Testosterone and Radiotherapy for Prostate Cancer

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Round Table 8
Outline

- Introduction
- Effects of Radiation on Testosterone (TST)
- Testosterone Replacement Therapy after Radiotherapy of Prostate Cancer
- Take Home Messages
External-Beam Radiotherapy (EBRT)

- Introduction of linear accelerators
- Till mid 1980s, conventional techniques
- 3 Dimensional-Conformal Radiotherapy (3D-CRT)
- Intensity-Modulated Radiotherapy (IMRT)
- Stereotactic Radiotherapy
- Protons
EBRT for Prostate Cancer (PCa.)
Radiation-Induced Testicular Injury

- Orchiectomy in 35 pts after EBRT compared to 43 not treated
- Testicular atrophy (loss seminiferous epithelium, decreased spermatogenesis, fibrosis...): 71% vs 28%, respectively
- More common within 3 yrs of EBRT (89% vs 53%)
  
  Daniell and Tam, Cancer 1998;83:1174-79

- 33 pts after EBRT vs 55 after Radical Prostatectomy (RP)
- TST, DHTST, FTST levels 30% lower after EBRT; LF and FSH increased 50% and 100%, respectively

  Daniell et al. Cancer 2001;91:1889-95

Retrospective evaluations, old techniques, larger fields
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Radiation-Induced Testicular Injury (cont’d)

- Prostate-only fields (68-72 Gy): mean Testicular Dose (TD) is 2.1 Gy
  Boehmer et al. Strahlenther Onkol 2005;181:179-84

- Pelvic nodal fields (45-50 Gy+25 Gy boost): mean TD is 4.3-9.1 Gy

- Hypogonadism is clinically appreciated at a TD of 2-4 Gy
  Bruheim et al. IJROBP 2008;70:722-27

- A TD <0.7 Gy has no long-term effects on TST level
  Kinsella et al. IJROBP 1989;7:718-24

- TD can be minimized by: photon energy <10 MV, smallest port size for fiducial tracking, avoidance of (elective) pelvic nodal fields
  King et al. IJROBP 2010;77:484-89
Incrocci L.

King et al. IJROBP 2010;77:484-89
Radiotherapy and TST

- Prospective study, n=666 after EBRT (no ADT)
- TST and PSA at baseline, 3-6 mos after EBRT
- TST decreased at 6 mos to 83% of baseline values
- Only 60% recovered to baseline levels
- Lower nadir TST levels in large fields and pre-treatment low TST levels
- No relationship between TST levels and biochemical relapse

Low incidence of new biochemical and clinical hypogonadism following hypofractionated stereotactic body radiation therapy (SBRT) monotherapy for low- to intermediate-risk prostate cancer

N=26, 5x7.25 Gy
Testosterone and Prostate Cancer: Revisiting Old Paradigms

Hendrik Isbarn a, *, Jehonathan H. Pinthus b, Leonard S. Marks c, Francesco Montorsi d, Alvaro Morales e, Abraham Morgentaler f, Claude Schulman g

Table 1 – Reports addressing the effect of testosterone therapy in symptomatic hypogonadal men after definitive prostate cancer treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample size, n</th>
<th>PCa treatment</th>
<th>Start of TRT after PCa treatment</th>
<th>Follow-up</th>
<th>Cases of BCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaufman and Graydon [29]</td>
<td>7</td>
<td>RP</td>
<td>Mean: 2.7 yr</td>
<td>Mean: NR</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range: 0–108 mo</td>
<td>Range: 1–12 years</td>
<td></td>
</tr>
<tr>
<td>Agarwal and Oefelein [28]</td>
<td>10</td>
<td>RP</td>
<td>Not reported</td>
<td>Mean: 19 mo</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Range: 9–29 mo</td>
<td></td>
</tr>
<tr>
<td>Khera et al [25]</td>
<td>21</td>
<td>RP</td>
<td>Mean: 54 mo</td>
<td>Median: 12 mo</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range: 1–181 mo</td>
<td>Range: 1–60 mo</td>
<td></td>
</tr>
<tr>
<td>Nabulsi et al [27]</td>
<td>22</td>
<td>RP</td>
<td>Mean: 26 mo</td>
<td>Mean: 24 mo</td>
<td>1/22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range: 2.5–118 mo</td>
<td>Range: 14–30 mo</td>
<td></td>
</tr>
<tr>
<td>Davilla et al [24]</td>
<td>20</td>
<td>RP: 14</td>
<td>Mean: 74 after RP; 57 mo after EBRT</td>
<td>Mean: 12 mo after RP; 9 mo after EBRT</td>
<td>None after RP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EBRT: 6</td>
<td></td>
<td>Range: NR</td>
<td></td>
</tr>
<tr>
<td>Morales et al [69]</td>
<td>5</td>
<td>EBRT</td>
<td>Not reported</td>
<td>Mean 14.6 mo</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Range: 6–27 mo</td>
<td>(according to ASTRO criteria)</td>
</tr>
<tr>
<td>Sarosdy [26]</td>
<td>31</td>
<td>Brachytherapy (with or without EBRT)</td>
<td>Median: 24 mo</td>
<td>Mean 14.6 mo</td>
<td>None (according to ASTRO criteria)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range: 6–54 mo</td>
<td>Range: 18–108 mo</td>
<td>PSA &lt;0.1 in 74%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PSA &lt;1.0 in 100%</td>
</tr>
</tbody>
</table>

ASTRO = American Society for Therapeutic Radiation Oncology; BCR = biochemical recurrence; EBRT = external beam radiotherapy; NR = not reported; PCa = prostate cancer; RP = radical prostatectomy; TRT = testosterone therapy.
Testosterone Replacement for Hypogonadism After Treatment of Early Prostate Cancer With Brachytherapy

Michael F. Sarosdy, MD
Cancer 2007;109:536–41

• TRT initiated at a median 2 (0.5-4) yrs after BT
• Transient PSA rise in one patient
• Median follow-up 5 yr

<table>
<thead>
<tr>
<th>PSA, ng/mL</th>
<th>No. of patients (%)</th>
</tr>
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<tbody>
<tr>
<td>&lt;0.1</td>
<td>23 (74.2)</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>30 (96.7)</td>
</tr>
<tr>
<td>&lt;1.0</td>
<td>31 (100)</td>
</tr>
</tbody>
</table>

In conclusion, the current report indicates that TRT may be used with caution and close follow-up in hypogonadal patients after they receive prostate brachytherapy for localized, early-stage prostate cancer. Assessment of baseline testosterone should be
Testosterone administration to men with testosterone deficiency syndrome after external beam radiotherapy for localized prostate cancer: preliminary observations

Alvaro Morales, Angela M. Black and Laurel E. Emerson

- N=5, age 65 (52-75) yrs with severe hypogonadism
- Treated after PSA level reached nadir
- Mean follow-up was 14.5 (6–27) mos
- TST increased from 5.2 to 17.6 nmol/L
- At last follow-up, none had evidence of cancer recurrence (PSA, DRE)
- One had transitory PSA rise
- Pts reported improvement of symptoms (erectile function and libido, decreased hot flushes and fatigue)
Testosterone administration to men with testosterone deficiency syndrome after external beam radiotherapy for localized prostate cancer: preliminary observations

Alvaro Morales, Angela M. Black and Laurel E. Emerson

This report should not be construed as evidence of the safety of TRT in men treated with EBRT for prostate cancer, because of the very few men under observation. It is, to our knowledge, the first series of its kind. We need to accumulate additional information on the safety and efficacy of TRT in men with severe TDS occurring spontaneously in the ageing population or as a result of neoadjuvant ADT before definitive curative treatment for localized prostate cancer, because of the significant impact that hypotestosteronaemia has on quality of life and longevity, particularly in those apparently cured of their primary cancer.

testosterone therapy. The patients must be aware of the advantages and disadvantages of the treatment. PSA levels must have reached a nadir before starting treatment and the follow-up must be particularly close.
Davila et al.

Analysis of the PSA response after testosterone supplementation in patients who have previously received management for their localized prostate cancer.

J Urol (suppl) 2008;179:428; **Abstract** 1247

- N=6
- Mean 57 mo after EBRT
- Mean follow-up was 9 mo
- No biochemical failures
Testosterone replacement therapy in the setting of prostate cancer treated with radiation

AW Pastuszak1,4, AM Pearlman2,4, G Godoy1, BJ Miles3, LI Lipshultz1 and M Khera1

International Journal of Impotence Research (2012), 1–5

- N=13, age 68 (62-77) yrs
- Retrospective data
- Brachytherapy or external-beam radiotherapy
- Median follow-up 30 (2-67) mos
- No PSA increase
- Improvement of hypogonadal symptoms
Testosterone Replacement Therapy (TRT) Facts

- PubMed:
- 50+ papers, from UK to US to Brazil, almost all of them reviews
- On Radiotherapy 20+, same
- In a Medicare database of about 150K PCa. pts, only 0.8% received TRT
- TRT not associated with overall or cancer-specific mortality, or with ADT salvage

Kaplan et al. JSM 2014;11:1063-70

- European Association of Urology Guidelines on PCa.:
  - In hypogonadal men who were successfully treated for Pca., TST suppletion can be considered after a prudent interval
Conclusion and Questions

- Optimal timing?
- A prospective randomized trial of TRT after primary treatment of low-stage PCa. would require thousands pts and long, costly follow-up
- Data do not support the statement that TRT is contraindicated after treatment of PCa.
- Selected pts, with significant symptoms of hypogonadism, may receive TRT
- Definition of PSA-no residual disease prior to start TRT: 2 ug/L?
- Monitoring PSA and DRE is fundamental. Timing? Every 3 mos?
To date 6 studies have provided information on a total of 111 men treated with RP, brachytherapy or external beam radiation therapy. Biochemical recurrence was noted in 1.8% (2 men), a recurrence rate no higher than published series in favorable groups. The absence of recurrence in 31 men treated with brachytherapy provides some reassurance that T therapy may not present undue risk even when the prostate remains in situ. There are no data to indicate that a delay in initiation of T therapy impacts outcome. Caution must be exercised in drawing conclusions from this limited clinical experience of T therapy after treatment of PCa.
Take Home Messages

- TST decreases after radiotherapy for PCa.
- Hypogonadism is clinically appreciated at a testicular dose of 2-4 Gy
- Data do not support the statement that TRT is contraindicated after treatment of PCa.
- Selected pts, with significant symptoms of hypogonadism, may receive TRT
- Proper counselling and monitoring of PSA and DRE are mandatory