Small Scale Modeling and Dosimetry for the Salivary Gland: Application to $^{177}$Lu- and $^{225}$Ac-PSMA Therapy

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Salivary Gland Dosimetry

Historical interest from salivary gland toxicity from $^{131}$I therapy of thyroid cancer.

A serious issue which affects patient quality of life (xerostomia, sialadenitis leading to dysphagia, tooth decay, etc.)

Salivary gland dose estimations from standard dosimetric methods are insufficient to explain clinically observed salivary gland toxicity.

More recently PSMA-radiolabeled constructs have been used for prostate and renal cancer.

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*a* Jentzen et al. EJNMMI '10

*b* Walter et al. JNM '07
$^{131}\text{I}$ study

9 Patients received ~24 MBq of $^{124}\text{I}$

Head and neck PET scans were performed at 0.5, 1, 2, 4 (PET/CT), 24, 48, and 72 or 96 h.

- Data acquired at University of Duisburg-Essen

3D-RD dosimetry

- BED $^a$

- external proximal sources of dose (lymph nodes, tumors) $^a$

- localized uptake – non-uniform activity and dose

Jentzen et al. EJNMMI '10

$^a$ Hobbs et al. QJNMMI '13
Small scale (alpha) dosimetry?

Traditional absorbed fraction dosimetry may fail to predict toxicity for TAT.

- limited range of $\alpha$-particles and localization of activity below in vivo imaging resolution and organ FSU scale.

- BUT not all TAT needs small scale, $\beta$RPT ($^{131}$I, $^{177}$Lu) may also need small scale dosimetry.
Small scale (Macro to micro) dosimetry

1. Use simple geometrical shapes as anatomy for MC-generated S-values

2. Measure (isotope) activity conc $a_{ij}(t)$ in compartments AND whole organ

3. Multiply by fraction of occupancy $f_i$ to apportion fraction of activity $g_i$ to compartments

Hobbs et al. Phys Med Biol ’12
SG Small-scale dosimetry

\(^{131}\text{I} \text{Problem: SG mean absorbed dose too low to explain toxicity}\)

- From literature \(^{131}\text{I} \text{ uptake}^a \text{ and } ^{177}\text{Lu-PSMA uptake}^b \text{ is localized to striated ductal cells}\)
- Saliva created and stored in acinar cells

Create a geometrical model to simulate uptake and dose in ductal cells:

- Simple geometrical shapes: spheres for acini, cylinders for ductal cells

\(^{a}\text{Gates et al. Laryngoscope ’67}\)
\(^{a}\text{Mishkin, Semin Nucl Med ’81}\)
\(^{b}\text{Rupp et al. JNMMI ’19}\)
Ductal cell S values

**Ductal cell dimensions:**

Ductal cells make up 5.1% of salivary gland; acinar cells constitute 60%.

Model as cylinder:
- 54.5 μm diameter, with 20 μm thick cells
- 700 μm long
- S-values for different isotopes and saliva/cell to cell as a function of distance (shells every 50 μm)

Run GEANT4 MC
SG Matrix model

Assume homogenous distribution
GEANT4 to place ductal cells in matrix inside sphere.
Increase matrix size from 10x10x10 to 250x250x250, where unit is size of ductal cell. Assume uniform distribution of acinar cells.
Two models – simple MC and kernel convolution
Radioiodine SG Matrix model

Ratio of ductal cell AD to average cell AD varies as a function of sphere size and isotope

For $^{131}$I in range of SG size, ratio is $\sim 3.7$. (For self-dose only)

For $^{211}$At, ratio is $\sim 14.1$.

BED is now a factor. Range from 3-25 Gy.

Toxicity to salivary glands expected in the range of 20-25 Gy
PSMA SG Matrix model

For $^{225}$Ac in range of SG size, ratio is $\sim 14$. (For self-dose only)

For $^{212}$Pb, ratio is $\sim 11.5$.

For $^{177}$Lu, ratio is 5 - 5.5.

Set an upper limit of dose based on the assumption of uptake in the ductal cells.

For uptake in acinar cells ratio is 1 - 1.5
Input data?

Conflicting and partial input.

- PSMA expression is on intercalated ductal cells in humans (need to add these?)
- PSMA staining in murine models in acini
- Acinar damage in murine models
- Uptake of radiolabeled PSMA constructs depends on construct – may vary localized uptake
Input data?

Recent publication suggests non-targeted uptake consistent with striated cells not intercalated cells.

Consistent with some murine αCamera imaging

Data using excised SGs is from single time point.

– striated cell uptake related to salivary gland flow can vary over time.

a Rupp et al. JNMMI ’19
Much more chaotic for SGs than most organs – depends on needs for and use of saliva ($^{131}$I) – may involve re-localization as a function of time (PK model)

Controversy over use of sialogogic agents (lemon drops) whether increase or decrease AD (may increase uptake and also evacuation)
Other caveats (general)

Distribution of ductal cells, both striated and intercalated. 
Tree-like branching?
Hot spots exist on PET images.
Accumulation of saliva? Or distribution of ductal cells
Construct variability
TAT-specific caveats

Evacuation of daughter isotopes ($^{221}$Fr, $^{213}$Bi)

Radiobiology for $\alpha$-particles – need to think in terms of cell-specific radiobiological parameters instead of organ values

RBE value related to EQD2 or BED
Conclusions

Preliminary results suggest validity for $^{131}$I toxicity

Set upper limit for PSMA AD values – need better input data and radiobiological parameters

Salivary Glands considered parallel organ from external beam.

Xbeam covers geometry, RPT driven by physiology – serial for RPT?
Acknowledgements

NIH grants R01 CA 116477 (Hobbs), R01 CA 114377 (Sgouros)

G. Sgouros, D Pkyku, A McGuffie, NAM Josefsson, S Roy - Johns Hopkins University

W Jentzen, A Bockisch – University of Duisburg-Essen
THANK YOU FOR YOUR ATTENTION!
Relative Biological Effectiveness

RBE definition:

$$RBE = \left. \frac{D_L}{D_H} \right|_{SF}$$

Low-LET response

$$SF = e^{-\alpha_L D_L - \beta_L D_L^2}$$

Alpha response:

$$SF = e^{-\kappa D_H}$$
Observation

Alpha-particle rRBE results are typically given as a range of values which span the measured range of dosimetric end points. Uncertainty in which value to use in which circumstances arises, which is problematic for conversions and potential combination therapies.
Values and dependency

RBE is dose dependant:

\[
RBE(D_L) = \frac{\kappa}{\alpha_L + \beta_L D_L}
\]

\[
RBE(D_H) = \frac{-\alpha_L - \sqrt{\alpha_L^2 + 4\beta_L D_H}}{2\beta_L D_H}
\]
Idea

EQDX, and more specifically, EQD2 is proposed as the standard by the ICRU. Should be understood as 2 – Gy fraction equivalent of external beam is standard for all radiation.

N.B.: BED is called EQD0 in this formalism

Bentzen et al. Radiother Oncol ’12
Illustration of equivalence

Comparison of different therapeutic regimens in the EQD2 framework
EQD2 – RBE2

Definition:

\[ EQDx = D_L \frac{\alpha_L + \beta_L d_L}{\alpha_L + \beta_L X} \]

Convert to EQD2, ratio is now called RBE2:

\[ RBE_2 = \frac{\kappa}{\alpha_L + 2\beta_L} \]
Application

2 different cell lines:
- murine breast cancer: NT2.5
- human breast cancer: MDA-MB-231
## Results

<table>
<thead>
<tr>
<th>Cell line</th>
<th>$\alpha$ (Gy$^{-1}$)</th>
<th>$\beta$ (Gy$^{-2}$)</th>
<th>$\kappa$ (Gy$^{-1}$)</th>
<th>$\alpha/\beta$ (Gy)</th>
<th>$RBE_{max}$</th>
<th>$RBE_2$</th>
<th>$RBE$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT2.5</td>
<td>0.118</td>
<td>0.0452</td>
<td>1.22</td>
<td>2.61</td>
<td>10.4</td>
<td>5.9</td>
<td>2.4 - 9.0</td>
</tr>
<tr>
<td>MDA-MB-231</td>
<td>0.187</td>
<td>0.0408</td>
<td>1.21</td>
<td>4.57</td>
<td>6.5</td>
<td>4.5</td>
<td>2.4 - 6.0</td>
</tr>
</tbody>
</table>

RBE different single values for each cell line

Should include uncertainty

Variations, e.g. DNA double strand break repair inhibition should have own $RBE_2$
RBE\textsubscript{RPT} comparison

RBE from \textit{in vivo} RPT comparisons:

\[
RBE\textsubscript{RPT}(G, D\textsubscript{RPT}) = \frac{\kappa}{\alpha + G \cdot \beta \cdot D\textsubscript{RPT}}
\]

Dose and kinetics dependency. Suggestion: convert to EQD2:

\[
EQDX = D\textsubscript{RPT} \frac{\alpha + G \cdot \beta \cdot D\textsubscript{RPT}}{\alpha + X \cdot \beta}
\]
RBE<sub>RPT</sub> comparison

G factor:

\[ G(\infty) = \frac{2}{D^2} \int_0^\infty \int_0^t \dot{D}(t) \dot{D}(w) e^{-\mu(t-w)} \, dw \, dt \]

Knowledge of \( \alpha \), \( \beta \) and G can lead to calculation of \( \kappa \).

Resolution of \emph{in vivo} end point versus \emph{in vitro} SF values – micro scale and cell type parameters
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Registration based on PET activity images
- Poor quality attenuation maps
- Good salivary gland definition for early time points
- Thyroid remnant or nodule uptake for late time points
- 4 h time point shared both characteristics (and registered to CT)

Jentzen et al. EJNMMI '10
SG dosimetry

Activity adjusted with RCs from UDE
Run MC (3D-RD)<sup>a</sup>
Collect energy, convert to dose rate
Hybrid trapezoid-exponential fit
Numerical integration for BED<sup>b</sup>

BEDs only ~5 % high than ADs due to low values (0.4 -4) Gy

<sup>a</sup> Prideaux et al. JNM ’07
<sup>b</sup> Hobbs et al. Med Phys ’09
SG dosimetry

For patients with proximal sources of high uptake - run MC for both self-dose and neck region

Long-term dose contribution from external sources, up to 50 % of total dose, not sufficient to explain discrepancies

AD 32 SGs: 0.7 – 5.3 Gy: expected toxicity range 20 - 25 Gy

Hobbs et al. QJNMMI ‘13