Collection of Recorded Radiotherapy Seminars

http://humanhealth.iaea.org
Combining radiation and hormone therapy in localized prostate cancer: where are we?

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Department of Radiation Oncology
McGill University, Montreal, Canada
Most Common Malignancy in Men

USA data
Time Trends in Incidence and Mortality

Canadian Cancer Society - 2009

Age-Standardized Incidence Rates

Age-Standardized Mortality Rates
Prostate Cancer is a Spectrum

Many prognostic factors

Risk Groups - Canadian Consensus

**Low Risk**
T1c, T2a and
Gleason score ≤ 6 and
PSA ≤ 10 ng/ml

**Intermediate Risk**
T2b or
Gleason score 7 or
PSA >10-20 ng/ml

**High Risk**
T2c or higher
Gleason score 8-10
PSA > 20 ng/ml

McGill
Why patients fail RT?

• Large tumors
• Intrinsic resistance
• Metastatic disease
How can local control be increased with RT?

• Higher radiation doses
• Decreasing tumoral volume
• Optimizing RT biology
Prostate Cancer and Hormones

- Huggins e Hodges - initial work
- Mainstay of treatment for metastatic disease
- Response to hormonal therapy ± 90%
- Induces apoptosis reducing intracellular concentration of dihidrotestosterone (+80%)
- How about Hormones and RT?
**Experimental Studies**


% tumor eradicated with

<table>
<thead>
<tr>
<th>Therapy</th>
<th>50 Gy</th>
<th>70 Gy</th>
<th>90 Gy</th>
<th>TCD 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT only</td>
<td>0</td>
<td>0</td>
<td>67</td>
<td>89 Gy</td>
</tr>
<tr>
<td>Orchietomy + RT 1 day after</td>
<td>14</td>
<td>91</td>
<td>100</td>
<td>60 Gy</td>
</tr>
<tr>
<td>Orchietomy + RT 12 days after</td>
<td>84</td>
<td>100</td>
<td>100</td>
<td>42 Gy</td>
</tr>
<tr>
<td>Orchietomy + RT at recurrence</td>
<td>0</td>
<td>40</td>
<td>100</td>
<td>73 Gy</td>
</tr>
<tr>
<td>RT + orchiectomy 12 days after</td>
<td>0</td>
<td>48</td>
<td>100</td>
<td>75 Gy</td>
</tr>
</tbody>
</table>
RT and Androgen Ablation
Mechanisms of Interaction

• Cyto reduction
• Synergism (apoptosis)
• Improved nutritional status
• Cell distribution to a “resting phase”

McGill
Hormone therapy was not very friendly

- DES
- Orchiectomy
- Introduction of LHRH analog in the 80’s
Publications: Prostate, Radiotherapy, Hormone
What is the end-point?

- Overall survival
- Disease-free survival
- Cancer-specific survival
- Biochemical-free survival
- Metastases-free survival
- Toxicity-free survival
RT and Hormone Therapy

- Does it improve survival?
- Neoadjuvant or adjuvant? Both?
- Who should get it?
- Toxicity
- Costs

McGill
Neoadjuvant Hormone Therapy

• 5 randomized trials
  – RTOG 8610 (JCO 2008)
  – Laverdiere (J Urol 2004)
  – D’Amico (JAMA 2004)
  – TROG 96-01 (Lancet Oncol 2005)
  – RTOG 94-08 (unpublished - ASTRO 2009)

• Several differences in patient selection and end-points
  – Mixed population

McGill
Some considerations regarding studies

- **RTOG 86-10**
  - Tumor ≥ 5 x 5 cm
  - T3 = 70%
  - Gleason ≥7 in 70%
  - H (2 mos) + RT/H (2 mos)
  - Pre-PSA era*
  - TAB
  - LN + OK

- **Quebec**
  - T2-T3 (65% T2), N0
  - H (3 mos) + RT
  - H (3 mos) + RT/H (2 mos) + H (5 mos)
  - Gleason ≤ 6 in 75%
  - PSA ?
  - TAB

*Median PSA=26.3 ng/ml
Some considerations regarding studies

• D’Amico
  T1b-T2b, N0
  PSA 10-40 ng/mL
  Gleason ≥ 7
  TAB
  H (3 mos) + RT/H (3 mos)
  T2b = 30%
  Gleason ≥ 7 = 62%
  Gleason ≥ 8 = 15%
  PSA 20-40 = 12%

• TROG 96-01
  T2b - T4, N0
  H (2 mos) + RT/H (1 mos)
  H (5 mos) + RT/H (1 mos)
  TAB
  PSA ≥ 20 = 38%
  T3-4 = 40%
  Gleason 8-10 = 17%
  High risk = 83%
# RTOG 94-08 Schema

<table>
<thead>
<tr>
<th>STTRAFY</th>
<th><strong>PSA</strong></th>
<th><strong>STRATIFY</strong></th>
<th><strong>RANDOMIZE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. &lt;4</td>
<td>Grade (Differentiation)</td>
<td>Arm 1</td>
</tr>
<tr>
<td></td>
<td>2. 4-20</td>
<td>1. Well</td>
<td>Neoadjuvant TAS two months before and during RT (66.6 Gy)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Moderate</td>
<td>Arm 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Poor</td>
<td>Radiation Therapy Alone (66.6 Gy)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nodal Status</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. N0 (surgical)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. NX</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Prostate re-biopsy to be done 2 years post-treatment.*
Case Status

From October 1994 to April 2001, 2028 patients were enrolled. (average of 26 patients per month)

<table>
<thead>
<tr>
<th></th>
<th>Hormones +RT</th>
<th>RT alone</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients entered</td>
<td>1013</td>
<td>1015</td>
<td>2028</td>
</tr>
<tr>
<td>Eligible (with on-study information)</td>
<td>987</td>
<td>992</td>
<td>1979</td>
</tr>
</tbody>
</table>

Median Follow-up (Alive pts.) 9.1 years 9.2 years

- Median age was 71.
- Pretreatment characteristics were well balanced.
- Unacceptable deviations in the delivery of radiation or hormones occurred in 5% and 4% of patients.
# Neoadjuvant Trials

<table>
<thead>
<tr>
<th>Study</th>
<th># Pts</th>
<th>RT (Gy)</th>
<th>Median FU</th>
<th>Local Failure</th>
<th>bNED</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG¹ 8610</td>
<td>456</td>
<td>65-70</td>
<td>12 yrs</td>
<td>RT</td>
<td>RT 20%*</td>
<td>RT 34%</td>
</tr>
<tr>
<td>Quebec²</td>
<td>161</td>
<td>64</td>
<td>5 yrs</td>
<td>RT</td>
<td>RT 42%*</td>
<td>HRT 66%</td>
</tr>
<tr>
<td>D’Amico³</td>
<td>206</td>
<td>70</td>
<td>4.5 yrs</td>
<td>RT 66%*</td>
<td>RT 78%*</td>
<td>HRT 88%</td>
</tr>
<tr>
<td>TROG⁴ 96-01</td>
<td>802</td>
<td>66</td>
<td>5.9 yrs</td>
<td>RT 28%*</td>
<td>RT 38%*</td>
<td>RT 91%</td>
</tr>
<tr>
<td>RTOG⁵ 94-08</td>
<td>1979</td>
<td>66.6</td>
<td>9 yrs</td>
<td>RT 40%</td>
<td>RT 59%*</td>
<td>RT 57%</td>
</tr>
</tbody>
</table>

* p<0.05  

Definition of Risk Subgroups

**Low Risk** (685 pts.)
Gleason \(\leq 6\) with PSA \(\leq 10\) and not T2b

**Intermediate Risk** (1068 pts.)
Gleason 7 or
Gleason \(\leq 6\) and either PSA 10 - 20 or T2b

**High Risk** (226 pts.)
Gleason 8-10
## Low Risk Group – RTOG 94-08

### 8 Year Outcomes and Hazard Ratios

<table>
<thead>
<tr>
<th></th>
<th>Hormones + RT</th>
<th>RT Alone</th>
<th>HR</th>
<th>(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Risk (n=685)</td>
<td>76%</td>
<td>73%</td>
<td>1.07</td>
<td>(0.83, 1.39)</td>
</tr>
<tr>
<td><strong>Disease-Specific Survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Risk</td>
<td>98%</td>
<td>99%</td>
<td>0.64</td>
<td>(0.21, 1.93)</td>
</tr>
<tr>
<td><strong>Biochemical Failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Risk</td>
<td>20%</td>
<td>30%</td>
<td>1.53</td>
<td>(1.13, 2.06)</td>
</tr>
</tbody>
</table>

*Phoenix Definition

No benefit with the addition of HT
## Neoadjuvant Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Category</th>
<th>Interstitial Fractionation</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG</td>
<td>0% (?)</td>
<td>69.5% (T2)</td>
</tr>
<tr>
<td>Quebec</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston</td>
<td>79%</td>
<td>16%</td>
</tr>
<tr>
<td>TROG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG</td>
<td>54%</td>
<td></td>
</tr>
</tbody>
</table>

*Intermed.*

1. IJROBP 2001
2. J Urol 2004
3. JAMA 2004
4. Lancet Oncol 2005
5. ASTRO 2009
bNED Survival

RTOG (2001)

- Failed/Total
  - RT+Hormones: 170/201
  - RT Alone: 194/203
  - p < 0.0001

Years from Date of Randomization

Quebec

- Survival distribution

- Log-rank test p < 0.0001
- Pairwise log-rank tests:
  - Arm 1 vs. Arm 2: p < 0.0001
  - Arm 1 vs. Arm 1-2: p < 0.0001
  - Arm 2 vs. Arm 1-2: p < 0.0001

Boston

- Survival Free of Salvage Therapy, %

- Log-Rank P = 0.002

Time, y

TROG

- Biochemical failure-free survival (%)

- Time since end of radiotherapy (years)
Biochemical Failure
Phoenix Definition

EVENT / TOTAL
- Hormone + RT: 246 / 987
- RT Alone: 393 / 992

p-value < 0.0001

41% for Hormone + RT
26% for RT Alone

PATIENTS AT RISK
- Hormone + RT: 987
- RT Alone: 992

YEARS FROM RANDOMIZATION
- 0: 987
- 2: 843
- 4: 681
- 6: 521
- 8: 380
- 10: 182
- 12: 52

PATIENTS AT RISK
- Hormone + RT: 987
- RT Alone: 992
Overall Survival

D’Amico

RTOG

TROG
Overall Survival

- **Overall Survival Rate**
  - Hormone + RT: 62%
  - RT Alone: 57%

- **Events / Total**:
  - Hormone + RT: 359 / 987
  - RT Alone: 404 / 992

- **p-value**: 0.0309

- **Patients at Risk**:
  - Hormone + RT: 987
  - RT Alone: 992

- **Years from Randomization**:
  - Hormone + RT: 926, 844, 714, 560, 278, 86
  - RT Alone: 931, 825, 692, 528, 270, 86

- **Graph** showing the survival rate over time for patients treated with Hormone + RT and RT Alone.
## Analysis by Risk Group

### 8 Year Outcomes and Hazard Ratios

<table>
<thead>
<tr>
<th></th>
<th>Hormones + RT</th>
<th>RT Alone</th>
<th>HR</th>
<th>(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>72%</td>
<td>66%</td>
<td>1.23</td>
<td>(1.02, 1.49)</td>
</tr>
<tr>
<td>(n=1068)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disease-Specific Survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>98%</td>
<td>92%</td>
<td>2.44</td>
<td>(1.47, 4.04)</td>
</tr>
<tr>
<td><strong>Biochemical Failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>25%</td>
<td>42%</td>
<td>1.79</td>
<td>(1.45, 2.21)</td>
</tr>
</tbody>
</table>

*Phoenix Definition*
Further details on D’Amico’s trial

- Faster than usual death rate in control group
- Higher number of unrelated deaths in control group
- Secondary analysis (JAMA 2008) shows program only benefited “well” patients
Does the duration of neoadjuvant therapy matter?

378 men randomized to 3 vs 8 months

26% low risk
43% intermediate risk
31% high risk

Biochemical Response vs Duration of Hormonal Therapy

Alexander et al. IJROBP 2009
A PHASE III TRIAL TO EVALUATE THE DURATION OF NEOADJUVANT TOTAL ANDROGEN SUPPRESSION (TAS) AND RADIATION THERAPY (RT) IN INTERMEDIATE-RISK PROSTATE CANCER

SCHEMA (6/7/04)

<table>
<thead>
<tr>
<th>PSA</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ≤10</td>
<td>Arm 1</td>
</tr>
<tr>
<td>2. &gt;10-20</td>
<td>TAS (LHRH agonist and Casodex or Eulexin) x 8 weeks followed by RT³ with concurrent TAS (LHRH agonist and Casodex or Eulexin).</td>
</tr>
<tr>
<td>3. &gt;20 to ≤100</td>
<td>Arm 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 2-4</td>
<td>TAS (LHRH agonist and Casodex or Eulexin) x 28 weeks followed by RT⁸ with concurrent TAS (LHRH agonist and Casodex or Eulexin).</td>
</tr>
<tr>
<td>2. 5-6</td>
<td></td>
</tr>
<tr>
<td>3. 7-10</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor stage</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. T1b-2</td>
<td></td>
</tr>
<tr>
<td>2. T3-4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior Hormones</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No</td>
<td></td>
</tr>
<tr>
<td>2. Yes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
</table>

- T1b-4 Gleason 2-6 PSA >10 but ≤100
- T1b-4 Gleason 7 PSA <20
- T1b-1c Gleason 8-10 PSA <20

Sample size: 1540
Neoadjuvant Hormonal Therapy

Summary

- Decreases local failure
- RT doses relatively low
- Improved bNED
- No benefit for low risk disease
- 2 trials show benefit in overall survival (50-80% intermediate risk)
Do we need hormone if RT dose is higher?

Quebec PCS III Trial

Randomize

Intermediate Risk
T2b or GS 7
or PSA 10-20

RT 70 Gy + Hormone

RT 76 Gy + Hormone

RT 76 Gy
RTOG 0815

EBRT alone: 79.2 Gy
EBRT + Brachytherapy: 45 Gy + 110 Gy
45 Gy + 10.5 Gy x 2
Adjuvant Hormonal Therapy

- 4 randomized trials
  - RTOG 85-31 Pilepich et al. IJROBP 2005
  - EORTC 22863 Bolla et al. Lancet 2002
  - RTOG 92-02 Horwitz et al. JCO 2008
  - Quebec L-200 Laverdiere et al. J Urol 2004

- Higher risk patients
  - Mixed population
    - T stage
    - Post-op
    - N positive
    - Low/Intermediate Risk
Some considerations regarding studies

- **RTOG 85-31**
  Pre-PSA era
  T3
  T1-2 if pN+
  Post-op, if high risk
  RT + goserelin for life
  GS >7 = 32%
  N+ = 29%
  Post-op = 15%

- **EORTC 22863**
  T3-T4
  T1-2 if grade 3
  Pelvic N + OK
  RT + H (3 yrs)
  PSA >20 ng/ml in >50%
  T3-4 = 91%
  GS 7-10 = 35%
  N+ = 4%
Some considerations regarding studies

- **RTOG 92-02**
  - T2c-4
  - PSA < 150 ng/ml
  - Pelvic N+ OK
  - H (2 mos) + RT/H (2 mos)
  - H (2 mos) + RT/H (24 mos)
  - T3-4 = 55%
  - GS >7 = 26%
  - PSA >30 ng/ml = 33%

- **Quebec L-200**
  - T2-3
  - H (3 mos) + RT/H (2 mos)
  - H (3 mos) + RT/H (5 mos)
  - T3 = 30%
  - GS ≥7 = 30%
  - Median PSA = 9.4 ng/ml
## Adjuvant Hormonal Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th># Pts</th>
<th>Median FU</th>
<th>Local Failure</th>
<th>Distant Mets</th>
<th>bNED</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG¹ 8531</td>
<td>977</td>
<td>11 yrs</td>
<td>RT 38%*</td>
<td>RT 39%*</td>
<td></td>
<td>RT 39%</td>
</tr>
<tr>
<td>EORTC² 22863</td>
<td>415</td>
<td>5.5 yrs</td>
<td>RT 16%*</td>
<td>RT 29%*</td>
<td></td>
<td>RT 45%*</td>
</tr>
<tr>
<td>RTOG³ 9202</td>
<td>1554</td>
<td>5.8 yrs</td>
<td>HRT 22%*</td>
<td>HRT 15%*</td>
<td></td>
<td>HRT 32%*</td>
</tr>
<tr>
<td>Quebec⁴ (L-200)</td>
<td>296</td>
<td>3.7 yrs</td>
<td>HRT 70%</td>
<td>HRT 70%</td>
<td></td>
<td>HRT 51%</td>
</tr>
</tbody>
</table>

* p<0.05

Adjuvant Hormonal Therapy

Summary

- Prolonged use of hormonal therapy beneficial for high risk patients
- Optimal duration of hormonal therapy still unknown
- Increased toxicity and Costs

McGill
Hormonal Therapy Has Side Effects

Acute
Hot flushes
Loss of libido
Erectile dysfunction

Late
Anemia
Muscle loss
Fatigue
↓ physical activity
Depression
Osteoporosis
Cardiac

Sanda et al. NEJM 2008
For how long should we prescribe hormonal therapy in high risk patients??

• 4 months?
• 6 months
• 24/28 months?
• 36 months?
• Longer?
Impact of the Duration of Adjuvant Hormonal Therapy in Patients With Locally Advanced Prostate Cancer Treated With Radiotherapy: A Secondary Analysis of RTOG 85-31

Luis Souhami, Kyounghwa Bae, Miljenko Pilepich, and Howard Sandler

ABSTRACT

Purpose
Radiation Therapy Oncology Group 85-31 was a randomized trial of androgen suppression for life for patients with locally advanced prostate cancer. However, not all patients continued on the protocol-mandated long-term hormonal therapy despite no evidence of recurrence. We correlated duration of adjuvant hormonal therapy and outcomes among patients who prematurely discontinued hormonal therapy.

Patients and Methods
The protocol mandated pelvic radiotherapy followed by goserelin given indefinitely or until disease progression. There were 189 analyzable patients. Patients were divided in groups based on the tertile of hormonal therapy duration (HTD) as follows: ≤ 1 year, more than 1 year and ≤ 5 years, and more than 5 years. Overall survival (OS), disease-free survival (DFS), cause-specific mortality, local failure (LF), and distant metastasis (DM) were studied. Kaplan-Meier estimation and Cox proportional hazards regression model were used for OS and DFS, and Fine and Gray’s regression model was used for the other outcomes.

From the McGill University Health Center, Montreal, Quebec, Canada; Radiation Therapy Oncology Group, Philadelphia, PA; University of California Medical Center, Los Angeles, CA; and University of Michigan, Ann Arbor, MI.

Submitted March 31, 2008; accepted December 2, 2008; published online ahead of print at www.jco.org on March 23, 2009.

Supported by National Cancer Institute Grants No. Radiation Therapy Oncology Group U10 CA21661, Community Clinical Oncology Program U10 CA37422, and Stat U10 CA321115.

Presented at the 43rd Annual Meeting of the American Society of Clinical Oncology, June 1-5, 2007, Chicago, IL.
Material and Methods

RTOG 85-31 Eligibility

- Adenocarcinoma of the prostate
- Clinical stage T3 or pN+
- T1-2 eligible if regional lymph nodes positive
- Post-prostatectomy patients eligible if:
  - capsular penetration +,
  - margin + or
  - seminal vesicle +
- KPS ≥ 60
- Written informed consent
- PSA determination was not mandatory

PELVIC RT + LIFE-LONG ANDROGEN SUPPRESSION (Arm 1)

PELVIC RT (Arm 2)

Pelvic RT: 60-66 Gy
Hormonal therapy: Goserelin 3.6 mg monthly for life

www.rtog.org
Between 1987 and 1992, 977 patients entered the RTOG 85-31 trial.

Of these, 446 pts received protocol HT (arm 1).

322 pts (72%) discontinued HT,
- 133 (41%) due to death, disease progression, other HT were excluded

189 pts (59%) comprised the study cohort
### Distribution of Hormone Duration

Patients were divided into 3 groups based on the tertile of HTD.

<table>
<thead>
<tr>
<th>Hormone Duration (Yrs)</th>
<th>Nº of Patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>67</td>
<td>35.5</td>
</tr>
<tr>
<td>1&lt; and ≤ 5</td>
<td>61</td>
<td>32.25</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>61</td>
<td>32.25</td>
</tr>
</tbody>
</table>
Results

Hormone Duration in Arm 1 (years)
Median: 2.2 (range: 0.003-13.5)
Tertiles of HTD:
1 year 33%
5 years 67%

The median follow-up time of surviving patients is 11.3 years
RTOG 85-31 - Secondary Analysis

Overall Survival

Disease-Specific Survival

Souhami et al. J Clin Oncol 2009
Cause-Specific Survival

Local-Regional Failure

Distant Failure

Patients at Risk

HTD <= 1 1 < HTD <= 5 5 < HTD

p-value (Gray's) = 0.02

p-value (Gray's) = 0.03

p-value (Gray's) = 0.006
Landmark Analysis

No. patients at risk
HTD ≤ 1 | 45 | 45 | 40 | 27 | 13
1 < HTD ≤ 5 | 39 | 39 | 36 | 24 | 6
5 < HTD | 61 | 61 | 58 | 49 | 19

Log-rank $P = .20$

Souhami et al. JCO 2009
### Causes of Death for Cause-Specific Mortality

<table>
<thead>
<tr>
<th></th>
<th>HTD ≤ 1 (n=42)</th>
<th>1 &lt; HTD ≤ 5 (n=40)</th>
<th>5 &lt; HTD (n=27)</th>
<th>Total (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Due to Prostate Cancer</td>
<td>13</td>
<td>31</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>Due to Second Primary</td>
<td>6</td>
<td>14</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Due to Other Causes</td>
<td>16</td>
<td>38</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td>17</td>
<td>7</td>
<td>18</td>
</tr>
</tbody>
</table>
Conclusions

- Prolonged HTD of > 5 years appears to be significantly associated with improvements in all end-points studied

- Based on these data, decreasing HTD to < 5 years may have a detrimental effect in patients with unfavorable prostate cancer
Prostate Cancer
T1c-T2b, N1-2 or pN1-2
or T2c-T4, N0-2 (UICC 1992)
MO
PSA <150 ng/ml

Stratify:
Institution
T stage
PSA level
Gleason score

Pelvic RT + 6 months ADT
30 months LHRH
Observation

End-point: overall survival
Non-inferiority - (HR ≤1.35)

## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Short ADT</th>
<th>Long ADT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age</strong></td>
<td>70 yr</td>
<td>69 yr</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td>23%</td>
<td>24%</td>
</tr>
<tr>
<td><strong>T3</strong></td>
<td>75.5%</td>
<td>73%</td>
</tr>
<tr>
<td><strong>N0</strong></td>
<td>91%</td>
<td>91%</td>
</tr>
<tr>
<td><strong>Gleason</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>47%</td>
<td>45%</td>
</tr>
<tr>
<td>7</td>
<td>30.5%</td>
<td>30%</td>
</tr>
<tr>
<td>≥8</td>
<td>18.5%</td>
<td>19.5%</td>
</tr>
<tr>
<td><strong>Median PSA</strong></td>
<td>18.8 ng/ml</td>
<td>18.8 ng/ml</td>
</tr>
</tbody>
</table>

EORTC 22961 - Bolla et al NEJM 2009
## Survival status and cause of death

Median follow-up = 6.4 years

<table>
<thead>
<tr>
<th></th>
<th>SADT</th>
<th>LADT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=483)</td>
<td>(n=487)</td>
</tr>
<tr>
<td>Death</td>
<td>132 (27%)</td>
<td>98 (20%)</td>
</tr>
<tr>
<td>Prostate Ca deaths</td>
<td>47 (9.7%)</td>
<td>28 (5.7%)</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>31 (6.5%)</td>
<td>25 (5%)</td>
</tr>
</tbody>
</table>

5-year prostate-specific mortality HR=1.71 - (p=0.002)

EORTC 22961 Bolla et al NEJM 2009
Overall survival

85.3% (98.2% CI: 80.5-89.0)

80.6% (98.2% CI: 75.4-84.8)

HR(SADT/LADT): 1.43 (96.4% CI: 1.04-1.98)

P-Value: 0.6543 (H1: SADT non inferior)

P-value: 0.0191 (H1: LADT superior)

Number of patients at risk:

<table>
<thead>
<tr>
<th>Years</th>
<th>Short ADT</th>
<th>Long ADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>483</td>
</tr>
<tr>
<td>1</td>
<td>470</td>
<td>452</td>
</tr>
<tr>
<td>2</td>
<td>452</td>
<td>409</td>
</tr>
<tr>
<td>3</td>
<td>409</td>
<td>332</td>
</tr>
<tr>
<td>4</td>
<td>332</td>
<td>235</td>
</tr>
<tr>
<td>5</td>
<td>235</td>
<td>122</td>
</tr>
<tr>
<td>6</td>
<td>122</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>17</td>
<td>4</td>
</tr>
</tbody>
</table>
Biochemical Progression-free Survival

HR: 2.29
(98.2% CI: 1.81-2.90)

P-Value: < 0.0001
(difference)
Clinical Progression Free Survival

- 81.8% (95% CI: 76.7, 85.9)
- 69% (95% CI: 63.2, 74)

HR: 1.93 (95% CI: 1.49-2.51)
P-Value: < 0.0001 (difference)

Disease status

<table>
<thead>
<tr>
<th></th>
<th>Short ADT (N=483)</th>
<th>Long ADT (N=487)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local progression</td>
<td>29 (6.0)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Nodal progression</td>
<td>15 (3.1)</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>Distant progression</td>
<td>78 (16.1)</td>
<td>31 (6.4)</td>
</tr>
<tr>
<td>Any Clinical progression</td>
<td>97 (20.1)</td>
<td>40 (8.2)</td>
</tr>
<tr>
<td>Biochemical progression</td>
<td>148 (30.6)</td>
<td>62 (10.7)</td>
</tr>
<tr>
<td>Clinical PFS (Clinical progression or death)</td>
<td>155 (32.1)</td>
<td>89 (18.3)</td>
</tr>
<tr>
<td>Biochemical PFS (Clinical or biological progression or death)</td>
<td>205 (42.4)</td>
<td>106 (21.8)</td>
</tr>
</tbody>
</table>
Conclusions

- The study was designed to demonstrate non-inferior survival with 6 months ADT compared to 3 years adjuvant ADT after irradiation for patients with locally advanced prostate cancer,
- Observed survival data indicate that non-inferiority cannot be confirmed.
- Progression-free survival was also shorter on SADT.
Quebec PCS IV
High-Risk Prostate Cancer

T3-T4
Gleason >7
PSA >20

RANDOMIZE

ADT 36 months + RT
ADT 18 months + RT

ADT: Androgen Deprivation Therapy
RT: Pelvis 44 Gy + Prostate 26 Gy
(RT to start at 4th month of ADT)

Accrual target: 630 patients
Median demanded increment in survival was ~10%
Adjuvant Hormonal Therapy Summary

- Prolonged use of hormonal therapy beneficial for high risk patients
- Short use of hormonal therapy appears beneficial for intermediate risk
- Optimal duration of hormonal therapy still unknown
- Toxicity is increased
- Health costs is an issue
- Closed studies
  - 36 months vs 6 months (EORTC)
  - 36 months vs 18 months (Quebec)
Where do we go from here?

- **Intermediate Risk Patients**
  - Higher RT dose vs. RT plus hormones
  - Genetic & Molecular markers

- **High Risk Patients**
  - Optimal duration of hormonal therapy
  - Chemotherapy (RTOG 0561, NCIC PR-12)
  - Genetic & Molecular markers

McGill