Conservative Management of Localized Prostate Cancer

Andrew Loblaw  BSc, MD, MSc, FRCPC, CIP

Department of Radiation Oncology
Sunnybrook Health Sciences Centre
University of Toronto

Brampton Us-Too Group
November 13, 2007
Objectives

1. To understand the philosophy of active surveillance versus watchful waiting
2. To review the outcomes of patients on active surveillance at Sunnybrook
3. To variety, pros and cons of different treatment options
The Future of Prostate Cancer
Lead Time Bias and Prostate Cancer

1950-1970’s

NATURAL HISTORY PROSTATE CANCER: 10 y

- Clinically Detectable
  - Metastases
- Asymptomatic
  - Metastases
- Symptomatic
  - Androgen Sensitive
- Symptomatic
  - Androgen Resistant
  - Death

Watchful Waiting

Castrate Therapies
Lead Time Bias and Prostate Cancer

1980-1990’s

NATURAL HISTORY PROSTATE CANCER: 13 y

- PSA Abnormal
- Clinically Detectable
- Asymptomatic Metastases
- Symptomatic Metastases
- Androgen Sensitive
- Symptomatic Metastases
- Androgen Resistant
- Death

Local Therapies → PSA Failure → Castrate Therapies
Lead Time Bias and Prostate Cancer

2000-2010

NATURAL HISTORY PROSTATE CANCER: 16+ y

PSA Abnormal
Clinically Detectable
Asymptomatic Metastases
Symptomatic Metastases
Androgen Sensitive
Symptomatic Metastases
Androgen Resistant
Death

Local Therapies

Castrate Therapies

PSA Failure
No “Normal” PSAs

![Graph showing risk of prostate cancer based on prostate-specific antigen (PSA) concentration. The x-axis represents PSA concentration in ng/mL, and the y-axis represents the risk of prostate cancer in percent. The graph includes bars for all prostate cancers and high-grade cancer.]
Background

• The number of men diagnosed with prostate cancer each year has increased over the last decade
  - In 1992, Canadian incidence 15,300
  - In 2005, Canadian incidence expected to be 20,500
  - Age-adjusted incidence has risen from 440 to 480 / 100,000 men from 1992-2001

• A greater proportion of men are being diagnosed
Background

• The chance of diagnosing “clinically insignificant prostate cancer” (CIPC), may be increased

• Studies report the proportion of men who are diagnosed with this entity to be 7-25%, depending on the definition used

• Autopsy series of men who died of other causes reveal the upper limit of the incidence of CIPC, since none of these men died of prostate cancer

• The incidence increases with age
  – 30% in 40’s – 50’s
  – 55% in 60’s
  – 64% in 70’s
A RANDOMIZED TRIAL COMPARING RADICAL PROSTATECTOMY WITH WATCHFUL WAITING IN EARLY PROSTATE CANCER

LARS HOLMBERG, M.D., PH.D., ANNA BILL-AXELSON, M.D., FRED HELGESEN, M.D., JAARKO O. SALO, M.D., PH.D., PER FOLMER, M.D., MICHAEL HAGGMAN, M.D., PH.D., SWEN-OLOF ANDERSSON, M.D., PH.D., ANDERS SPANGBERG, M.D., CHRISTER BUSCH, M.D., PH.D., STEG NORDLING, M.D., PH.D., JUNI PALMGREN, PH.D., HANS-OLIV ADAM, M.D., PH.D., JAN-Erik JOHANSSON, M.D., PH.D., AND BO JOHAN NORDLÉN, M.D., PH.D.,
FOR THE SCANDINAVIAN PROSTATIC CANCER GROUP STUDY NUMBER 4

Figure 2. Cumulative Hazard Rate of Death from Prostate Cancer.

Figure 3. Cumulative Hazard Rate of Development of Distant Metastasis.
Surveillance vs WW

PSA

100

50

10

Symptoms
Hormone Treatment

Treatment for Cure

Time
Prostate Growth Characteristics

Active Surveillance

Continue Surveillance

Radical Treatment
Sunnybrook Active Surveillance Program
Acknowledgements

To the 460 men who volunteered for the AS Study

Radiation Oncology
• D. Loblaw
• R. Choo
• C. Danjoux
• G. Morton

Urology
• L. Klotz
• R. Nam
• S. Sharir

Radiation Therapy Research
• L. Holden

Clinical Trials & Epidemiology
• L. Zhang
• A. Mamedov
Active Surveillance Cohort

1. Men (> 18 years old) with histopathologically confirmed adenocarcinoma of prostate within 12 months of study entry

2. No previous treatment

3. Clinical stage T1b-T2b N0 M0 (1997 TNM classification)

4. PSA < 15 ng/ml

5. Refused radical treatment
Baseline Investigations

1. History and Physical examination
2. Central pathology review
3. PSA, Creatinine, PAP
4. CXR
5. Bone scan and CT abdomen/pelvis at MD’s discretion
Follow-up

• Physical including DRE q3 mo
• Bloodwork (PSA, Cr, PAP) q3 mo
• TRUS q6mo
• Bone Scan q1y x 2, then q2y (q1y if PSA > 15)
• Prostate rebiopsy 12-18 mo post-acrual
Intervention

• Treatment individualized according to age, extent of disease, co-morbidities if any of:
  - $\text{PSA}_{\text{Adt}}^*$ < 2 y (statistically significant) on $\geq 3$ measures, $\geq 6$ months, PSA $\geq 8$
  - Gleason Grade $\geq 4+4$
  - Max dimension of clinical nodule $\geq$ doubles
  - Patient request

*Doubling Time Calculation: Linear regression of $\ln(\text{PSA})$ on time
Results

• n = 231
• Age at enrollment 71 y median, range 49 – 84 y
• Gleason ≤ 6: 78%, Gleason 7: 22%
• iPSA < 10: 84%, 10-15: 16%
Results

• 134/231 (58%) patients remained on surveillance
  - Patient choice 16%
  - Grade progression 4%
  - Clinical progression 9%
  - PSA dt criteria 10%

• As of Feb 2007, the median follow-up was 6.8 y (95% CI: 6.0 – 7.4y)

• Crude CSS analysis (January 2006): 98.8% (418 / 423)
  - Deaths occurred at 3.7, 5.1, 5.2, 5.3, 5.5 years after enrollment

• 24 (17.9%) have died of other causes; 6 (4.5%) have been lost to follow-up
PSA Thresholds

Time (years)
First-Last Doubling Time

PSA

PSAdt = 0.6y  PSAdt = 0.7y  PSAdt = 1.9y  PSAdt = 2y

PSAdt = 15.0y

Time (years)
Linear Regression Doubling Time

PSA

PSAdt = 0.6y   PSAdt = 1.0y   PSAdt = 1.6y   PSAdt = 2y

PSAdt = 1.4y   PSAdt = 2.5y

Time (years)
General Linear Mixed Modeling

- Allows for individual predictors of intercept and slope to be integrated into model

- For high risk line:
  \[ \ln(PSA) = 1.003 \times \ln(baseline\ PSA) + 0.112 \times \text{time} + 0.041 \times \text{time}^2 \]

- For low risk line:
  \[ \ln(PSA) = 1.03 \times \ln(baseline\ PSA) - 0.0056 \times \text{Age} + 0.046 \times \text{Gleason} + 0.081 \times \text{time} + 0.0038 \times \text{time}^2 \]

Zhang L, Loblaw DA, Klotz L. J Urol 2006
Figure 1: Risk Profiles (GLMM model)
Patient A: High risk for progression
– intervene
Patient B: Average risk for progression
– continue follow-up q3mo
Patient C: Low risk for progression
– relax follow-up to q6mo
Comparing PSA Triggers For Treatment For Men With Prostate Cancer On Active Surveillance

D. Loblaw\textsuperscript{1}, L. Zhang\textsuperscript{2}, L. Klotz\textsuperscript{3}

\textsuperscript{1}Departments of Radiation Oncology, \textsuperscript{2}Clinical Trials and Epidemiology and \textsuperscript{3}Surgery, Sunnybrook Health Sciences Centre, University of Toronto

ASCO Prostate 2007
Objectives

• To compare commonly used PSA triggers for radical treatment for men with prostate cancer on active surveillance
## Results

<table>
<thead>
<tr>
<th>PSA Trigger</th>
<th>Patients Triggered (%)</th>
<th>Median / pt (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSAt = 10</td>
<td>42/114 (37%)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1-24)</td>
</tr>
<tr>
<td>PSAt = 20</td>
<td>14/134 (10%)</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1-9)</td>
</tr>
<tr>
<td>PSAdt first-last</td>
<td>52/134 (39%)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1-11)</td>
</tr>
<tr>
<td>LR PSAdt</td>
<td>52/134 (39%)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1-11)</td>
</tr>
<tr>
<td>Actual PSAv &gt; 2y</td>
<td>66/134 (49%)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1-10)</td>
</tr>
<tr>
<td>Calc PSAv &gt; 2y</td>
<td>65/134 (49%)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1-10)</td>
</tr>
<tr>
<td>GLMM PSAdt &lt; 2y</td>
<td>0/134</td>
<td></td>
</tr>
</tbody>
</table>
Baseline data for patient 3. Institution: TSRCC
Age: 79.0 years; Gleason: 6 (mean value used)

<table>
<thead>
<tr>
<th>Start</th>
<th>End</th>
<th>YYYY-MM-DD</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1995-10-20</td>
<td>8.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1996-02-23</td>
<td>8.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1996-05-16</td>
<td>6.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1996-09-19</td>
<td>8.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1996-11-28</td>
<td>7.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1997-02-27</td>
<td>10.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1997-03-27</td>
<td>8.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1997-05-22</td>
<td>9.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1997-09-04</td>
<td>7.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1997-11-20</td>
<td>10.70</td>
</tr>
</tbody>
</table>

Select PSA metric:
- Velocity (lin.model)
- Doubl.Time (exp.model)

Summary: PSA doubling time = 6.4 years.

For the 3.5-year period PSA level was fluctuating between progression and non-progression lines therefore the patient should have ongoing close monitoring.
ASURE

• Active SURveillance REsearch program
• Platform of lifestyle, nutriceutical and pharmaceutical interventions to slow prostate growth
Capsaicin
Prostate Hypofractionation
Dose Escalated Radiation Therapy

Pollack
IJ ROBP
2002

Zeitman
JAMA
2005

Sathya
JCO
2005

Peeters
JCO
2006

Fig 1. Probability of biochemical or clinical failure (BCF) by randomized treatment arm. EBRT, external-beam radiation therapy.
What is the $\alpha/\beta$ of prostate cancer?

- **Brenner and Hall, 1999** $n=367$
  - Ext beam vs I-125 implant
    $\alpha/\beta = 1.5$ (95% C.I. 0.8-2.8)

- **Fowler et al, 2001** $n=735$
  - Ext Beam vs I-125/Pd-103 vs HDR
    $\alpha/\beta = 1.49$ (95% CI 1.25-1.76)
  - Overall $n = 2158$

- **Lukka et al, 2003** $n=936$
  - NCIC PR5 52.5 Gy/20 vs 66 Gy/33 RCT
    $\alpha/\beta = 0.9$

- **Yeoh et al, 2003** $n=120$
  - Australian 64 Gy/32 vs 55 Gy/20 RCT
    $\alpha/\beta = 2.6$

Weighted $\alpha/\beta = 1.3$
Little Punches

vs

One Big KO!

Conventional

HART

HART
# Hypofractionated Radiotherapy Protocols Open

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Trial</th>
<th>Phase</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>pHART3</td>
<td>1/2</td>
<td>5 f / 5 wk</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>HDR single</td>
<td>2</td>
<td>16 f / 5 wk</td>
</tr>
<tr>
<td></td>
<td>PROFIT</td>
<td>3</td>
<td>20 f / 4 wk</td>
</tr>
<tr>
<td>High Risk</td>
<td>pHART2</td>
<td>2</td>
<td>25 f / 5 wk</td>
</tr>
</tbody>
</table>
Advances in Technology
Radiotherapy Advances

CT Plan → LINAC

Gold seed insert → IMRT Plan
Better Control
Fewer visits
• more convenient for patient
• Higher capacity for RT centre
Less side effects
Prostate Brachytherapy

Monotherapy

Low Risk Cancer
T1/T2, Gleason 6, PSA <10

Combined with External Beam

Permanent

Temporary

Intermediate / high risk
Minimally Invasive Surgery
Concomitant Boost to Prostate

• CTV = prostate only
• PTV = 4 mm (for intrafraction prostate motion)*
• Dose = 22.5 Gy in 25 fractions
• (total dose to prostate = 67.5 Gy in 25 fractions)
  • Equivalent to 82Gy / 41f
• Step & Shoot IMRT technique (7 – 9 fields)
• Daily on-line correction for prostate fiducial marker position prior to beam on time

Recurrent Prostate Cancer

After Radical Radiotherapy
Post-Radiotherapy Failure

• Local therapies
  – Radical prostatectomy
  – Cryotherapy
  – HiFU
  – Seed brachytherapy*

• ANDROGEN DEPRIVATION THERAPY
  – ASCO Androgen Sensitive Guideline 2006
    Update available April 2007
## Patterns of Care Survey

<table>
<thead>
<tr>
<th>Trigger PSA (ng/mL) for starting ADT</th>
<th>1994 Canada</th>
<th>2000 USA</th>
<th>2004 Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>20</td>
<td>28</td>
<td>53</td>
</tr>
<tr>
<td>10-20</td>
<td>18</td>
<td>50</td>
<td>36</td>
</tr>
<tr>
<td>20-50</td>
<td>32</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>&gt;50</td>
<td>24</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
### Prostate Cancer Mortality

**Review:** Timing of ADT in Prostate Cancer  
**Comparison:** 01 Timing of ADT  
**Outcome:** 02 Prostate Cancer Mortality

<table>
<thead>
<tr>
<th>Study or Subcategory</th>
<th>Immediate ADT (n/N)</th>
<th>Deferred ADT (n/N)</th>
<th>RR (random); 95% CI</th>
<th>Weight %</th>
<th>RR (random)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Untreated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Byer VACURG 1</td>
<td>139/469</td>
<td>173/484</td>
<td>0.83</td>
<td>19.58</td>
<td>(0.69 to 1.00)</td>
<td></td>
</tr>
<tr>
<td>Kirk MRC PR03</td>
<td>241/469</td>
<td>287/469</td>
<td>0.84</td>
<td>27.26</td>
<td>(0.75 to 0.94)</td>
<td></td>
</tr>
<tr>
<td>Studer SAKK 88-08</td>
<td>23/96</td>
<td>34/92</td>
<td>0.65</td>
<td>6.06</td>
<td>(0.42 to 1.01)</td>
<td></td>
</tr>
<tr>
<td>Studer EORTC 30891</td>
<td>94/492</td>
<td>99/493</td>
<td>0.95</td>
<td>13.87</td>
<td>(0.74 to 1.23)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1,526</strong></td>
<td><strong>1,538</strong></td>
<td></td>
<td><strong>66.76</strong></td>
<td><strong>0.84</strong></td>
<td><strong>(0.77 to 0.92)</strong></td>
</tr>
<tr>
<td>Total events: 497 (Immediate ADT), 593 (Deferred ADT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 2.25 (P = .52), I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 3.82 (P = .0001)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subcategory</th>
<th>Immediate ADT (n/N)</th>
<th>Deferred ADT (n/N)</th>
<th>RR (random); 95% CI</th>
<th>Weight %</th>
<th>RR (random)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>02 N+ Postsurgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Messing ECOG</td>
<td>7/47</td>
<td>25/51</td>
<td>0.30</td>
<td>2.46</td>
<td>(0.15 to 0.64)</td>
<td></td>
</tr>
<tr>
<td>Schroder EORTC 30846</td>
<td>55/119</td>
<td>54/115</td>
<td>0.98</td>
<td>12.51</td>
<td>(0.75 to 1.30)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>166</strong></td>
<td><strong>166</strong></td>
<td></td>
<td><strong>14.98</strong></td>
<td><strong>0.57</strong></td>
<td><strong>(0.18 to 1.87)</strong></td>
</tr>
<tr>
<td>Total events: 62 (Immediate ADT), 79 (Deferred ADT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 9.06 (P = .003), I^2 = 89.0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 0.92 (P = .36)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subcategory</th>
<th>Immediate ADT (n/N)</th>
<th>Deferred ADT (n/N)</th>
<th>RR (random); 95% CI</th>
<th>Weight %</th>
<th>RR (random)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>03 Bicalutamide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McLeod EPCP</td>
<td>151/1,114</td>
<td>189/1,170</td>
<td>0.84</td>
<td>18.26</td>
<td>(0.69 to 1.02)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1,114</strong></td>
<td><strong>1,170</strong></td>
<td></td>
<td><strong>18.26</strong></td>
<td><strong>0.84</strong></td>
<td><strong>(0.69 to 1.02)</strong></td>
</tr>
<tr>
<td>Total events: 151 (Immediate ADT), 189 (Deferred ADT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 1.74 (P = .08)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Immediate ADT (n/N)</th>
<th>Deferred ADT (n/N)</th>
<th>RR (random); 95% CI</th>
<th>Weight %</th>
<th>RR (random)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,806</td>
<td>2,874</td>
<td>0.83</td>
<td>100.00</td>
<td>(0.74 to 0.94)</td>
<td></td>
</tr>
<tr>
<td>Total events: 710 (Immediate ADT), 861 (Deferred ADT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 10.84 (P = .09), I^2 = 44.6%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 2.95 (P = .003)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Favors Immediate ADT** | **Favors Deferred ADT**
# Overall Mortality

**Review:** Timing of ADT in Prostate Cancer  
**Comparison:** 01 Timing of ADT  
**Outcome:** 01 Overall Mortality

<table>
<thead>
<tr>
<th>Study or Subcategory</th>
<th>Immediate ADT (n/N)</th>
<th>Deferred ADT (n/N)</th>
<th>RR (random); 95% CI</th>
<th>Weight %</th>
<th>RR (random)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>01 Untreated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Byer VACURG 1</td>
<td>413/469</td>
<td>438/484</td>
<td>31.30</td>
<td>0.97</td>
<td>(0.93 to 1.02)</td>
<td></td>
</tr>
<tr>
<td>Kirk MRC PR03</td>
<td>434/469</td>
<td>438/469</td>
<td>43.43</td>
<td>0.99</td>
<td>(0.96 to 1.03)</td>
<td></td>
</tr>
<tr>
<td>Studer SAKK 88-08</td>
<td>87/96</td>
<td>85/92</td>
<td>9.68</td>
<td>0.98</td>
<td>(0.90 to 1.07)</td>
<td></td>
</tr>
<tr>
<td>Studer EORTC 30891</td>
<td>257/492</td>
<td>284/493</td>
<td>5.87</td>
<td>0.91</td>
<td>(0.81 to 1.02)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1,526</td>
<td>1,538</td>
<td>90.27</td>
<td>0.98</td>
<td>(0.95 to 1.01)</td>
<td></td>
</tr>
<tr>
<td>Total events: 1191 (Immediate ADT), 1245 (Deferred ADT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2_s = 3.64 \ (P = .30)$, $I^2 = 17.7%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 1.46 \ (P = .14)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>02 N+ Postsurgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Messing ECOG</td>
<td>17/47</td>
<td>28/51</td>
<td>0.38</td>
<td>0.66</td>
<td>(0.42 to 1.04)</td>
<td></td>
</tr>
<tr>
<td>Schroder EORTC 30846</td>
<td>72/119</td>
<td>71/115</td>
<td>1.86</td>
<td>0.98</td>
<td>(0.80 to 1.20)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>166</td>
<td>166</td>
<td>2.25</td>
<td>0.85</td>
<td>(0.58 to 1.24)</td>
<td></td>
</tr>
<tr>
<td>Total events: 89 (Immediate ADT), 99 (Deferred ADT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2_s = 2.52 \ (P = .11)$, $I^2 = 60.3%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 0.86 \ (P = .39)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>03 Bicalutamide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McLeod EPCP</td>
<td>458/1,114</td>
<td>462/1,170</td>
<td>7.48</td>
<td>1.04</td>
<td>(0.94 to 1.15)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1,114</td>
<td>1,170</td>
<td>7.48</td>
<td>1.04</td>
<td>(0.94 to 1.15)</td>
<td></td>
</tr>
<tr>
<td>Total events: 458 (Immediate ADT), 462 (Deferred ADT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 0.79 \ (P = .43)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>2,806</td>
<td>2,874</td>
<td>100.00</td>
<td>0.98</td>
<td>(0.95 to 1.01)</td>
<td></td>
</tr>
<tr>
<td>Total events: 1,738 (Immediate ADT), 1,806 (Deferred ADT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2_s = 6.63 \ (P = .36)$, $I^2 = 9.5%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 1.33 \ (P = .18)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Risk of Fracture after Androgen Deprivation for Prostate Cancer

Vahakn B. Shahinian, M.D., Yong-Fang Kuo, Ph.D., Jean L. Freeman, Ph.D., and James S. Goodwin, M.D.

Figure 1. Unadjusted Fracture-free Survival among Patients with Prostate Cancer, According to Androgen-Deprivation Therapy.

The survival curves start at 12 months after diagnosis, and androgen deprivation was initiated within 6 months after diagnosis. GnRH denotes gonadotropin-releasing hormone. The number of doses is the number administered within 12 months after diagnosis.
Diabetes and Cardiovascular Disease During Androgen Deprivation Therapy for Prostate Cancer

Nancy L. Keating, A. James O’Malley, and Matthew R. Smith

Table 2. Rate of Incident Diabetes, Coronary Heart Disease, and Myocardial Infarction, and Sudden Death Associated With Androgen Deprivation Therapy, Unadjusted

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Incident Diabetes</th>
<th>Incident CHD</th>
<th>Myocardial Infarction</th>
<th>Sudden Cardiac Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>20.9 (20.3 to 21.5) &lt;ref&gt;</td>
<td>61.3 (60.2 to 62.4) &lt;ref&gt;</td>
<td>10.9 (10.5 to 11.3) &lt;ref&gt;</td>
<td>9.0 (8.6 to 11.1) &lt;ref&gt;</td>
</tr>
<tr>
<td>GnRH agonist</td>
<td>29.0 (27.3 to 30.7) &lt;.001</td>
<td>72.3 (69.4 to 62.4) &lt;.001</td>
<td>13.5 (12.5 to 14.5) &lt;.001</td>
<td>12.9 (11.9 to 13.9) &lt;.001</td>
</tr>
<tr>
<td>Orchiectomy</td>
<td>24.5 (22.1 to 26.9) .005</td>
<td>63.3 (48.9 to 67.7) .39</td>
<td>13.2 (11.6 to 14.8) .01</td>
<td>12.5 (10.9 to 14.1) &lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; ref, reference; GnRH, gonadatropin-releasing hormone.

*P values based on two-sample hypotheses tests evaluating whether the rate for men during GnRH agonist treatment differed from the rate under no treatment and whether the rate for men treated with orchiectomy differed from the rate under no treatment. Patients with prevalent diabetes and coronary heart disease did not contribute data to the rates for incident diabetes and coronary heart disease, respectively.
**ELAAT Study Schema**

<table>
<thead>
<tr>
<th><strong>Randomize</strong></th>
<th><strong>Immediate LHRH</strong></th>
<th><strong>Deferred LHRH</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized Prostate Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic biochemical failure post RT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Outcomes**
- Time to Androgen Independent Disease
- Cause specific survival
- Overall survival
- Quality of Life
- Complications of Advanced Malignancy
- Bone Fractures