Radiobiology for Radiosurgery

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Increased curve separation = “Therapeutic Gain”

Reducing treatment volume with SBRT techniques separates curves
Paired Sigmoid Shaped Dose-Response Curves

- Good for representing drug dose, radiation dose, etc.
- Therapeutic gain of any modifying factor depends upon how it changes the relative separation of the response and complication curves
- A fair and thorough comparison of different technique requires data for both curves for each
• Gamma linoleic acid acts as a radiation protector for CNS tissue
• Sims & Plowman  Br J NSrg 2001: 15: 28-34  62 pts with AVM >10cc at St Bart’s London. Radiosurgery to 17.5 Gy LINAC
  – No linolenic acid: 20% perm morbidity, 41% oblit
  – With linolenic acid: 0% perm morbidity. 5% oblit
• Conclusion: No gain in the therapeutic ratio
  • Protects the target (AVM) as much as normal tissue
If you protect *(or sensitize)* the normal tissue to the same degree as the target tissue with a radiation protector *(or sensitizer)* there is no change in the therapeutic ratio, only the dose at which the same effects occur.
AVM Dose-Response

- No Embolization (n=450)
- Embolized (n=65)

% Obliterated vs Marginal Dose (Gy)

FU $\geq$ 60 Months, n=515
Logistic Model, $\alpha/\beta = -45.9$
Maximum Obliteration at 23 Gy
95.7% with no embolization
91.8% with prior embolization
AVM Radiosurgery: Brain tolerance

Risk of Persistent Neurological Sequelae
Post-SRS by Location & 12-Gy Volume

% With Post-SRS ARE

12-Gy Volume
<table>
<thead>
<tr>
<th>Tumor Diameter</th>
<th>RTOG Dose</th>
<th>Dose for 10% Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4 cm</td>
<td>15.0 Gy</td>
<td>13.5 Gy</td>
</tr>
<tr>
<td>2-3 cm</td>
<td>18.0 Gy</td>
<td>16.0 Gy</td>
</tr>
<tr>
<td>&lt;2 cm</td>
<td>24.0 Gy</td>
<td>21.0 Gy</td>
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</table>

% with Late Neurological Sequelae Post-Radiosurgery

(n = 156)
Minimum Tumor Dose (marginal dose) in Gy

% Tumor Control Probability

- Sensitive (90%)
- Resistant (10%)
- Combined population

90% control

flat range of the dose-response curve for the combined population

10% resistant tumors
The Four R's of Radiobiology

- Repair of Sublethal Damage
- Redistribution throughout parts of the cell cycle (with different sensitivities)
- Repopulation of cells between successive radiation treatments
- Reoxygenation of hypoxic cells
The Four R's of Radiobiology

- Redistribution of cells throughout parts of the cell cycle (with different sensitivities)

- Not important since cells are hard to synchronize: they get stuck in G0
Cells are more sensitive to killing by radiation during mitosis and in late-G1/early S.

1. Multiple fraction XRT may catch more cells in mitosis.
2. Taxanes arrest cells at the border of G2 and M where radiation sensitivity is high.

FIG. 7-9. Forms of age response for (A) cells with short G1, represented by Chinese hamster cells, and (B) cells with long G1, represented by HeLa cells. The times have been adjusted so that the S period has a comparable length on the x-axis for both cell lines. (From Sinclair WK: Dependence of Radiosensitivity Upon Age. In Proceedings of the Carmel Conference on Time and Dose Relationships in Radiobiology as Applied to Radiotherapy. BNL Report 50203(C-57), 1959, p. 97-107.)
The Four R's of Radiobiology

- **Repair** of Sublethal Damage
- **Redistribution** throughout parts of the cell cycle (with different sensitivities)
- **Repopulation** of cells between successive radiation treatments
- **Reoxygenation** of hypoxic cells
It takes three times as much radiation dose to kill fully hypoxic tumor cells.
Oxygenated cells are easily killed during the first XRT fractions.

Hypoxic-viable cells survive first XRT fractions but become oxygenated and then more sensitive to XRT.
Effects of Hypoxia In Radiosurgery

• Poorer tumor control with radiosurgery of brain metastases that show heterogeneous enhancement
High concentrations of hypoxic radiation sensitizers can completely replace oxygen’s enhancement of cell killing by radiation.

Most hypoxic cell sensitizers have been too toxic to give in high enough doses to improve responses in the clinic, or enough re-oxygenation already occurs.
Densely ionizing radiation is more likely to cause double-stranded DNA breakage unaffected by fractionation and less dependent on oxygen.
The specifics of radiation’s affects on cells are more complex than free radicals directly damaging DNA and killing the cell.
Tumor Response to Radiotherapy Regulated by Endothelial Cell Apoptosis

Monica Garcia-Barros,¹ Francois Paris,¹ Carlos Cordon-Cardo,² David Lyden,³ Shahin Rafii,⁵ Adriana Haimovitz-Friedman,⁴ Zvi Fuks,⁴* Richard Kolesnick¹*†

About 50% of cancer patients receive radiation therapy. Here we investigated the hypothesis that tumor response to radiation is determined not only by tumor cell phenotype but also by microvascular sensitivity. MCA/129 fibrosarcomas and B16F1 melanomas grown in apoptosis-resistant acid sphingomyelinase (asmase)–deficient or Bax-deficient mice displayed markedly reduced baseline microvascular endothelial apoptosis and grew 200 to 400% faster than tumors on wild-type microvasculature. Thus, endothelial apoptosis is a homeostatic factor regulating angiogenesis-dependent tumor growth. Moreover, these tumors exhibited reduced endothelial apoptosis upon irradiation and, unlike tumors in wild-type mice, they were resistant to single-dose radiation up to 20 grays (Gy). These studies indicate that microvascular damage regulates tumor cell response to radiation at the clinically relevant dose range.
Conclusions: Endothelial Response

• The radiation response, at least to single fraction radiation, appears to be determined primarily from the host endothelial cells (not the tumor cells)

• Varied radioresistance of different tumors may correlate with how tumor cells modify the response of adjacent endothelial cells
The Four R's of Radiobiology

- Repopulation of cells between successive radiation treatments (Accelerated after 2-3 wks)
- The one advantage of single fraction treatment for rapidly growing tumors
The Four R's of Radiobiology

- **Repair** of Sublethal Damage
  - Mostly complete in 4-6 hr
  - Biphasic: 1/2 fast component with 30 minute T1/2
Single stranded DNA breakage means double hit kinetics (it takes two adjacent breaks to kill a cell).

Double stranded DNA breakage means single hit kinetics.
In this example, 4 Gy given in one fraction is as effective as 8 Gy given in daily 2 Gy fractions.
Cell survival with radiation delivered in small (2 Gy) daily fractions

Normal tissues may be better able to repair sublethal radiation damage

Fractionation necessary because traditional RT irradiates a large volume of normal tissue
Ablative Radiotherapy

- Radiation therapy traditionally given in many small fractions over several weeks, in order to maximize biological effect on tumor, minimize effects on normal tissue.
- It is thought that normal tissues are better able to repair radiation damage than most cancerous tissues.
- Concept of therapeutic gain- fractionation increases the relative effect of radiation on cancer vs normal tissue.
Ablative Radiotherapy

• Traditional fractionated radiation therapy doses ~ 2 Gy/day
• Shoulder on cell survival curve- cells able to recover from sublethal damage
• Ablative radiotherapy – doses > 10 Gy/day
• Tumor cell repopulation accelerates during course of fractionated RT- large doses delivered over a short period may be much more effective at cell kill
Ablative Radiation

• Advantage of ablative radiation comes from
  – Biology- large fractions are more effective in killing tumor cells and injuring supporting vasculature
  – Geometry- more accurate localization reduces irradiation of tissue around tumor
Ablative Radiotherapy

- Traditional radiation therapy doesn’t kill cancer cells, but damages their DNA so they cannot divide and grow.
- Fewer, higher dose fractions disrupt cell functions and destroy associated blood vessels that support the cancer.
- Also more effective at killing normal tissue- volume of normal tissue irradiated must be tightly limited.
- Tumor shrinkage may be enhanced with radiosurgery by avoiding injury to tissue-resident immune system cells that phagocytize injured tumor.
What does radiobiology tell us?

- The degree to which a tissue is spared injury by fractionation is represented in the linear quadratic formula by the alpha/beta ratio.
  - Alpha cell killing is the component that is less effected by fractionation, hence a high \( \alpha/\beta \) ratio means that alpha cell killing predominates and fractionation has less of an effect.
  - If the surrounding tissue has a lower \( \alpha/\beta \) ratio than the target or tumor tissue, then increasing fractionation improves the therapeutic ratio.
Linear Quadratic Formula

- Biologically Equivalent Dose (BED or ETD)
  - BED = (Total Dose) x [Relative effectiveness factor]
  - BED = (n d) x [1 + d/(a/b)] - (repopulation factor)
    - where d= dose/fraction, n= #fractions, a/b = alpha/beta ratio
    - Early reacting (fast growing) a/b=10, Late (slow) a/b=2
      - BED extrapolates to the dose equivalent for LDR brachytherapy
- To equate one XRT course to another (example: 2-Gy per fraction), divide by another relative effectiveness factor (Normalized Total Dose)
  - NTD$_{2\text{Gy}}$ = (n d) [1 + d/(a/b)] / [1 + 2 Gy/(a/b)]
AVM Obliteration: $\alpha/\beta$

- Logit expression (with sex)
  - Angio alone: $\alpha/\beta = -46 \pm 10$
  - MR + Angio: $\alpha/\beta = -42 \pm 9$

- Standard Probit Model (without sex)
  - Angio alone: $\alpha/\beta = -55 \pm 10$
  - MR + Angio: $\alpha/\beta = -51 \pm 10$
<table>
<thead>
<tr>
<th>End point</th>
<th>Number</th>
<th>Alpha/beta</th>
</tr>
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<tbody>
<tr>
<td>V neuropathy</td>
<td>45/218 acoustics</td>
<td>-43.2 to -52.2</td>
</tr>
<tr>
<td>VII neuropathy</td>
<td>31/218 acoustics</td>
<td>-39.9 to -55.2</td>
</tr>
<tr>
<td>Hearing change</td>
<td>57/218 acoustics</td>
<td>-38.3 to -52.7</td>
</tr>
<tr>
<td>Imaging changes</td>
<td>90/355 AVM</td>
<td>-29.7 to -44.0</td>
</tr>
<tr>
<td>Symptomatic edema</td>
<td>30/355 AVM</td>
<td>-42.4 to -47.0</td>
</tr>
</tbody>
</table>
Problem with LQ model: LQ overestimates cell kill at high fractional doses

Park et al (IJROBP 2008) propose ‘universal survival curve’- LQ at low doses, multitarget model (straight line on log plot) at high doses

Cell survival curve for H460 NSCLC cells, from Park et al, IJROBP 2008
Normal tissue type and architecture affects tolerance

Parallel tissues (e.g., peripheral lung, liver)
- Often low radiation tolerance for whole organ
- Toxicity is mainly related to volume irradiated, tolerance related to volume spared
- Nature’s defense: redundancy of function

Serial tissues (spinal cord)
- Toxicity is mainly dose related
- Nature’s defense: inherent radiation resistance
- In some serial tissues (cord, esophagus), tolerance improved if entire circumference of tissue is not irradiated
The Four R's of Radiobiology (three reasons for fractionation)

- **Repair** of Sublethal Damage
- **Redistribution** throughout parts of the cell cycle (with different sensitivities)
- **Reoxygenation** of hypoxic cells
- **Repopulation** of cells between successive radiation treatment
Treatment volume is the single most important factor effecting the risk of complications from radiosurgery (within the range of radiation doses commonly used)
Other factors besides volume that effect complications

- Location
  - Brainstem locations are worse
- Histology
  - 30% post-radiosurgery imaging changes for AVM vs. 10% for tumors
- Minimum tumor or target dose
- How well the treatment volume fits the target volume
- Accuracy of normal structure drawings