Implications of Heterogenous Dose Distributions for Radiopharmaceutical Therapy Revisited

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I’m the co-founder and CSO of Voximetry, LCC a Middleton-based nuclear medicine dosimetry company.
When radiopharmaceutical therapy fails to produce significant improvement in local control it is primarily due to:

- Tumor selectivity
- Limited radiation tolerance of normal tissues
- Tumor radiosensitivity
- Heterogeneous uptake within the tumor (i.e. heterogeneous dose)
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  - Tumor radiosensitivity
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Patient-specific dosimetry can help!
RAPID (Radiopharmaceutical Assessment Platform for Internal Dosimetry)

Diagnostic Image Acquisition → Image Registration Amira → ROI Contouring Amira

PET to Therapeutic Activity Conversion Matlab → Source Distribution Definition

Activity Integration Matlab → Dose Calculation Geant4 Monte Carlo

PET/CT/MRI Data

123I Absorbed Dose (Gy/Gd)

0-6
No Two Tumors Are Alike

μPET/CT  SPECT/CT

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>No. Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone (NonTarget)</td>
<td>1</td>
</tr>
<tr>
<td>SCV Node</td>
<td>2</td>
</tr>
<tr>
<td>Lung (Left)</td>
<td></td>
</tr>
<tr>
<td>Lung (Right Upper)</td>
<td>9</td>
</tr>
<tr>
<td>Lung (Left Lower)</td>
<td></td>
</tr>
<tr>
<td>Lung (Right Lower, NonTarget)</td>
<td></td>
</tr>
<tr>
<td>Lung (Left Ant, NonTarget)</td>
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<tr>
<td>Lung (Right Additional)</td>
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</tr>
<tr>
<td>Adrenal (Left)</td>
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</tr>
<tr>
<td>Adrenal (Right)</td>
<td></td>
</tr>
<tr>
<td>Liver (Left)</td>
<td></td>
</tr>
<tr>
<td>Liver (NonTarget)</td>
<td></td>
</tr>
<tr>
<td>Breast (Right)</td>
<td>4</td>
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<tr>
<td>Axial Node (Left, Sup)</td>
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</tr>
<tr>
<td>Axial Node (Left, Mid)</td>
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</tr>
<tr>
<td>Axial Node (Left, Inf)</td>
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</tr>
<tr>
<td>Liver (Center)</td>
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<tr>
<td>PeriPortal</td>
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<tr>
<td>Gastrohepatic Node</td>
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</tbody>
</table>

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Leiomyosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Rectal</td>
<td>1</td>
</tr>
<tr>
<td>Synovial Sarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Triple negative breast</td>
<td>1</td>
</tr>
</tbody>
</table>

Drug distribution depends on physiological make-up of tumor microenvironment

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The dose of radiation D sterilizes a proportion of cells and the loge proportion of surviving cells or cell kill in the exposed population is described by the linear quadratic (LQ) model.

\[ -\alpha D - \beta D^2 \]

\[ \alpha = 1 \text{ log per Gy} \]
\[ \beta = 0.333 \text{ per Gy}^2 \]
\[ \alpha/\beta = 3 \text{ Gy} \]

**High:** rapidly proliferating tissues (tumors and early-responders)

**Low:** slowly proliferating tissues (late-responders)
**BED – Biologically Effective Dose**

- The radiation dose that would cause the same loge cell kill if the dose were delivered with a very small dose rate low enough so that all repairable damage has time to repair.

\[
\text{BED} = D \times RE
\]

\[
RE = (1 + g \beta D / \alpha)
\]

Dose protraction factor*

\[
g = \frac{2}{D^2} \int_0^T \dot{d}(t)dt \int_0^t \dot{d}(w)e^{-\mu(t-w)}dw
\]

*Assumes \( \dot{d} = \dot{d}_0 \)

\* \( g \rightarrow 0 \) at low dose rates
BED – Biologically Effective Dose

- The radiation dose that would cause the same loge cell kill if the dose were delivered with a very small dose rate low enough so that all repairable damage has time to repair.

\[
BED = D \times RE - (\tau \times t/\alpha)
\]

\[
RE = (1 + g \beta D / \alpha)
\]

\[
g = \frac{2}{D} \int_0^T \dot{d}(t)dt \int_0^t \dot{d}(w)e^{-\mu(t-w)}dw
\]

*Assumes \( \dot{d} = \dot{d}_0 \)

Repopulation rate constant

Dose protraction factor*

\[\alpha/\beta = 10 \text{ Gy} \]

\[T_{1/2} = 3, 2, 1, 0.5, 0.25 \text{ h} \]

\[\dot{d} < 30 \text{ cGy/hr} \]

\[\dot{d} (\text{cGy/hr}) \]

\[\dot{d} \rightarrow 0 \text{ at low dose rates} \]
BED – Biologically Effective Dose

- The radiation dose that would cause the same $\log_e$ cell kill if the dose were delivered with a very small dose rate low enough so that all repairable damage has time to repair.

\[ \text{BED} = D \times \text{RE} \]

\[ \text{RE} = (1 + g\beta D / \alpha) \]

\[ g = \frac{2}{D^2} \int_0^T d(t) dt \int_0^t d(w)e^{-\mu(t-w)} dw \]

*\( g \to 0 \) at low dose rates
Tumor Dose Heterogeneity

SPECT/CT of $^{177}$Lu-DOTATATE

Ilan et al. JNM, 56(3) 2015
EUD – Equivalent Uniform Dose

- The non-uniform distribution of BED (or dose) that would produce the same log\(_e\) cell kill as the uniform value of BED (or dose)

\[
EUD = -\frac{1}{\alpha} \ln(SF(\alpha)) = -\frac{1}{\alpha} \int_0^\infty p(\psi) e^{-\alpha \psi} d\psi
\]

where \(\psi\) is the BED, \(p(\psi)\) is the probability density function of differential DVH with respect to \(\psi\), and:

\[
SF(\alpha) = \int_0^\infty p(\psi) e^{-\alpha \psi} d\psi \rightarrow \text{total survival probability}
\]
EUD – Equivalent Uniform Dose

- As the distribution becomes more nonuniform, the EUD (hence therapeutic effect) decreases
- The overall loss of therapeutic effectiveness depends on the mean BED and is proportionally worse for greater mean values

\[
\% \text{ Diff}_{60-\text{Gy}} = 76\%
\]
\[
\% \text{ Diff}_{10-\text{Gy}} = 29\%
\]

*assumes dDVH is normally distributed
EUD – Equivalent Uniform Dose

Loss in $\log_e$ cell kill is proportionally worse for radiosensitive tumors
Discussion Points

- Models such as LQ that reflect the biological effect of the RPT agent on tumor (and normal) cells should be more meaningful than absorbed dose.

- Despite several efforts correlations between BED or EUD and effect have been difficult to detect.

- New models that better reflect the tumor microenvironment should be investigated.
Discussion Points

Radiation

Cytokine release

Temporary local depletion of lymphocytes (suppressor and effector)

Increased immune infiltrate

Phenotypic changes in cells surviving radiation

Immunogenic cell death

Dendritic cell maturation, antigen cross-presentation, and diversification of T cell response
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