To treat or not to treat: When to treat!
A case presentation

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A case presentation

- Pt. 76 y. – Mild LUTS (07/1999)
- Rectal exam. and sonography: cT2c
- PSA : 21 ng/ml
- Transrectal biopsies
  - Gleason 7 (4+3) / 8 of 12 biopsies +
- Staging : CT and bone scan: negative
- Definite staging : cT2cNoMo
A case presentation

• General Health Status
  – Comorbidities
    • Mild hypertension – treated
    • NIDDM – compensated
    • Mild depression
  – Other variables
    • Normal nutritional and cognitive status
    • No dependancy and/or geriatric syndromes
• Social status
  • Married, middle class, urban
How can we treat this patient?
How can we treat this patient

EAU Guidelines
AUA guidelines
NCCN Guidelines
....
# EAU guidelines for the management of localized prostate cancer

<table>
<thead>
<tr>
<th>STAGE</th>
<th>TREATMENT</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Watchful waiting</td>
<td>Standard treatment for well- and moderately differentiated tumors and (&lt;10)-year life expectancy. In patients with (&gt;10)-year life expectancy, restaging with TRUS and biopsy is advised (grade B recommendation)</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
<td>Optional in young patients with a long life expectancy, especially for poorly differentiated tumors (grade B recommendation)</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>Optional in younger patients with a long life expectancy, especially for poorly differentiated tumors. Higher complication risks after TURP, especially with interstitial radiation (grade B recommendation)</td>
</tr>
<tr>
<td></td>
<td>Hormonal</td>
<td>Not an option (grade A recommendation)</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>Not an option (grade C recommendation)</td>
</tr>
<tr>
<td>T1b-T2b</td>
<td>Watchful waiting</td>
<td>Asymptomatic patients with well- and moderately differentiated tumors and a life expectancy &lt; 10 years. Patients who do not accept treatment-related complications (grade B recommendation)</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
<td>Standard treatment for patients with life expectancy &gt; 10 years who accept treatment-related complications (grade A recommendation)</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>Patients with a life expectancy &gt; 10 years who accept treatment-related complications. Patients with contraindications for surgery. Unfit patients with 5-10 years of life expectancy and poorly differentiated tumors (combination therapy is recommended; see below) (grade B recommendation)</td>
</tr>
<tr>
<td></td>
<td>Hormonal</td>
<td>Symptomatic patients who need palliation of symptoms unfit for curative treatment (grade C recommendation). Antiandrogens are associated with poorer outcome in comparison with watchful waiting are not recommended (grade A recommendation)</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>Neoadjuvant hormonal therapy (NHT) + radical prostatectomy: no proven benefit (grade A recommendation). NHT + radiotherapy: better local control. No proven survival benefit (grade B recommendation). Hormonal (3 years) + radiotherapy: better than radiotherapy in poorly differentiated tumors (grade A recommendation)</td>
</tr>
<tr>
<td>T3-4</td>
<td>Watchful waiting</td>
<td>Option in asymptomatic patients with T3, well-differentiated and moderately differentiated tumors, and a life expectancy &lt; 10 years (grade C recommendation)</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
<td>Optional for selected patients with T3a and a life expectancy &gt; 10 years (grade C recommendation)</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>T3 with &gt; 5-10 years of life expectancy. Dose escalation &gt; 70 Gy seems to be of benefit. If this is not available, a combination with hormonal therapy could be recommended (see below) (grade A recommendation)</td>
</tr>
<tr>
<td></td>
<td>Hormonal</td>
<td>Symptomatic patients, extensive T3-T4, high PSA level (&gt;25 ng/mL), unfit patients. Better than watchful waiting (grade A recommendation)</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>Radiotherapy + hormonal seems better than radiotherapy alone (grade A recommendation). NHT + radical prostatectomy: no proven benefit (grade B recommendation)</td>
</tr>
</tbody>
</table>
**EAU Guidelines 2007 cT2NoMo**

- **Watchfull waiting**
  - Asymptomatic patients with well, and moderately differentiated tumors and a life expectancy <10 years.
  - Patients who do not accept treatment related complications

- **Radical prostatectomy**
  - Standard treatment for patients with a life expectancy >10 years who accept treatment related complications

- **Radiotherapy**
  - Patients with a life expectancy >10 years who accept treatment related complications.
  - Patients with contraindications for surgery
  - Unfit patients with 5-10 years of life expectancy and poorly differentiated tumors.(combination therapy is recommended)

- **Hormones**
  - Symptomatic patients who need palliation of symptoms unfit for curative treatment. Antiandrogens are associated with poorer outcome compared to watchfull waiting and are not recommended

- **Combination**
  - ...NHT+ RT : better local control....Hormonal (3 years) +RT: better than RT in poorly differentiated tumors
How should we treat this patient?
How should we treat this patient

Tumor characteristics
Age
General Condition
Life Expectancy
Patient preference
Should we treat this patient?

Watchfull waiting?

- Pt. 76 y. – Mild LUTS
- Rectal exam. and sonography: cT2c
- PSA: 21 ng/ml
- Transrectal biopsies
  - Gleason 7 (4+3) / 8 of 12 biopsies +
- Staging: CT and bone scan: negative
- Definite staging: cT2cNoMo
D’Amico Prostate Cancer risk classification

Cancer-Specific Mortality After Surgery or Radiation for Patients With Clinically Localized Prostate Cancer Managed During the Prostate-Specific Antigen Era

By Anthony V. D’Amico, Judd Moul, Peter R. Carroll, Leon Sun, Deborah Lubeck, and Ming-Hui Chen


The risk groups were defined using the pretreatment serum PSA level, biopsy Gleason score, and 2002 AJCC tumor category. Specifically, low-risk patients had a PSA level of 10 ng/mL or less, a biopsy Gleason score of 6 or less, and 2002 AJCC category T1c or T2a disease. Intermediate-risk patients had a PSA of more than 10 ng/mL and not more than 20 ng/mL, a biopsy Gleason score of 7, or 2002 AJCC category T2b disease. Finally, high-risk patients had a PSA more than 20 ng/mL, a biopsy Gleason score of 8 to 10, or 2002 AJCC category T2c disease.
Prostate Cancer specific mortality after treatment
Localized prostate cancer

Radical prostatectomy  Radiation therapy

Low risk  Intermediate risk  High risk

Only patients with high-risk disease are likely to receive curative treatment

<table>
<thead>
<tr>
<th>D’AMICO RISK CLASSIFICATION</th>
<th>10-YEAR MORTALITY IN MEN 70+</th>
</tr>
</thead>
</table>
| Low risk (PSA ≤ 10ng/mL and Gleason score ≤ 6 and T1c or T2a) | Overall: ≈ 20%  
Due to prostate cancer: ≈ 0% |
| Medium risk (PSA 10-20 ng/mL or Gleason = 7 or T2b) | Overall: ≈ 40%  
Due to prostate cancer: ≈ 10% |
| High risk (PSA >20ng/mL or Gleason score >7 or T2c) | Overall: ≈ 60%  
Due to prostate cancer: ≈ 30% |

Death of other causes  
Death of prostate cancer

D‘Amico A et al. JCO 2003, 21: 2163-2172
Can we treat this patient surgically? Radical prostatectomy?

- Pt. 76 y. – Mild LUTS
- Rectal exam. and sonography: cT2c
- PSA: 21 ng/ml
- Transrectal biopsies
  - Gleason 7 (4+3) / 8 of 12 biopsies +
- Staging: CT and bone scan: negative
- Definite staging: cT2cNoMo
- Good General Health – moderate operative risk
Can we treat this patient surgically?  

Radical prostatectomy?

- EAU Guidelines
  - Standard treatment
  - Life expectancy > 10 years
  - Accepting treatment related complications
- D’Amico data
  - Favorable for surgery in high risk patients
Median life expectancy

![Bar chart showing median life expectancy across different age groups. The chart highlights a decrease in life expectancy with age, with the highest median life expectancy at 60 years.]
Life expectancy - Percentiles

Fit.

Median/Vulnerable

Frail and terminal

nb d'années restantes

Age (années)
Can we treat this patient surgically?

Radical prostatectomy?

• EAU Guidelines
  – Standard treatment
  – Life expectancy > 10 years
  – Accepting treatment related complications
• D’Amico Data
• But ........
  – General Health status ?
  – Per and early postoperative morbidity ?
  – Late postoperative problems
A case presentation

• General Health Status – 76 Y
  – Comorbidities
    • Mild hypertension – treated
    • NIDDM – compensated
    • Mild depression
  – Other variables
    • Normal nutritional and cognitive status
    • No dependancy and/or geriatric syndromes
• Social status
  – Married, middle class, urban
Can we treat this patient safely with a Radical prostatectomy?
This clinical case has to be considered as ‘vulnerable’

- Simplified Senior adult health status assessment.
- Lodovico Balducci, MD. & Jean-Pierre Droz, MD.
- “SIOG prostate Cancer in senior adult patients guidelines”
Senior adults with localized prostate cancer

Life Expectancy Evaluation

Group 1 (Healthy)
- Comorbidity (CISR-G): grade 0 or 1 or 2
- Independent in IADL
- No denutrition

Group 2 (Vulnerable, i.e. reversible problem)
- Comorbidity (CISR-G): at least one grade 3
- Dependent in ≥ 1 IADL
- Denutrition

Group 3 (Frail, i.e. non reversible problem)
- Comorbidity (CISR-G): several grade 3 or at least one grade 4
- Dependency: Impairment of at least one ADL
- Cognitive impairment
- Repeated delirium
- Severe denutrition

Group 4 (Terminal illness)
- Terminal
- Bedridden
- Major comorbidities
- Cognitive impairment

• Standard treatment as for younger patients
• Standard treatment as for younger patients except prostatectomy
• Symptomatic management including specific treatments (hormones, RTUP...)
• Only palliative treatment

Readaptation
The optimal treatment for this patient is Radiotherapy?

- EAU Guidelines
  - Life expectancy > 10 years
  - Accepting treatment related complications
  - Unfit patients with 5-10 years of life expectancy and poorly differentiated tumors (combination therapy is recommended)
  - Patients with contraindications for surgery
The definite treatment for this patient

Radiotherapy combined with hormones

• EAU Guidelines
  – Combined with hormones during 3 years
    • Better than RT in poorly differentiated tumors
    • Proven overall survival benefit
  – Neo adjuvant:
    • better local control, no benefit in O.S
Combined RT and HT – Bolla study

- Log-rank test $p < 0.0001$
- Hazard ratio 0.51
- (95% CI 0.36–0.73)

- Overall survival (%) vs. Time since randomisation (years)

- Number of patients at risk:
  - Radiotherapy alone:
    - 81, 208, 199, 177, 146, 106, 70, 46, 30, 16
    - 50, 207, 197, 183, 166, 142, 93, 71, 43, 24

- Combined treatment:
Further clinical course

• Conformal Radiotherapy – 72 GY – 08/99
• Hormonal treatment:
  – Goserelin 10.8 every three months (Zoladex)
  – Bicalutamide 50 mg 1 month (Casodex)
• Oncological Follow up
  – Every three months – Clinical/PSA
  – Cyproterone 50mg (Androcur)– hot flushes since 12/99
Biochemical recurrence

- TAP/CT: 2 LN external left iliac artery 7 and 8 mm
- Tc-99m bone scan: negative

PSA (ng/mL)

Zoladex LA + Androcur
What is the proposed strategy?

1. Nothing
2. Stop Androcur and wait
3. Stop Androcur and replace immediately by Casodex 50 mg
4. Stop Androcur and replace immediately by Estracyt 50 mg (estramustine phosphate)
5. Add Avodart 0.5 mg (dutasteride)
6. Start docetaxel
# Anti-androgen withdrawal syndrome

<table>
<thead>
<tr>
<th>Total</th>
<th>Drug</th>
<th>Patients (n)</th>
<th>% of patients with 50% PSA response</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scher et al</td>
<td>Flut</td>
<td>57</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>Small et al</td>
<td>Flut</td>
<td>82</td>
<td>15</td>
<td>3.5</td>
</tr>
<tr>
<td>Figg et al</td>
<td>Flut</td>
<td>21</td>
<td>33</td>
<td>3.7</td>
</tr>
<tr>
<td>Herrada et al</td>
<td>Flut</td>
<td>39</td>
<td>28</td>
<td>3.3</td>
</tr>
<tr>
<td>Schellhammer et al</td>
<td>Flut</td>
<td>8</td>
<td>50</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Bical</td>
<td>14</td>
<td>29</td>
<td>NR</td>
</tr>
<tr>
<td>Nieh</td>
<td>Bical</td>
<td>3</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>224</strong></td>
<td><strong>25</strong></td>
<td></td>
</tr>
</tbody>
</table>

Flut + flutamide; Bical = bicalutamide; NR = not recorded
Second-line hormonal manipulations

Adding a second line of hormones

<table>
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<tr>
<th>Total</th>
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<th>Patients (n)</th>
<th>% &gt; 50% PSA response</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelly et al</td>
<td>Hydrocortisone</td>
<td>30</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Storile et al</td>
<td>Dexamethasone</td>
<td>38</td>
<td>61</td>
<td>NR</td>
</tr>
<tr>
<td>Tannock et al</td>
<td>Prednisone</td>
<td>81</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>Dawson et al</td>
<td>Hydrocortisone + AAW</td>
<td>34</td>
<td>29</td>
<td>1.8</td>
</tr>
<tr>
<td>Sartor et al</td>
<td>Aminoglutethimide + AAW + hydrocortisone</td>
<td>29</td>
<td>48</td>
<td>4</td>
</tr>
<tr>
<td>Small et al</td>
<td>Ketoconazole + hydrocortisone</td>
<td>50</td>
<td>63</td>
<td>3.5</td>
</tr>
<tr>
<td>Small et al</td>
<td>Ketoconazole + hydrocortisone + AAW</td>
<td>20</td>
<td>55</td>
<td>8.5</td>
</tr>
<tr>
<td>Dawson et al</td>
<td>Megestrol acetate</td>
<td>149</td>
<td>12</td>
<td>NR</td>
</tr>
<tr>
<td>Osborn et al</td>
<td>Megestrol acetate</td>
<td>14</td>
<td>14</td>
<td>NR</td>
</tr>
<tr>
<td>Scher et al</td>
<td>High-dose bicalutamide</td>
<td>51</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Joyce et al</td>
<td>High-dose bicalutamide</td>
<td>31</td>
<td>23</td>
<td>NR</td>
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AAW = anti-androgen withdrawal
Biochemical recurrence

- TAP/CT: 2 LN external left iliac artery 7 and 8 mm
- Tc-99m bone scan: negative

PSA (ng/mL)

Zoladex LA + Androcur  Zoladex LA

Stop Androcur
Clinical course after AA withdrawal

- Biochemical progression
- Asymptomatic
- Patient agreed to be included into a clinical trial - Atrasentan
- He agrees to have bone scans and CT scans every two months
Atrasentan - Study M00-244

Non-metastatic
PSA rising
Atrasentan vs. placebo
Further clinical course

- Patient has to stop trial medication
- Strictly asymptomatic
- MRI of the axial skeleton confirms two metastases
Asymptomatic Biochemical Progression

What is our strategy now?

1. Zometa 4 mg monthly
2. Estracyt per os
3. Docetaxel 75 mg/m² q/3 weeks
4. Surveillance until symptoms appear
Evolution to Symptomatic HRPC

- The patient initially decides to have surveillance
- He comes back after four months
- He has moderate but recurrent pain in the back.
Biochemical recurrence

PSA (ng/mL)

Study drug

Zoladex LA
Symptomatic HRPC

What is our strategy now?

1. Zometa 4 mg monthly
2. Estracyt per os
3. Docetaxel 75 mg/m² q/3 weeks
4. Radionuclide drugs
5. Palliative radiotherapy
6. Other?