Tyrol Prostate Cancer Demonstration Project: Early Detection, Treatment, Outcome, Incidence and Mortality

Wolfgang Horninger, Jasmin Bektic, Georg Schäfer, (1) Wilhelm Oberaigner, Helmut Klocker, (2) Peter Boyle, Georg Bartsch

Europäisches Prostatazentrum Innsbruck, Universitätsklinik f. Urologie
(1) Tiroler Tumorregister, Innsbruck, Österreich
(2) International Agency for Research on Cancer, WHO Lyon, France
Mortality
Incidence & Mortality of Prostate Cancer in Austria

- **Incidence 2007:** 5,085 new cases
- **Incidence 2003:** 5,408 new cases
- **Mortality 2007:** 1,066 deaths
- **Mortality 2003:** 1,160 deaths

Source: Statistik Austria
Prostate cancer is the most common major cancer in the United States and the second most lethal cancer in men. Prostate cancer strikes 1 in 6 men.

### Estimated New Cases*

<table>
<thead>
<tr>
<th>Type</th>
<th>Cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>186,320</td>
<td>25%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>114,690</td>
<td>15%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>77,250</td>
<td>10%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>51,230</td>
<td>7%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>35,450</td>
<td>5%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>34,950</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>33,130</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>25,310</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>25,180</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18,770</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td>745,180</td>
<td>100%</td>
</tr>
</tbody>
</table>

### Estimated Deaths

<table>
<thead>
<tr>
<th>Type</th>
<th>Deaths</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>90,810</td>
<td>31%</td>
</tr>
<tr>
<td>Prostate</td>
<td>28,660</td>
<td>10%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>24,260</td>
<td>8%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>17,500</td>
<td>6%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>12,570</td>
<td>4%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>12,460</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>11,250</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>9,950</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>9,790</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,100</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td>294,120</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths, Males, United States 2008*
“Baby Boomers”

Prostate Cancer Incidence:

2008: 186,000/ year

2015: 380,000/ year
Possibilities to enhance prognosis and mortality of Cancer?

- Prevention
- better therapy of locally advanced or metastatic stages
- early detection and effective therapy of curable stages
Prostate Cancer

- no Prevention
- no curative therapy for locally advanced or metastatic stages
- one possibility to enhance prognosis and decrease mortality of Prostate Cancer: Early detection with PSA
Dept. of Urology, University of Innsbruck, Austria
Program of Early detection of PCa with PSA - since 1988
(organized with exact data collection & documentation since 1993)
Early detection in Tyrol, Austria

PSA-testing was made freely available by Social insurance company University Hospital of Innsbruck
Early detection of Prostate Cancer in Tyrol, Countrywide project

General Practitioners
Medical Examiners
Urologists
Pathologists
Tyrol Blood Bank of the Red Cross
PSA – Early detection tools

1988

- PSA, DRE, perineal punch biopsy, transrectal aspiration biopsy
- Radiation(64 Gray), rad. Prostatectomy (10 cases/year)
Early detection in Tyrol, Austria

- **age related t-PSA – reference levels**
  - 40-49 years: 0-2.5 ng/ml
  - 50-59 years: 0-3.5 ng/ml
  - 60-69 years: 0-4.5 ng/ml
  - 70-79 years: 0-6.5 ng/ml
  1993 - Okt. 1995

- **rate of organ confined, curable PCa 1993-1995:**
  25%
Early detection in Tyrol, Austria

- **low t- PSA — reference levels**
  - 40-49 years: 0-1.25 ng/ml
  - 50-59 years: 0-1.75 ng/ml
  - 60-69 years: 0-2.25 ng/ml
  - 70-79 years: 0-3.25 ng/ml
  since Oct. 1995

- **t- PSA: low specificity:**
  - increase of biopsies
  - high number of negative, unnecessary biopsies
### free PSA, 1995

<table>
<thead>
<tr>
<th>Study</th>
<th>Cutoff value</th>
<th>Saving of unnecessary biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catalona et al., 1994</td>
<td>25%</td>
<td>20%</td>
</tr>
<tr>
<td>Horninger et al., 1995</td>
<td>20%</td>
<td>45.2%</td>
</tr>
</tbody>
</table>
complex PSA, 2002

- further enhancement of specificity compared to t-PSA alone
- mainly at low t-PSA levels
- saving of 14% unnecessary biopsies at a Cutoff of 2.1ng/ml
PSA - Velocity

Longitudinal PSA changes in men with and without prostate cancer

A.P. Berger, H. Klocker, J. Bektic, H. Steiner, A. Pelzer, G. Bartsch, M. Deibl*, W. Horninger

Department of Urology, Medical University of Innsbruck, Austria,
*Department of Statistics, Medical University of Innsbruck, Austria,

The Prostate, 2005 Aug 1;64 (3):240-245
Neuronal Artificial Networks
FOR DEMO PURPOSES
ONLY

Xaim

Input Form
Applications Menu

Prostate Biopsy Likelihood

Predicted Biopsy Outcome

Patient ID: No Patient ID Provided

<table>
<thead>
<tr>
<th>DRE Result</th>
<th>Race</th>
<th>Age</th>
<th>PSA Ratio</th>
<th>Total PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>White</td>
<td>51</td>
<td>.15</td>
<td>7.8</td>
</tr>
</tbody>
</table>

XAIM recommends that accepted medical procedures be followed and any PSA reading over 4 or a suspicious DRE be followed up with a biopsy.
**decreasing number of prostate bx / year**

<table>
<thead>
<tr>
<th>year</th>
<th>number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>557</td>
</tr>
<tr>
<td>2000</td>
<td>555</td>
</tr>
<tr>
<td>2001</td>
<td>536</td>
</tr>
<tr>
<td>2002</td>
<td>602</td>
</tr>
<tr>
<td>2003</td>
<td>518</td>
</tr>
<tr>
<td>2004</td>
<td>417</td>
</tr>
<tr>
<td>2005</td>
<td>366</td>
</tr>
<tr>
<td>2006</td>
<td>472</td>
</tr>
<tr>
<td>2007</td>
<td>437</td>
</tr>
<tr>
<td>2008</td>
<td>392</td>
</tr>
</tbody>
</table>
Prostate biopsy: technique

optimized preembedding:
every biopsy was marked outside and embedded straightened in a separate tissue chamber

Informed consent period of 19 years

1985
Sextant Biopsy
Ten Systematic Biopsies
Additional 5 Contrast-Enhanced-Colour-Doppler-Ultrasound Biopsies

Detection rate
PSA 2-4 ng/ml 24%
PSA 4-10 ng/ml 40.2%
62-year-old man (PSA: 4.1 ng/mL) with biopsy proven Gleason 7 cancer.
48-year-old man (PSA: 2.9 ng/mL) Gleason 9 left apex.
Early detection in Tyrol, Austria
Therapy( 2008)

T1, T2: radical Prostatectomy (83.3%)  
Radiation ( 4.7%)  
Brachytherapy (12.0%)  

T3 Radiationtherapie & AA

N+, M+ Androgenablation

NO „WATCHFUL WAITING“
RADICAL PROSTATECTOMY

- oncologic operation
- reconstructive operation

- preserve continence
- preserve potency („nerve sparing“)
Robotic Prostatectomy
### RADICAL PROSTATECTOMY: MORBIDITY AND MORTALITY, 1988 – 2007: 2,033 patients

<table>
<thead>
<tr>
<th>Morbidity/Mortality</th>
<th>0.0%</th>
<th>0.6%, since 2000: 0.1%</th>
<th>0.0%</th>
<th>0.7%</th>
<th>3.0%</th>
<th>79.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (30 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ureteral injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleedings requiring intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion rate:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continence (no pads)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(12 months postop.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3 months postop.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt; 50</th>
<th>50-59</th>
<th>60-69</th>
<th>≥ 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continence</td>
<td>95</td>
<td>95</td>
<td>93</td>
<td>85</td>
</tr>
<tr>
<td>Potency: bilateral nerve sparing, 2 years follow-up, ± PDE-5 inhibitor</td>
<td>94</td>
<td>86</td>
<td>72</td>
<td>52</td>
</tr>
</tbody>
</table>
PSA – Early Detection Tools 2009

1988

- t-PSA, DRE, perieal punch biopsy, aspiration biopsy
- 64 Gray Radiation, radical Prostatektomy (10 cases /year)

2009

- t-PSA, f-PSA, c-PSA, p-PSA, PSA-density, PSA TZ-density, PSA-Velocity, ANN, transrectal sonographie (25 MHz): contrast enhanced, colour doppler targeted biopsies, endorectale MR coils, Elastography
- 3D-conformal Radiation, intensity modulated Radiation (81Gy), Brachytherapie, GnRH-Analoga, Androgenreceptorblocker continence- & poteny preserving radical Prostatectomy (150-180 cases/year)
### STAGE MIGRATION

Percentage of organ confined PCa (R.P., Innsbruck)  
Number of metastatic disease at diagnosis in Tyrol (1993-2007)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>organ-confined PCa (%)</td>
<td>25.7</td>
<td>55.8</td>
<td>65.7</td>
<td>66.9</td>
<td>79.1</td>
<td>82.1</td>
<td>82.4</td>
<td>82.0</td>
<td>83.9</td>
<td>79.8</td>
<td>78.6</td>
<td>82.9</td>
<td>78.6</td>
</tr>
<tr>
<td>metastatic PCa (n)</td>
<td>23</td>
<td>21</td>
<td>11</td>
<td>6</td>
<td>5</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>8</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
Prostate cancer mortality rates in the county of Tyrol and in the Republic of Austria excluding the county of Tyrol; Age 40 - 79

<table>
<thead>
<tr>
<th>40-79 years</th>
<th>Expected</th>
<th>Observed</th>
<th>SMR</th>
<th>IC95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>45</td>
<td>45</td>
<td>100</td>
<td>(73, 134)</td>
</tr>
<tr>
<td>1996</td>
<td>47</td>
<td>37 (-21%)</td>
<td>79</td>
<td>(55, 108)</td>
</tr>
<tr>
<td>1997</td>
<td>50</td>
<td>33 (-32%)</td>
<td>66</td>
<td>(46, 93)</td>
</tr>
<tr>
<td>1998</td>
<td>52</td>
<td>30 (-42%)</td>
<td>57</td>
<td>(39, 82)</td>
</tr>
<tr>
<td>1999</td>
<td>55</td>
<td>37 (-33%)</td>
<td>68</td>
<td>(48, 93)</td>
</tr>
<tr>
<td>2000</td>
<td>57</td>
<td>32 (-44%)</td>
<td>56</td>
<td>(39, 80)</td>
</tr>
<tr>
<td>2001</td>
<td>58</td>
<td>44 (-25%)</td>
<td>77</td>
<td>(56, 103)</td>
</tr>
<tr>
<td>2002</td>
<td>59</td>
<td>44 (-26%)</td>
<td>74</td>
<td>(54, 100)</td>
</tr>
<tr>
<td>2003</td>
<td>61</td>
<td>32 (-48%)</td>
<td>52</td>
<td>(36, 74)</td>
</tr>
<tr>
<td>2004</td>
<td>63</td>
<td>28 (-55%)</td>
<td>44</td>
<td>(29, 64)</td>
</tr>
<tr>
<td>2005</td>
<td>65</td>
<td>30 (-54%)</td>
<td>46</td>
<td>(31, 66)</td>
</tr>
<tr>
<td>2006</td>
<td>67</td>
<td>34 (-49%)</td>
<td>51</td>
<td>(35, 71)</td>
</tr>
<tr>
<td>2007</td>
<td>69</td>
<td>41 (-41%)</td>
<td>59</td>
<td>(43, 81)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected</th>
<th>Observed</th>
<th>SMR</th>
<th>IC95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>44</td>
<td>35</td>
<td>79</td>
<td>(55, 111)</td>
</tr>
<tr>
<td>2003</td>
<td>46</td>
<td>36</td>
<td>79</td>
<td>(55, 109)</td>
</tr>
<tr>
<td>2004</td>
<td>48</td>
<td>31</td>
<td>65</td>
<td>(44, 92)</td>
</tr>
<tr>
<td>2005</td>
<td>50</td>
<td>30</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>53</td>
<td>34</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>55</td>
<td>33</td>
<td>55</td>
<td></td>
</tr>
</tbody>
</table>
Trends in the mortality rates in Tyrol and the rest of Austria were compared within the Poission regression model

\[
\log (\text{rate}) = \beta_0 + \beta_1 (\text{year} - 1993) I (\text{year} \geq 1993) + \beta_3 \text{Tyrol} + \beta_4 \text{Tyrol} x (\text{year} - 1993) + \beta_5 \text{Tyrol} x (\text{year} - 1993) I (\text{year} \geq 1993)
\]
Mortality

• in the time frame 1996 to 2007, 999 PCa deaths would have been expected in Tyrol, however only 622 had been observed

• in Tyrol, in the last 12 years there were 377 PCa deaths less observed than expected
Between 1993 and 2002, the truncated (40-79) age standardised prostate cancer mortality rate in the United States has decreased by an average of 4.7% per year.

In Austria, excluding Tyrol, the decline was 3.2% per year (1996-2007).

In Tyrol it was 7.3% per year (1996-2007).

The shift of stage in the PSA era followed by effective therapy translated into a decrease of prostate cancer mortality.
Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*
PSA-based screening reduced the rate of death from PCa by 20% according to a prospective, randomized European PCa study.

- eight countries: Belgium, Finland, France, Italy, Netherlands, Spain, Sweden, Switzerland
- 162,000 men aged 55-69
- 50% of the participating men was offered PSA screening at an average of once every 4 years, the other half was the control group
- the primary outcome was the rate of death from PCa
- diagnosis & therapy: according to the local guidelines
PSA-based screening reduced the rate of death from PCa by 20%
to prevent one death from prostate cancer

- 1410 men would need to be screened
- 48 cases of prostate cancer would need to be treated

- Costs ?
- Benefit / Harm ?
Prostate cancer: Early detection: Yes/ No ??

- **with restriction:**
- **Yes** in regions (centers) with experience in epidemiology, in interpretation of PSA values, in diagnosis & therapy

- **Yes** to a „individualized Early Detection“ (informed consent of patients, General Practitioners, Medical Examiners.....)

- **No** to uncritical mass screening
Early detection of PCA - disadvantages

- Specificity of PSA & Isoforms: max. 45%, still too much unnecessary biopsies
- Underdiagnosis: 18.9%, >pT3a or pos. margin
- 5-7% Incontinence, 20-30% E.D. after R.P.
Where to go

- „Mammography“ for prostate cancer
- Molecular signature
- Navigational minimal invasive surgery
Where to go

Molecular signature
Individualized prostate cancer diagnosis and therapy

- Identification of new markers
  - Identification of new markers for prognosis
  - Identification of new markers for the disease, who do not need curative intent.
  - Identification of new markers of risk of progression after treatment
- Stratification of risk groups for progression
- Stratification of patients for therapeutic modalities

Genomics / Proteomics
Innsbruck Biorepository

- 7074 patients
- >2000 radical prostatectomy
- biopsy cores 96,036 (blocks)

Methodology:
- Sally Isaacs, Johns Hopkins

Analysis methods:
- sonography, CT, MRT, PET

Clinical data:
- Family history
- Treatment & follow up
- Imaging

Frozen tissue
- Paraffin-tissue
- Plasma lymphocytes
- Serum samples

Period of 19 years (1988-2007)
Computational System Biology of Prostate Cancer (IMGUS)

Data Warehouse

Web-based portal for collecting project relevant clinical and -omics data

Life Science Data Integration

Extract / Transform / Load: ETL

Data Integration Layer

Data Management Layer

KIS
Clinical Data
Firma
Anschrift
Befunde
Zusammen

HIS/CMS
Labor & Clinical Data
RILabor (Tumormarker, Hormone, PSA, Brkt, Fis, ISB, ISB, ...
Histoanatomie, Immunostruktur, Biochemik
Zytologische Forschungs-labor
Pathologische Befunde

TumorDB

KEGG, BREND A ...

IDB
Annotationen

Genomics
Proteomics
Metabonomics

External Documents
Publications...

Life Science Data Integration
Laser microdissection → genetic fingerprint

Gleason 4,5

Gleason 6 versus 8, 9, 10

Gleason 3+4 versus 4+3

Pre and post radical prostatectomy
PCa –Proteinanalysis/Proteomics

BIOREPOSITORY

serum, tissue

protein profiles with mass spectroscopy

<table>
<thead>
<tr>
<th>studies</th>
<th>sensitivity %</th>
<th>specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adam et al.</td>
<td>83</td>
<td>97</td>
</tr>
<tr>
<td>Petricoin et al.</td>
<td>95</td>
<td>78-83</td>
</tr>
<tr>
<td>Qu et al.</td>
<td>97-100</td>
<td>97-100</td>
</tr>
<tr>
<td>Innsbruck</td>
<td>93-100</td>
<td>97-100</td>
</tr>
</tbody>
</table>

normal

BPH

PCa
Where to go

• minimal invasive therapy
minimal invasive therapy:
targeted molecular therapy, microbubbles as a vehicles for medicaments (Antisense), Phase I Study

visualisation and cracking with ultrasound 1.75 MHz
future perspective

• Individualized (personalized) medicine: departure from traditional prostate cancer diagnosis (e.g. phenotype of the cancer cell)

• Each tumor is individual (DNA, proteins and metabolites) and needs individual treatment

• Which tumors should be treated and with what?
Incidence of prostate cancer in Tyrol

- less (unnecessary) prostate biopsies
- higher detection rate
- decreasing incidence

SDR = altersstandartisierte Rate/100,000

SDR Rates [x100,000]

Period


130.1 84.7 87.1
Prostate Cancer Mortality: Age-Period-Graph for Tyrol and Austria without Tyrol
PCa „The (far,far) Future“

- die Diagnose & Therapie d. PCA wird nicht mehr nur über den Phänotyp der Krebszelle gestellt
- Individuelle personenbezogene Medizin
- Jeder Tumor ist individuell (DNA, Proteine & Metabolite)
- und braucht(oder auch nicht) eine individuelle Therapie
The controversy surrounding screening for prostate cancer with PSA revolves around three key issues.

- Does PSA identify clinically significant prostate cancer in the majority of cases?
There ist too much “overdiagnosis”
  - Draisma GR et al JNCI, 2003
  - Etzione R et al JNCI 2002

CON:

Estimates of 30 % to 50 % or are exaggerated: Etzione: computer simulation model of PSA-testing of a hypothetical cohort of 2 mill. men who were 60 to 84 years old in 1988.

In clinical series overdiagnosis occurs:

<table>
<thead>
<tr>
<th>Tyrol Study</th>
<th>tPSA 2-10 ng/ml</th>
<th>8.7%*</th>
<th>17.6% **</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tPSA 2-10 ng/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tPSA 2-10 ng/ml</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Epstein et. al., JAMA, 1994
**pT2a, G1 < 7
+Ohori (unimportant disease)

<table>
<thead>
<tr>
<th>tPSA 2-10 ng/ml</th>
<th>2.7-8.6%</th>
</tr>
</thead>
</table>

+Graif, Th, W. Catalona, 2006, J. Urol

Contrary, in clinical series also in the low PSA approach underdiagnosis accours.

<table>
<thead>
<tr>
<th>tPSA 2-4 ng/ml</th>
<th>18.9%***</th>
</tr>
</thead>
<tbody>
<tr>
<td>tPSA 10ng/ml</td>
<td>36.7%***</td>
</tr>
</tbody>
</table>

Graif, Th, W. Catalona, 2006, J. Urol

| tPSA 2-10ng/ml | 26-31%*** |

*** (≥pT3 or pos. surg. margins)

Accepted, J. Urol, July, 2007
**TUMOR BIOLOGY IN LOW PSA (1.25-3.25ng/ml)**

**DISEASE: radical prostatectomy**

---

<table>
<thead>
<tr>
<th></th>
<th>unifocal PCa</th>
<th>multifocal PCa</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>28 (35%)</td>
<td>52 (65%)</td>
</tr>
<tr>
<td>total PSA (range)</td>
<td>2.7ng/ml (1.3-4.0)</td>
<td>3.3ng/ml (1.4-4.0)</td>
</tr>
<tr>
<td>tumor volume (range)</td>
<td>0.43cc* (0.01-2.6)</td>
<td>0.88cc* (0.13-1.86)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>mean t-PSA (ng/ml)</th>
<th>mean % f-PSA</th>
<th>mean Gleason Score</th>
<th>mean tumor volume (cc)</th>
<th>mean KI67 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>diploid</td>
<td>14 (64)</td>
<td>3.8</td>
<td>19.6*</td>
<td>5.07</td>
<td>0.44</td>
<td>4.08*</td>
</tr>
<tr>
<td>tetraploid</td>
<td>8 (36)</td>
<td>4.9</td>
<td>11.7*</td>
<td>6.25</td>
<td>0.55</td>
<td>7.80*</td>
</tr>
</tbody>
</table>

* statistically significant

Prostate cancers in young men less likely to be harmless, and it is unlikely that all cases labelled as “overdiagnosis” are harmless.

---

No index tumor assessment of tumor; volume needs morphometry of the whole specimen („Stamey - Issue“)
Overdiagnosis and overtreatment are weighed out by a decrease in mortality:

Therefore:
• Overdiagnosis is a result in older men when using PSA cut off levels, only

• Intelligent use of PSA: artificial network, PSA velocity, % free, pro PSA

• Deal with the risks of possible overdiagnosis: carefully selecting patients for treatment and ensuring high-quality effective treatment
Overdiagnosis

- Computational System Biology
- Navigational minimal invasive surgery
The Innsbruck Prostate Tumor Bank

- ~400,000 patients
- 1988 to 2007 period
- 7074 radical prostatectomies
- 96,036 biopsy cores

Methodology:
Sally Isaacs, John Hopkins

Imaging:
Sonography, CT, MRT, PET

Clinical Data

Family History

Plasma Samples

Blood Lymphocytes

Paraffin Tissue

Frozen Tissue

Tumor Bank

Period of 19 years

Radical prostatectomy: 1896, biopsy cores 96,036 (blocks)

Radical prostatectomy: 682 since 1988

7074 patients who have undergone biopsy
The controversy surrounding screening for prostate cancer with PSA revolves around three key issues

- Does aggressive intervention with surgery or radiation alter the outcome in men diagnosed with clinically significant disease?
• **L. Holmberg, A. Bill-Axelson., N.E.J.M., 2003**  
  
  **A. Bill-Axelson, L. Holmberg, N.E.J.M., 2005**  
  
  **These two studies show strong evidence, that surgery reduces local progression (67 %) and progression to metastatic disease (40 %) and death from prostate cancer by 50 %. Also an overall survival benefit was demonstrated (40%).**

• **Yu-Ning Wong et. al. JAMA 2006**  
  
  This study shows a statistically significant survival advantage with radical prostatectomy/radiation therapy for low and intermediate risk cancer in elderly men aged 65 to 80 years. (44.630 men with organ confined, well or moderately differentiated prostate cancer, 12-year study period).
The controversy surrounding screening for prostate cancer with PSA revolves around three key issues:

• Does diagnosis and treatment seriously impinge quality of life?
MORBIDITY OF 7074 TRANSRECTAL ULTRASOUND GUIDED (TRUS) BIOPSIES OF THE PROSTATE

<table>
<thead>
<tr>
<th>1993 - 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minor complications</strong></td>
</tr>
<tr>
<td>haematuria &gt; 1 day</td>
</tr>
<tr>
<td>haemospermia</td>
</tr>
<tr>
<td>rectal bleeding</td>
</tr>
<tr>
<td><strong>Major complications</strong></td>
</tr>
<tr>
<td>pain</td>
</tr>
<tr>
<td>severe rectal bleeding</td>
</tr>
<tr>
<td>fever &gt; 38°C with hospitalisation</td>
</tr>
<tr>
<td>epididymitis, prostatitis</td>
</tr>
<tr>
<td>urinary retention</td>
</tr>
</tbody>
</table>
### RADICAL PROSTATECTOMY: MORBIDITY AND MORTALITY, 1998 – 2007: 2,033 patients

<table>
<thead>
<tr>
<th>Mortality (30 days)</th>
<th>0.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal injury</td>
<td>0.6%, since 2000: 0.1%</td>
</tr>
<tr>
<td>Ureteral injury</td>
<td>0.0%</td>
</tr>
<tr>
<td>Bleedings requiring intervention</td>
<td>0.7%</td>
</tr>
<tr>
<td>Transfusion rate:</td>
<td>3.0%</td>
</tr>
<tr>
<td>Continence (no pads)</td>
<td>95.7%</td>
</tr>
<tr>
<td>(12 months postop.)</td>
<td>81.1%</td>
</tr>
<tr>
<td>(3 months postop.)</td>
<td>79.1%</td>
</tr>
<tr>
<td>Potency &lt; 65 years, since 2000</td>
<td>79.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt; 50</th>
<th>50-59</th>
<th>60-69</th>
<th>≥ 70</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continence</strong></td>
<td>95</td>
<td>95</td>
<td>93</td>
<td>85</td>
</tr>
<tr>
<td><strong>Potency: bilateral nerve sparing, 2 years follow-up, + PDE-5 inhibitor</strong></td>
<td>94</td>
<td>86</td>
<td>72</td>
<td>52</td>
</tr>
</tbody>
</table>
Ecological data suggest that 10 % to 30 % of the geographic variation in mortality rates may relate to variations in access to medical care \(^1\). A key feature of this study setting is that patients in Tyrol have equal access to all therapeutic resources (surgery, radiotherapy and hormonal therapy) and that diagnosis and therapy are free of charge for everyone.
The decline in mortality in the targeted age range which started in 1996, is comparable with that seen in other screening programs with high compliance. It is likely that much of this decline in mortality rates is due to earlier detection and successful treatment of prostate cancer. However, an important corollary implication of our study is that screening is only the first step in the optimal management of prostate cancer patients.
Although randomized, controlled trials evaluating the effectiveness of PSA and digital rectal screening in reducing prostate cancer mortality have been performed for several years, they have not produced results yet. Furthermore, the randomized design may be threatened by extensive non-adherence to the assigned intervention group, e.g. controls seeking PSA testing could lead to widespread contamination of the control group. (Zelen, 1986)
European randomized study/ Tiroler PSA Screening Programm

-20%

-40% (seit 5 Jahren -50%)
• **There is too much “overdiagnosis”**

  – Draisma GR et al JNCI, 2003
  – Etzione R et al JNCI 2002

• **Estimates of 30 % to 50 % or are exaggerated: Etzione:** computer simulation model of PSA-testing of a hypothetical cohort of 2 mill. men who were 60 to 84 years old in 1988.
There ist too much “overdiagnosis”

<table>
<thead>
<tr>
<th>Tyrol Study</th>
<th>tPSA 2-10 ng/ml</th>
<th>8.7%*</th>
<th>17.6% **</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tPSA 4-10 ng/ml</td>
<td>2.7-8.6%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*Epstein et. al., JAMA, 1994  
** pT2a, G1 < 7  
+Ohori (unimportant disease)  

Contrary, in clinical series also in the low PSA approach underdiagnosis accours.

<table>
<thead>
<tr>
<th>Tyrol Study</th>
<th>tPSA 2-4 ng/ml</th>
<th>18.9%***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tPSA 4-10 ng/ml</td>
<td>36.7%***</td>
</tr>
</tbody>
</table>

| tPSA 2-10 ng/ml | 26-31%*** | Graif, Th. W. Catalona, 2006, J. Urol |

J. Urol., 2007

*** (pT3 or pos. surg. margins)
**Overdiagnosis and overtreatment are weighed out by high quality treatment: Tyrol early detection program**

<table>
<thead>
<tr>
<th>Table: Radical prostatectomy, Dept. of Urology, Univ. Innsbruck, Austria 1988 - 2008: 2153 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality (30 days)</strong></td>
</tr>
<tr>
<td><strong>Rectal injury</strong></td>
</tr>
<tr>
<td><strong>Ureteral injury</strong></td>
</tr>
<tr>
<td><strong>Bleedings requiring intervention</strong></td>
</tr>
<tr>
<td><em><em>Continence</em> (no pads)</em>*</td>
</tr>
<tr>
<td>(12 months postop.)</td>
</tr>
<tr>
<td>(3 months postop.)</td>
</tr>
<tr>
<td><em><em>Potency</em> &lt; 65 years, since 2000</em>*</td>
</tr>
</tbody>
</table>

* in a patient reported outcome study to an independent third party.
Prostate cancer mortality rates: Tyrol early detection program 1970-2007
Nomenclature of the prostatic cancer disease who should not be treated

- indolent
- insignificant
- unimportant
- irrelevant
## Nomenclature: Insignificant Cancer

<table>
<thead>
<tr>
<th>References</th>
<th>No. Pts</th>
<th>Insignificant Criteria</th>
<th>% Insignificant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goto et al</td>
<td>66</td>
<td>0.5 or less cc, no Gleason pattern 4 or 5, organ confined</td>
<td>12</td>
</tr>
<tr>
<td>Lerner et al</td>
<td></td>
<td>Less than 0.5 cc, noot „poorly differentiated“ diploid</td>
<td>9</td>
</tr>
<tr>
<td>Humphrey et al</td>
<td>78</td>
<td>Less than 0.5cc, no Gleason pattern 4 or 5, organ confined</td>
<td>23</td>
</tr>
<tr>
<td>Epstein et al</td>
<td>157</td>
<td>Less than 0.5cc, no Gleason pattern 4 or 5, organ confined</td>
<td>26</td>
</tr>
<tr>
<td>Carter et al</td>
<td>240</td>
<td>Less than 0.5cc, no Gleason pattern 4 or 5, organ confined</td>
<td>29</td>
</tr>
<tr>
<td>Epstein et al</td>
<td>163</td>
<td>Less than 0.5cc, no Gleason pattern 4 or 5, organ confined</td>
<td>30</td>
</tr>
</tbody>
</table>
number of tumor foci max.
dimension of cancer (2.2 mm)
Gleason score 2 to 5

Latent cancer – extrapolation to insignificant disease?

PSA
Volume of gland (PSAD)
Tumor volume

W. A. Sakr et al. 1996
Identification of small volume and contralateral disease

- Contrast enhanced ultrasonography
- Dynamic MRI
- Sono, RT-Elastography
- Spectroscopy
- 3D – US Reconstructive Software
- Tansperineal 3D Mapping Biopsy

- We need “Mammography” for Prostate cancer
Nomogram for predict the probability of insignificant cancer in an individual patient

Partin  
Kattan  
Thompson  
Steyerberg
Critical issues: Active surveillance

- How great is the risk that prostate cancer is at the edge of the window of opportunity (cure)?
- How great is the risk, that prostate cancer is at the edge of the window of opportunity (morbidity).
- What is the risk of dedifferentiation of the tumor over time?
- Although in the different studies the definition of low-risk prostate cancer is similar, it is not identical:
  - What parameters can reliably predict the development of lethal prostate cancer:
  - Do we know trigger points for treatment?
  - At which intervals should patients be reassessed?
For men with low risk prostate cancer it was recently proposed that ablative treatment to the affected side may decrease morbidity.
Where to go: new nomenclature

- Invasive – non invasive cancer
- Metastatic – non metastatic cancer
- Lethal – non lethal cancer
Computational System Biology of Prostate Cancer (IMGUS)
The Innsbruck Prostate Tumor Bank

- ~400,000 plasma samples
- ~400,000 serum samples
- 7074 blood lymphocytes
- paraffin - tissue
- frozen tissue
- family history
- imaging
- clinical data
- treatment & follow up

Methodology: Sally Isaacs, John Hopkins

Sonography, CT, MRT, PET

Radical prostatectomy: 1896, biopsy cores 96,036 (blocks)

Radical prostatectomy: 682

Since: 1988, 1896 radical prostatectomy, 7074 patients, who have undergone biopsy
Part 2 Discussion
• **These nomograms (using clinical and pathological information) for prediction of clinically insignificant prostate cancers are between 64% and 79% accurate.**

• **The definition of indolent cancer is based on old pathological criteria (Gleason score 6 or less, organ confined disease and tumor volume less than 0.5 cc) and imaging, which at the time can not diagnose small volume disease.**
• Consequently it might be difficult to accurately discriminate between clinically insignificant and significant disease, unless more accurate prediction tools are introduced.

• Pathological indolent disease is only a surrogate for the more important clinical endpoint of progression-free or overall survival.

• Old pathological criteria have to be replaced by molecular profiles or panels of tumormarker to characterize the biological behavior and novel markers for disease severity.
Part 3
Discussion
**Critical issues: Active surveillance**

- How great is the risk that prostate cancer is at the edge of the window of opportunity (cure)?
- How great is the risk, that prostate cancer is at the edge of the window of opportunity (morbidity).
- What is the risk of dedifferentiation of the tumor over time?
- Although in the different studies the definition of low-risk prostate cancer is similar, it is not identical:
  - What parameters can reliably predict the development of lethal prostate cancer?
- Do we know trigger points for treatment?
- At which intervals should patients be reassessed?
Part 4
Discussion
<table>
<thead>
<tr>
<th></th>
<th>No. positive core</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Number of patients</td>
<td>234</td>
</tr>
<tr>
<td>Mean Age (Years)</td>
<td>60.9 (42–76)</td>
</tr>
<tr>
<td>Prostate volume (cc)</td>
<td>38.8 (16–98)</td>
</tr>
<tr>
<td>Clinical Stage T1c</td>
<td>211 (90.2%)</td>
</tr>
<tr>
<td>Clinical Stage T2</td>
<td>23 (9.8%)</td>
</tr>
<tr>
<td>PSA at diagnosis (ng/ml)</td>
<td>5.21 (1.57–24.4)</td>
</tr>
<tr>
<td>PSA density (ng/ml/cc)</td>
<td>0.14 (0.03–0.53)</td>
</tr>
<tr>
<td>Biopsy Gleason Sum ≤ 6</td>
<td>207 (89%)</td>
</tr>
<tr>
<td>Biopsy Gleason Sum &gt; 7</td>
<td>27 (11%)</td>
</tr>
<tr>
<td>Organ-confined disease</td>
<td>225 (96%)</td>
</tr>
<tr>
<td>Unilateral disease</td>
<td>68 (29%) *</td>
</tr>
<tr>
<td>Bilateral disease</td>
<td>166 (71%)</td>
</tr>
</tbody>
</table>
Single positive biopsy core (Gleason 6) has 70% sensitivity, 57% specificity, 29% PPV and 89% NPV. Its combination with PSA and Gleason sum has 60% sensitivity, 68% specificity, 44% PPV and 81% NPV

Ho. H. et al 2009