Radiobiological Effects of Hypofractionation:
Unique Aspects of Tumor Response to High Dose Per Fraction Radiotherapy—
SBRT as Ablative Therapy

Dr. Jimm Grimm, PhD
Holy Redeemer Hospital
with the support of 74 other physicians, physicists, and radiobiologists

Part 2 of 2
Conflict of Interest

- Dr. Grimm founded www.DiversiLabs.com and developed the DVH Evaluator (This conflict has been disclosed on the AAPM website since 2011)
WG SBRT

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Outline of Presentation

• Part 2
  – SBRT Lung TCP
    • A few hints about possible radiobiological explanations
  – NTCP for anatomical structures near Lung
  – SBRT Liver TCP
Learning Objectives

1. Common SBRT fractionation schemes and current evidence for efficacy
2. Evidence for normal tissue tolerances in hypofractionated treatments
3. Clinically relevant radiobiological effects at large fraction sizes
• WGSBRT is extensively reviewing all the SBRT literature
  – A bit too ambitious for one lecture at summer school
• Therefore, this presentation is just a sampling of the literature that we are reviewing
• We will consider a few key aspects here, but can’t be as comprehensive as the whole project
• We will see the need for improved reporting standards
This talk focuses primarily on these Physical Factors data where models have emerged for SBRT.
This talk focuses primarily on dose response models that have emerged for SBRT.
Conventionally Fractionated Lung TCP, Martel 1999

• University of Michigan Medical Center
• 76 patients, non-small cell lung cancer
  – includes all patients treated from 1986 to 1992 who have CT-based treatment plans that were evaluable for tumor dose information
• Daily fraction size of 1.8–2.0 Gy
• Isocenter doses ranging from 64 to 82 Gy (corrected)
Martel 1999
Logistic Model

\[
TCP = \frac{1}{1 + \left(\frac{D_{50}}{D}\right)^K}
\]

- \(D\) = isocenter dose
- \(D_{50}\) = isocenter dose needed to achieve a 50% probability of tumor control
- \(K = 4\gamma\) where \(\gamma\) = normalized slope at \(D_{50}\)
Reconstruction of Martel et al.'s data from the dose escalation study in non–small-cell lung cancer at the University of Michigan (17). The plot is against total dose in 2 Gy fractions, given 5F per week. Scales below those doses show overall time in days, biologically effective dose (BED) as given allowing for repopulation, and equivalent BED if no repopulation occurred. (Reprinted from Mehta M, Serringer R, Mackie R, et al., A new approach to dose escalation in non–small-cell lung cancer. Int J Radiat Oncol Biol Phys 2001;49:23–33, with permission of Elsevier Inc.).
In the Martel 1999 NSCLC article, what isocenter dose was required to achieve 50% progression free survival at 30 months:

- 4% 1. 60 Gy
- 7% 2. 74 Gy
- 87% 3. 84 Gy
- 2% 4. 94 Gy
- 0% 5. 156 Gy
In the Martel 1999 NSCLC article, what isocenter dose was required to achieve 50% progression free survival at 30 months:

• Correct answer:

• 3. 84 Gy

Even 74Gy is Challenging
RTOG 0617  74Gy Arm

Patient-Reported Quality of Life Outcomes Shed Light on Poor Survival in an RTOG Trial Evaluating Increased Radiotherapy Dose for Lung Cancer

Atlanta—Results of a quality of life (QOL) analysis presented today during a plenary session of the 2013 Annual Meeting of the American Society for Radiation Oncology (ASTRO) show that, at 3 months after the start of treatment, almost half of patients with stage III non-small cell lung cancer (NSCLC) who received a higher dose of radiotherapy (RT) with chemotherapy reported a clinically meaningful decline in QOL compared with less than a third of those who received a standard dose of radiation with chemotherapy.
BED_{10} \geq 100\text{Gy} 
Onishi 2007

- 257 Patients from 14 Institutions in Japan
- Stage I NSCLC
- A total dose of 18 to 75 Gy at the isocenter in 1 to 22 fractions

**TABLE 1. Patient Pretreatment Characteristics**

<table>
<thead>
<tr>
<th>Total cases: 257</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: 39–92 yr (median, 74)</td>
</tr>
<tr>
<td>Performance status: PS 0, 109; PS 1, 103; PS 2, 39; PS 3, 6</td>
</tr>
<tr>
<td>Pulmonary chronic disease: 168 positive, 89 negative</td>
</tr>
<tr>
<td>Histology: 111 squamous cell, 120 adenocarcinoma, 26 other</td>
</tr>
<tr>
<td>Stage: 164 IA, 93 IB</td>
</tr>
<tr>
<td>Tumor diameter: 7–58 mm (median, 28)</td>
</tr>
<tr>
<td>Medical operability: 158 inoperable, 99 operable</td>
</tr>
</tbody>
</table>
FIGURE 4. Overall survival rate in operable patients according to the biological effective dose (BED). OS, overall survival rate; CI, confidence interval.

SBRT Lung TCP
Guckenberger 2009

- 159 lesions in 124 patients
- 118 mets
- CTV and PTV margin dose instead of isocenter dose
- Still compared to the 100Gy BED\textsubscript{10} baseline
- Median followup 14 month
100Gy \text{BED}_{10}

- 100Gy is a round number that has been applied to both:
  - Isocenter dose
  - Margin dose

- Always check definitions!

Fig 2a, D95 BED$_{10}$ to 3D PTV

$D_{95} = 84.7$ Gy
BED$_{10}$ (LQ) 95% Control @14 months

Guckenberger 2009, IJROBP May; 74:47-54
Fig 2b, D95 BED$_{10}$ to 4D CTV

$D_{95} = 115.9$Gy
BED$_{10}$ (LQ)
95% Control @14 months

Guckenberger 2009, IJROBP
May; 74: 47-54
95% 14 Month Local Control

- 3D PTV: 84.7 Gy BED\textsubscript{10} = 38 Gy in 3 fractions
- 4D CTV: 115.9 Gy BED\textsubscript{10} = 46 Gy in 3 fractions

- CTV D95 is about 20% higher than PTV D95
- May want a bit higher dose for more durable LC
- Author conclusion: “Doses of $>100$ Gy BED to the CTV based on 4D dose calculation resulted in excellent local control rates for image guided SBRT of primary early-stage NSCLC and pulmonary metastases.”
Mehta 2012
Pooled Analysis

- Stage I NSCLC
- 2-year followup required
- Data from 42 studies
  - 2696 total cases
  - About 1000 conventional cases
  - About 1500 SBRT cases
- Prescriptions converted to isoBED using LQ and USC
  - Least Squares fitting of
  - Logistic Model for both

Table 3: Demographics, radiation therapy details, and tumor control

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>2696</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>73 (22-95)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>704 (26%)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>847 (31%)</td>
</tr>
<tr>
<td>NOS</td>
<td>1145 (42%)</td>
</tr>
<tr>
<td>T stage</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>1585 (56%)</td>
</tr>
<tr>
<td>T2</td>
<td>1128 (40%)</td>
</tr>
<tr>
<td>NOS</td>
<td>96 (3%)</td>
</tr>
<tr>
<td>Operable</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>421 (14%)</td>
</tr>
<tr>
<td>No</td>
<td>2531 (86%)</td>
</tr>
<tr>
<td>RT technique</td>
<td></td>
</tr>
<tr>
<td>3D-CRT</td>
<td>1046 (39%)</td>
</tr>
<tr>
<td>SBRT</td>
<td>1640 (61%)</td>
</tr>
<tr>
<td>Absolute dose range, Gy</td>
<td></td>
</tr>
<tr>
<td>3D-CRT</td>
<td>48-102.9 (1.2-4 Gy/fx)</td>
</tr>
<tr>
<td>SBRT</td>
<td>20-66 (4.4-26 Gy/fx)</td>
</tr>
<tr>
<td>No. of fractions, range</td>
<td></td>
</tr>
<tr>
<td>3D-CRT</td>
<td>12-49</td>
</tr>
<tr>
<td>SBRT</td>
<td>1-10</td>
</tr>
<tr>
<td>Median aBED, Gy</td>
<td>105.6</td>
</tr>
<tr>
<td>aBED range, Gy</td>
<td>59.6-286.6</td>
</tr>
</tbody>
</table>

3D-CRT, 3-dimensional conformal radiation therapy; aBED, average biological effective dose; NOS, not otherwise specified; RT, radiation therapy; SBRT, stereotactic body radiation therapy.
About 1000 conventional cases…
About 1500 SBRT cases…
Pooled 2500 cases...
Logistic Model, LQ, $\alpha/\beta=8.6\text{Gy}$…
$D_{iso} = 151.1\text{Gy}$
$BED_{8.6} (\text{USC})$
95% Control @2 years

$D_{iso} = 192.9\text{Gy}$
$BED_{8.6} (\text{LQ})$
95% Control @2 years
95% 2 Year Local Control

- USC: 151.1 Gy BED_{8.6} = 22.6Gy * 3 fractions
- LQ: 192.9 Gy BED_{8.6} = 19.6Gy * 3 fractions
≈ 20Gy * 3 fractions

Physical dose

According to the model in Mehta 2012, what prescription dose resulted in 95% local control at 2 years?

0%  1. 10Gy * 3 fractions
1%  2. 12Gy * 3 fractions
0%  3. 15Gy * 3 fractions
99% 4. 20Gy * 3 fractions
0%  5. 24Gy * 3 fractions
According to the model in Mehta 2012, what prescription dose resulted in 95% local control at 2 years?

• Correct answer

• 4. 20Gy * 3 fractions


• Caveats: dose calculation algorithm, isocenter versus margin dose, many other factors – see the next slide…
Many Other Factors May Affect Outcomes

- Patient age, gender, smoking, comorbidities
- Gating/tracking/immobilization/delivery system
- Dose calculation algorithm/heterogeneity correct
- D95%, min dose, max dose, isodose, margin
- GTV size, CTV/ITV/PTV size
- Duration of each treatment
- Surgery, Chemotherapy or other treatments
Which of the following factors may affect outcomes?

1. Patient gender
2. Tumor size
3. Operable/Inoperable
4. Dose calculation algorithm
5. All of the above

97% 5. All of the above
Which of the following factors may affect outcomes?

- Correct answer

- **5. All of the above**


Reporting Standards

- It is often hard to prove which factors are most significant because of lack of reported details
  - Dose per patient
  - PTV D95, GTV min dose, Isocenter dose, etc.
  - Explicitly state Endpoints
  - Supplemental electronic material can be used to share more detailed information
  - Too few events in each article – hard to combine them if the reporting isn’t clear or if definitions vary too much
Why are reporting standards important?

1. Small numbers of events in individual series (1%)
2. Facilitates later analysis of clinical outcome data (2%)
3. Gets everyone speaking the same language (1%)
4. Not important; just pass peer-review (1%)
5. 1, 2, and 3 are correct (96%)
Why are reporting standards important?

• Correct answer

• 5. 1, 2, and 3 are correct

WG SBRT Thoracic TCP Group

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- Timothy Solberg, PhD
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- Chang Song, PhD
- Ellen Yorke, PhD

- Analyzing all this data and more
- Comparing BED models
- Comparing dose response models
- Multivariate analysis to determine which factors significantly affect outcomes
Possible Radiobiological Explanations: Immunogenic Response

Possible Radiobiological Explanations: Vascular Damage

J. Denekamp, Acta Radiologica Oncol, 23, p217, 1984
C. Song, Rad Res, 177, p323, 2012
Single Endothelial Cell?

Figure 22-23  Capillaries

(A) Electron micrograph of a cross section of a small capillary in the pancreas. The wall is formed by a single endothelial cell surrounded by a basal lamina.
Thoracic NTCP

- Example: Rib Fractures / Chestwall Pain
Much Data Exists Regarding Rib / Chestwall Tolerance for SBRT


- ...
Much Data Exists Regarding Rib / Chestwall Tolerance for SBRT

- ...  
- Many more still coming...
Pettersson 2009

• One of the first articles published on the topic actually has enough data to get almost a complete set of dose tolerance limits

• Linac based SBRT
• Individual Ribs
Patient Characteristics

- 68 patients, inoperable, stage I, NSCLC
- 33 patients with complete treatment records and radiographic follow-up exceeding 15 months (median: 29 months)
- 13 fractures were found in 7 patients (of 81 ribs)
- Did not generally heal
- Most of the rib fractures radiographic only; not a great deal of pain
Pettersson 2009  G1-3 Rib Tolerance

Treatment Characteristics

- 45 Gy in 3 fractions
- $\alpha/\beta=3$ Gy, LQ model is “built into” logistic dose response model
- Elekta Body Frame
- Cadplan 6.4.7 or Eclipse 7.2.24, Varian
- Pencil beam convolution algorithm using the modified Batho method for inhomogeneity correction
Endpoint

- “most of the rib fractures were only detected radiographically”
- “some patients had a long lasting moderate pain with need for analgesics”

- Would be CTCAE Grade 1-2, or maybe 1-3
  - Mostly Grade 1

$D_{2cc} \leq 49.8\text{Gy}$
50% Risk G1-3

$D_{2cc} \leq 27.2\text{Gy}$
5% Risk G1-3
\[ D_{20\%} \leq 40.8\text{Gy} \]

50% Risk G1-3

\[ D_{20\%} \leq 19.3\text{Gy} \]

5% Risk G1-3