The LQ Formulation – from Model to Practice in Prostate Cancer

Mark Ritter MD, PhD
University of Wisconsin - Madison

In Honor of Jack Fowler

Radiobiological provocateur, innovator and teacher extraordinaire
Models for fractionation and time

D = (NSD)(T^0.11)(N^0.24)

Tumor control dose


Early vs Late
Overall Time

Jack’s influence on models for fractionation and overall time

HDR Brachytherapy
- GYN; Breast

Proliferation
Normal tissue vs tumor response

H & N HyperFx

Prostate HypoFx
UW GYN HDR Brachytherapy Program
- Past and present Faculty -

* JACK FOWLER
* DOLORES BUCHLER
* BRUCE THOMADSEN
* JUDY STITT
* DAN PETEREIT
* BHUDATT PALIWAL
* RUPAK DAS
* SCOTT TANNEHILL

The Clinical Application of LQ to Prostate Cancer

Mouse skin rx

Douglas & Fowler 1976

\[ E = \alpha D + \beta Dd \]

\[ 1/D = \alpha/E + (\beta/E) d \]

Clinical data

Thames, Withers
Peters, Fletcher: 1982
Barendsen, 1981

Prostate – Ext beam vs I-125

Duchesne, Peters, 1999
Brenner & Hall, 1999
Fowler, Chappell, Ritter, 2001

Dasu, 2007
Outline:

- Why hypofractionation for prostate cancer?
  - Can hypofractionation be employed to improve the therapeutic ratio?
- What clinical hypofractionation trials have been completed or are underway?
- What are the potential benefits and pitfalls of extreme, so-called SBRT or SABR hypofractionation?
- What SBRT treatments are currently underway?

Localized Prostate Cancer: Available Treatment Modalities

- Surveillance: (No Dose option)
- Radiotherapy: Brachytherapy: LDR / HDR
  - High dose EBRT (IMRT)
  - Hypofractionation (including SBRT)
- Surgery: Radical Retropubic
  - Laparoscopic / Robotic
- Cryosurgery
- HIFU
Dose Escalation - Rationale

- Conventional radiation therapy (66-70 Gy) fails to achieve local control in many higher risk patients.
- Local failure can lead to the development of distant metastases.
- Dose escalation improves tumor control but at the risk of higher complications.

Better treatment planning and delivery technology including image guidance

Dose escalation becomes feasible, but accomplished by increasing the number of radiation fractions, often to 40 or more.

Time, cost and resource intensive
Does prostate cancer have therapeutically exploitable radiobiology that might allow a more efficient treatment?

* Slow proliferation
  * low labeling indices and long potential doubling times (Haustermans et al., 1997)
  * long PSA doubling times often observed in new or failing patients

* A hypothesized low $\alpha/\beta$ ratio $\sim 1.5$ Gy
  * Implant versus external beam data
    [Duchene & Peters, 1999; Brenner and Hall, 1999; Fowler, Ritter, Chappell, 2003; others]
  * HDR implant data (Brenner and Martinez)
  * External beam monotherapy data from different fraction arms

At the time, this was contrary to the prevailing belief that hyperfractionation was a potentially generally applicable approach for improving therapeutic ratio.

Large fraction radiotherapy – “a dangerous and unsettling idea”:


Mechanistic basis for prostate prostate hypofractionation?

Many tumors have higher growth fractions than late responding normal tissues.

Tumors with lower growth fractions may have better interfraction repair.

Prostate tumors often contain unusually small growth fractions (Haustermans, Begg, Fowler, 1997): $T_{pot} > 20$ days

Rationale

High fraction-size sensitivity

Normal organs $\alpha/\beta = 3$

Tumor $< 3$

Hypofractionation

Tumor $> 3$

Hyperfractionation
Increasing Therapeutic Advantage with Increasing Hypofractionation

\[ \text{EQD}_2^2 = \frac{1 + \frac{d}{\alpha/\beta}}{1 + \frac{2}{\alpha/\beta}} \]

- \( n \) = \# fractions
- \( d \) = fraction size
- Prostate tumor \( \alpha/\beta = 1.5 \)
- Late tissue \( \alpha/\beta = 3 \)

Decrease normal tissue toxicity while maintaining constant tumor control.

- \( \alpha/\beta \) values:
  - Tumor: 1.5
  - Normal: 3.0
LQ and $\alpha/\beta$ Estimation Uncertainties

- $\alpha/\beta$ uncertainties: Large error bars
- Model uncertainties: Deviation from LQ at large fraction sizes... differing tumor cell kill mechanisms, tumor vasculature
- Impact of tumor grade, ADT, proliferation
- Consequential late effects secondary to excessively short schedules
- Fewer fractions = reduced reoxygenation and cell cycle redistribution.

Tumor EQD$_2$ versus Hypofractionation

What would happen if $\alpha/\beta$ were higher than currently suspected?
Does LQ remain valid at very large fraction sizes?

YES

NO

Less efficacy than predicted by LQ at large fraction sizes, approximated by a higher $\alpha/\beta$.

The LQ Model -- Good Enough?

The LQ is unlikely to be mechanistically correct, but is probably adequate for moderate hypofractionation and perhaps with some modifications, for extreme hypofractionation

- Similar predictions to other mechanistic cell killing models
  - saturable repair, repair-misrepair, lethal-potentially lethal models
- Good agreement with most in vitro and in vivo laboratory fractionation experiments
- Is reasonably well validated, experimentally and theoretically, up to about 4-5 Gy/fraction and may be good enough at higher fraction sizes
- No catastrophes to date when the LQ model has been applied prudently in the clinic, but need cautious steps and adequate follow-up.

Brenner, Semin Radiat Oncol 18:234-239 © 2008
Jack’s take:

“What’s a poor, confused prostate radiation oncologist to do? GO SIMPLE: Stay with LQ but perhaps adjust the alpha/beta upward as a compromise to best approximate both the low end and the high end of the fraction size spectrum.”

Hypofractionated regimens are short. Standard fractionation regimens are long.....

so, does clonogen proliferation have a role?

<table>
<thead>
<tr>
<th>Tumor</th>
<th>$D_{p}e_{q}^{\text{eq}}$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Various head and neck$^{21}$</td>
<td>0.8 (0.5,1.1)</td>
</tr>
<tr>
<td>Tonsil$^{24}$</td>
<td>0.73 (0.6,0.9)</td>
</tr>
<tr>
<td>Various$^{25}$</td>
<td>0.64 (0.42,0.86)</td>
</tr>
<tr>
<td>Nonsmall cell lung$^{26}$</td>
<td>0.45 (0.3,0.6)</td>
</tr>
<tr>
<td>Larynx$^{27}$</td>
<td>0.74 (0.3,1.2)</td>
</tr>
<tr>
<td>Medulloblastoma$^{28}$</td>
<td>0.52 (0.29,0.75)</td>
</tr>
<tr>
<td>Esophagus$^{29}$</td>
<td>0.59 (0.18,0.99)</td>
</tr>
</tbody>
</table>

6% increase in biochemical failures for a one week increase in duration of treatment

Thames et al. Radiotherapy and Oncology 96 (2010) 6–12
Proliferation

\[ E_{QD_2} = \frac{D(\alpha/\beta + d)}{(\alpha/\beta + 2)} - d_{\text{prolif}}(T - T_{\text{delay}}) \]

\[ \delta_{\text{prolif}} = 0.31 \pm 0.056 \text{ Gy/d (95% CI 0.20-0.42)}. \]


What is the value for $T_{\text{delay}}$?
- Thames: $T_{\text{delay}} \geq 7$ weeks
- DeAmbrosia: $T_{\text{delay}} = 30-35$ days.

Impact of modeling proliferation into alpha/beta estimates

\[
\begin{array}{c|c|c}
\text{Study} & \alpha/\beta & \text{95% CI} \\
\hline
\text{without prolif.} & 0.47 [-.55, 1.5] & \\
\text{with prolif} & 1.93 [-.27, 4.14] & \\
\end{array}
\]

* assuming $\delta_{\text{prolif}} = 0.31 \text{ Gy/d}$

Vogelius IR, Bentzen SM; 2013
Practical Time–Dose Evaluations, or How to Stop Worrying and Learn to Love Linear Quadratics

Jack F. Fowler

“This chapter is written mainly for those who say “I don’t understand this $\alpha/\beta$ business – I can’t be bothered with Linear Quadratic and that sort of stuff”. Well, it might seem boring--depending on your personality--but it is easy, and it makes so many things in radiation therapy wonderfully and delightfully clear.”

Technical Basis of Radiation Therapy: Practical Clinical Applications

10/31/89
Courtesy of Randy Jirtle, Duke University
Hypofractionation Trials: Schedules and Equivalent Doses

<table>
<thead>
<tr>
<th>REFERENCE</th>
<th>No. PTs</th>
<th>Dose/rx size/# rx</th>
<th>Total Equivalent Dose in 2 Gy fractions (EQD2)</th>
<th>Intermed. risk 2 Grade 2 Late Toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liversy et al 10 Manchester</td>
<td>705</td>
<td>50 Gy/3.15 Gy/16 fx</td>
<td>66 Gy 61.3 Gy 60 56 (5 yr) 5 9</td>
<td></td>
</tr>
<tr>
<td>Akimoto et al 13 Guma</td>
<td>152</td>
<td>69 Gy/2 Gy/23 fx</td>
<td>88.7 Gy 82.8 Gy 33 25 ---</td>
<td></td>
</tr>
<tr>
<td>Tsuji et al 14 Chiba</td>
<td>201</td>
<td>60 Gy/0.25 Gy/40 fx (carbon lens)</td>
<td>90.5 Gy 82.1 Gy 30 97 2 6</td>
<td></td>
</tr>
<tr>
<td>Higgins et al 15 Edinburgh</td>
<td>300</td>
<td>52.5 Gy/2.52 Gy/26 fx</td>
<td>61.9 Gy 59.1 Gy 12 55 --- 30</td>
<td></td>
</tr>
<tr>
<td>Sobie et al 17 Jette, Belgium</td>
<td>36</td>
<td>56 Gy/3.5 Gy/16</td>
<td>80 Gy 72.8 Gy 44 --- --- ---</td>
<td></td>
</tr>
<tr>
<td>Martin et al 18 Princess Margaret</td>
<td>92</td>
<td>60 Gy/5 Gy/20 fx</td>
<td>77.2 Gy 72 Gy 36 85 4 3</td>
<td></td>
</tr>
<tr>
<td>Kupelian et al 19 Cleveland Clinic</td>
<td>779</td>
<td>70 Gy/2.5 Gy/28 fx</td>
<td>80 Gy 77 Gy 45 85 4.5 5.3</td>
<td></td>
</tr>
<tr>
<td>Ritter et al 20 Wisconsin</td>
<td>160</td>
<td>54.7 Gy/3.94 Gy/12 fx</td>
<td>82.5 Gy 85.1 Gy 77 Gy 77 Gy 75 Gy 38 24 14</td>
<td></td>
</tr>
<tr>
<td>Lueke et al 21 NCIC</td>
<td>406</td>
<td>52.5 Gy/2.5 Gy/28 fx</td>
<td>61.5 Gy 59.1 Gy 66 Gy 66 Gy 66 40 1.3 1.9</td>
<td></td>
</tr>
<tr>
<td>Yeh et al 22 Adelaide</td>
<td>108</td>
<td>55 Gy/2.5 Gy/20 fx</td>
<td>66.8 Gy 63.2 Gy 64 Gy 64 Gy 64 Gy 48 57.4 55.5 Alternate scoring Alternate scoring</td>
<td></td>
</tr>
<tr>
<td>Petrich et al 23 Fox Chase</td>
<td>150</td>
<td>70.2 Gy/2.7 Gy/36 fx</td>
<td>84.2 Gy 76 Gy 70 Gy 70 Gy --- --- ---</td>
<td></td>
</tr>
<tr>
<td>PIDC [<a href="http://www.rscengineer.org/protocols/414/91481541">www.rscengineer.org/protocols/414/91481541</a>]</td>
<td>Ongoing on 1067 pts</td>
<td>70 Gy/2.5 Gy/28 fx 73.8 Gy/1.8 Gy/41 fx</td>
<td>80 Gy 69.6 Gy 77 Gy 70.8 Gy --- --- ---</td>
<td></td>
</tr>
<tr>
<td>CHIP - MRC</td>
<td>Ongoing on 2100 pts</td>
<td>57 Gy/2 Gy/19 fx 60 Gy/2 Gy/20 fx</td>
<td>73.3 Gy 77.2 Gy 68.4 Gy 72 Gy --- --- ---</td>
<td></td>
</tr>
</tbody>
</table>

A Phase I/II Trial of Increasingly Hypofractionated Radiation Therapy for Prostate Cancer

Investigators

Mark Ritter
Jack Fowler University of Wisconsin
Rick Chappell
Jeffrey Forman Wayne State University
Patrick Kupelian M.D. Anderson, Orlando
Daniel Peterit Rapid City, S. Dakota
Colleen Lawton Medical College of Wisconsin

Acknowledgements

Data management: Nick Anger, Wendy Walker, Heather Geye

NIH-R01CA106835; PO1 CA106835
A Five Institution, Phase I/II Hypofractionation Trial

347 patients
Median follow-ups of 80, 64 and 50 months

<table>
<thead>
<tr>
<th>Fract. Level</th>
<th># pts</th>
<th>Dose per Fx (Gy)</th>
<th># Fxs</th>
<th>Total dose (Gy)</th>
<th>Tumor EQD$_{2\alpha/\beta=1.5}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>101</td>
<td>2.94</td>
<td>22</td>
<td>64.68</td>
<td>82.6</td>
</tr>
<tr>
<td>II</td>
<td>111</td>
<td>3.63</td>
<td>16</td>
<td>58.08</td>
<td>85.1</td>
</tr>
<tr>
<td>III</td>
<td>135</td>
<td>4.3</td>
<td>12</td>
<td>51.6</td>
<td>85.5</td>
</tr>
</tbody>
</table>

Predicted late toxicities equivalent to 76Gy in 2 Gy fractions

Biochemical PFS vs Hypofractionation Level

<table>
<thead>
<tr>
<th>Hypofrac Level</th>
<th># pts</th>
<th>Median F/U</th>
<th>5-Yr % bPFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.94 x 22 Fxs</td>
<td>101</td>
<td>80 months</td>
<td>90.6±13.3</td>
</tr>
<tr>
<td>3.63 x 16 Fxs</td>
<td>111</td>
<td>64 months</td>
<td>92.6±2.7</td>
</tr>
<tr>
<td>4.3 x 12 Fxs</td>
<td>135</td>
<td>50 months</td>
<td>93.5±2.6</td>
</tr>
</tbody>
</table>

Log Rank (Mantel-Cox): p = 0.990

Quality of Life scores

RTOG 0938: Randomized phase II: 4.3 Gy x 12 versus 7.25 Gy x 5 fractions
As on pp 96 & 197, updated to 4-5y results

-50 = 2.1 Gy

TCD50 = 65.6 Gy

Prostate Ca - Intermediate risk: 10 - 19.9 ng/ml

MSK5y
FoxCh5y
MDA4..5y
Beaumont5y

LogitFit
%

bNED

Equiv total dose in 2 Gy fractions (\(\alpha/\beta = 1.5\) Gy)

\[ \alpha/\beta = 10 \quad 3 \quad 1.5 \]

\[ \alpha/\beta = 3 \quad 1.5 \]

NCIC (Lukka)
66 Gy/33 fx
52.5 Gy/20 fx

Christie
\[ \alpha/\beta = 33.5/6.7\] Gy/5 fx

PMH
60 Gy/3 Gy/20 fx

70 Gy/2.5 Gy/28 fx

Kupelian; UW

2 Gy per fraction curve

If one assumes an \(\alpha/\beta\) of 1.5, clinical outcomes match LQ predictions.

Hypofractionation

Low dose hypersensitivity

Linear Quadratic Radiobiology

Microvascular damage? Immune stimulation? Stromal damage?

Estimated dose per fraction (Gy)
Stereotactic Body Radiation Therapy

SBRT Considerations

- Immobilization
- Image guidance
  - Motion
    - Interfraction
    - Intrafraction
      - Imaging-to-treatment interval
  - Respiration
    - prone versus supine
    - body fix or respiratory gating

The New York Times

Popular Prostate Cancer Therapy Is Short, Intense and Unproven.

By GINA KOLATA  MARCH 20, 2017

Faster  5 treatments vs 40  ✓

Cheaper  $13,645 versus $21,023  (Medicare claims: Yu, 2014)  ✓
            $22,152 versus $35,431  (Hodges, 2012)

Better  ?
### Selected prostate SBRT trials with more than minimal follow-up

<table>
<thead>
<tr>
<th>Institution</th>
<th>Platform</th>
<th>Dose</th>
<th>Median FU years</th>
<th>Risk group</th>
<th>Pts</th>
<th>5-Year bDFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virginia Mason (71)</td>
<td>Gantry-based linac</td>
<td>6.7 Gy × 5</td>
<td>3.4</td>
<td>Low</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Stanford (73)</td>
<td>CyberKnife</td>
<td>7.25 Gy × 5</td>
<td>2.7</td>
<td>Low and low-intermediate</td>
<td>61</td>
<td>94</td>
</tr>
<tr>
<td>Stanford, Naples (75)</td>
<td>CyberKnife</td>
<td>7-7.25 Gy × 5</td>
<td>5</td>
<td>Low and low-intermediate</td>
<td>41</td>
<td>93</td>
</tr>
<tr>
<td>Winthrop Hospital (76)</td>
<td>CyberKnife</td>
<td>7-7.25 Gy × 5</td>
<td>6</td>
<td>Low</td>
<td>324</td>
<td>97</td>
</tr>
<tr>
<td>San Bortolo (80)</td>
<td>CyberKnife</td>
<td>7 Gy × 5</td>
<td>3</td>
<td>Low, intermediate, and high</td>
<td>153</td>
<td>91</td>
</tr>
<tr>
<td>Pooled eight institutions (74)</td>
<td>CyberKnife</td>
<td>38–40 Gy in 4–5 fs</td>
<td>3</td>
<td>Low, intermediate</td>
<td>841</td>
<td>95</td>
</tr>
<tr>
<td>Katz and Kang (51)</td>
<td>CyberKnife</td>
<td>7-7.25 Gy × 5</td>
<td>5</td>
<td>High</td>
<td>125</td>
<td>81</td>
</tr>
<tr>
<td>Multi-Institution (82)</td>
<td>CyberKnife</td>
<td>5 Gy × 5</td>
<td>3</td>
<td>Intermediate</td>
<td>137</td>
<td>97</td>
</tr>
<tr>
<td>Sunnybrook (77)</td>
<td>Gantry-based linac</td>
<td>7 Gy × 5</td>
<td>4.7</td>
<td>Low</td>
<td>84</td>
<td>97</td>
</tr>
<tr>
<td>Twenty-first century (77)</td>
<td>Gantry-based linac</td>
<td>8 Gy × 5</td>
<td>5</td>
<td>Low</td>
<td>98</td>
<td>99</td>
</tr>
</tbody>
</table>

Meier, Front. Oncol 2015

6 x 6 Gy 232 pts (1962 – 84). Olivier treated in 1967 (Similar to the 5 x 7.25 Gy regimen commoned today). EQD2: 77.25 Gy vs. 90.75 Gy


PACE trial (UK)
(1,700 patients)

<table>
<thead>
<tr>
<th>RANDOMIZED SBRT TRIALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBRT Arm</td>
</tr>
<tr>
<td>Widmark:</td>
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<tr>
<td></td>
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<tr>
<td>RTOG 0938:</td>
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<tr>
<td></td>
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<tr>
<td>U. Miami</td>
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</tbody>
</table>

A UW Phase I/II Trial of Stereotactic Body Radiotherapy (SBRT) for Prostate Cancer with a Simultaneous Integrated Boost to MRI-identified Intraprostatic Tumors (NCT02470897)

- Prostate MRI: Identify prostate borders, tumor(s), urethra
- Planning CT: target and normal organ contours on CT/MRI fusion

- 8 Gy for 5 fractions delivered every other week day
- IMRT/VMAT except to exclusion zone and MRI-identified intra-prostatic cancers
- Exclusion zone: urethra, adjacent bladder and rectal borders constrained to 3.25 Gy per fraction (or 8 Gy to any region overlapping with an MRI-detected tumor)
- Tumor SIB volume: MRI-identified, lesions simultaneously boosted up to 8 Gy per fx (8 Gy/Fx if overlapping exclusion zone)
Newer research directions in the management of prostate cancer

**Imaging**
- improved staging;
- ablation of oligometastases

**Immuno-radiation therapy**

Jack’s Legacy
- Profound and continuing impact on the field of Radiation Oncology and on countless research careers.
- A kind, generous and enthusiastic mentor to many, myself included.
- Contagious enthusiasm for research and for life.

May 2006