When and how long do you need hormone treatment for Prostate Cancer and what are its side-effects

Thomas Steuber

SAMO Interdisciplinary Workshop on urogenital Tumors,
*Luzern14.09.2012*
• Mechanisms of Hormonal therapy

• Hormonal therapy of non metastatic PCa
  - localized (T1-T2)
  - locally advanced PCa (T2-T4)
  - biochemical recurrence

• Hormonal therapy of metastatic PCa

• Therapeutic strategies

• Side effects of Hormonal therapy

• Hormonal therapy despite Hormonal resistance?
• Mechanisms of Hormonal therapy

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Mechanism of Hormononal Therapy

- Hypothalamus
  - GnRH
  - Feedback
  - Down-Regulation
  - ↓ Testosteron
  - ↑ LH, FSH
  - Testes
  - Prostate
  - Hypophy

Graphs:
- Percentage change vs. weeks post injection
- Treatment: Degarelix 240/160 mg, Degarelix 240/80 mg, Leuprolide 7.5 mg

70-80% normal
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• 19,271 men, SEER Data-Base

• T1-T2 PCa btw. 1992-2002

• No local therapy

• Stratification; „high-use ADT HSA“ vs. „low-use“ ADT HSA

• Instrumental variable Analysis, CSS and OS

„...clinicians should carefully consider the rationale for initiating immediate ADT in elderly patients with T1-T2 prostate cancer“.

Lu-Yao et al, JAMA, July 9, 2008—Vol 300, No. 2
• EORTC 30891, prospective randomized trial
  – n = 985
  – Follow-up = 7.8 Jahre

• T2–T4 M0 (new diagnosed, no distant metastasis,)
  – Immediate ADT (n = 493)
  – ADT in case of Symptomy or systemic progression(n = 492)

No significant difference in cancer-specific survival

Studer U et al., JCO 2006; 24: 1868
• If patient and physician refuse treatment in curative intent, patient should be counseled to undergo immediate ADT or watchful waiting followed by palliative ADT in case of symptomatic/metastatic progression.

• Content of discussion should be
  - palliative character of treatment
  - side effects of ADT
  - Advantage in PFS but inconsistency with respect to OS

S3-Guideline Prostate Cancer, Version 2.0; 2012
if you consider immediate ADT for locally advanced PCa, you should combine with local (radio-) therapy
Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial

Anders Widmark, Olbjørn Kløpp, Anne Solberg, Jan-Erik Damber, Anders Angelsen, Per Fransson, Jo-Åsmund Lund, Ilker Tasdemir, Morten Hoyer, Fredrik Wiklund, Sophie D Fosså, for the Scandinavian Prostate Cancer Group Study 7 and the Swedish Association for Urological Oncology 3

12.3 % benefit in CSS for ADT plus Radiation after 10 years

Widmark et al., Lancet 2009; 373
**Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial**

Padraig Warde*, Malcolm Mason*, Keyue Ding, Peter Kirkbride, Michael Brundage, Richard Cowan, Mary Gospodarowicz, Karen Sanders, Edmund Kostashuk, Greg Swanson, Jim Barber, Andrea Hiltz, Mahesh K B Parmar, Jinka Sathy, John Anderson, Charles Hayter, John Hetherington, Matthew R Sydes¹, Wendy Parulekar¹, for the NCIC CTG PR.3/MRC UK PR07 investigators

11% benefit in CSS for ADT plus Radiation after 7 years

Warde et al., Lancet 2011; 378
...but delayed mPFS when ADT is started at PSA <5 ng/ml (p<0.004) or PSA <10 ng/ml (p= 0.003) in men with Gleason >7 or PSA-DT <12 months

Moul et al., J Urol, 2004; 171:1141
Hormonal therapy for biochemical recurrence?

„Androgen deprivation therapy is no standard for biochemical recurrence or biochemical progression following local therapy“

„Hormonal therapy should be considered for
- PSA-DT < 3 months
- local recurrence
- metastatic progression

S3-Guideline Prostate Cancer, Version 2.0; 2012
Treatment modality in relation to “Cancer of the Prostate Risk Assessment risk score” and Age

Bechis et al., JCO 2011
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“For patients with asymptomatic, metastatic prostate cancer, hormonal therapy can be offered“

“For patients with symptomatic, metastatic prostate cancer, hormonal therapy should be offered“
• Mechanisms of Hormonal therapy

• Hormonal therapy of non metastatic PCa
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Monotherapy – surgical/chemical Castration

Hormonal therapy

- Surgical Castration
- GnRH-Agonists
- GnRH-Antagonist

GnRH vs. Orchiectomie

- equivalent, reversible, 20% failure

GnRH Agonist vs. Antagonist

- equivalent (p = 0.05)


Tombal et al. Eur Urol 2010
Hormonal therapy

Non-steroidal Antiandrogens (Bicalutamid 150 mg)

M0, not significant

S3: „For Patients with metastatic PCa ... therapy with non steroidal Antiandrogen can be offered. Grad 0“

Tyrell et al, Eur Urol 1998; 33
S3: “After counseling the patient about missing long-term data, intermittent hormonal therapy can be considered. Grad 0”
- Prospektive randomized trial

- 1386 patients with BCR after radiotherapy, 1999 - 2005

- Intermittant ADT (690) vs. Continous ADT (696), median follow-up 6.9 yr

- GnRH-Analogue for 4 months, intermittent ADT when PSA<4 ng/ml

- Non – inferiority hypothesis, Cox multivariable Analysis, OS

Crook et al, New Eng J Med, September 2012; 367
Who can be treated with IAD?

• Requirement: significant PSA↓ after 6 months:

<table>
<thead>
<tr>
<th>No prior treatment</th>
<th>&lt; 4 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA Recurrence following Radiation</td>
<td>&lt; 0.5 - 1 ng/mL</td>
</tr>
<tr>
<td>PSA Recurrence following RP</td>
<td>&lt; 0.5 ng/mL</td>
</tr>
</tbody>
</table>

• Precaution:
  - Patients with high initial-PSA (>500ng/ml) or fast PSA-doubling time (PSA-DT < 6 Monate)
  - Patients with high grade PCA
  - Patients with large tumor burden
Conclusion, Hormonal therapy

- **low risk-group:**
  - biochemical progression after local Tx
  - T1-T4, M0
  - M1 asymptomatisch
  - small Tumor burden
  - Slow PSA-Dynamic

- **high risk-Konstellation:**
  - M1, high tumor burden
  - symptomatic Patient
  - PSA>400
  - PSA-DT 3-6 Monate

- **ww, deferred ADT**
- **Monotherapy (GnRH-Agonist/Antagonist, Bicalutamid)**
- **intermittant ADT**

- **immediate ADT**
- **continous ADT**
- **combined ADT**
Side effects of Hormonal therapy

• Gynäkomastie/Pain as side effect of Bicalutamid (150 mg) (up to 70%)
  Prevention: Radiatio Mamillae, Therapy: Tamoxifen 10 mg

• Hot flashes
  Therapy: Östrogene, Gestagene, steroidal Antiandrogen (Androcour)

• Osteoporosis
  Prevention: Excercising, Ca+ Bisphosphonate, Denosumab 60 mg s.c.(Prolia®)

• Erektile Dysfunction
  Therapy: PDE5-Inhibitor, SKAT

• Loss of Libido, Depression

• Influence on fat metabolism, Increase body fat, increase LDL, Cholesterin and Triglycerides
  Prevention: Diet, physical excercises

• Insulin resistanzce (= causes Diabetes Mellitus Type 2)

• Increase cardiovascular death?
• **Increased risk**

Observation:

Randomised:

• **No increased risk**

Observation:

Randomised:
SEER-Medicare-Ergebnisse according to duration of treatment

<table>
<thead>
<tr>
<th>Duration of LHRH-Agonist</th>
<th>Diabetes Mellitus</th>
<th>Myocard Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–4 Monate</td>
<td>$p &lt; 0.001$</td>
<td>$p = 0.19$</td>
</tr>
<tr>
<td>5–12 Monate</td>
<td>$p &lt; 0.001$</td>
<td>$p = 0.21$</td>
</tr>
<tr>
<td>13–24 Monate</td>
<td>$p &lt; 0.001$</td>
<td>$p = 0.42$</td>
</tr>
<tr>
<td>≥ 25 Monate</td>
<td>$p &lt; 0.001$</td>
<td>$p = 0.24$</td>
</tr>
</tbody>
</table>

Duration of ADT significantly correlates with incidence of diabetes, not with heart attack risk!
Add Antiandrogen

Hormon Insensitive Prostate Cancer

Mean response

36 months

4-6 months

4-6 months

5-6 months

4-8 months

CRPC

Non hormonal therapy, e.g. Chemotherapy

10-12 months
Prostate Cancer can maintain AR signaling after becoming CRPC

AR Signaling still happens, even in patients with castrate levels of testosterone (<50 ng/dl or <1.7 nmol/)

How?

Androgen receptor up-regulation by gene-amplification or other mutations

Overexpression of key enzymes P-450C 17 (CYP 17)
Involved in extragonadal androgen biosynthesis

Intratumoral Synthesis of testosterone

Why go back for ADT in castration resistant disease?
• Because ADT is the most effective treatment we have for advanced Pca
• These patients are not truely hormon refractory but castration resistant
• Lower testosterone levels or targeting AR signaling can significantly improve outcomes
Importance of maintaining castrate levels in CRPC: Survival

- Retrospective analysis (N = 341) showed discontinuation of medical castration predictive of shorter survival

### Wisconsin Clinical Cancer Center study C08586
(N = 38): median OS significantly longer with maintained castrate testosterone levels (P = .01)
- Orchiectomy: 9.9 mo
- Hormone therapy discontinued prior to study: 3.6 mo

Taylor CD et al, J Clin Oncol, 1993; 11
Androgen Priming before cytotoxic therapy for CRPC is associated with worse outcome.

- 85 men with progressive PC refractory to orchietomy
- Treated with aminoglutethimide and hydrocortisone and administered cyclic IV CT
- Randomised to receive either androgen priming or no additional treatment for 3 days before and on the day of CT

Overall Survival Kaplan-Meier Curve

\( P = .0047, \text{ Mantel-Cox} \)

Manni A et al, J Clin Oncol, 1988; 23
Baseline Testosterone, predictor of response to Abirateron in CRPC

Distribution of Androgen Levels at Baseline

- Although eligibility criterion for serum testosterone levels was <50 ng/dL, most patients had <15 ng/dL

Ryan et al. AACR Conference 2012: Abstract LB-434 (Oral presentation)
Coding “high hormones” (HH, above Median) vs. “low hormones” (LH, below Median)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH (IU/L)</td>
<td>227</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>11.8</td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>134</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>131.4</td>
</tr>
<tr>
<td>Testosterone (ng/dL)</td>
<td>5.0</td>
</tr>
<tr>
<td>Androstenedione (ng/dL)</td>
<td>23.7</td>
</tr>
<tr>
<td>DHEA (µg/dL)</td>
<td>16</td>
</tr>
</tbody>
</table>

Ryan et al. AACR Conference 2012; Abstract LB-434 (Oral presentation)
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>0.667</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>0.679</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>DHEA</td>
<td>0.691</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

- Therapy effect robust
- All other biomarkers significant (LDH, Hgb, ALP, PSA)

Ryan et al. AACR Conference 2012; Abstract LB-434 (Oral presentation)
OS Significantly Longer in HH vs. LH Groups: Testosterone

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>AA HH vs. AA LH</th>
<th>AA HH vs. PL HH</th>
<th>AA LH vs. PL LH</th>
<th>PL HH vs. PL LH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.64 (0.53-0.77)</td>
<td>0.81 (0.64-1.03)</td>
<td>0.69 (0.56-0.85)</td>
<td>0.51 (0.39-0.67)</td>
<td></td>
</tr>
</tbody>
</table>

HH, high hormone; LH, low hormone; PL, placebo

Ryan et al. AACR Conference 2012; Abstract LB-434 (Oral presentation)
Continuation of ADT with GnRH analogues in patients with CRPC is recommended by guidelines.

EAU Guidelines 2012: „It is recommended to continue ADT with GnRH analogues despite PSA progression“
<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone acetate</td>
<td>Selective and irreversible inhibitor of the 17,20 lyase activity of CYP17, a critical enzyme in androgen biosynthesis, which blocks nongonadal androgen production</td>
<td>Approved&lt;sup&gt;2,3&lt;/sup&gt;</td>
</tr>
<tr>
<td>MDV3100/enzalutamide</td>
<td>AR antagonist that blocks AR transfer to the nucleus</td>
<td>Phase 3 studies</td>
</tr>
<tr>
<td>TAK-700/orteronel</td>
<td>Selective reversible nonsteroidal androgen synthesis inhibitor of the 17,20 lyase activity</td>
<td>Phase 3 studies</td>
</tr>
<tr>
<td>ARN-509, AZD3514, ASP9521, TOK-001</td>
<td>In earlier stages of development</td>
<td>Phase 1 and 2 studies</td>
</tr>
</tbody>
</table>
New Concept 1: Cytochrom P17 (CYP17) – Blockage

Mineralocorticoid-Antagonist Eplerenone
Prednison

Randomisierte, multinationale, doppelblinde und placebo-kontrollierte Phase III Multicenterstudie (147 Standorte in 13 Länder; USA, Europa, Australien, Kanada)

- 1195 Patienten mit progredientem, M1 CRPC
- 1-2i vorherige Chemotherapien
- Randomisiert 2:1
- Stratifikation durch:
  - ECOG(0-1 versus 2)

Abirateron Acetat 1000 mg täglich
Prednison 5 mg zweimal täglich
Placebo täglich
Prednison 5 mg zweimal täglich

Primärer Endpunkt: OS (25% Verbesserung; HR 0,8)

de Bono et al. Ann Oncol 2010: Abstract LBA5 (Oral presentation at ESMO)
Targeting Androgen Synthesis
Cougar-301: Abiraterone in Docetaxel Pretreated Metastatic CRPC

**Study design:** 1,195 patients with mCRPC pretreated with docetaxel were randomised to abiraterone acetate + prednisone or placebo + prednisone (testosterone maintained <50 ng/dL via ongoing medical castration or surgical castration)

![Graph showing survival rates with Abiraterone and PBO](image)

- **OS**
  - **Abiraterone:** 14.8 mo
  - **PBO:** 10.9 mo
- **HR**
  - **Abiraterone:** 0.646 (95% CI, 0.54-0.77)
  - **PBO:**

All secondary endpoints favoured the treatment group:
- **Time to PSA progression** (10.2 vs 6.6 mo; \( P < .001 \))
- **PFS** (5.6 vs 3.6 mo; \( P < .001 \))
- **PSA response rate** (29% vs 6%, \( P < .001 \))

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**Notes:**
- a Defined by investigator assessment of progression by soft tissue or progression by bone scans with \( \geq 2 \) new lesions not consistent with tumour flare.
- b Defined as PSA decline of \( \geq 50\% \) confirmed by a second PSA decline at least 4 weeks later.
COU-AA-302 Phase III Trial; Abirateron for mCRPC prior to Chemotherapie

Phase 3 multizenter, randomisierte, doppel blind, Plazebo kontrollierte Studie durchgeführt an 151 Zentren in 12 Ländern; USA, Europe, Australia, Canada

<table>
<thead>
<tr>
<th>Patienten</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Progressive chemo-naive mCRPC Patienten (Planned N = 1088)</td>
</tr>
<tr>
<td>• Asymptomatisch oder mild symptomatisch</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RANDOMISIERT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RANDOMISIERT</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA 1000 mg täglich Prednisone 5 mg BID (Actual n = 546)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RANDOMISIERT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plazebo täglich Prednisone 5 mg BID (Actual n = 542)</td>
</tr>
</tbody>
</table>

Endpunkte

Co-Primärendpunkte:
• Radiologische Progressionsfreiheit
• Gesamtüberleben

Sekundäre Endpunkte
• Zeit zum Opiat-Gebrauch (Tumor bedingt)
• Zeit bis zur Chemotherapie
• Zeit bis zur ECOG-PS Verschlechterung
Targeting Androgen Synthesis
Cougar-302: Abiraterone in Chemotherapy-Naïve Patients

- Study design: Phase 3 multicentre RCT: CT-naïve patients were randomised to abiraterone + prednisone or PBO + prednisone (testosterone maintained <50 ng/dL via ongoing medical castration or surgical castration)

Progression-Free Survival at 18 Mo

<table>
<thead>
<tr>
<th>Time to Progression or Death, mo</th>
<th>Progression-Free Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>0%</td>
</tr>
<tr>
<td>12</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>0%</td>
</tr>
<tr>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

Abiraterone + Prednisone: Median PFS = NR, HR = 0.43 (95% CI, 0.35-0.52); P < .0001
PBO + Prednisone: Median PFS = 8.3 mo
### Side Effects mainly attributed to mineralocorticoid excess

<table>
<thead>
<tr>
<th></th>
<th>AA (n = 791)</th>
<th>Placebo (n = 394)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>30.5%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>17.1%</td>
<td>3.8%</td>
</tr>
<tr>
<td>LFT Abnormalities</td>
<td>10.4%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9.7%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Cardio vascular disorders</td>
<td>13.3%</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

---

• 4 Tablets a 250 mg (1000 mg)
• taken on an empty stomach
  (AUC may vary according to fat consume)
• Prednison / Prednisolone 5 mg bid
Enzalutamide (MDV3100) binds the AR more tightly than the anti-androgen bicalutamide, blocks nuclear translocation more effectively and prevents DNA binding\(^1,2\)

Adapted from:
1. Scher H I, et al. Results From the Phase 3 Affirm Study. Presented at ASCO-GU, 02 February 2012
AFFIRM: A Phase 3 trial of Enzalutamide vs. Placebo in Post-Chemotherapy treated CRPC

**Patient population:**
1199 patients with progressive CRPC

*Failed docetaxel chemotherapy

**Randomized 2:1**

**Enzalutamide 160 mg daily n = 800**

**Placebo N = 399**

**Primary Endpoint**
Overall Survival

Clinicaltrials.gov identifier: NCT00974311

Modifiziert nach: Scher HI, ASCO GU 2012; de Bono JS, ASCO 2012
Enzalutamide prolonged survival by a median of 4.8 months in the phase 3 AFFIRM trial.
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio for Death (95% CI)</th>
<th>Overall Survival Median (mo) Enzalutamide/Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>0.63 (0.53–0.75)</td>
<td>18.4 / 13.6</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>0.63 (0.46–0.87)</td>
<td>— / 12.4</td>
</tr>
<tr>
<td>≥65</td>
<td>0.63 (0.51–0.78)</td>
<td>18.4 / 13.9</td>
</tr>
<tr>
<td>Baseline ECOG PS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>0.62 (0.52–0.75)</td>
<td>— / 14.2</td>
</tr>
<tr>
<td>2</td>
<td>0.65 (0.39–1.07)</td>
<td>10.5 / 7.2</td>
</tr>
<tr>
<td>Baseline mean pain score on BPI-SF (question #3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>0.58 (0.47–0.74)</td>
<td>— / 16.2</td>
</tr>
<tr>
<td>≥4</td>
<td>0.71 (0.54–0.94)</td>
<td>12.4 / 9.1</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>0.64 (0.50–0.82)</td>
<td>17.4 / 12.3</td>
</tr>
<tr>
<td>Other</td>
<td>0.63 (0.49–0.81)</td>
<td>— / 14.4</td>
</tr>
<tr>
<td>Number of prior chemotherapy regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.59 (0.48–0.73)</td>
<td>— / 14.2</td>
</tr>
<tr>
<td>≥2</td>
<td>0.74 (0.54–1.03)</td>
<td>15.9 / 12.3</td>
</tr>
<tr>
<td>Type of progression at study entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA progression only</td>
<td>0.62 (0.46–0.83)</td>
<td>— / 19.5</td>
</tr>
<tr>
<td>Radiographic progression ± PSA progression</td>
<td>0.64 (0.52–0.80)</td>
<td>17.3 / 13.0</td>
</tr>
<tr>
<td>Baseline value &gt;median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td>0.62 (0.50–0.78)</td>
<td>15.3 / 10.3</td>
</tr>
<tr>
<td>LDH</td>
<td>0.61 (0.50–0.76)</td>
<td>12.4 / 8.5</td>
</tr>
</tbody>
</table>
• Timing and Strategy of ADT crucial

• Benefits should be balanced against harms /side effects

• CRPC ≠ Hormon resistance

• New ADT concepts
  - Androgen targeting through Lyase inhibition (Abirateron, Oteronel)
  - AR targeting by 2. Generation Antiandrogens (MDV-3100)
Hormonal therapy, use it with sound judgement …

…to keep our patients in the game!!!
Vielen Dank

Elbphilharmonie, Hamburg 2014???
Case discussions
• 52 yr healthy male, PSA 14 ng/ml, cT2b,
• Biopsy Gleason 4+4, 6/12 positive cores, right
• Bone scan negative, MRI nodule involvement right, along external illiac artery

Therapy??
• PLND, discontinue RP in case of LN-metastasis, Hormonal therapy

• RP and extended PLND

• HDR-Brachytherapy

• Tomotherapy plus adjuvant hormonal therapy (3 yrs)
• RP and extended PLND
Platinum Priority – Prostate Cancer

*Editorial by Urs E. Studer, Laurence Collette and Richard Sylvester on pp. 762–763 of this issue*

**Survival Benefit of Radical Prostatectomy in Lymph Node–Positive Patients with Prostate Cancer**

Engel et al., Eur Urol. 2010 May;57(5):754-61. Epub 2010 Jan 20
Cancer Specific Survival, RP- vs. RP+

Median follow-up: 98 Monate
Verstorben PCa: 46 Patienten (29%)

Gesamtkohorte matched Pair (pos.LN, Bx-Gleas, PSA 1:1)

• DaVinciRP with unilateral nerve sparing (left) NeuroSafe-technic (Schlomm et. al, Eur Urol 2012) extended PLND
• Full recovery of continence, sexual active with PDE-5 inhibitor
• Histology: pT3b, Gleason 4+3, pN1 (2/25)
  • Adjuvant therapy?
Case No 1, adjuvant ADT

- Improved CSS and overall survival

- However, small sample size (n = 98)

- Initiation of ADT in deferred arm very late

Lancet Oncology 2006; June 6(7)
• Patient refused adjuvant ADT

• Biochemical recurrence after 8 months (nadir <0.01)

• Therapy?
Case No 1,

- Watchful waiting
- Salvage radiotherapy
- Immediate salvage ADT, GnRH analogue
- Immediate salvage ADT, Bicalutamid
Case No 1,

- Salvage radiotherapy

- After that, PSA dropped from 0.8 ng/ml to 0.6 ng/ml

- Subsequent PSA-test (after 6 weeks 1.2 ng/ml)

  - Therapy?
• Watchfull waiting

• Immediate salvage ADT, GnRH analogue

• Immediate salvage ADT, Bicalutamid

• Therapy?
Case No 1,

- Watchful waiting
- After 1 year, PSA of 10 ng/ml
- Bone scan showed 1 Metastasis
  - Therapy
Case No 1,

- Watchful waiting
- Immediate salvage ADT, GnRH analogue
- Immediate salvage ADT, Bicalutamid
- Radiation of bone metastasis
- Bisphosphonates/Rank_ligand-Inhibition?
Case No 1,

- Immediate salvage ADT, Bicalutamid
- Rank_ligand-Inhibition (Denosumab, Prolia s.c.)
- PSA drop 0,6 ng/ml
Case No 1,

- Watchful waiting
- After 1 year, PSA of 10 ng/ml
- Bone scan showed 1 Metastasis
- Therapy?