LET-guided Adverse Event Initialization Study and LET-guided Robust Optimization in Proton Therapy

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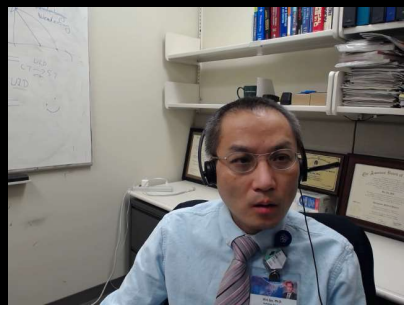
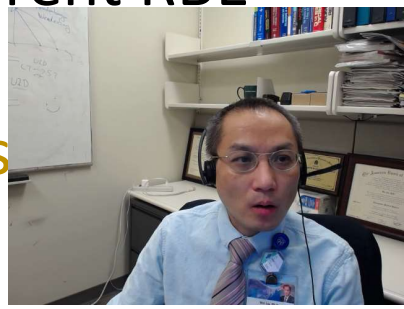


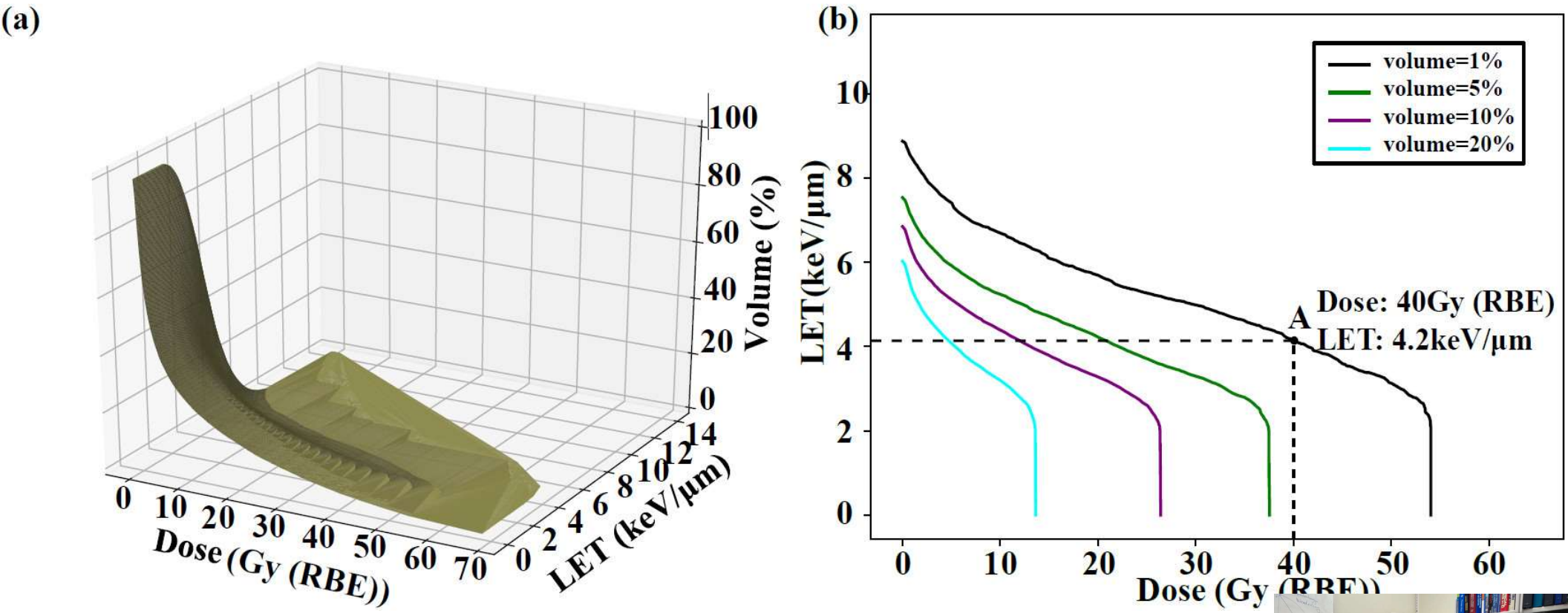
Background

- The LET effect to patient outcome is unclear
- The parameters of the current RBE models have many uncertainties
- Different RBE models give very different results
- Current IMPT planning ignores LET information (assuming an LET independent and fixed RBE of 1.1) and exclusively relies on physical dose
- The ignorance of LET distribution may result in unanticipated AEs and undesirable patient outcome

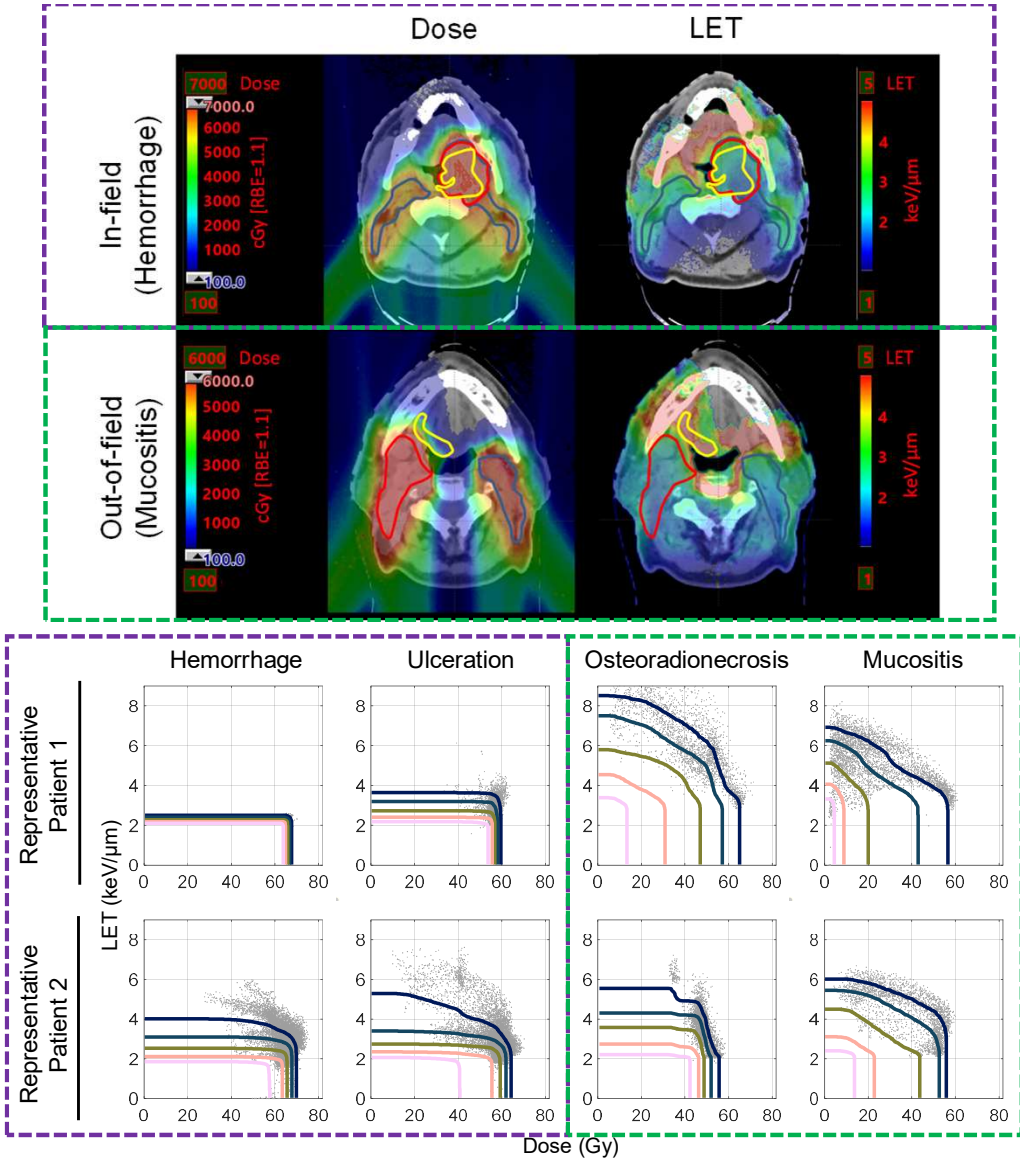
- It is important to address the uncertainties in the current RBE models, use well-defined physics quantities like dose to correlate patient outcomes data, and combine dos for IMPT evaluation and treatment planning

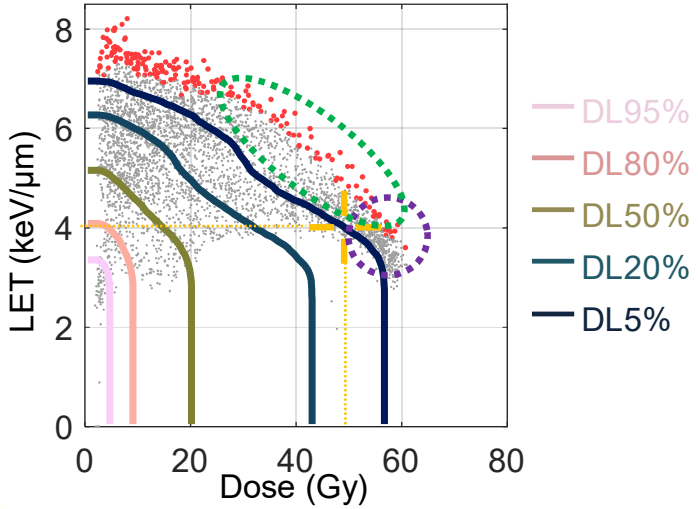


Solution 1: Dose LET Volume Histogram (DLVH)



- DLv%, represent the percentage volume of a structure that has of at least d Gy and an LET of at least l keV/μm
- Present dose and LET in one plot and their interplay





Both dose and LET are important in AE

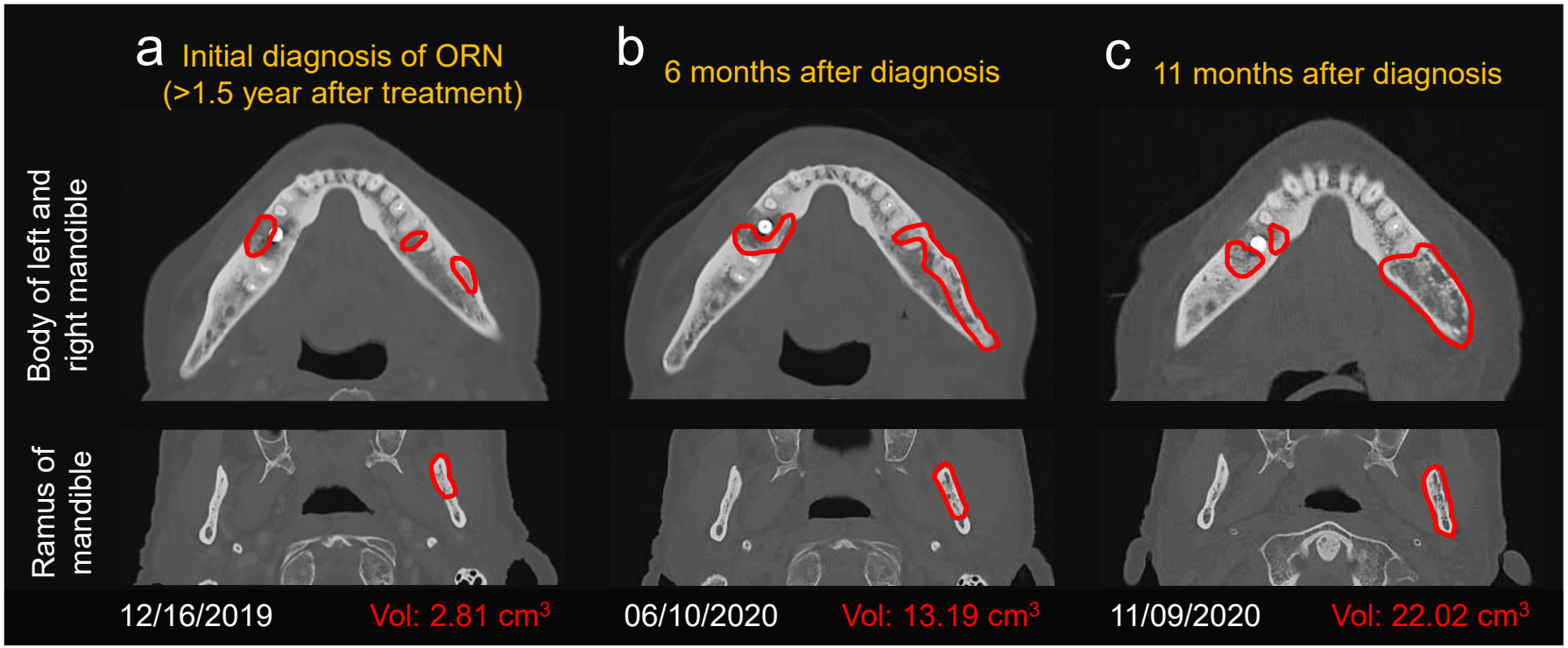
Motivation for seed spot analysis

Assumptions used in the voxel-based analysis for LET-related adverse event studies might not hold:

1. all the damaged voxels were presumably induced from the dosimetric effect (i.e., dose and LET)
2. voxels were independent from each other within the AE regions of the same patients

Only a **sub-population** of the **independent** voxels within the AE regions were dosimetrically important!

Progression of AE regions

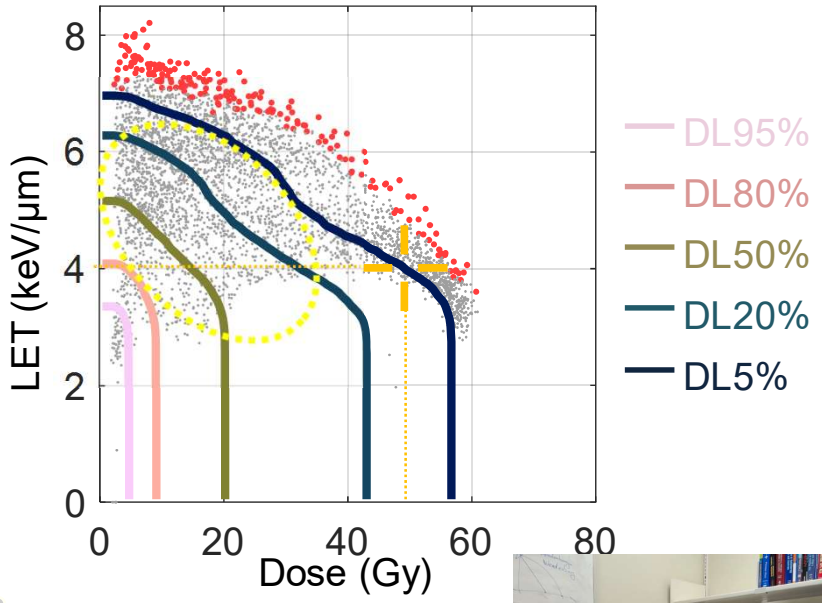


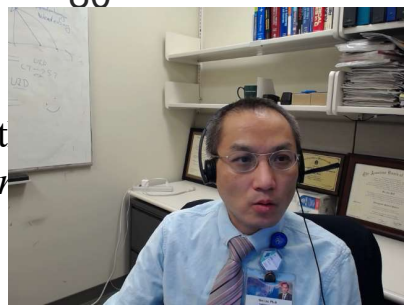
Volume of AE region increased about **10 times within 11 months**

"**Necrotic regions evolve over time and expand to include nearby voxels with low local probal**
Niemierko *et al.* Brain necrosis in adult patients after proton therapy: Is there evidence for depende
energy transfer? *International journal of radiation oncology, biology, physics* 2021;109:109-119.

"The assumption of any regression methods requiring independent data points might not hold". And the inclusion of low dose/LET voxels within AE regions "increased the "noise" level of data."
Niemierko *et al.* Brain necrosis in adult patients after proton therapy: Is there evidence for dependency on linear energy transfer? *International journal of radiation oncology, biology, physics* 2021;109:109-119.

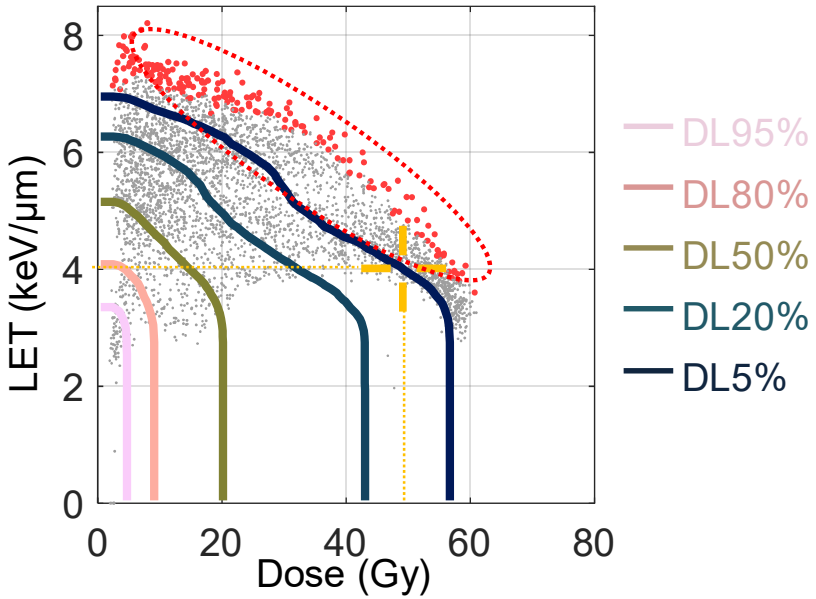
- AE region forms in two stages: dosimetric + biological
- Origin: dosimetric effect; Expansion: biological processes
- Voxels in AE are not independent
- **Solution 2:** Important to find independent seed spots (origin lesion*)

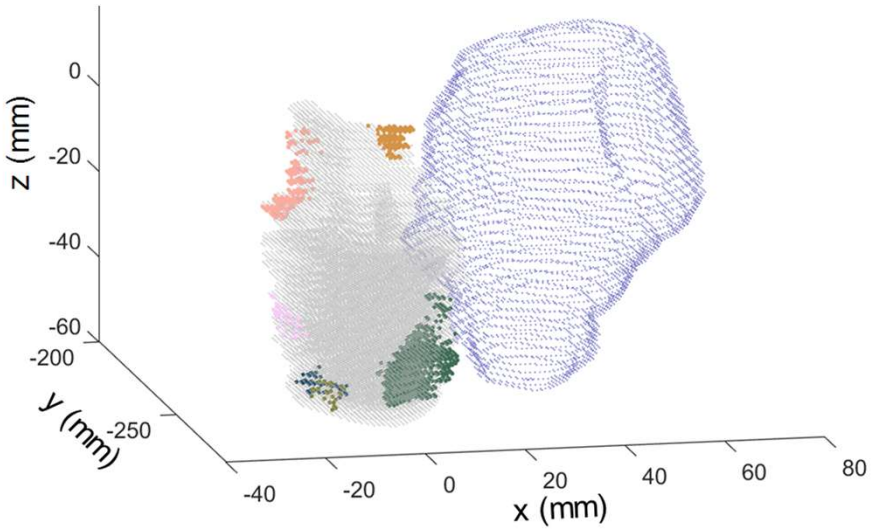




* Bahn E, Bauer J, Harrabi S, et al. Late contrast enhancing brain lesions in proton-treated patients wit glioma: Clinical evidence for increased periventricular sensitivity and variable rbe. *International Jourr Radiation Oncology* Biology* Physics* 2020;107:571-578.

Seed spot analysis

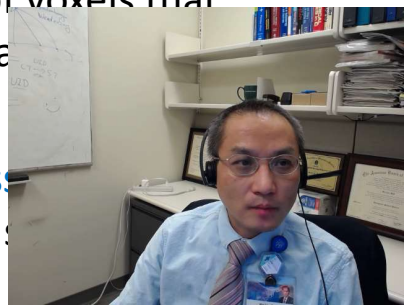




- Assumption: top edge are critical voxels that forms seed spots

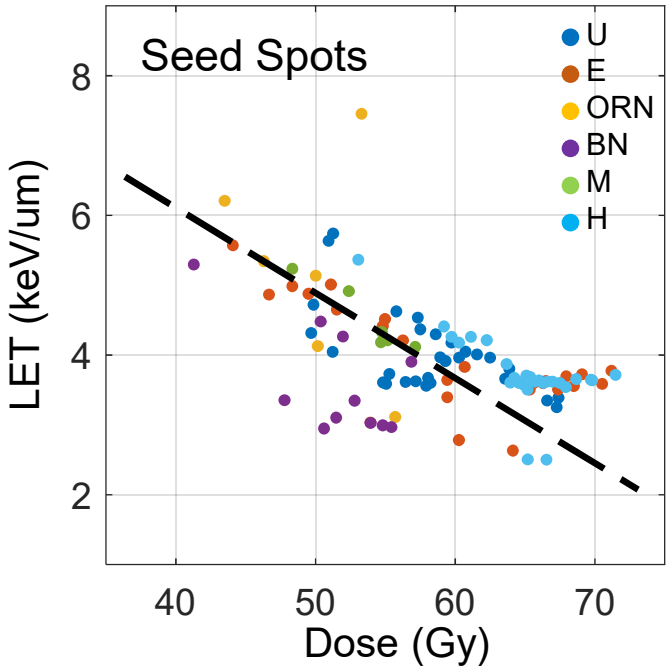
- Cluster to find spatially independent seed spots
- Resembles the patch-based methods in medical imaging analysis
- Find independent spatial clusters of voxels that possess similar characteristics or pa a dosimetry perspective.

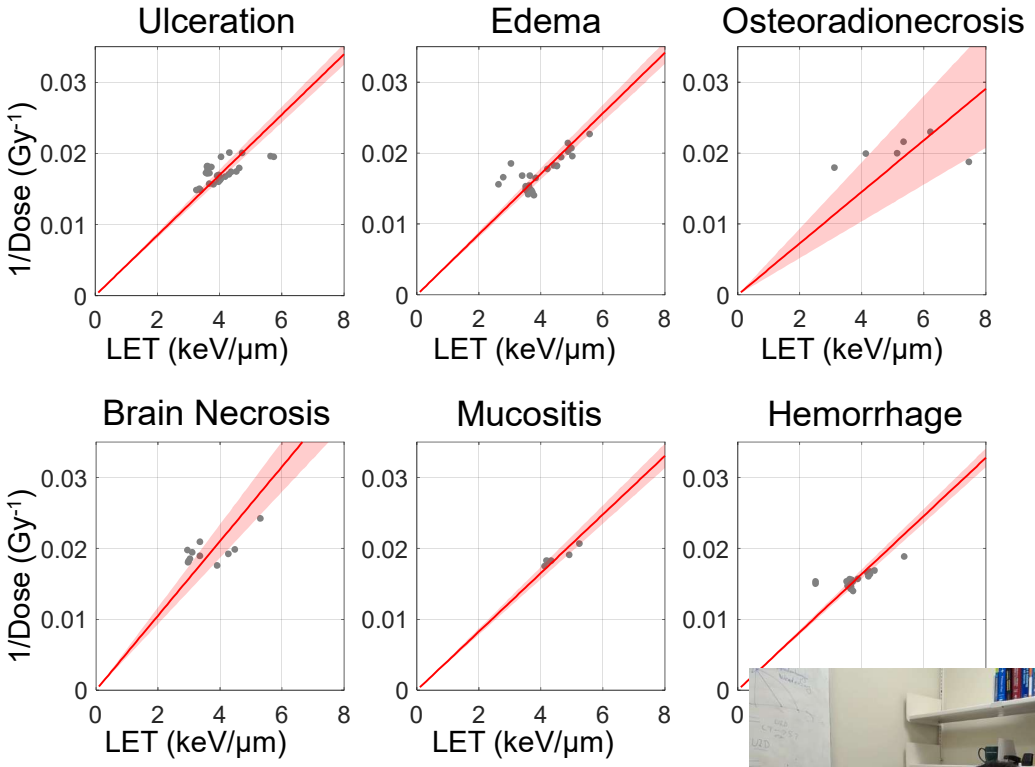
- Seed spot analysis can mitigate the confounding impact from complex biological proces
- Boost the independent data points and fewer patients are required in patient outcome



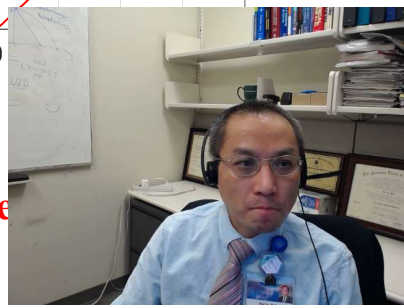
Modelling of seed spot distribution using **the dose LET product (xBD)** ($D \geq 40$ Gy)

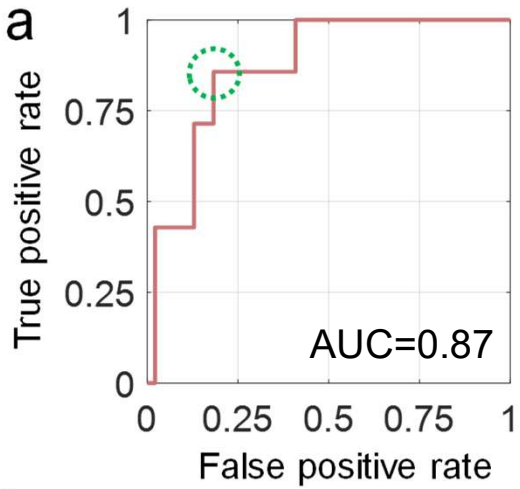
- **Caution: based on a very limited number of patients with AEs.**

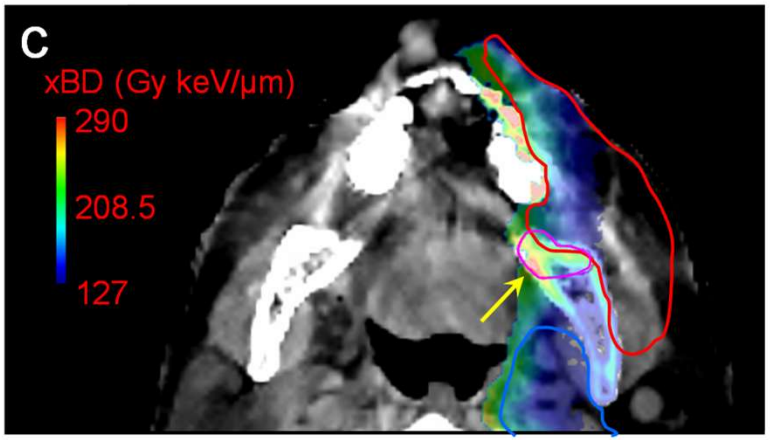


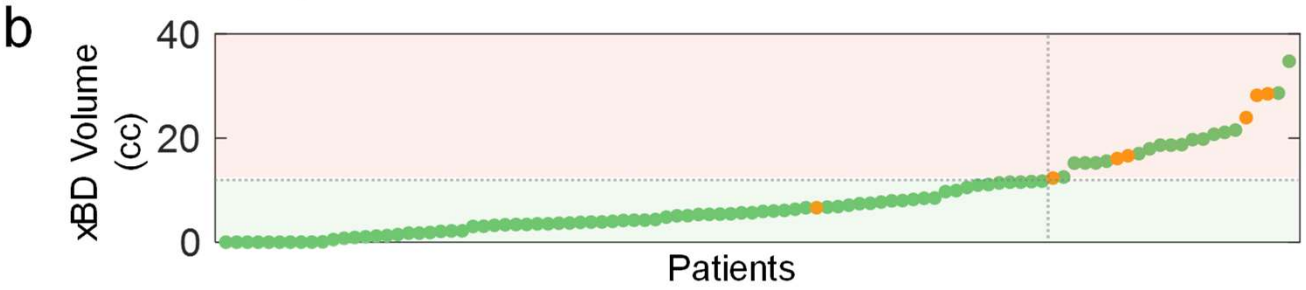


The product of dose and LET (xBD) was found to be a good dose-LET descriptive feature









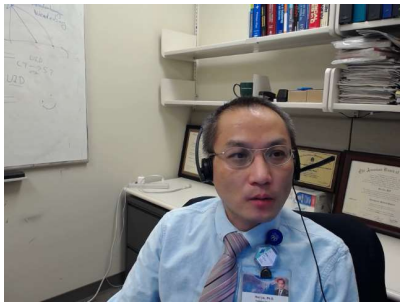
Validation

Patient cohort: 100
Osteoradionecrosis of the mandible: 7
Control: 93

$$V\left(xBD \geq 127.3\ Gy \cdot \frac{keV}{\mu m}\ and\ D \geq 42Gy\right) < 11$$

The xBD based predictive model could be used to predict mandible osteoradionecrosis reas

Clinical Translation DEMOs



GPU-based Real-Time Virtual Particle Monte Carlo

a new concept to avoid simulating secondary particles in proton dose calculation

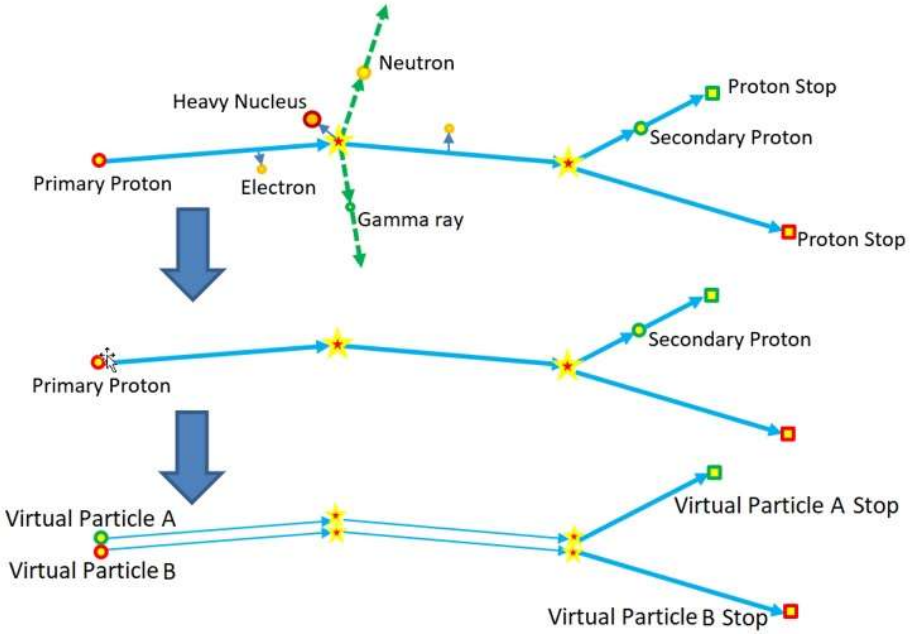
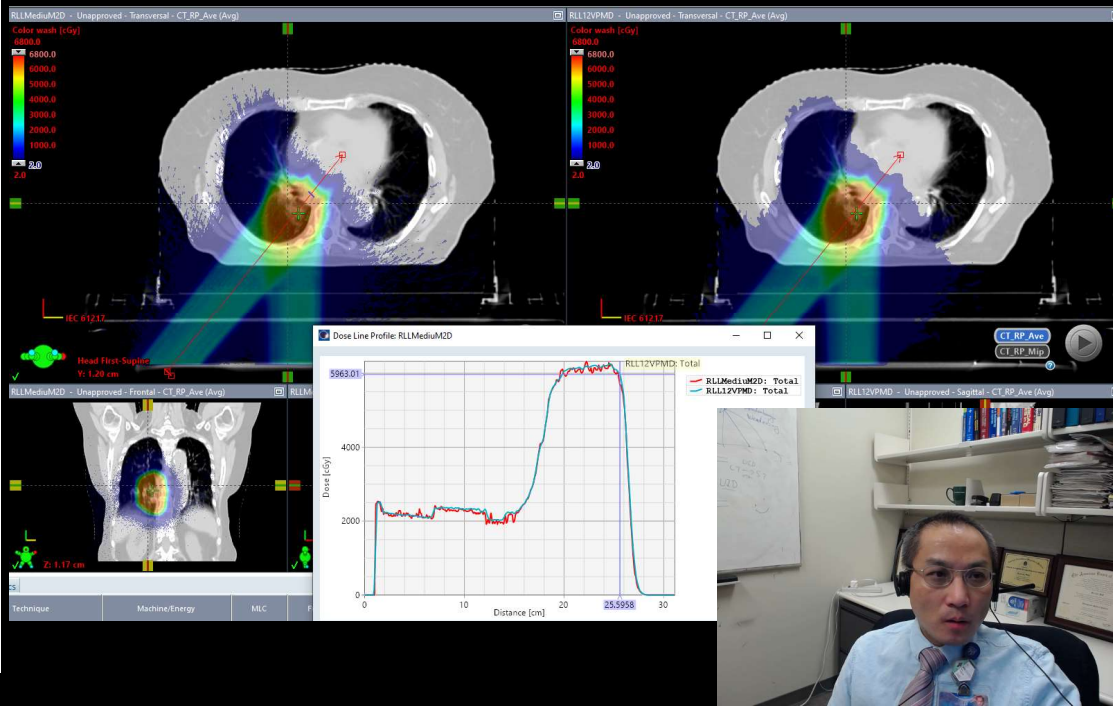
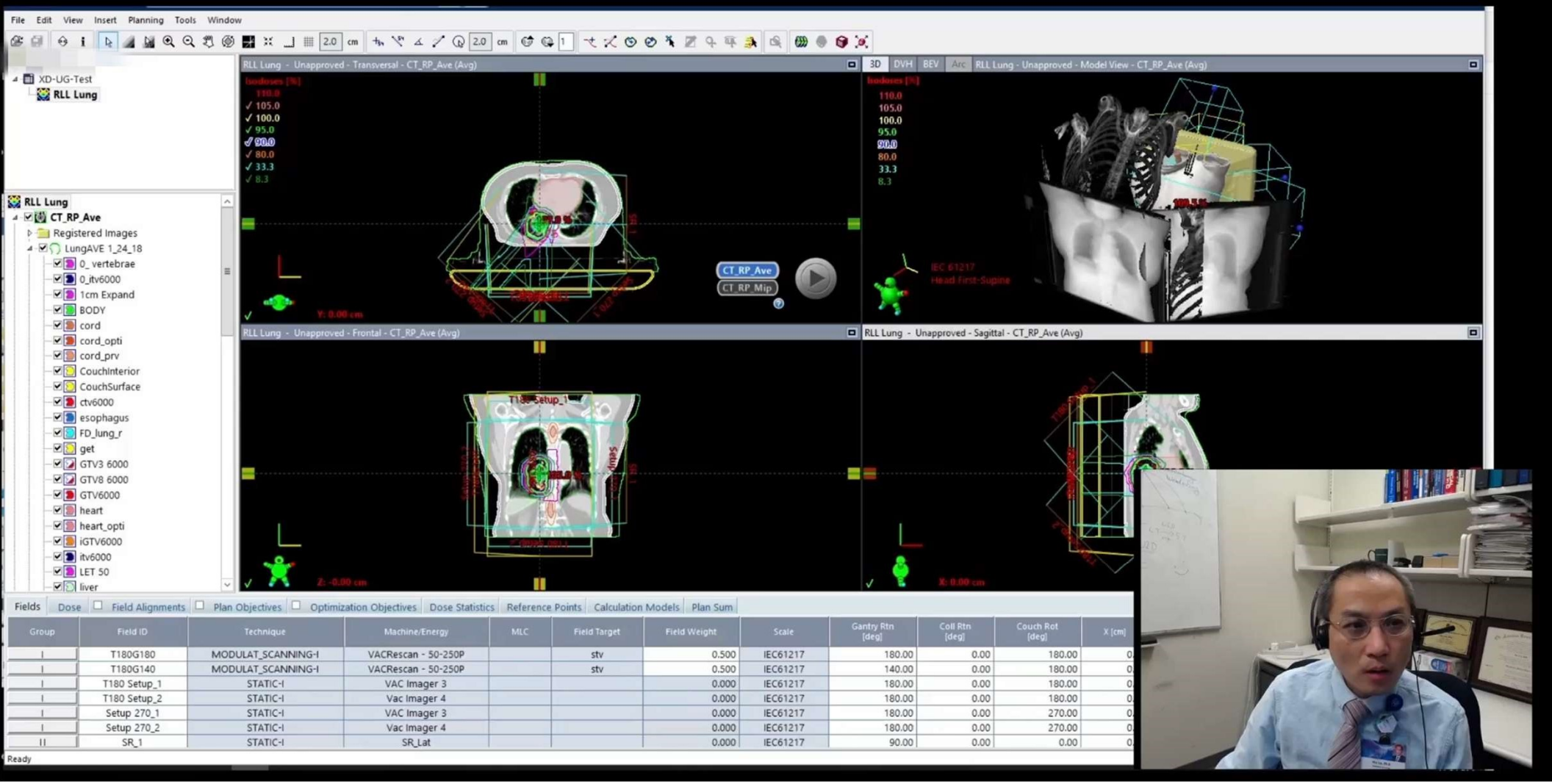


Figure 1. The way to convert the track histories of a realistic proton and its secondaries in a conventional Monte Carlo simulation into two virtual particles. First, analyze the tracks by ignoring neutrons and gamma rays, locally depositing the dose of electrons, heavy ions and nuclear fragments, and converting the tracks of deuterons into tracks of protons. Then we regard the tracks of primary and secondary protons as tracks of two virtual particles, which all start at the starting position of the primary proton, not the forked position where the secondary particles are generated.

- Simulating speed: **29.3M protons/sec/node**
- For most plans, it only takes **2-3 seconds** to finish calculation.

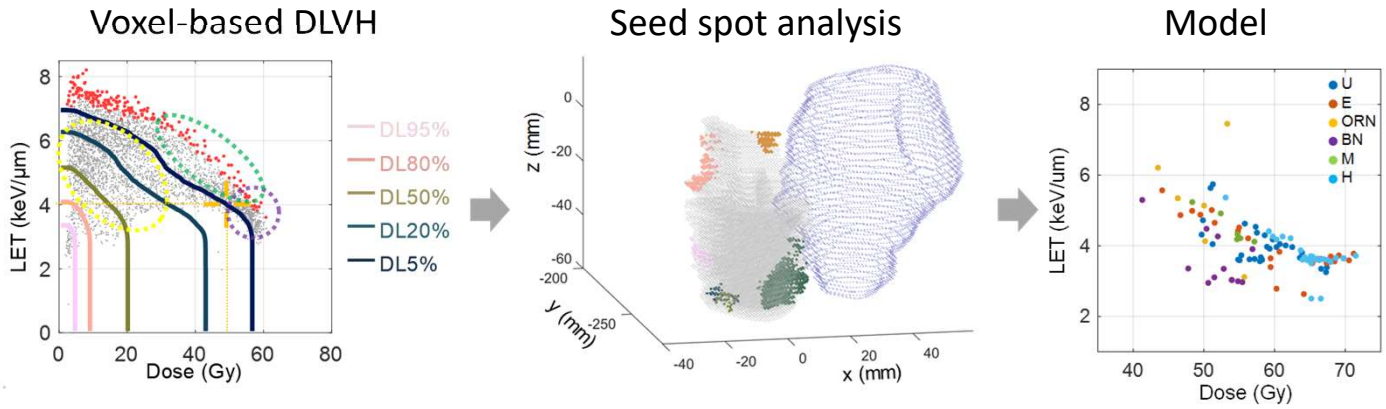


Demo: xBD-based robust optimization



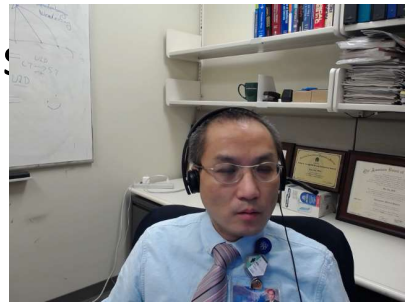
Group	Field ID	Technique	Machine/Energy	MLC	Field Target	Field Weight	Scale	Gantry Rtn [deg]	Coll Rtn [deg]	Couch Rot [deg]	X [cm]
I	T180G180	MODULAT_SCANNING-I	VACRescan - 50-250P		stv	0.500	IEC61217	180.00	0.00	180.00	0.
I	T180G140	MODULAT_SCANNING-I	VACRescan - 50-250P		stv	0.500	IEC61217	140.00	0.00	180.00	0.
I	T180 Setup_1	STATIC-I	VAC Imager 3			0.000	IEC61217	180.00	0.00	180.00	0.
I	T180 Setup_2	STATIC-I	Vac Imager 4			0.000	IEC61217	180.00	0.00	180.00	0.
I	Setup 270_1	STATIC-I	VAC Imager 3			0.000	IEC61217	180.00	0.00	270.00	0.
I	Setup 270_2	STATIC-I	Vac Imager 4			0.000	IEC61217	180.00	0.00	270.00	0.
II	SR_1	STATIC-I	SR_Lat			0.000	IEC61217	90.00	0.00	0.00	0.

Summary



- Developed DLVH and seed spot analysis for AE initialization studies
- Both **dose** and **LET** are important in the AE initialization
- The product of dose and LET (**xBD**) is a good dose-LET descriptive feature for seed spots.

- Established an xBD volume constraint for mandible osteoradionecrosis
- **Caution: based on a very limited number of patients with AEs.**



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