A new Kind of Ray: The last 100 Years

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IMRT Fellowship, MDACC
A Brief History of Radiation

• Wilhelm Roentgen discovered X-rays on November 8, 1895, while experimenting with a gas-filled cathode tube
  - He noted an image of the bones of his hand projected on a screen when placed between the tube and the fluorescent screen
  - He wrote a carefully reasoned explanation of the phenomenon within two months

Early radiograph taken by Roentgen, January, 1896.
Brief History of Radiation Therapy

• The first patient was treated with radiation in 1896, two months after the discovery of the X-ray.
• Back then, both doctors and non-physicians treated cancer patients with radiation.
• Rapid technology advances began in the early 1950s with cobalt units followed by linear accelerators a few years later.
• Recent technology advances have made radiation more effective and precise.
Prostate Cancer
Case presentation/ Prostate

- 60 yom with organ confined CAP T1c stage II, PSA - 10, gl 3+3 involving 1/6 cores
Questions

• The first debate RP vs RT for this low risk group pt

• The second debate Dose escalation with 3D RT for this pt

• 3D vs IMRT
Paulson et al 1982/ 1st debate

97 pts T1/T2 N0 CAP randomized to RP vs EBRT.
  - balanced group of 4 pts to either RP or RT.

• 41 pts under went RP.
  - either perineal or suprapubic route.

• 56 pts received EBRT
  - RT given to large pelvis 45-50 Gy, to prostate boost 20 GY, total dose 65-70 Gy.

• Treatment failure – elevation of acid phosphatase x2, DM to bones/parenchyma.

• End point – time to first evidence of treatment failure.
Concl:
• Prostatectomy better than EBRT.

Flaws:
• Peculiar randomization.
• Differences in clinical stages.
• Analysis as treatment given.
• Local control not mentioned.
• Study inconclusive.

D’Amico et al 1998

• Between 1989 and 1997
  – 1872 pts with localized CAP stage T1c-T2b, retrospectively analyzed
  – **RP vs ERRT vs implant**

• Pts were stratified into risk groups
  – **low risk**: T1c or T2a and PSA ≤ 10 and gl ≤ 6
  – **intermediate risk**: T2b or PSA > 10 and ≤ 20 or gl 7
  – **high risk**: T2c or PSA > 20 or gl > 8.

• 1992 AJCC Staging – H&P, PSA, CT/MRI, BS, TRUS guided needle bx
  – Radiologic/bx info not used to determine clinical stage
D’Amico et al 1998

- Surgical treatment
  - RP and bilat pelvic LN sampling.

- EBRT was given with at least 10 MV and conformal 4 fld tech to 66-67 Gy

- Implant was given by Pd-103, with a peripheral loading tech to 115 Gy MPD.

- Pts in each risk groups were analyzed for time to PSA failure as a function of treatment they received.
D’Amico et al 1998

- Low risk pts no significant diff in outcome across all tx modalities, **RP, EBRT, Implant**
- Inter risk pts did significantly worse if managed by implant alone
- High risk pts did significantly better txed using RP or EBRT

<table>
<thead>
<tr>
<th>[relative to RP]</th>
<th>low risk</th>
<th>inte risk</th>
<th>high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RR</strong></td>
<td>bFS (%)</td>
<td>RR</td>
<td>bFS (%)</td>
</tr>
<tr>
<td>EBRT</td>
<td>1.1</td>
<td>85</td>
<td>0.8</td>
</tr>
<tr>
<td>Implant</td>
<td>1.1</td>
<td>85</td>
<td>3.1</td>
</tr>
<tr>
<td>HTx+Implant</td>
<td>0.5</td>
<td>85</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Conclusions/ 1st debate

• Data presented indicated that all available treatment modalities may be acceptable for low risk CAP pts for PSA free survival

• However, it is possible that significant difference in QOL may exist between the treatment modalities
Pollack et al 2002/ 3DCRT 2nd debate

• 304 pts with CAP T1-3Nx/N0 randomized to
  > RT dose 70 Gy vs 78 Gy.
• Median pretreatment PSA was 7.8 ng/ml, failure was defined as ASTRO consensus panel.
• RT given initially 4 flds to 46 Gy then 6 flds 3D CRT to boost, dose specified to isocenter
• No pts received neoad/adj androgen ablation
• Primary end point FFF, secondary end point DM, OS.
Pollack et al 2002/ 3DCRT

- FFF/OS results at 6 yrs

<table>
<thead>
<tr>
<th>Doses</th>
<th>PSA &lt; 10 (%)</th>
<th>PSA &gt; 10 (%)</th>
<th>all pt (%)</th>
<th>OS all (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 Gy</td>
<td>75</td>
<td>43</td>
<td>64</td>
<td>87</td>
</tr>
<tr>
<td>78 Gy</td>
<td>75</td>
<td>62</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>p value</td>
<td>ns</td>
<td>0.01</td>
<td>0.03</td>
<td>0.67</td>
</tr>
</tbody>
</table>
Pollack et al 2002/ 3DCRT

- Late toxicity results at 6 yrs

<table>
<thead>
<tr>
<th>Doses</th>
<th>Rectal gr ≥ 2 (%)</th>
<th>Bladder gr ≥ 2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 Gy</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>78 Gy</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>p value</td>
<td>0.001</td>
<td>ns</td>
</tr>
</tbody>
</table>
Pollack et al 2002/ 3DCRT

- Gr 2 or higher late rectal complications
- Toxicity related to Volume of rectum

Conclusion
- Dose escalation 8 Gy improved FFF for prostate pts
- However, higher dose increased rectal toxicity

IMRT is a new technology in RT that delivers radiation precisely to the tumor while relatively sparing the surrounding normal tissues.

Combines two advance concepts to deliver 3D conformal radiation
- inverse treatment planning with computer optimization
- computer controlled intensity modulation of the radiation beam

Potential advantages
- to create multiple targets
- multiple critical avoidance
- new accelerated fractionation scheme
Zelefsky et al 2002/ IMRT

- 1996-2001, 772 pts with clinically localized CAP txed IMRT.

- T1-2, PSA ≤ 10, gl ≤ 6
  - favorable - 3 present
  - intermediate - 2 present
  - unfavorable - 0-1 present

- RTOG scale to grade toxicity.

- Isocentric 5 flds, inverse plan, 15 MV, 81-86 Gy to PTV.
Zelefsky et al 2002/ IMRT

- Results: actuarial PSA free survival
- Median f/u 24 m (6 - 60 m)

<table>
<thead>
<tr>
<th>Risk</th>
<th>3D CRT (64.8-70.2 Gy)</th>
<th>3DCRT (75.6-86.4 Gy)</th>
<th>IMRT (81-86.4 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>group</td>
<td>at 5 yrs (%)</td>
<td>at 5 yrs (%)</td>
<td>at 3 yrs (%)</td>
</tr>
<tr>
<td>fav</td>
<td>77</td>
<td>90</td>
<td>92</td>
</tr>
<tr>
<td>int</td>
<td>50</td>
<td>70</td>
<td>86</td>
</tr>
<tr>
<td>unfav</td>
<td>21</td>
<td>47</td>
<td>81</td>
</tr>
</tbody>
</table>
Zelefsky et al 2002/ IMRT

- Results: acute and late toxicity
- Median f/u 24 m (6 - 60 m)

<table>
<thead>
<tr>
<th>Tox grade</th>
<th>acute</th>
<th>late</th>
<th>acute</th>
<th>late</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>GI (%)</td>
<td>74</td>
<td>GI (%)</td>
<td>89</td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>9</td>
<td>38</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>1.5</td>
<td>28</td>
<td>9.5</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Figure 2. Actuarial incidence of grade 2 and higher late rectal toxicity according to dose and mode of treatment delivery.
Zelefsky et al 2002/ IMRT

- **Conclusions:**
  - Short term bFS of pts treated with IMRT is comparable with 3D CRT at similar dose level
  - IMRT reduced acute and late rectal toxicity significantly compared with 3D CRT
  - Report confirms the safety of high dose IMRT in a large number of CAP pts
Case Presentation/ Prostate Tx

• After careful consideration all his options including RP and RT, the pt decided to proceed with RT

• He received RT to Prostate + SV to 55.8 Gy, followed by a boost dose to a final dose to 75.6 Gy, utilizing IMRT technique
Case Presentation/ Prostate Tx
Case Presentation/ Prostate Tx
Ongoing Clinical Trial

- Most reports indicate that the alpha-beta ratio is between 1 and 3. If this hypothesis is in fact true, then hypofractionated regimens (less frequent, larger fractions) may be more efficacious and less costly.

- To date the preliminary results from two randomized trials examining fractionation schedules for prostate cancer have been published.


Ongoing Clinical Trial

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0415

A PHASE III RANDOMIZED STUDY OF HYPOFRACTIONATED 3D-CRT/IMRT VERSUS CONVENTIONALLY FRACTIONATED 3D-CRT/IMRT IN PATIENTS WITH FAVORABLE-RISK PROSTATE CANCER
RTOG protocol/QD IMRT over 5 weeks

- Low risk Prostate Cancer pt. receiving IMRT randomized between 8 ½ weeks vs 5 ½ weeks

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>Arm 1 (Minimum PTV prescription)</th>
<th>Arm 2 (Minimum PTV prescription)</th>
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<tbody>
<tr>
<td>1. Gleason 2-4</td>
<td>3D-CRT or IMRT: 73.8 Gy in 41 fractions</td>
<td>3D-CRT or IMRT: 70 Gy in 28 fractions</td>
</tr>
<tr>
<td>2. Gleason 5-6</td>
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<table>
<thead>
<tr>
<th>PSA</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>1. &lt; 4 ng/mL</td>
<td></td>
</tr>
<tr>
<td>2. 4- &lt; 10 ng/mL</td>
<td></td>
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<table>
<thead>
<tr>
<th>Radiation Modality</th>
</tr>
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<tbody>
<tr>
<td>1. 3D-CRT</td>
</tr>
<tr>
<td>2. IMRT</td>
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</table>
Cancer death rates 1930-2003


*Age-adjusted to the 2000 US standard population.
Conclusions/ Prostate

- All available treatment modalities such as RP, EBRT, or Implant may be acceptable for low risk CAP pts
- RT dose escalation with IMRT improves bFS in prostate cancer pts
Conclusions/ Prostate

• IMRT reduced GI toxicity in prostate cancer pts

• Phase III clinical trial underway to determine
  - whether hypofractionated IMRT provides equivalent local tumor control compared to conventional RT in the local management of low risk Prostate cancer.
  - We are now enrolling patients with low risk Prostate cancer in local clinical trial at the local hospital in Panama City, FL.
Conclusions

- IMRT is the latest radiation technique
- X-rays have come a long way in last 100 yrs, now actively contributing to cure of cancers
The End

Thanks

• Dr. Buchholz, MD Anderson Can Cnt
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