Department of Medical Physics
UNIVERSITY OF WISCONSIN – MADISON
SCHOOL OF MEDICINE AND PUBLIC HEALTH

RED
RADIOLOGICAL ENGINEERING
& DESIGN LABORATORY

Implications of Heterogenous Dose Distributions for Radiopharmaceutical Therapy Revisited

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Disclosures

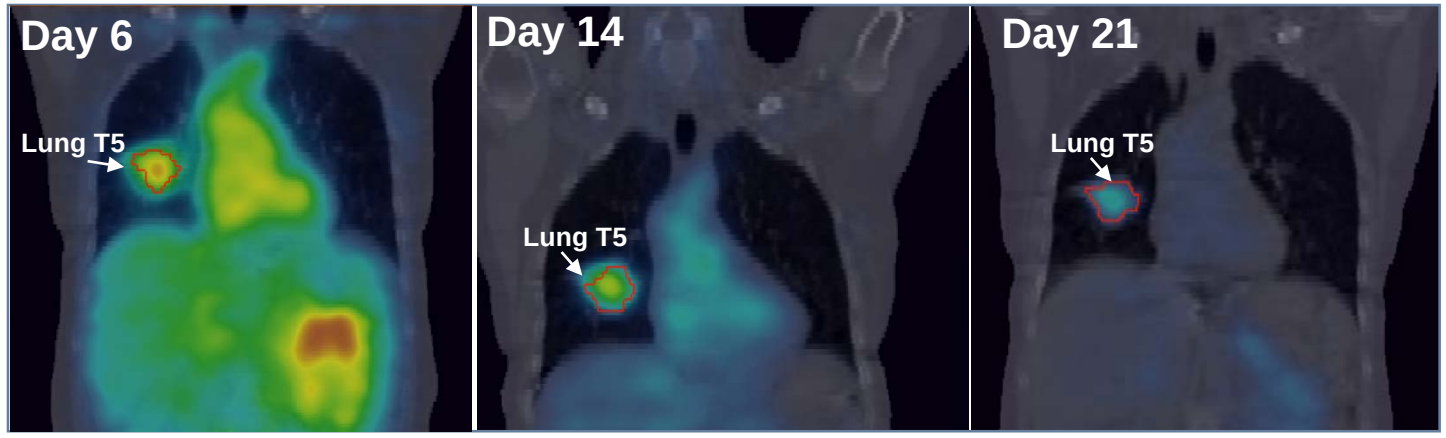
I’m the co-founder and CSO of Voximetry, LCC a Middleton-based nuclear medicine dosimetry company.

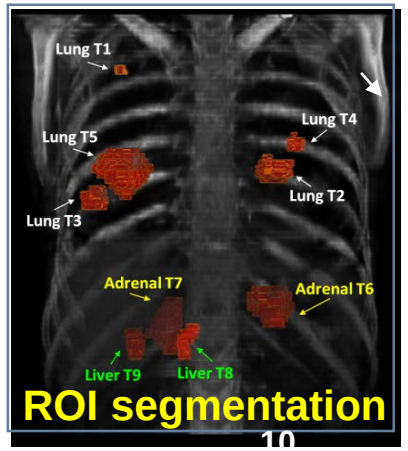
Background

- When radiopharmaceutical therapy fails to produce significant improvement in local control it is primarily due to:

Patient-specific dosimetry can help!

  - Tumor selectivity
  - Limited radiation tolerance of normal tissues
  - Tumor radiosensitivity
  - Heterogeneous uptake within the tumor (i.e. heterogeneous dose)





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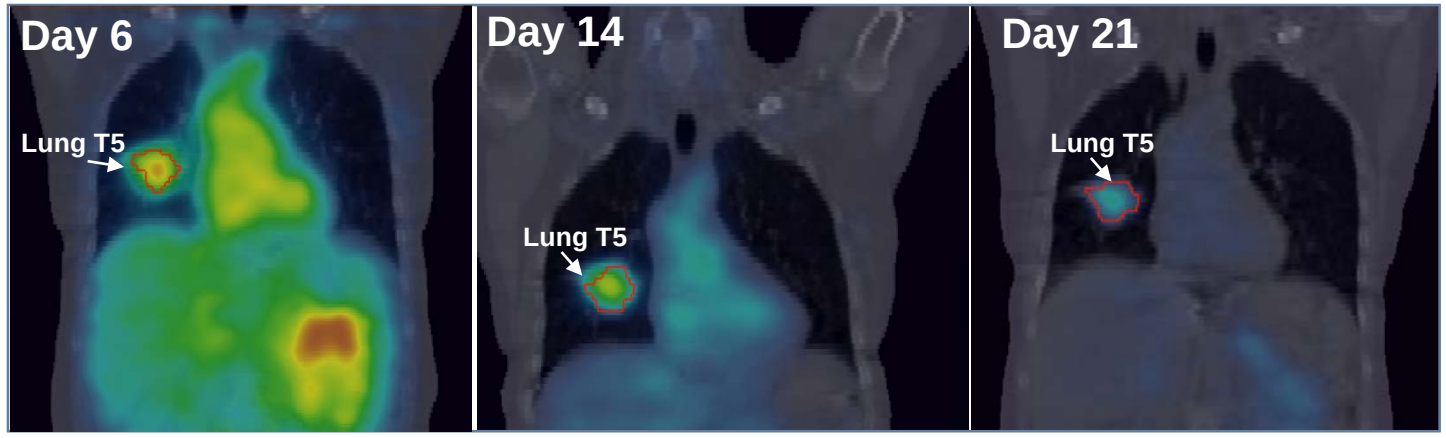

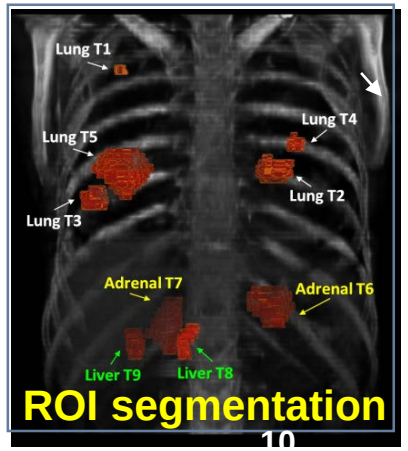

RAPID

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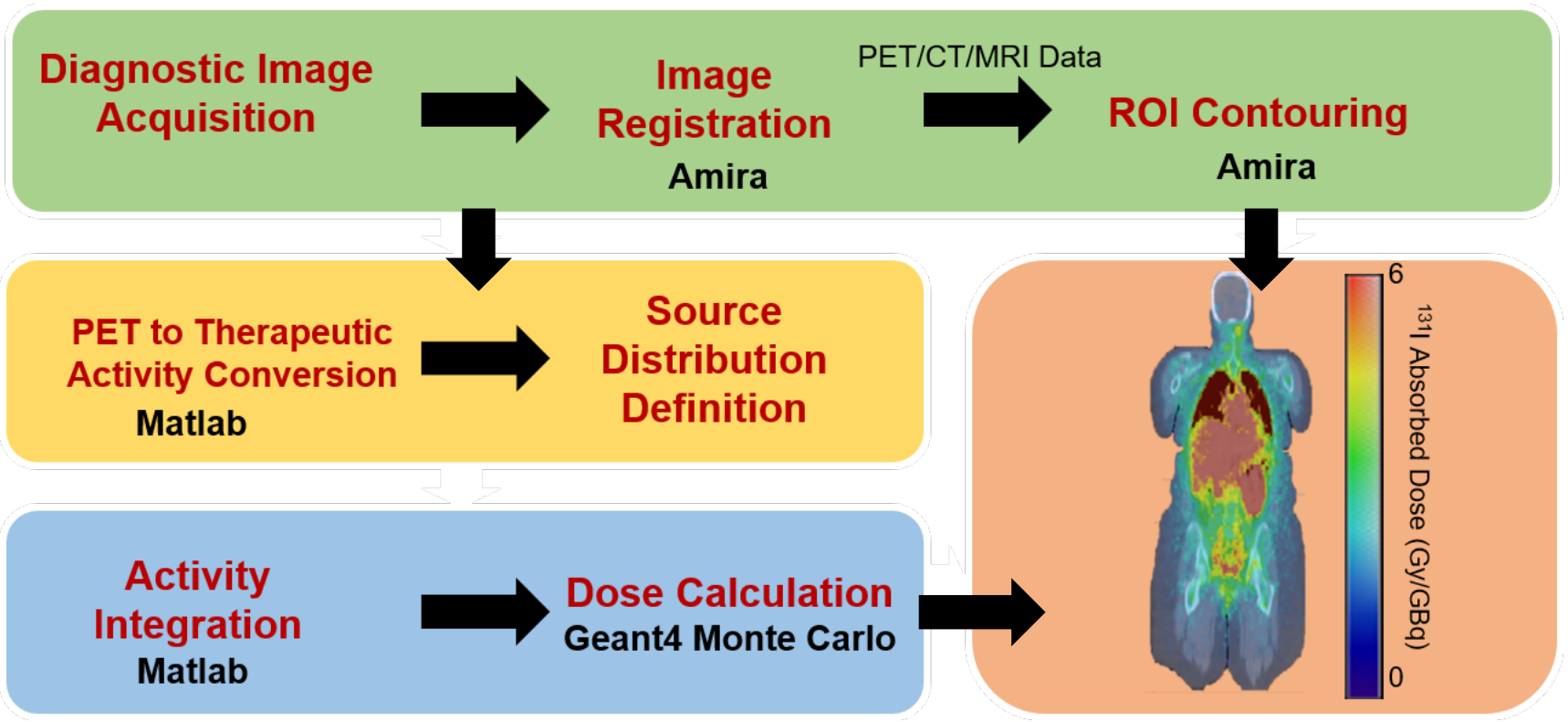
RAPID (Radiopharmaceutical Assessment Platform for Internal Dosimetry)



No Two Tumors Are Alike

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μPET/CT

PDX

Cell Line	No. Mice
NB1691	4
CHLA20	4
Rh30	4
TC71	3
hNET-NB1691	8
TU138	6
SCC22B	**4**
SCC6	**4**
SCC2	**2**
SCC47	**2**
SCC1483	**2**
UW1	**6**
UW13	**4**
UW64	**4**
UW22	**6**
UW25	**4**
UW36	**4**
4T1	3
A549	3
B78	12
EL-4	7
HCT116	3
Hut-102	3
LLC	3
MyCap	3
Panco2	3
Colon Adenocarcinoma	3
SCC22B	2

121

SPECT/CT

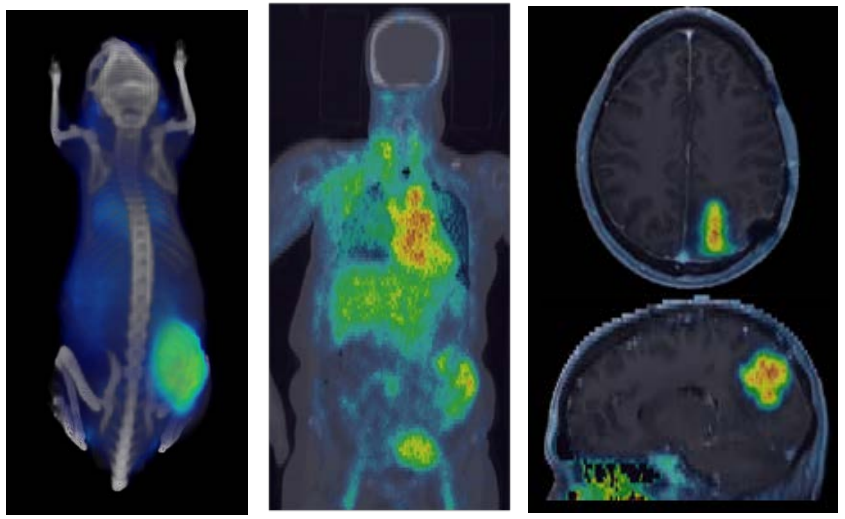
Cancer Type	No. Tumors
Bone (NonTarget)	1
SCV Node	2
Lung (Left)	
Lung (Right Upper)	9
Lung (Left Lower)	
Lung (Right Lower, NonTarget)	
Lung (Left Ant, NonTarget)	
Lung (Right Additional)	
Adrenal (Left)	
Adrenal (Right)	
Liver (Left)	
Liver (NonTarget)	
Breast (Right)	4
Axial Node (Left, Sup)	
Axial Node (Left, Mid	
Axial Node (Left, Inf)	
Liver (Center)	3
PeriPortal	
Gastrohepatic Node	

20

PET/CT

Cancer Type	No. Tumors
Leiomyosarcoma	1
Rectal	1
Synovial Sarcoma	1
Triple negative breast	1

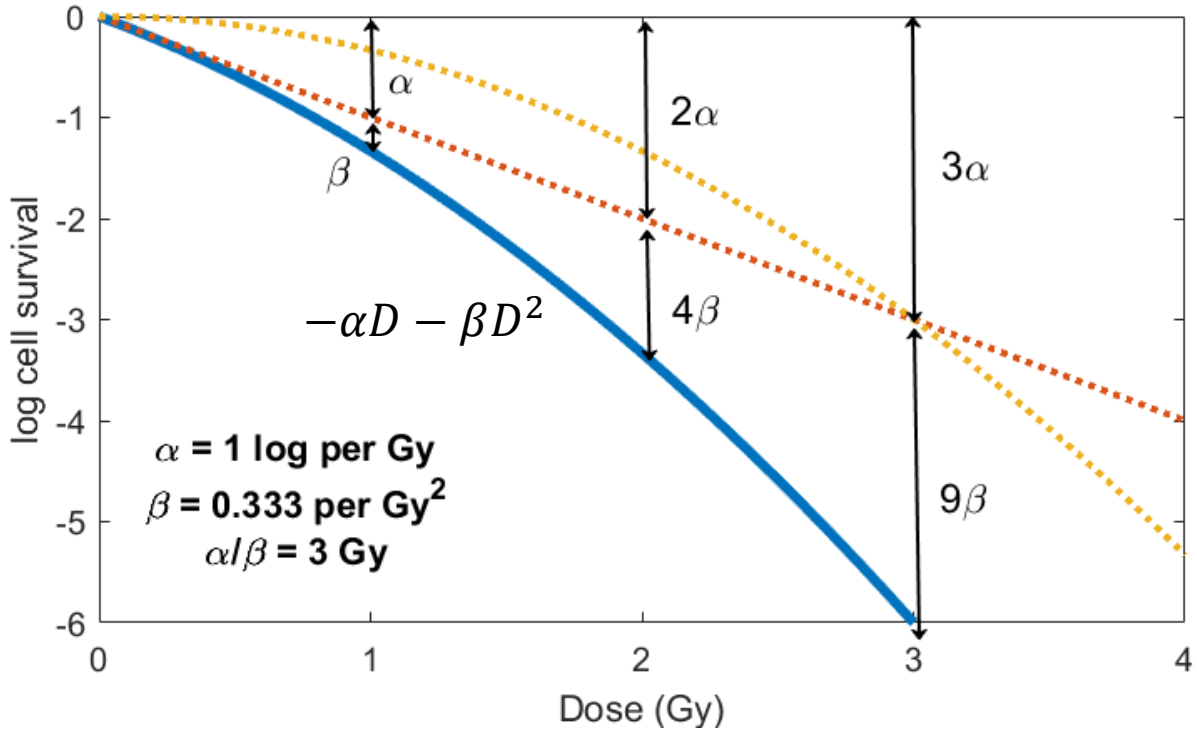
4



Drug distribution depends on physiological make-up of tumor microenvironment

LQ Model

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



α/β

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

Low: slowly proliferating tissues (late-responders)

α: Intrinsic radiosensitivity ($\log_e$ of number of cells sterilized via non-repairable damage per dose)

β: Repair capacity ($\log_e$ of the number of cells sterilized in a repairable manner per dose-squared)

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.

absorbed dose relative effect

$$BED = D \times RE$$

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

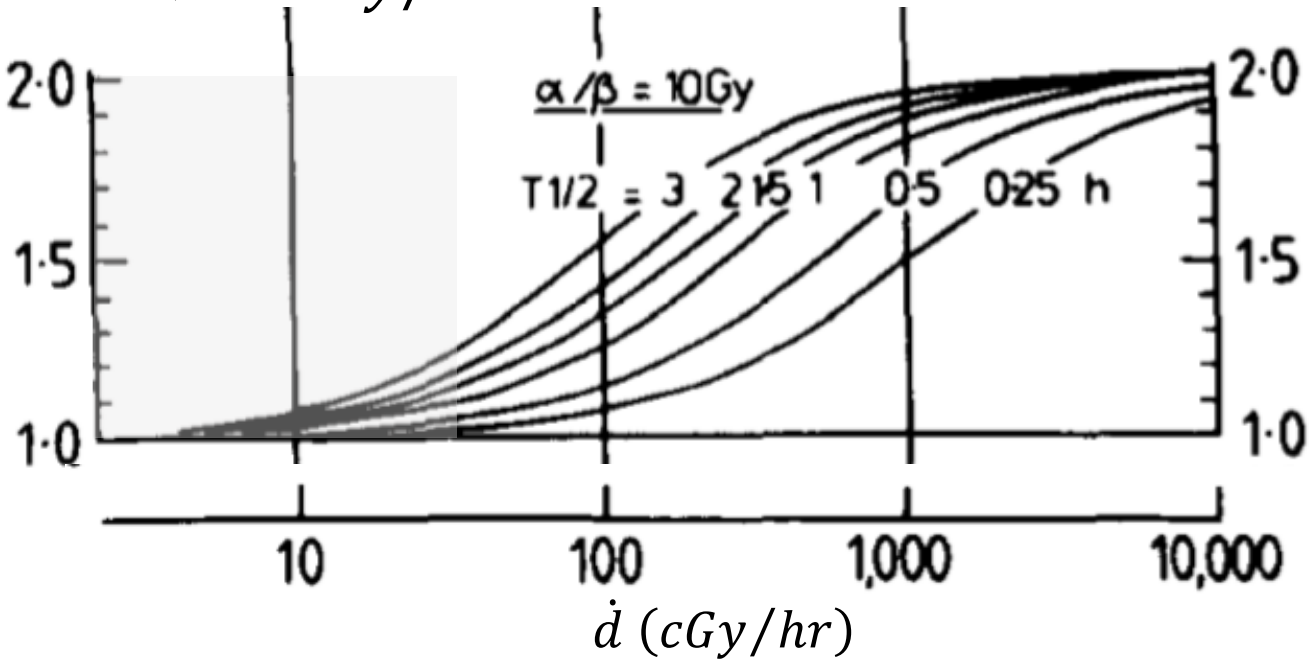
Dose protraction factor*

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

*$g \rightarrow 0$ at low dose rates

*Assumes $\dot{d} = \dot{d}_0$

$\dot{d} < 30\ cGy/hr$



BED – Biologically Effective Dose

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Repopulation rate constant

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

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

Dose protraction factor*

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

*$g \to 0$ at low dose rates

*Assumes $\dot{d} = \dot{d}_0$

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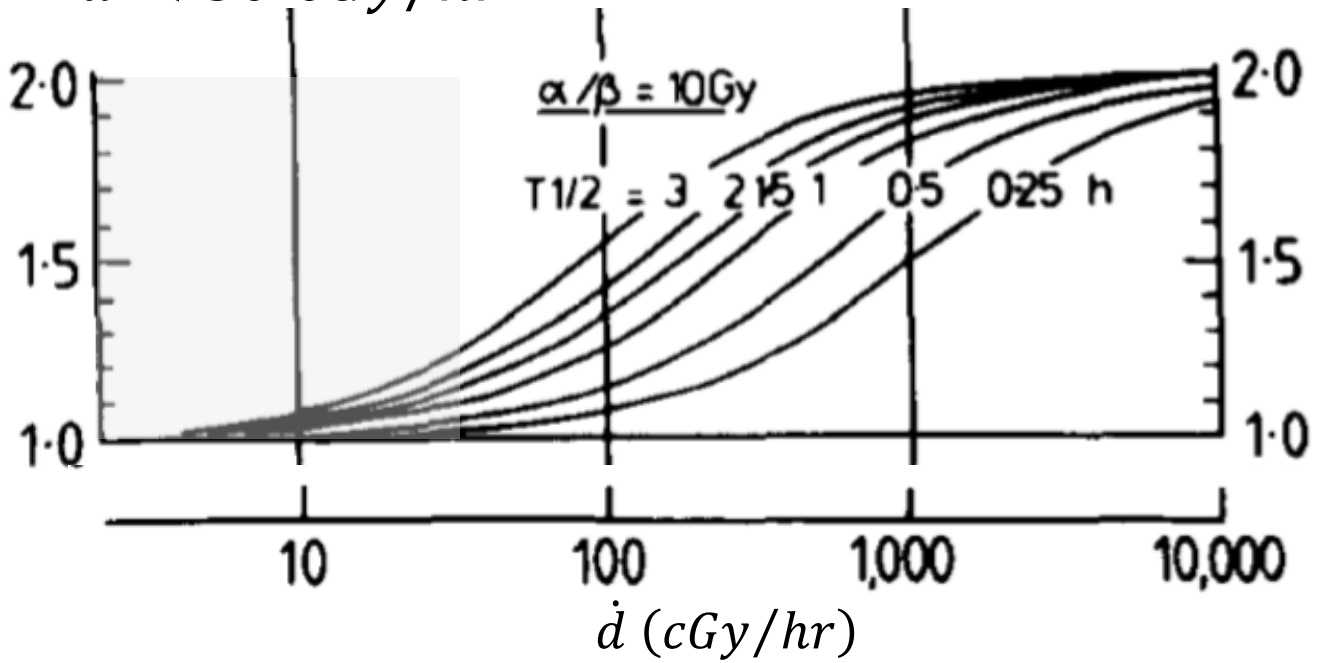

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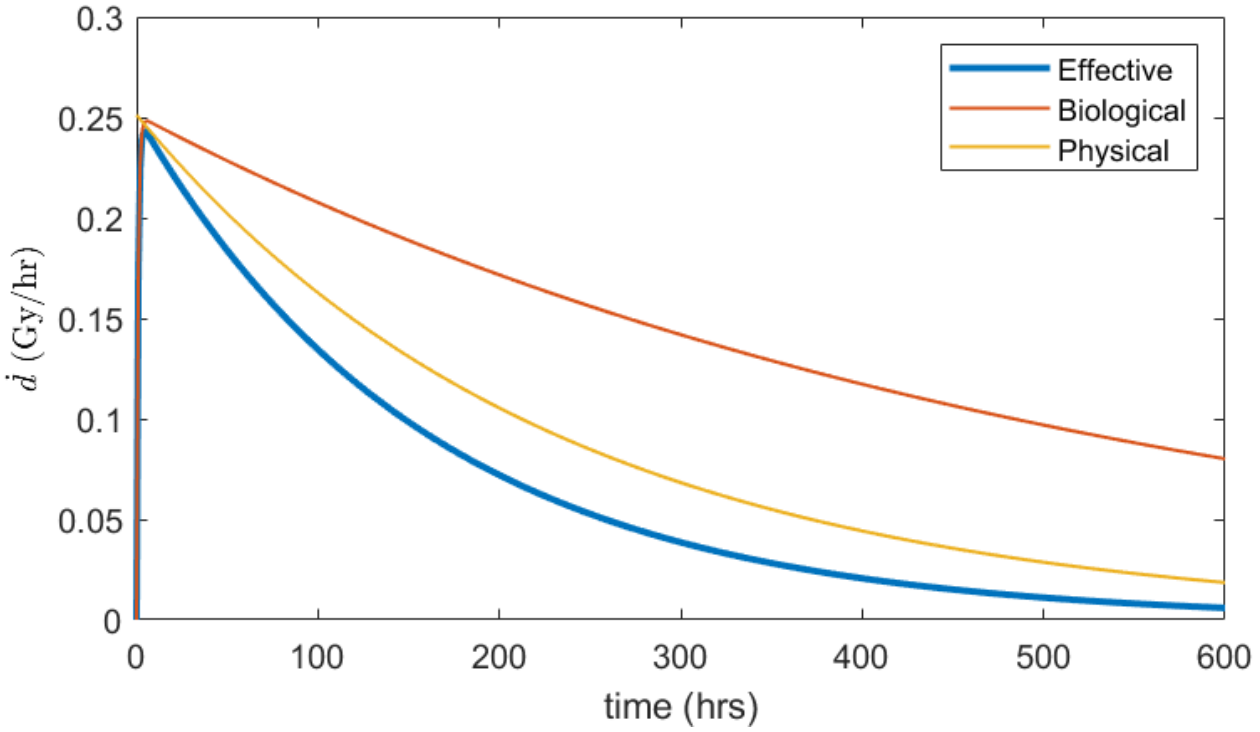
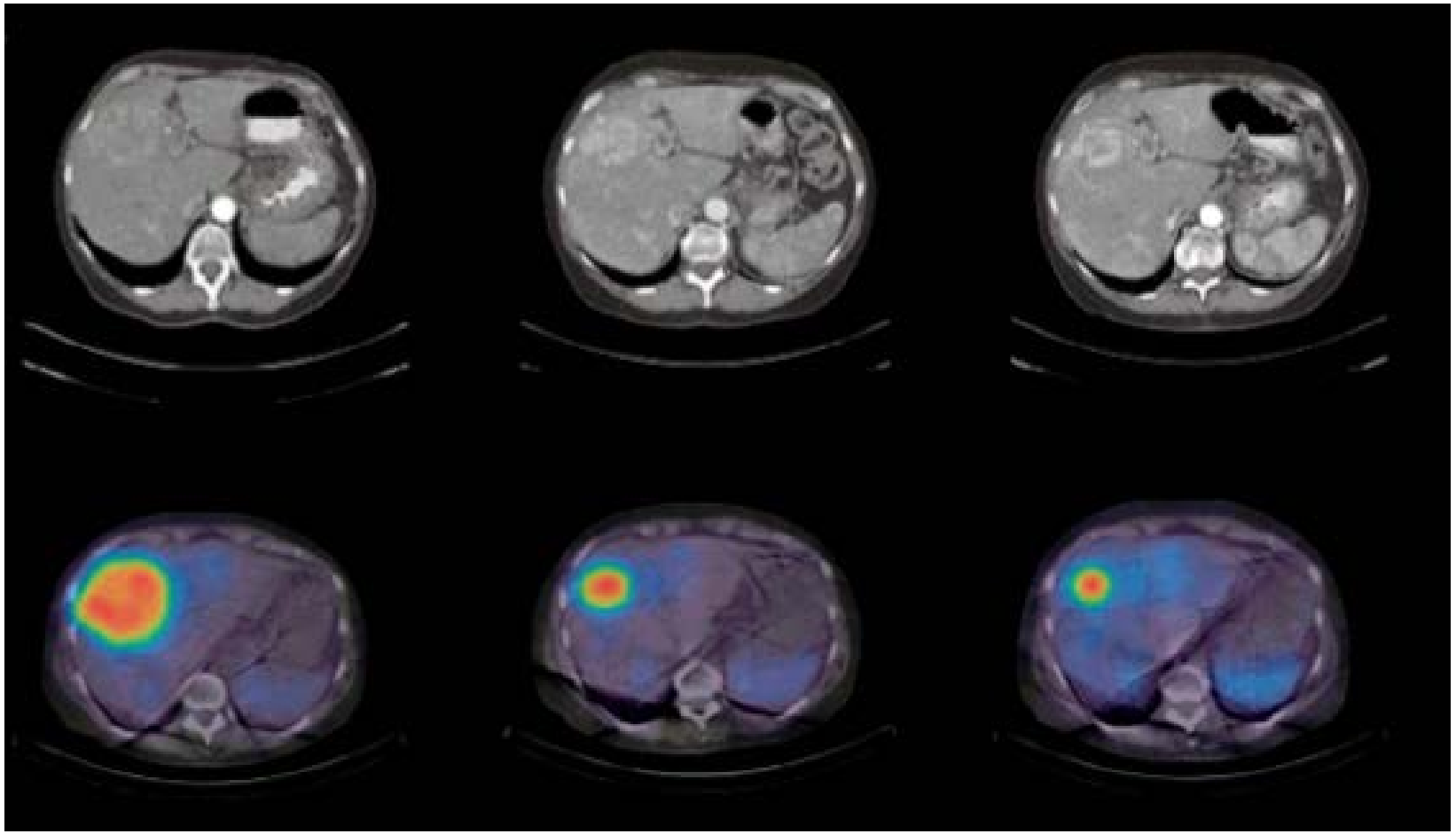


Tumor Dose Heterogeneity

SPECT/CT of ^{177}Lu-DOTATATE



Ilan et. al JNM, 56(3) 2015

EUD – Equivalent Uniform Dose

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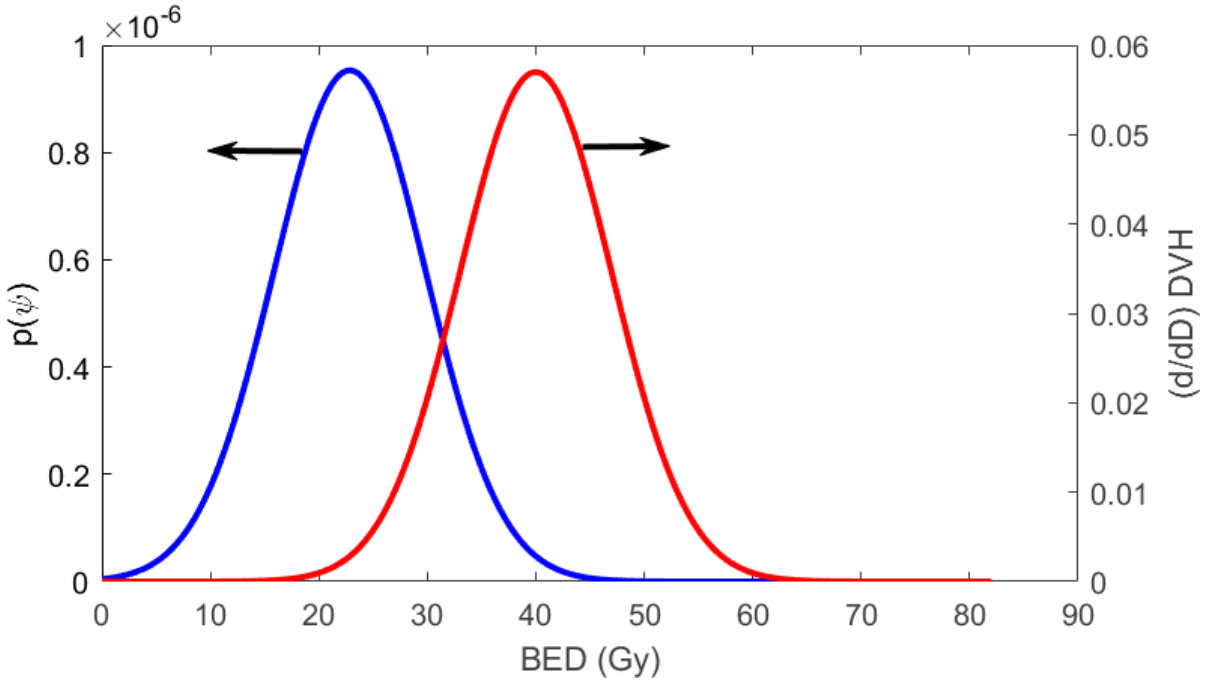
- The non-uniform distribution of BED (or dose) that would produce the same $\log_e$ cell kill as the uniform value of BED (or dose)

$$EUD = -\frac{1}{\alpha} ln\big(SF(\alpha)\big) = -\frac{1}{\alpha} \overbrace{\int_0^\infty p(\psi)\, e^{-\alpha\psi} d\psi}^{\mathcal{L}(p(\psi))}$$

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

$SF(\alpha) = \int_0^\infty p(\psi)\, e^{-\alpha\psi} d\psi \rightarrow$ total survival probability



EUD – Equivalent Uniform Dose

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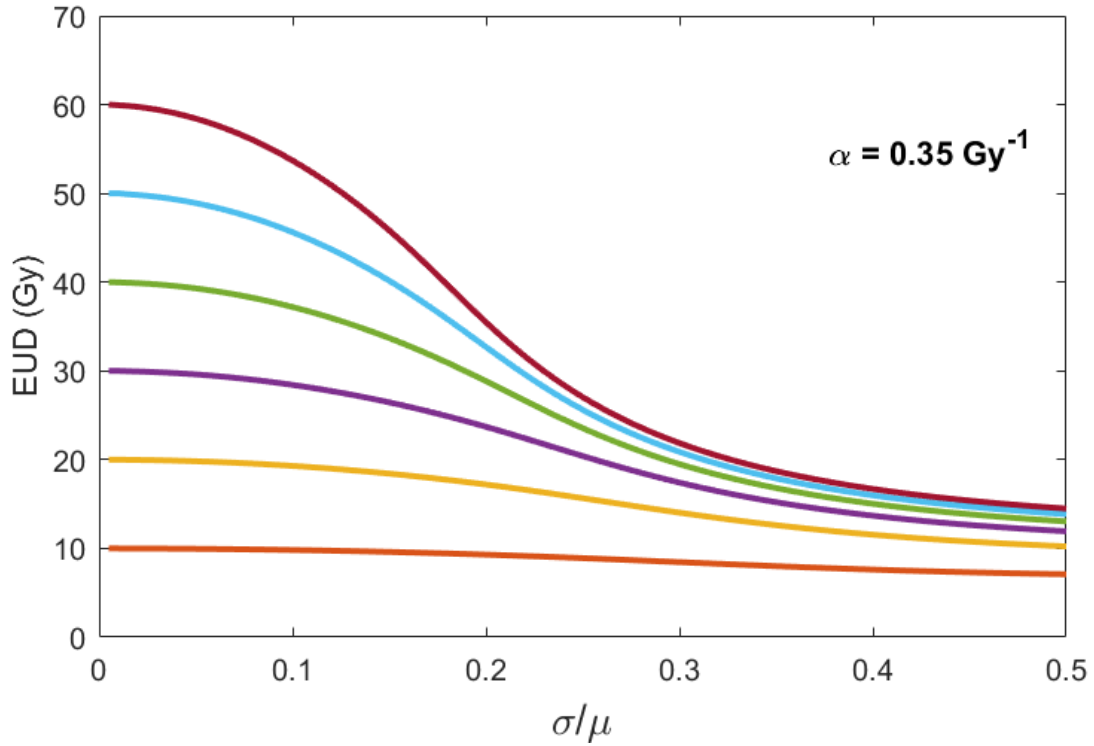
- EUD plotted out as a function of nonuniformity (σ/μ)*



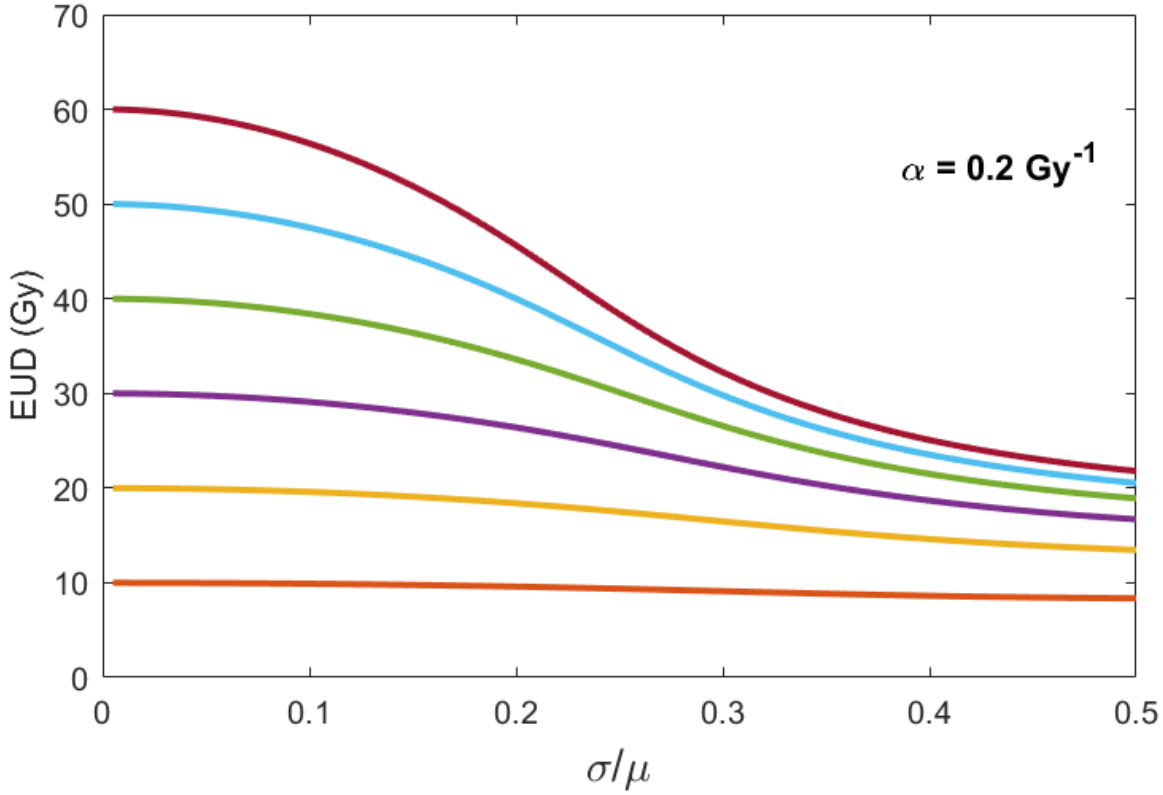
- As the distribution becomes more nonuniform the EUD (hence therapeutic effect) decreases
- The overall loss of therapeutic effectiveness depends on the mean BED and is proportionally worse for greater mean values

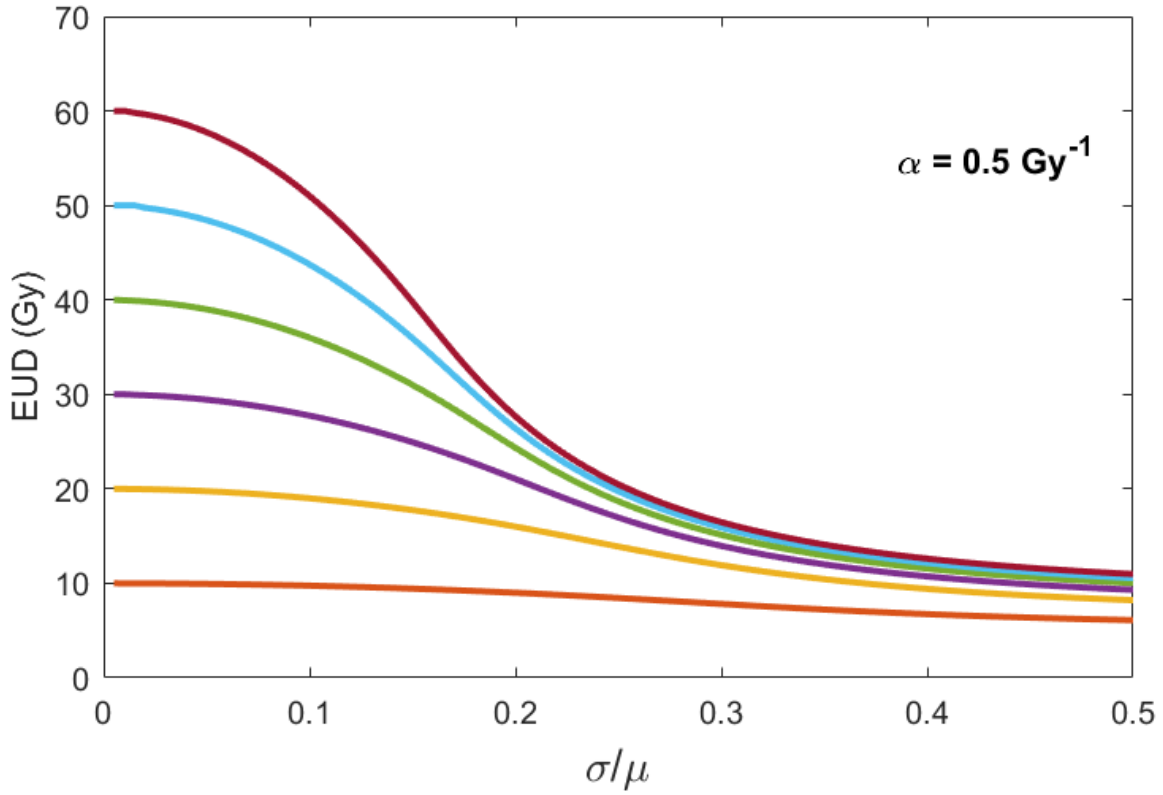
$$\%\ Diff_{60-Gy} = 76\%$$

$$\%\ Diff_{10-Gy} = 29\%$$

*assumes dDVH is normally distributed

EUD – Equivalent Uniform Dose





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

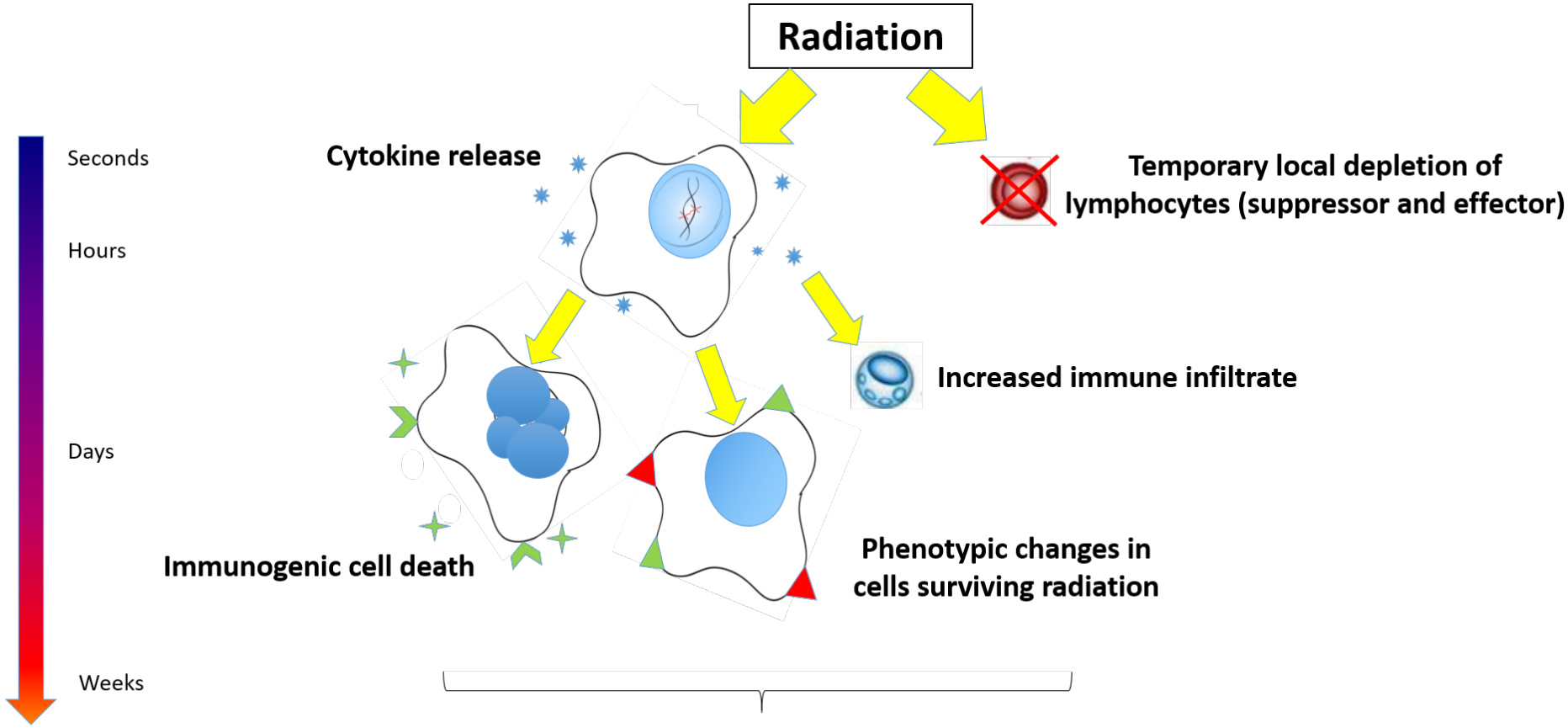
Discussion Points

- 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



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

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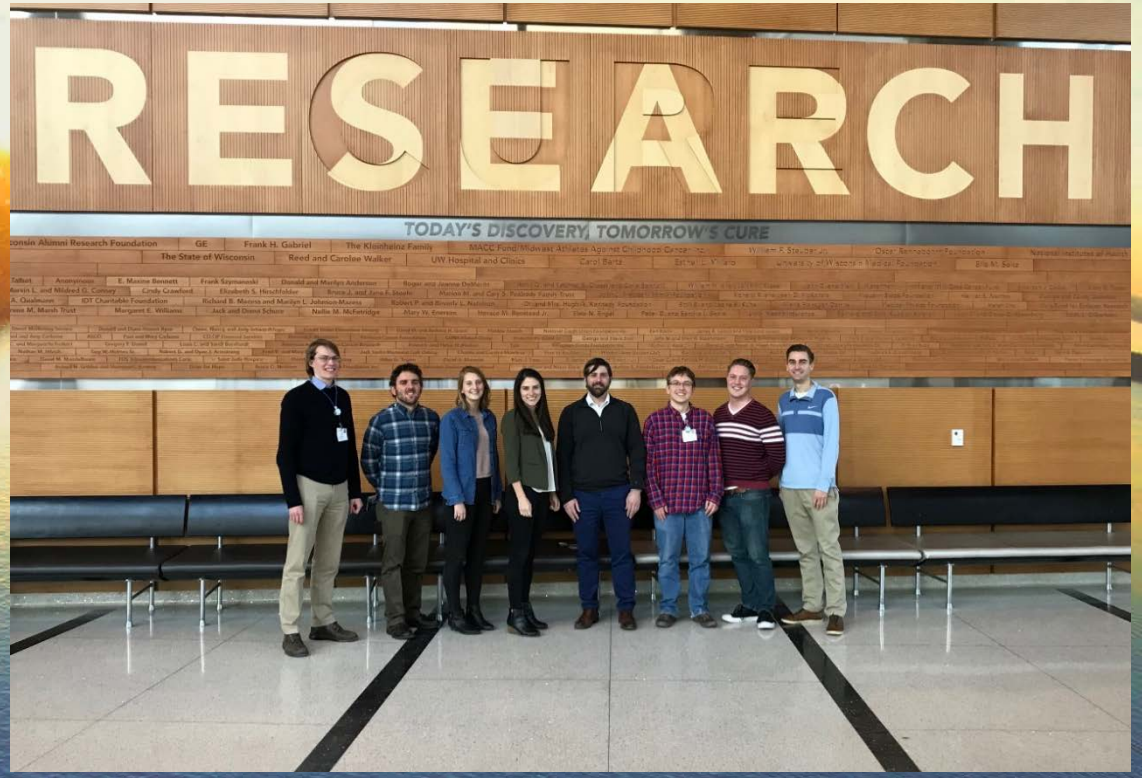

Thank You!

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