growth Rate and Progression

Cancer Progression

Onset of Cancer

Localized Disease

Metastatic Disease

Early Detection

Prostate Cancer Death

Life Expectancy

Natural Death
The patients know more about their diseases than me. I must get faster modem, higher speed internet access than them.