Spatial Mapping of the RBE of Scanned Particle Beams

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Background

- Clinical - Radiation Oncology
  - Proton Therapy
    - Brain (adults and children)
    - Base of skull
- Scientific
  - Neuroscience (not physics)
  - & now “particle” biology

Motivation to explore RBE
Goals for today…

- Biologic assays used to define RBE
  - Limitations and new directions
- Emphasize the need for involvement of physicists
  - Experimental design, setup, data analysis, reporting, grants etc.
- "Radiobiology from a clinician's perspective"

What is RBE?

- A comparison of two radiation types using whatever measure you want.
  - Typically cell kill (clonogenic survival)
    - Measured with established (but NOT standardized) techniques

Clonogenic survival assays
Limitations of clonogenic survival?

Can only be performed in cell lines which can grow in culture

Limitations of clonogenic survival?

- V79 cells
- CHO cells

Often in non-patient derived cells lines

Limitations of clonogenic survival?

Time and labor intensive.....
What is the RBE for proton therapy?

What does RBE depend on?
- dose
- alpha/beta
- end point
- BIOLOGY
- LET

Mid SOBP....
What can we control….

• RBE (and LET) increases with depth

Along the SOBP….

• How do we all deal with this with PSPT?
  – No single beams (except prostate)
  – Select angles
  – Don’t end in critical structure

What about IMPT?

This is a real opportunity
We need more and better data (for models)

High-throughput clonogenic assays

We must think about the physics!
Disclosures:

- Lawrence Bronk
- Fada Guan
- Uwe Titt
- Radhe Mohan
- Dragan Mirkovic
- Chris Peeler
- Darshana Patel
- Wenhu Cao
- Michael Gillin
- Ron Zhu
- Falk Poenisch
- Narayan Sahoo

- Steven Lin
- Erik Sulman
- Kathy Mason
- Ray Meyn
- Jeff Dinh

Funding:
- NCI
- R21
- U19
- CPRIT

“The Jig”

Drs. Guan & Titt

Scanning vs. PSPT

Guan & Bronk, Scientific Reports 2015
“IMPT in a dish”

Results

Models....

• What do all models attempt to describe?
  – A: Cell kill

Dr. Titt
Carbon???

Comparison of protons vs. carbon

Protons vs. Protons

Thank you to DKFZ/HIT
Other cancer cell models

GSC23 response

What about normal tissues?
What is necrosis?

• Not just cell kill
  – An active spreading process involving multiple cell types
• We are forcing models of clonogenic survival onto a complex process….

Normal tissues – “Rat brain organoids”

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Live, active neurons
Normal tissues – “organoids”

Sham 5.2 Gy, 16.7 keV/µm

Cell type and viability: 20 Gy

- Green: GFAP (glia)
- Red: beta III tubulin (neuron)
- Blue: CD68 (microglia)

3 keV/µm  10 keV/µm  16 keV/µm

Mapping Biologic Effect

- Repeat for numerous dose and LET combinations or use the ‘Jig’ to generate a surface plot
- Terminal fixation and histologic analysis
- Unirradiated 4 keV/µm  4 keV/µm  16 keV/µm
Animals…

Patients!!!

Pediatric ependymoma cohort
Critical issues

• Particle therapy is different
  – “It’s not just dose”
• Clonogenic survival
  – Is still the “gold” standard
• “Biology” makes correlations with physical factors challenging

We do understand the physics

• Technology is changing rapidly
  – IMPT...
• If we believe RBE (or LET) matters…
  – This can (and should) be incorporated with IMPT.
  – What models to use for treatment planning?
  – Are we ready to use this clinically?
• Heavy ions may have even more benefits

Needs to be more collaboration

• Physics is essential, especially for particles
  – Experimental design
    • MC based design
    • Minimization of uncertainties
  – Accurate data
    • Dose
    • LET
  – Team science
The Team!

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