A More Precise Way of Calculating the Dose Distribution at a Subcellular Level In Radioligand Therapy

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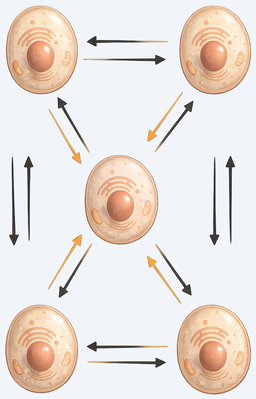
Introduction

- Radioligand therapy (RLT) selectively targets cancer cells while sparing normal tissue.[1]
- In RLT, a major limitation is the **one-size-fits-all dosing** strategy, where the administered activity is not tailored to each patient's in vivo activity biodistribution.

• Personalized RLT should account for:

- ✓ **Crossfire and bystander** effects.
- ✓ In vivo radioligand distribution, particularly random uptake among tumor clones.
- ✓ **Radiation type** and the linear energy transfer (LET).
- ✓ DNA lethal lesions (LLs) rather than absorbed dose.[2]



Crossfire and bystander effects

The Need: A framework for personalized subcellular dosimetry that accounts for stochastic radioligand distribution, radiation type, cross-fire, and bystander effects to optimize radioligand therapy.

Methods

❖ Monte Carlo Multi-cell Model:

A tumor surrounded by six layers of healthy cells was modeled in a PET voxel using TOPAS[3] to obtain the cell-wise absorbed dose.

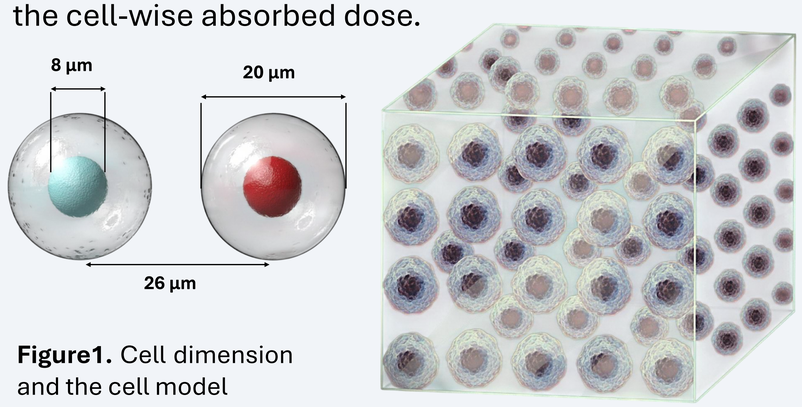


Figure1. Cell dimension and the cell model

❖ Random distribution of activity, dose, and DNA LLs

- 3D time-integrated activity (TIA) maps were generated by sampling from a normal distribution (patient-derived mean, CV = 30%) and convolved with **^{225}Ac**, **^{161}Tb**, and **^{177}Lu** cell dose kernels (CDKs).
- To further assess the effect of different radiation types, a modified linear-quadratic (LQ) model was used to **calculate DNA LLs** accounting for radiation quality and DNA repair.

❖ Cell Dose Kernel (CDK):

^{225}Ac, **^{161}Tb**, and **^{177}Lu** sources were randomly distributed within the cytoplasm of a central cell. Absorbed doses to the central and neighboring cells' nuclei were estimated as a function of distance.

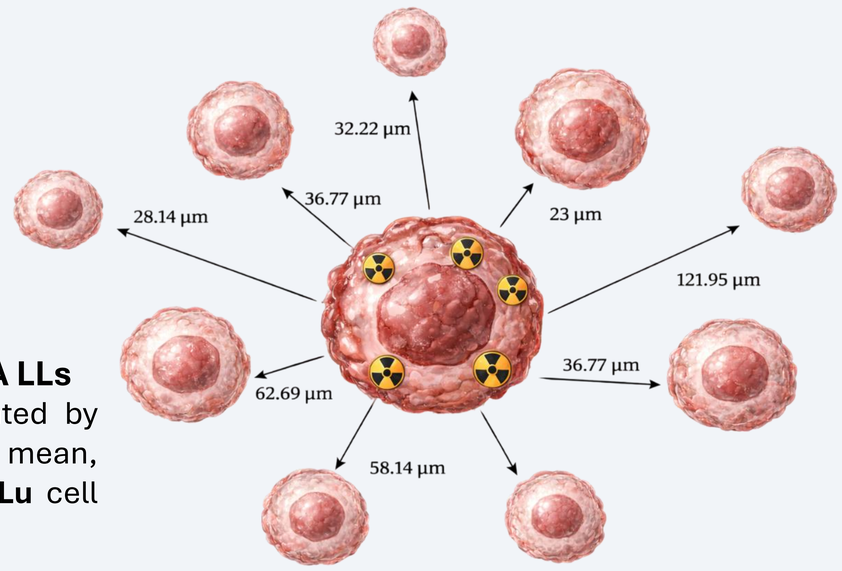


Figure2. Method used for the CDK construction

$$DNA\ Lethal\ Lesions = \alpha D + G\beta D^2$$

Results

3D ^{225}Ac CDK → 3D Convolution with **random TIA maps** → Calculating **DNA Lethal Lesions**

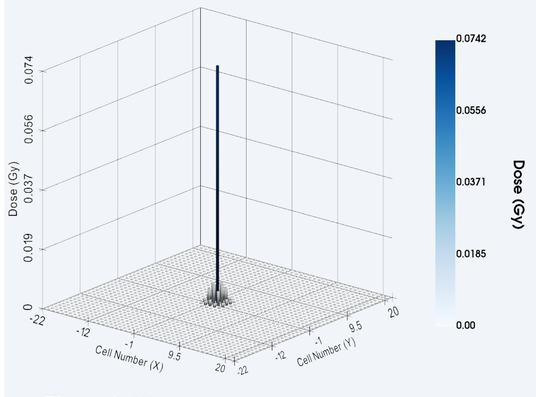


Figure3. ^{225}Ac Cell Dose Kernel (CDK).

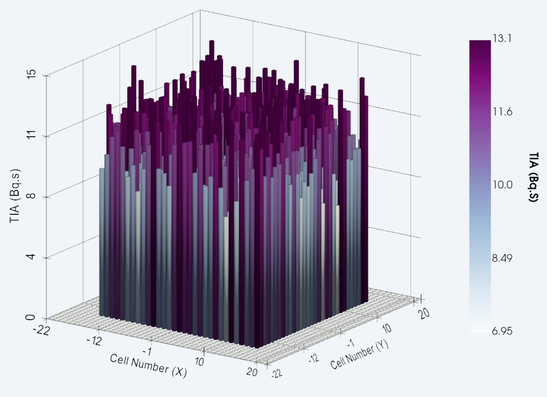


Figure 4. Patient-derived Randomly Generated TIA Map.

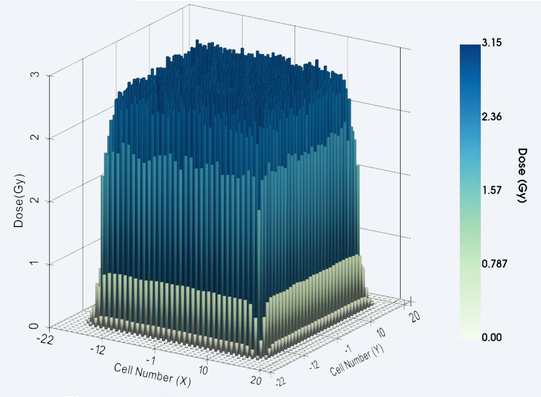
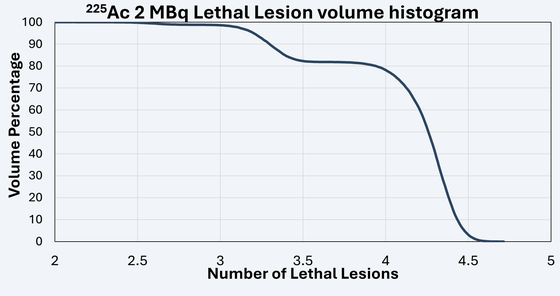


Figure 5. ^{225}Ac Dose Distribution Map (2 MBq).

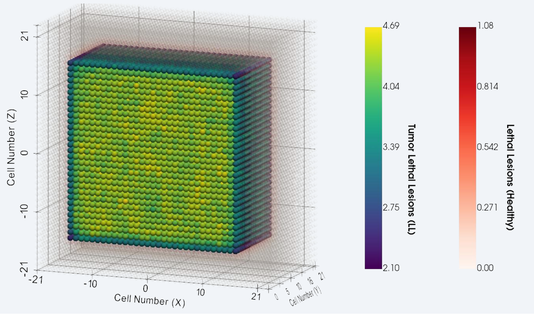
Applying the LQ model:

Maximum dose to a cell: 3.59 Gy
Mean dose to the tumor: 1.08 Gy

Mean lethal lesions across cells: 4.1



3D DNA LL Map in **tumor and healthy tissue** (half- cut view)



Conclusion

- The framework quantifies subcellular absorbed dose in patient-specific tumor models while accounting for **stochastic radioligand uptake**, **radiation type**, and **cross-fire and bystander effects.**
- Coupling these dose maps with the linear-quadratic (LQ) model predicts **cell-specific lethal DNA lesions throughout the tumor.**
- **This enables optimization of administered activity to maximize tumor control while minimizing normal tissue toxicity.**

Acknowledgments

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References

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