Long Term Risk of Radiation Therapy for Clinically Localized Prostate Cancer

Various Forms of Radiation Treatment
- External beam radiotherapy (EBRT)
  - 3-D conformal
  - Intensity-modulated radiotherapy (IMRT)
  - Proton Beam
- Brachytherapy
  - Permanent seed implants (I-125/Pd-103)*
    - As monotherapy
    - With EBRT
  - Temporary high-dose-rate (HDR) after loading implants
    - With EBRT
      - I-125=iodine 125; Pd-103=palladium 103

Short History Therapy for Localized Prostate Cancer
- Radium first clinically useful isotope 1898.
- Pasteau et al. made the first curative attempts with Brachytherapy for prostate ca. in 1909. Their first pt. Received 29 Radium Tx’s with the pt. NED @ 4 yrs
- Benjamin Barringer is considered to originator of the Transperineal Prostate Implant performed hundreds of implants beginning in 1915 (twenty in the first year!)
- Young et al. by 1914 devised a radium carrying cystoscopic instrument for greater accuracy.
- Herbst published results in JAMA (1919)
- Young et al. (1921) performed open perineal Brachytherapy approach
Short History Therapy for Localized Prostate Cancer

- Memmelaar (1949) reports the successful use of the RRP for treatment of prostate cancer.
- 1950’s & 1960’s believed that EBRT provided comparable results with less morbidity.
- Late 70’s early 80’s Walsh et al. - reduced blood loss, risk of incontinence & impotence with RRP.
- The “modern anatomic” RRP a few years older than 3DCRT & Brachytherapy older than both!

External Beam Radiotherapy (EBRT)

- Cobalt and high voltage radiotherapy was popular in the 1930’s to 1950’s but morbidity was significant.
- The first medical Accelerator in the Western Hemisphere was developed at Stanford
- Linac based treatment of Prostate Cancer was introduced at Stanford Hospital in 1956

| Radiation Sequelae in Prostate Cancer Patients +/- Blocking: Old Stanford Data |
|---------------------------------|------------------|-------|
|                                 | Intestinal       | Urologic | Other |
| Persistent                      |                  |         |       |
| 1/65 to 12/74 (N=431 pts)       | 5.1% (n=22)      | 7.7% (n=33) | 1.6% (n=7) |
| Transient severe                | 1.4% (n=6)       | 3.2% (n=14) | 0.2% (n=1) |
| Persistent                      |                  |         |       |
| 1/75 to 12/84 (N=289 pts)       | 2.4% (n=7)       | 4.8% (n=14) | 1.4% (n=6) |
| Transient severe                | 0.5% (n=2)       | 3.4% (n=7) | 0.3% (n=1) |

P Value = 0.0026 for reduction in radiation sequelae

3-D Conformal / IMRT (both forms of EBRT)

- Computed tomography (CT)- or magnetic resonance (MR)-based acquisition of prostate, seminal vesicle (SV), bladder & rectum
- Direct transfer of 3D images
- 3-D treatment planning software
- Beam’s eye view field shaping
- Volumetric dose calculations
- Linear accelerator radiation delivery
- Multi-leaf collimator (MLC) shaping
- Automated delivery of multiple radiation therapy (RT) fields
Prostate Cancer and Late Effects of Radiotherapy

- **Median Lobe - planning**
  - 1. I-125 seed
  - 2. Acquisition of prostate volume by TRUS for planning
  - 3. Outpatient implant procedure; TRUS guidance
  - 4. Postimplant assessment of implant quality by CT

- **Permanent Seed Implants**
  - I-125/Pd-103 Brachytherapy

- **ST Inverse SMLC**
  - 90 Gy, 75.6 Gy, 60 Gy, 50 Gy, 40 Gy, 30 Gy

- **Forward SMLC**

- **Prostate Cancer and Late Effects of Radiotherapy**
  - Grade 2 or higher Late rectal Complications
  - Pollack et al. UROLOG 2002

- **Fraction free of rectal reaction**
  - Months after radiotherapy
  - Median Lobe - planning
  - p = 0.0014

- **90 Gy, 75.6 Gy, 60 Gy, 50 Gy, 40 Gy, 30 Gy**
1. HDR afterloader; Ir-192 source on cable
2. Needle insertion under Ultrasound
3. Implant completed; CT planning

High-Dose-Rate Afterloading: Temporary Iridium-192 (Ir-192) Brachytherapy

Prostate Cancer and Late Effects of Radiotherapy

- Acute: GU
  - Frequency, Urgency, Nocturia
- Acute: GI
  - Diarrhea, rectal bleeding, Nausea
- Acute: Other
  - Fatigue
- Late: GU
  - Chronic Frequency, Urge Incontinence, Strictures
- Late: GI
  - Chronic Diarrhea, Chronic rectal bleeding, Fistula
- Late: Other
  - Impotence, Second Cancers, Hip Fractures

SANDA et al. NEJM 358:1250-61, 2008

Quality of Life and Satisfaction with Outcome among Prostate-Cancer Survivors

ABSTRACT

SANDA et al. NEJM 358:1250-61, 2008
Quality of Life Among Prostate-Cancer Survivors: Characteristics of Patients

Surgery vs Radiotherapy

SANDA et al. NEJM 358:1250-61, 2008

PROSTATE CANCER & Radiotherapy Complications - Late

- Late: GU are Dose and Volume Dependent
  - Chronic Frequency & Urge Incontinence: minimized by reducing exposure to the bladder
  - Strictures: minimized by reducing “hot spots”

- Late: GI are Dose and Volume Dependent
  - Chronic Diarrhea & Chronic rectal bleeding: minimized by reducing exposure to the bowel
  - Fistula: minimized by reducing “hot spots” between urethra and rectum

- Late: Other are Dose and Volume Dependent
  - Impotence: minimize dose to penile structures
  - Hip Fractures: minimize “hot spots” in femurs
  - Second Cancers: min. dose & volume to nl. tissues
Prostate Cancer and Late Effects of Radiotherapy


Table 1: Comparison of doses to small bowel and penile bulb between IMRT, WP, EF, and extended field (EF) EBRT plans for group 1 patients with rectal washouts exceeding 3 or 3.5 Gy.

<table>
<thead>
<tr>
<th>Group</th>
<th>IMRT</th>
<th>WP</th>
<th>EF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>V9 (Gy)</td>
<td>51.5 ± 6.2</td>
<td>206.6 ± 117.2</td>
</tr>
<tr>
<td>2</td>
<td>V15 (Gy)</td>
<td>64.9 ± 20.6</td>
<td>310.0 ± 370.0</td>
</tr>
<tr>
<td>3</td>
<td>V20 (Gy)</td>
<td>209.1 ± 33.7</td>
<td>390.1 ± 34.2</td>
</tr>
<tr>
<td>4</td>
<td>V22 (Gy)</td>
<td>678.2 ± 166.7</td>
<td>640.2 ± 132.3</td>
</tr>
<tr>
<td>5</td>
<td>Mean dose (Gy)</td>
<td>318.1 ± 5.2</td>
<td>176.2 ± 0.7</td>
</tr>
</tbody>
</table>

Note: IMRT = intensity-modulated radiation therapy; WP = whole pelvis; EF = extended field; V9 = volume receiving 9 Gy; V15 = volume receiving 15 Gy; V20 = volume receiving 20 Gy; V22 = volume receiving 22 Gy; Mean dose = mean dose to small bowel or penile bulb.

CLINICAL INVESTIGATION

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Cancer Incidence After Localized Therapy for Prostate Cancer

METHODS: Men with prostate ca identified from the SEER registry & distinguished by the type of treatment & occurrences of secondary ca. beginning 5 yrs after Dx.

RESULTS: Compared with men who received no prostate ca.-directed RT, men who received EBRT had an increased odds of Dx second Ca. at sites potentially related to RT (OR, bladder=1.63; and rectum=1.60).

RESULTS (contd.): Men who received EBRT also had higher odds of developing second ca. in areas not related to EBRT, including the cecum, transverse colon; brain, stomach, skin, and lung +bronchus (OR, 1.63; 1.85; 1.63; 1.38; 1.29; 1.25, respectively).

Men who received radioactive implants did not have a higher odds of secondary ca.

CONCLUSIONS: Men treated with EBRT had higher odds of developing second ca. in and out of field men who received radioactive implants had the lowest odds of developing second ca.

Radiation Therapy for Prostate Cancer Increases Subsequent Risk of Bladder and Rectal Cancer: A Population Based Cohort Study

PURPOSE: Est. the risk of secondary bladder & rectal ca. after prostate RT.

MATERIALS AND METHODS: 243K men in the SEER database post RP or RT between 1988-03.

RESULTS: RR of bladder ca. after EBRT, BT & EBRT+BT compared to RP was 1.88, 1.52 & 1.85.

Compared to the USA pop the incidence ratio for bladder ca. developing after RP, EBRT, BT & BT +EBRT was 0.99, 1.42, 1.10 and 1.39.

RR of rectal ca. after EBRT, BT and EBRT+BT compared to RP was 1.26, 1.08 and 1.21.

The incidence ratio for rectal ca. after RR, EBRT, BT and BT+EBRT was 0.91, 0.99, 0.68 and 0.86.

The use of external beam radiotherapy is associated with an increased risk of secondary malignancies. In this report the difference between the risk of bladder cancer following prostatectomy and EBRT was 144 per 100,000 person-years or 0.0014 per year or approximately 1.4% at 10 years. Taking into account other competing causes of death, the risk of second cancers at 10 years might be half this rate or approximately 0.7%.

Assuming a 5-year survival of 50% from a second cancer, the risk of death would be approximately 0.35% at 15 years. I might present it to a 70-year-old patient as “Your chances of dying from a second cancer due to EBRT at 15 years is probably less than your risk of dying after a radical prostatectomy (0.6%) within 30 days, but potency and erectile rates are better with EBRT.” Most patients could probably understand this comparison and make an informed decision.
Take-Home Points

• Modern radiotherapy is associated with better outcomes & fewer side-effects
• Choice of type of Radiotherapy depends on expertise, pt preference, & available technology
• Radiation Induced Complications (Impotence, Proctitis ...) are Dose and Volume Dependent
• Second Cancers occur as a late effect of RT but they are relatively uncommon & usually do not drive decisions about treatment

Cardiac Effects of Androgen Deprivation Therapy in Men with Prostate Cancer: How Real a Problem?

No Relevant Disclosures

Selected Series Addressing Risk of Cardiovascular Disease with Androgen Deprivation therapy

<table>
<thead>
<tr>
<th>Au. (yr)</th>
<th>Study design</th>
<th>Conclusions</th>
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<tbody>
<tr>
<td>Smith (2001)</td>
<td>Studied effects of ADT for 3 &amp; 6 mo., assessing arterial stiffness, body composition &amp; metabolism.</td>
<td>Partially reversible duration dependent arterial stiffening, increased insulin but no changes in lipids or glucose noted.</td>
</tr>
<tr>
<td>Keating (2006)</td>
<td>SEER data including 73,000 men with “locoregional disease” diagnosed 1992 thru 1999 followed thru 2001.</td>
<td>Use of ADT for 5-12 months or more associated with increased risk of sudden death but ADT not associated with increased MIs.</td>
</tr>
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<td>Keating (2008)</td>
<td>Pop-based cohort of men aged &lt;6 yrs with metastatic prostate ca. 1992-2002 followed to 2003. ADT early (&lt;4 mos. from Dx), delayed (&gt;4 mos.), or not at all.</td>
<td>Receipt of ADT was associated with improved survival (adjusted hazard ratio 0.69, 95% confidence interval 0.66-0.73). The benefit of early treatment did not differ from delayed treatment (P = 0.58).</td>
</tr>
</tbody>
</table>
The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. J.C. Smith 

Central Arterial waveforms at baseline and after ADT in 55 year old subject

Comparison of two groups. Group A, 3 mo LHRH; Group B continued LHRH (p<0.05)

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<td>D'Amico (2007)</td>
<td>Evaluated fatal MIs &amp; ADT in men enrolled onto 3 trials randomly assigned to EBRT with 0 vs 3 vs 6, 3 vs 8, or 0 vs 6 mo of ADT.</td>
<td>Men age &gt;65 yrs who received 6 mos of ADT experienced shorter times to fatal MIs (P = .017). No significant diff. (P = .97) 6 to 8 mos compared with 3 mos of ADT. D’Amico Concluded duration not important</td>
</tr>
<tr>
<td>Tsai (2007)</td>
<td>Captured database treated with prostatectomy, EBRT, brachy, or cryotheray for prostate ca.</td>
<td>ADT assoc. with increased risks of cardiac death in pts treated with prostatectomy. Among pts treated with EBRT, brachy, or cryo, no sign increase in cardiac events.</td>
</tr>
<tr>
<td>Efstathiou (2007)</td>
<td>RTOG 8531 (n=945)</td>
<td>No significant increase in risk of cardiovascular mortality</td>
</tr>
<tr>
<td>Roach (2008)</td>
<td>RTOG 8610 (n=456)</td>
<td>No significant increase in risk of fatal cardiac events</td>
</tr>
<tr>
<td>Efstathiou (2008)</td>
<td>RTOG 9202 (n=1554)</td>
<td>Longer ADT does not appear to increase the risk of cardiac mortality.</td>
</tr>
</tbody>
</table>

Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions.

D'Amico et al. JCO 25:2420-5, 2007

Regarding the influence of adjuvant suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarction: how real is the risk? Roach JCO 25:5325-6, 2007
Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610 Roach et al. JCO 26: 585-912008
Truth

“You can observe a lot just by watchin’”

Yogi Berra