Conformal Radiation Therapy of Prostate Cancer—What Can We Learn from the IMRT Experience?

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Why study IMRT?

- Large numbers of patients treated to date.
- Reasonably long follow-up.
- Dosimetry in high-dose area is “closer” to protons than with older techniques (2-D) or dissimilar techniques (brachytherapy), i.e., it is the closest, easily available analog we currently have to conformal proton beam radiotherapy.
Why study IMRT?

- When initiating proton beam treatment at a new facility with limited proton beam experience, IMRT-based data (and treatment planning, in terms of dose-constraints) provides the closest analog to planning and treating with protons.
Difficulties in extrapolating from IMRT to PBT

- IMRT is not monolithic! Numerous different techniques (static vs. dynamic, Tomotherapy), differing ways of prescribing dose (isocenter, CTV, PTV).
- Morbidity reporting is typically physician, not patient derived (also a problem for PBT).
- Effects of treating large volumes of tissue to low to moderate doses are poorly understood (obviously this is not an issue for PBT).
IMRT vs. Protons

- Not much of a contest! Particularly in terms of integral dose (we will always win!). But…
- Conceptually, treatment planning is identical for both modalities (i.e., maximal dose to target, minimal dose elsewhere)
- The rapid development and implementation of IMRT=lots of published data on toxicity, disease response, novel treatment approaches.
Where can we find Long-Term Data on IMRT Treatment in Prostate Cancer?

- Toxicity (both acute and late).
- Dose Escalation
- Hypofractionation.
IMRT as a “Data Mine” (and vice versa)

- IMRT of prostate cancer has concentrated on same areas as PBT-since RBE of protons and x-rays is similar, data from IMRT should be directly translatable to PBT.

- Conversely, conformal PBT dose-escalation data (PROG 9509) is being quoted extensively in the IMRT literature and used to justify dose-escalation.
Still, an x-ray does not a proton make…
Multifield
Conformal Proton Beam Dose Distribution
IMRT and Dose-Escalation

- Review of Non-Randomized (MSKCC) and Randomized (UTMDAH) Data.
- Review of IMRT Hypofractionation data.
- Review of IMRT-Intra-Prostatic Boosting.
Prospective Randomized Trial of dose-escalation.

1993-1998, 301 patients, Stages T1-T3, randomized between 70 Gy (150) and 78 Gy (151)

Median F/U 60 Months, Biochemical failure per ASTRO definition.
IMRT and Dose-Escalation - Randomized Data-UTMDAH

- Overall, Freedom From Failure (FFF) favored 78 Gy arm-70% vs. 60% at 6 years, p=0.03.

- Dose-escalation preferentially benefited those with pre-treatment PSA > 10 ng/ml-FFF 68% for 78 Gy vs. 43% 70 Gy, p=0.01.

- No dose-response benefit found for patients with pre-treatment PSA < 10 ng/ml. (Different from what was seen in PROG 9509).
Although no difference in overall survival seen, freedom from distant mets rate was higher for those with PSA levels > 10 who received 78 Gy (98 vs. 88% @ 6 years, p=0.056).

GI (Rectal) side effects greater in 78 Gy arm (26 vs. 12% ≥ Grade 2, p=0.001).

GU (Bladder) side effects similar between arms.

Rectal side effects correlated highly with proportion of rectum receiving > 70 Gy (more on this later).
IMRT and Dose-Escalation-Randomized Data-UTMDAH

Conclusions

1. Increasing dose from 70-78 Gy resulted in a highly significant improvement in Freedom From Failure for patients in intermediate and high risk groups.

2. Rectal toxicity was increased in the high-dose arm.
<table>
<thead>
<tr>
<th>Photons</th>
<th>Protons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose?</strong></td>
<td><strong>Int-high risk only</strong></td>
</tr>
<tr>
<td><strong>Toxicity?</strong></td>
<td><strong>Inc. GI toxicity</strong></td>
</tr>
<tr>
<td></td>
<td><strong>in high-dose arm</strong></td>
</tr>
<tr>
<td></td>
<td><strong>(&gt; Gr2)</strong></td>
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</table>
MDAH vs. PROG-Late Morbidity-Hi-Dose Arm

- Grade 2

<table>
<thead>
<tr>
<th></th>
<th>MDAH</th>
<th>PROG</th>
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<tbody>
<tr>
<td>GI</td>
<td>26% (8 Gr3)</td>
<td>18% (1 Gr3)</td>
</tr>
<tr>
<td>GU</td>
<td>13%</td>
<td>21%</td>
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</table>

- At MDAH, volume of rectum receiving > 70 Gy correlated with risk of GI morbidity-8/9 Gr 3 reactions in patients in whom rectal volume treated to ≥ 70 Gy was > 25%.
MDAH-Effect of dose on Metastasis-Free Survival

Fig. 3. Kaplan–Meier freedom from distant metastasis curves for patients with PSA > 10 ng/mL, by dose randomization (70 Gy vs. 78 Gy).
IMRT Dose-Escalation-Non-Randomized Data.

- Since few randomized studies have been performed in prostate cancer (or, for that matter, most other adult cancers), we are forced to rely heavily on retrospective data.
- Numerous retrospective series to choose from (including Patterns Of Care) = fertile ground for meta-analysis.
Meta-Analysis-
“A Systematic Overview of Radiation Therapy Effects in Prostate Cancer”

- Nilsson et. al., Karolinska Institute.
- Reviewed 295 Trials, studies included 152,614 patients.
- Broad Overview = Broad Conclusions.
Meta-Analysis-Conclusions

- Dose-Escalation can be performed safely using a variety of techniques (IMRT, Protons, seeds., etc.)
- Evidence that dose-escalation is beneficial in some patients (study published prior to results of PROG 9509).
3-D CRT/IMRT Dose Escalation-
Single Institution Experience.

- Memorial Sloan-Kettering has reported the greatest volume of single-institution data on dose-escalation and its effects on biochemical disease-free survival, post-radiation positive biopsy rates.

- Techniques have evolved from 3-D CRT in the mid-late 1980’s to IMRT. This allows some comparison of the reduction in morbidity between the two techniques.
MSKCC

- Systematic Dose-Escalation-64.8 Gy (96), 70.2 Gy (266), 75.6 Gy (320), 81.0 Gy (61).
- Biochemical Failure as per the ASTRO criteria.
- Post-Radiation biopsies in some (not all!) patients (136/743).
MSKCC-Subgroups vs. Biochemical Failure

![Graph showing PSA relapse free survival over months for different subgroups with statistical significance (p<0.001)]
MSKCC Subgroups vs. PROG

- **Graphs**
  - **PSA Relapse Free Survival**
    - Favorable (167)
    - Intermediate (269)
    - Unfavorable (307)
  - **Proportion Free From Biochemical Failure**
  - **Time From Randomization, y**
    - No. at Risk
      - High Dose: 116 116 114 111 105 69 29 14
      - Conventional Dose: 111 110 99 92 90 58 23 8
    - Low Risk
    - High Dose
    - Conventional Dose

- **Statistical Significance**
  - Gra’s test, P<0.001
MSKCC vs. PROG-Favorable Risk Only

MSKCC Data is confirmatory of dose-response effect seen in PROG 9509

C. Rossi-LLUMC   PTCOG 46
MSKCC-Effect of dose on positive biopsy rate

Table 5. Effect of dose on local control in 105 prostate cancer patients assessed by biopsies performed at ≥2.5 years after 3D-CRT*

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Negative</th>
<th>Treatment effect</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>66.6</td>
<td>7/23 (30%)</td>
<td>3/23 (13%)</td>
<td>13/23 (57%)</td>
</tr>
<tr>
<td>70.2</td>
<td>17/42 (41%)</td>
<td>6/42 (14%)</td>
<td>19/42 (45%)</td>
</tr>
<tr>
<td>75.6</td>
<td>8/25 (32%)</td>
<td>5/25 (20%)</td>
<td>12/25 (48%)</td>
</tr>
<tr>
<td>81.0</td>
<td>8/15 (53%)</td>
<td>6/15 (40%)</td>
<td>1/15 (7%)</td>
</tr>
</tbody>
</table>

* Patients included did not receive neoadjuvant androgen deprivation therapy.

† 75.6 Gy vs. 81 Gy, p = 0.005.

Biopsy Data, although limited, supports benefit of dose-escalation.
MSKCC-Update-IMRT

- All received 81 Gy.
- Biochemical relapse defined by both the ASTRO and Houston definitions (absolute nadir plus 2 ng/ml dated at the call).
- Morbidity as per RTOG Criteria.
Patients treated prone.

PTV=CTV (prostate) plus 1 cm, except 6mm along posterior border.

5-field IMRT technique, 15 MeV.

81 Gy Rx to PTV, in general < 5% of PTV received < 81 Gy.

ADT in 177 patients (vs. none in PROG).
Rectal Wall Volume exceeding 75.6 Gy limited to 30% (PROG constraint was no more than 30% of anterior wall could receive 79 CGE).

Similar constraints applied to bladder (PROG Bladder constraint was similar to PROG rectal constraint.).
MSKCC Update-bNED Survival vs. Risk Group
Why the difference in bNED survival despite similar doses?

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MSKCC Update-Morbidity

FIG. 2. Actuarial likelihood of late grade 2 or greater rectal toxicities and late grade 2 or greater urinary toxicities.
MSKCC vs. PROG-Late Toxicity

- ≥ Grade 2-5 year actuarial

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<th>PROG</th>
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<td>1.6%</td>
<td>18%</td>
</tr>
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<td>GU</td>
<td>12%</td>
<td>21%</td>
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Why difference in GI Toxicity?

1. Different definitions? Perhaps……
2. Reduced dose to anterior wall in MSKCC patients? Probably, but…
3. bNED Survival is poorer in MSKCC than PROG-could this be due to Geographic Miss courtesy of tighter rectal margins (0.6 cm vs. 1.2 cm)?
Non-Randomized and Randomized data support dose-escalation as a means of improving bNED survival. This is confirmatory of PROG data.

GI Morbidity is lower in some IMRT series than PROG, but so is bNED survival-this may be due to geographic miss incurred by very tight IMRT margins.

We still have not reached the Maximally Tolerated Dose (CJR’s opinion)=room for further dose-escalation.
Exploit difference in alpha/beta ratio between prostate cancer cells (1.5-3.0) and adjacent normal rectum.

Decrease treatment time.

Increase patient throughput.
IMRT-Based Hypofractionation—Kupelian et al.

- 100 patients, treated consecutively to 70 Gy @ 2.5 Gy/Fraction. Assuming a/b of 3.0, this is equivalent to 81 Gy @ 1.8 Gy/fx.
- 5-field IMRT technique, daily BAT localization.
- Median age 68 years, median PSA 8.1.
- Gleason ≤6 in 58%, ≥8 7%.
- 51% received neoadjuvant or adjuvant ADT.
- Patients compared to 310 consecutive patients treated 1995-2003 with 3-D CRT to 78 Gy/2 Gy fx.
IMRT-Based Hypofractionation - Kupelian et al.

bNED Survival as per ASTRO definition.
Hypofractionation vs. PROG-Low Risk

![Graph showing survival rates over time for different risk groups and dose levels.]

- **Low Risk**
- **Intermediate Risk**
- **High Risk**

<table>
<thead>
<tr>
<th>Time From Randomization, y</th>
<th>High Dose</th>
<th>Conventional Dose</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>116</td>
<td>111</td>
</tr>
<tr>
<td>1</td>
<td>116</td>
<td>110</td>
</tr>
<tr>
<td>2</td>
<td>114</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>111</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>105</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>69</td>
<td>58</td>
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<td>6</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>8</td>
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Gray's test P<0.001
Hypofractionation vs. PROG-
Intermediate to High Risk

(a)

Proportion-Free From Biochemical Failure

<table>
<thead>
<tr>
<th>Time From Randomization, y</th>
<th>High Dose</th>
<th>Conventional Dose</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>76</td>
<td>86</td>
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<tr>
<td>1</td>
<td>74</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>17</td>
</tr>
<tr>
<td>7</td>
<td>17</td>
<td>7</td>
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</table>

Gray's test $P=0.106$
Fig. 1. Biochemical relapse-free survival for all 100 patients treated with high-dose hypofractionated radiotherapy. Both biochemical failure definitions were used. Symbols represent censored patients.

Fig. 3. Biochemical relapse-free survival (ASTRO definition) for the 310 patients treated with three-dimensional conformal radiotherapy with the conventional schedule of 78 Gy at 2 Gy per fraction (median follow-up of 71 months). The outcomes are displayed by low-, intermediate-, and high-risk groups. Symbols represent censored patients.
Hypofractionated IMRT-Late Rectal Toxicity
All GR 2-3 = 11% at 5 years, Persistent GR 2-3 = 5% at 5 years

Fig. 4. Late rectal toxicity rates (RTOG Grades 2 and 3). (a) The Grade 3 only vs. the combined Grades 2 and 3 late rectal toxicity events. (b) All Grades 2 and 3 late rectal toxicity events vs. the Grade 2 or 3 events that were still persistent at last follow-up (i.e., 5% were still actually experiencing Grade 2 or 3 toxicity). Symbols represent censored patients.
Hypofractionated IMRT-Late Rectal Toxicity- Multivariate Analysis

Table 1. Multivariate analysis (Cox proportional hazards regression) of confounding factors affecting Grade 2 or 3 late rectal toxicity

<table>
<thead>
<tr>
<th>Factors</th>
<th>Chi-square</th>
<th>p value</th>
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<tbody>
<tr>
<td>Age (continuous variable)</td>
<td>4.29</td>
<td>0.038</td>
</tr>
<tr>
<td>Use of androgen deprivation (no vs. yes)</td>
<td>0.82</td>
<td>0.37</td>
</tr>
<tr>
<td>Coverage of seminal vesicles (no vs. yes)</td>
<td>0.18</td>
<td>0.67</td>
</tr>
<tr>
<td>Total rectal volume (continuous variable)</td>
<td>0.51</td>
<td>0.47</td>
</tr>
<tr>
<td>Percent rectal volume at 50 Gy (%) (continuous variable)</td>
<td>0.31</td>
<td>0.58</td>
</tr>
<tr>
<td>Percent rectal volume at 60 Gy (%) (continuous variable)</td>
<td>1.56</td>
<td>0.21</td>
</tr>
<tr>
<td>Percent rectal volume at 70 Gy (%) (continuous variable)</td>
<td>2.92</td>
<td>0.09</td>
</tr>
<tr>
<td>Actual rectal volume at 50 Gy (mL) (continuous variable)</td>
<td>0.13</td>
<td>0.72</td>
</tr>
<tr>
<td>Actual rectal volume at 60 Gy (mL) (continuous variable)</td>
<td>2.65</td>
<td>0.10</td>
</tr>
<tr>
<td>Actual rectal volume at 70 Gy (mL) (continuous variable)</td>
<td>4.79</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Absolute rectal volume (< vs > 10 cm3) was the only modifiable significant variable
Hypofractionated IMRT-Late Rectal Toxicity

Fig. 5. Late rectal toxicity rates (RTOG Grades 2 and 3) by the rectal volume receiving 70 Gy (Vr70) with a 10-mL cutoff. Symbols represent censored patients.

Limiting volume of rectum receiving 70 Gy to < 10 cc resulted in a 50% reduction in late GR 2-3 Toxicity
Hypofractionated IMRT - Conclusions

1. Treatment well tolerated.
2. 5-year bNED survival rates appear to be equivalent to standard fractionation (delivered both with IMRT and conformal PBT).
3. Rectal toxicity is a function of absolute rectal volume included in the high-dose area.
Hypofractionated IMRT-
Implications for PBT

1. If they can do it, we can do it! With our integral dose advantage, and identical RBE, if hypofractionation is feasible and effective in IMRT, at the very least we should be able to generate identical results.
IMRT and Intra-Prostatic Boosting

- Majority of post-radiation failures originate at the original tumor location.
- Dose-Escalation reduces local relapse rates, but also increases volume of normal tissue treated if boost volume is the entire prostate gland.
- MRI-MRS can be used to define dominant intra-prostatic lesion as target for boosting.
IMRT and Intra-Prostatic Boosting-Fesability

- De Meerleer et al (Ghent)-15 patients treated, all had palpable mass on DRE and/or PSA > 10.0.
- T2 weighted MRI of prostate to define dominant intraprostatic lesion (GTV MRI).
- Plans prepared with and without inclusion of GTVMRI into plan optimization. All patients treated using IMRT-GTVMRI plan.
IMRT and Intra-Prostatic Boosting-Fesability-
Normal prostate appearance on MRI

Fig. 1. Zonal anatomy of the prostate on transverse T2-weighted MR-image: high signal-intensity peripheral zone (PZ) and low signal-intensity central gland (CG). EC, endorectal coil.
Fig. 2. Transverse T2 weighted MR image showing the peripheral zone of the prostate, interrupted by a dark mass (red arrow). This mass is defined as the GTV$_{MRI}$. 
Intra-Prostatic Boosting-Results

- All patients treated to IMRT to dose of 78 Gy.
- No acute Grade 3 toxicities.
- One patient with acute Grade 3 GU toxicity.
- Including GTVmri into IMRT optimization resulted in a modest increase in prostate dose without compromising dose to CTV, PTV, and organs at risk.
Intra-Prostatic Boosting-Dosimetry

A. GTV_{mri} vs. Dose in Gray

B. CTV vs. Dose in Gray

C. Rectum vs. Dose in Gray
What can we learn from the IMRT Experience?-Conclusions

IMRT Data is both complimentary and confirmatory:

- Confirms importance of dose-escalation (validates PROG 9509, and vice versa).
- Confirms ability of highly conformal treatment to reduce normal organ toxicity to acceptable levels.
- Demonstrates potential advantages of treatment regimens particularly suited to protons (hypofractionation, intra-prostacic boosting)
Conclusions

- IMRT use is expanding far more rapidly (at present) than PBT, so we are going to have an increasing volume of data to “mine” in this area...