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Relative Biological Effectiveness-weighted Dose Sparing Using LET Optimization

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MOFFITT CANCER CENTER

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Disclosure

- This work was conducted at the University of Florida Proton Therapy Institute. The presenter is currently affiliated with Moffitt Cancer Center.
- No conflicts of interest to disclose.

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Learning Objectives

1. Understand the relationship between LET & RBE within proton plans.
2. Identify OAR that can potentially be affected by high LET for PBS proton left breast treatment.
3. Determine if LET optimization functions have a positive impact on OAR dose sparing with left breast proton treatment plans.

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1. Relationship between LET & RBE Within Proton Plans

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Constant RBE of 1.1

- **RBE (Relative Biological Effectiveness)**[1–6]
  - Ratio of the absorbed dose of a reference radiation to the dose of the test radiation required to produce the same biological effect

$$\frac{D_{Ref}}{D_{Test}}$$

- Reference: 250 kV X-rays or Co-60 gamma rays
- Test beam: Proton, Heavy ions, other type of radiations

Factors affecting RBE (↑)		
Physical Parameters	**Dose Schemes**	**Biological Factors**
• Linear energy transfer (LET↑) • Beam quality (particle types and energy spectra) • Beam delivery technique	• Dose per fraction (↓) • Total fractions • Dose rate and temporal delivery	• Tissue type and radiosensitivity (α/β↓) • Biological Endpoint • Oxygenation(↓) • Genomic heterogeneity

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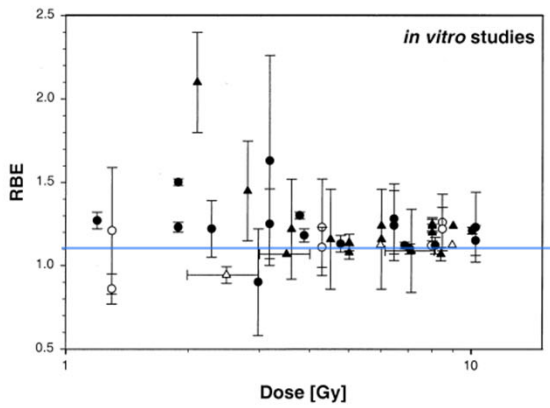
Constant RBE of 1.1

- **Rationale for Adopting a Fixed RBE of 1.1 in Clinical Proton Therapy**[1–5]
  - RBE of 1.1 was originally established in the early days of proton therapy (1970s)
  - Derived as an average of measured RBE values from in vivo experiments
  - Reference conditions for RBE derivation:
    - At the center of the target volume (at the center of SOBP)
    - A standard fraction dose of 2 Gy
    - Averaging across various biological endpoints
      (early/acute reactions for normal tissues, tumor growth delay, c.f. molecular endpoints)
    - Extensive use of mice for both normal tissue and tumor
  - Pragmatic and clinical rationales
    - Institutional consensus that RBE of 1.1 is not clinically unreasonable
    - Modest LET variation in proton beams
    - Lack of clinical counter evidence

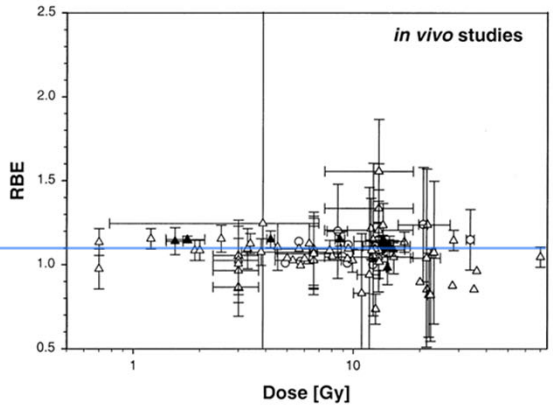
Constant RBE of 1.1

(Relative to Co-60)

- **Rationale for Adopting a Fixed RBE of 1.1 in Clinical Proton Therapy**[5]



Chinese hamster cell lines (● < 100 MeV, ▲> 100 MeV)
Other cell lines (○< 100 MeV, Δ > 100 MeV)



Jejunal crypt cells in mice (● < 100 MeV, ▲> 100 MeV)
Other tissues in mice (○< 100 MeV, Δ > 100 MeV)

Constant RBE of 1.1

- **Clinical Efficacy of Proton Therapy with Fixed RBE of 1.1**[6–9]
  - Accounting for 10% lower physical dose delivered by protons at the same prescribed dose
  - Most consistent advantage of protons is toxicity reduction(lower integral dose and OAR dose)
  - Comparable local control or no significant difference in overall survival or PFS

(Randomized trials)

> **Interpretation** IMPT showed non-inferiority to IMRT for progression-free survival, improvement in overall survival, similar disease control, and reduced high-grade toxicity relative to IMRT. Treatment-related and post-progression deaths occurred more frequently with IMRT. IMPT is a new standard-of-care treatment option for patients with oropharyngeal cancer.
>
> (H&N, The Lancet, 2026)

> **CONCLUSION** For locally advanced esophageal cancer, PBT reduced the risk and severity of AEs compared with IMRT while maintaining similar PFS.
>
> (Esophageal Cancer, JCO, 2020)

(Meta Analysis)

> $p = 0.540$) compared to photons. Conclusions: While long-term oncologic control appears comparable between proton and photon radiotherapy, exploratory analyses suggest that PBT is associated with improved odds of 1-year overall survival. This potential early bene-
>
> (NSCLC, Cancers, 2026)

> *Results:* A total of 230 studies matched inclusion criteria and, due to overlapped populations, 160 were included in the present analysis. Significant lower rates of G ≥ 2 acute GI incidence (2 % vs 7 %) and improved 5-year biochemical relapse-free survival (95 % vs 91 %) were observed in the PT arm compared to XRT. PT benefits
>
> (Prostate, Radiother Oncol, 2026)

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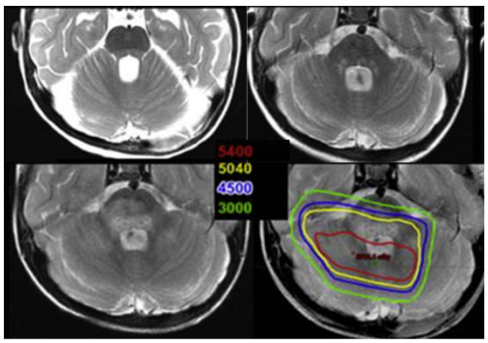
Variable RBE and LET Effects

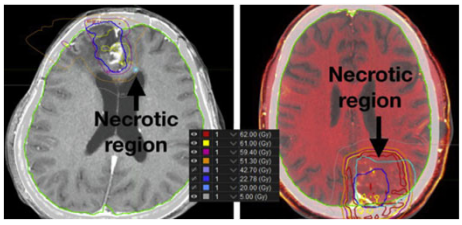
- **Clinical Motivation for Investigating LET Effects**[10,11]
  - Brainstem/Brain injury in pediatric & adult patients
    - Increased brainstem necrosis observed after proton therapy for pediatric posterior fossa tumors
    - Unexpected severity at conventional doses with RBE = 1.1
    - Need for new dose-volume models specific to proton brainstem tolerance

Post op



1.3 yo girl, Ependymoma, GTR (54Gy)

4.4 months post-proton RT (after intervention)



- Higher LET correlates with necrosis location

LET_d for necrosis: 5.6 keV/μm

LET_d for necrosis: 3.5 keV/μm

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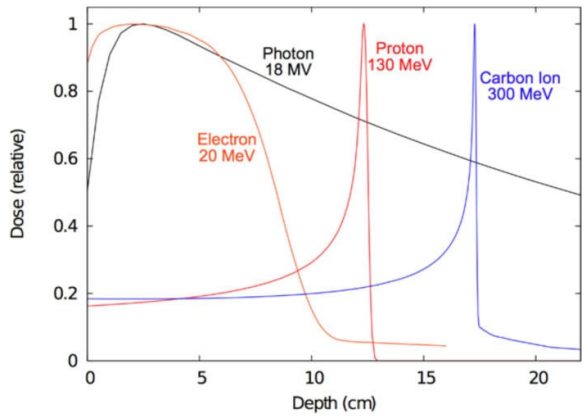
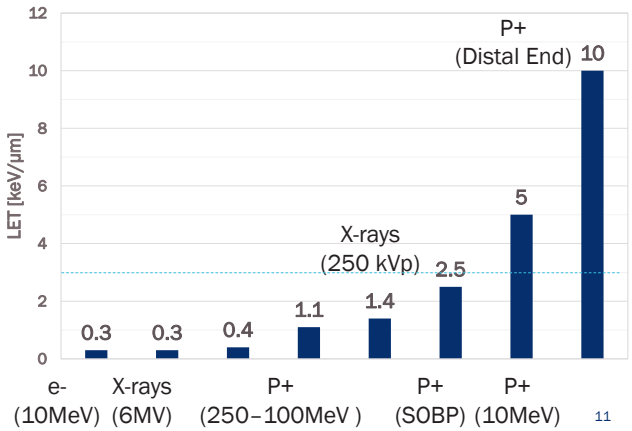
Variable RBE and LET Effects

Proton LET Characteristics Compared to Other Clinical Beams[2,3,12]

PDD across radiation modalities



Approx. LET for radiation modalities and energies



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Variable RBE and LET Effects

Phenomenological Variable RBE Models[13]

- Based on LQ model
- Using the in vitro data
- Fitting of empirical data of clonogenic cell SF
- $RBE_{max}(d \to 0)$, $RBE_{min}(d \to \infty)$
  [α, β, LET_d, $p_0, p_1, p_2, p_3, \ldots$]
- High RBE (↑) – d_{ion}(↓), α/β (↓), LET (↑)

LQ model: $\ln(S) = -\alpha d - \beta d^2$

RBE = d_{ph}/d_{ion}, $\alpha d_{ph} + \beta d_{ph}^2 = \alpha d_{ion} + \beta d_{ion}^2$

RBE = $\frac{d_{ph}}{d_{ion}} = \frac{\sqrt{\left(\alpha/\beta\right)_{ph}^2 + 4d_{ion}\left(\alpha/\beta\right)_{ph} RBE_{max} + 4RBE_{min}^2 d_{ion}^2} - \left(\alpha/\beta\right)_{ph}}{2d_{ion}}$

$RBE_{max} = \sqrt{\alpha_{ion}/\alpha_{ph}}$, $RBE_{min} = \sqrt{\beta_{ion}/\beta_{ph}}$

Models	Cell lines / Data set	Models	Cell lines / Data set
Carabe, Chen	V79 (44), V79 (14)	Belli	V79 (6), $RBE_{max,min}$= f (α(E),β(E))
Wilkens, Wedenberg	V79 (19)	Jones	Multiple (28), $RBE_{max,min}$= f (α,β)
McNamara	Multiple (285)	V79: Chinese hamster lung fibroblasts Majority of data from non-human cell lines Least amount of data for human normal tissues	
Rørvik	Multiple (85)		

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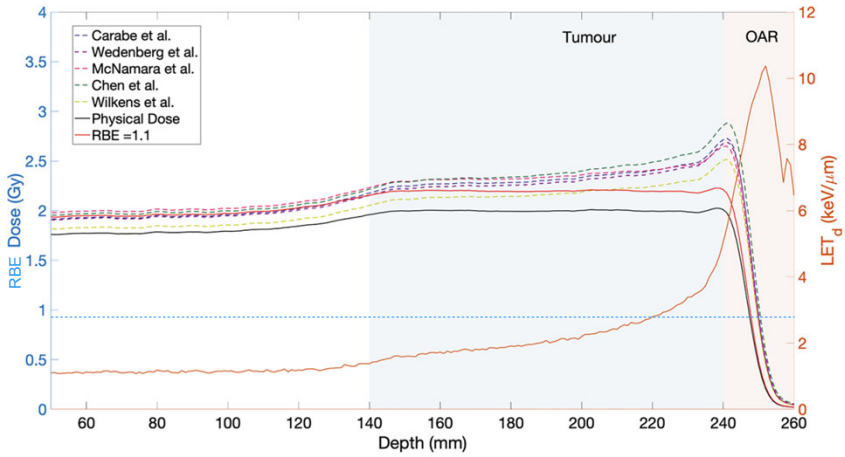
Variable RBE and LET Effects

- **Depth Profiles of LET and RBE Dose: Comparison of Models[13]**



- α/β = 2 Gy
- Proton beam range = 25 cm
- Water

Phenomenological RBE models ranked by predicated RBE magnitude	
Chen	Rørvik
	Lynghom
Carabe	
Wedenberg	
McNamara	
Wilkens	

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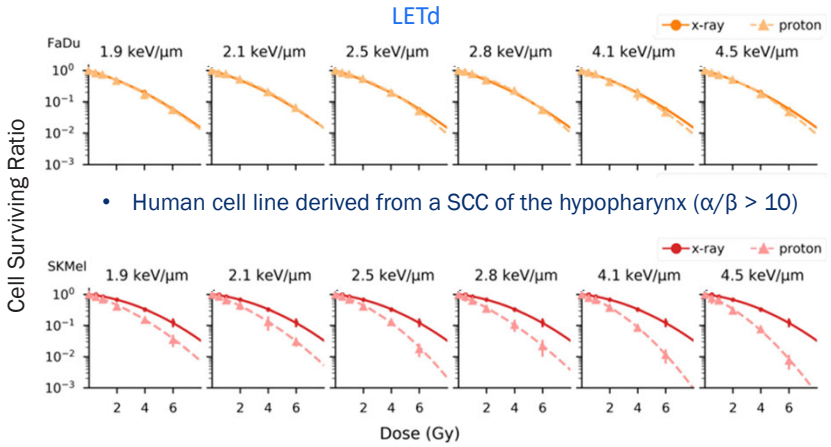
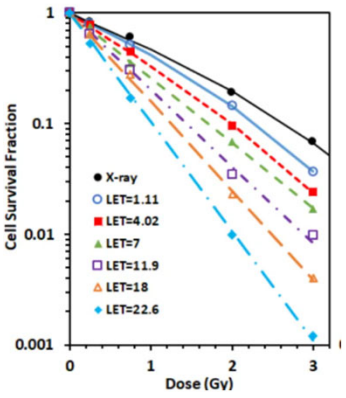
Variable RBE and LET Effects

- **In Vitro Evidence of LET effects Across Tumor/Normal Cell Lines[14,15]**



- Human cell line derived from a SCC of the hypopharynx (α/β > 10)
- Human malignant melanoma cell lines (α/β ~ 3)



- Human skin fibroblast cell line (α/β ~ 2.5)

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Variable RBE and LET Effects

- **Defensive & Offensive Strategies for LET-based RBE Dose Optimization**

  - Defensive strategy: high LET avoidance in OAR[16]
    - Focus on low α/β tissues (α/β = 2-3): nerve, brainstem, optic structures, spinal cord
    - High LET at distal end enhances biological effect even at lower physical doses
    - CNS (Pediatric/Adult) and H&N cases: sparing brainstem and optic structure doses
    - Spine/Chordoma cases: sparing spinal cord doses
    - Lung cases: sparing esophagus and heart doses

  - Offensive strategy: high LET targeting in tumors for therapeutic gain
    - Radiation-resistant/hypoxic tumors benefit from increased RBE
    - Low α/β tumors (α/β ≤3): prostate, sarcoma
    - Potential for RBE dose escalation in high-LET regions

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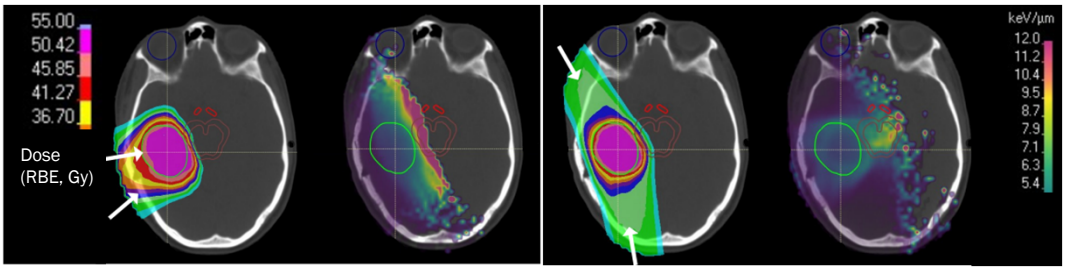
Variable RBE and LET Effects

- **RBE Dose Reduction at the Brainstem[16]**



Geometrically	Physically	Biologically
• Beam angle optimization to avoid distal beam stop at critical OAR	• Increasing beam number to distribute and reduce high LET dose concentration • LET optimization: adjusting beam energy and spot weights to minimize high LET and RBE dose in critical OAR	• Beam configuration guided by tissue radiosensitivity — prioritizing low α/β OAR such as nerve and brainstem

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2. OAR Considerations for High LET Effects in PBS Proton Left Breast Treatment

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OAR Sparing in PBS Proton Left Breast

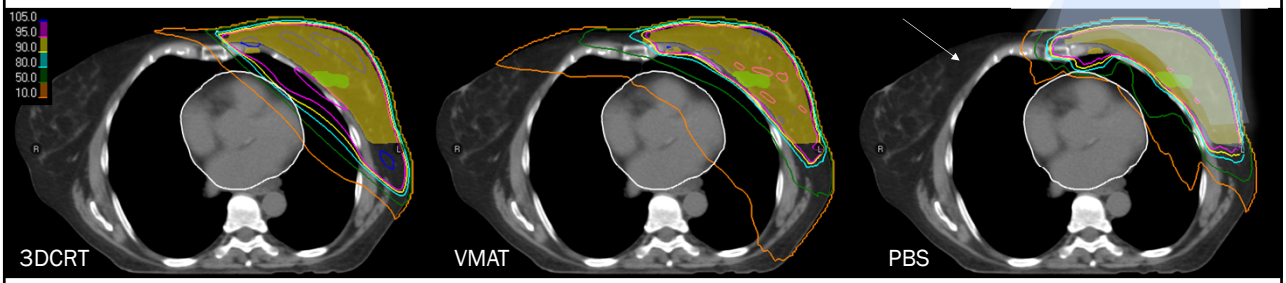
- **Dosimetric Comparison of Left Breast Treatment Techniques**
  - **OAR Sparing Opportunities with Protons**

Robustness optimization:
± 3.5 % / ± 5 mm (density/position uncertainty)

Lt Breast + Regional Nodes	
RBE Dose	50 Gy + 10 Gy
Initial Phase	2 Gy (RBE) x 25 fxs
Boost Phase	2 Gy (RBE) x 5 fxs

Mean Heart Dose [Gy]	
3DCRT	4.80
VMAT	4.20
PBS	0.24

Ipsilateral Lung, V20 [%]	
3DCRT	35.0%
VMAT	24.4%
PBS	24.5%



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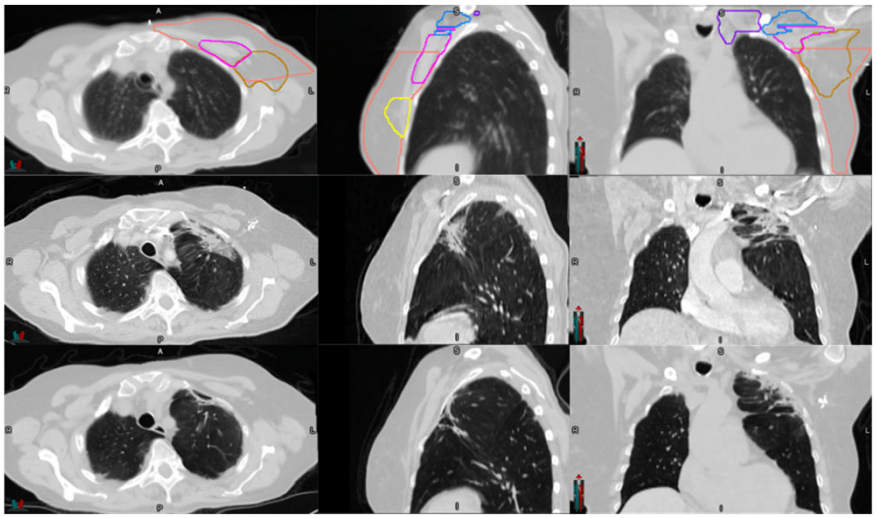
OAR Sparing in PBS Proton Left Breast

- **Reported Case: Pneumonitis Development Following PBS Proton[17]**



Lung window setting
[-1024 – 300 HU]

- Planning - Avg. CT
- Post-PBS treatment CT (C+) Follow-up: 1.5 months
  - Radiation pneumonitis (CTCAE, Grade 2)
- 2nd CT Follow-up: 3 months

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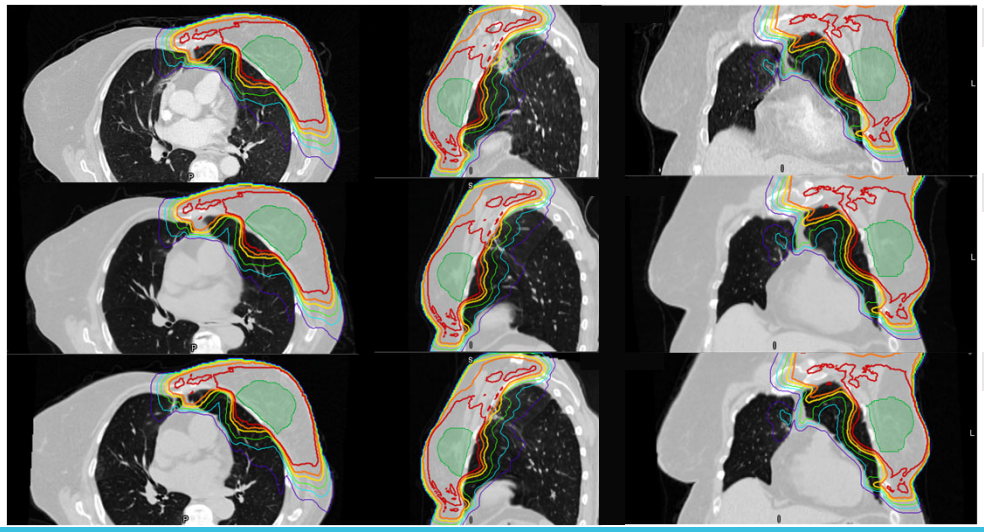
OAR Sparing in PBS Proton Left Breast

- **Mismatch Between Pneumonitis Location and Highest Physical Dose Region[17]**



FU: 1.5 m

FU: 3 m

FU: 4.5 m

Isodose
- 50 Gy
- 45 Gy
- 40 Gy
- 30 Gy
- 20 Gy
- 10 Gy

RBE (1.1)

Tumor bed
(Robustness optimization for tumor bed with high priority)

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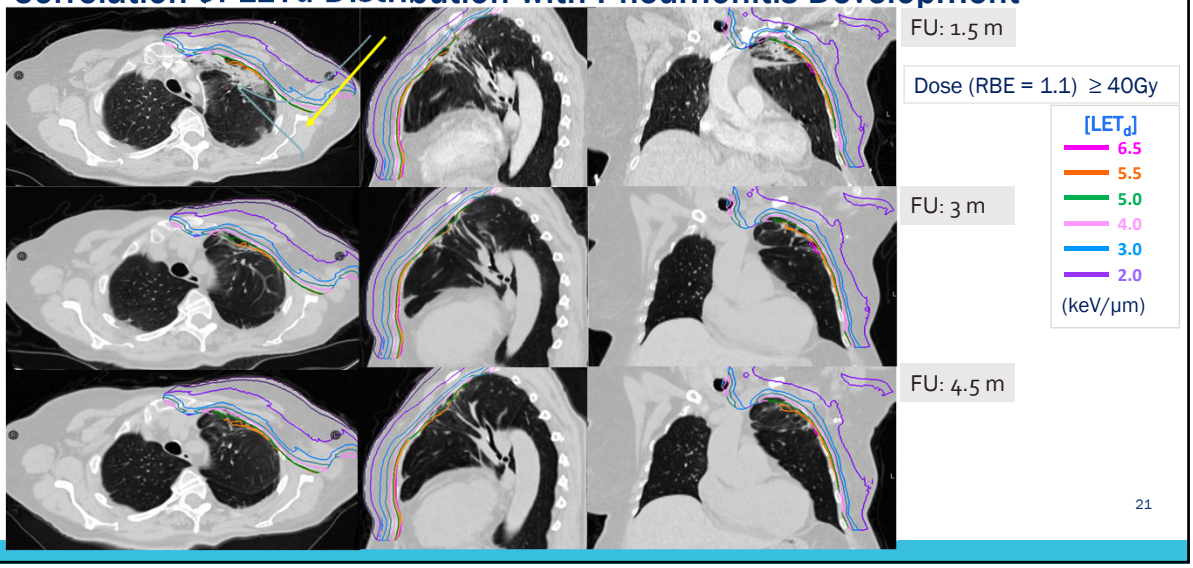
OAR Sparing in PBS Proton Left Breast

Correlation of LETd Distribution with Pneumonitis Development[17]



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OAR Sparing in PBS Proton Left Breast

Clinical Feasibility of LET Optimization for OAR Dose Reduction[18]

Objectives	• Reduce variable RBE dose to OAR while maintaining target coverage using LET optimization • Primary OAR dose reduction: Ipsilateral lung (D_{mean}) • Secondary OAR dose reduction: Heart (D_{mean}) and Humeral Joint (D_{max})
Patient Cohort	• 12 left-sided intact breast cancer patients (IDC or ILC — Stage 2A or 3A) • 4D CT simulation with consistent immobilization devices
PBS planning	• Maintaining current institutional treatment protocol (2 anterior fields) • Recalculating physical dose to vRBE dose: clinical plan ($Plan_{clinical}$) vs LET plan ($Plan_{LET\text{-}opt}$) • Identical robustness optimization uncertainty: density 3.5% / setup 5 mm
LET optimization	• Based on review of 40 left breast proton plans, maximum LET_d thresholds were established for 3 primary OARs: - Lung (< 8–10 keV/μm, $D_{RBE(1.1)} \geq 20$ Gy), - Heart (< 12–14 keV/μm, $D_{RBE(1.1)} \geq 1$ Gy) , - Humeral joint (5–6 keV/μm, $D_{RBE(1.1)} \geq 5$ Gy).
Dosimetric Comparison	• Variable RBE (vRBE) dose calculated using McNamara model incorporating LET_d • α/β values: breast target = 4 Gy, all OAR and normal tissues = 3 Gy
Statistical Analysis	• Paired t-test & Wilcoxon Signed-Rank (WSR) test applied based on data normality.

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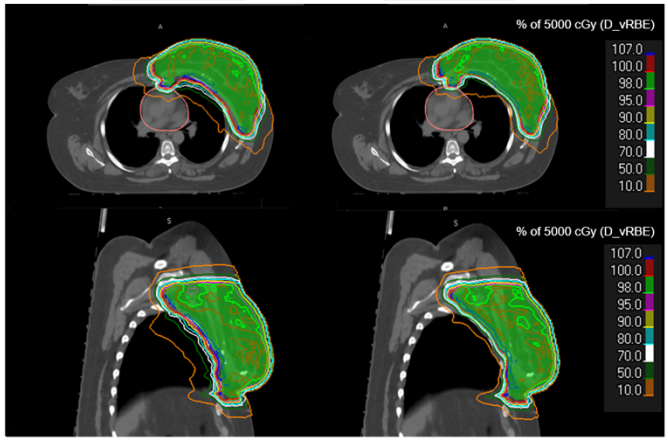
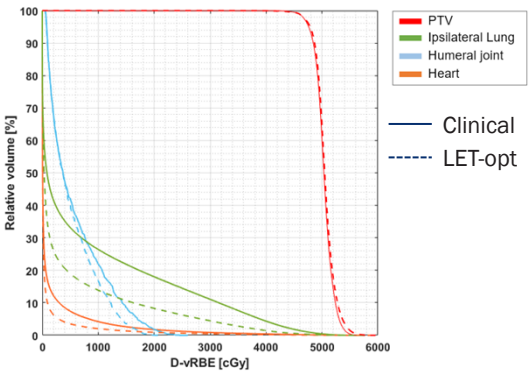
OAR Sparing in PBS Proton Left Breast

- Variable RBE Dose Comparison: Clinical Plan vs. LET Optimized Plan[18]

$Plan_{clinical}$ $Plan_{LET\text{-}opt}$



DVH Comparison



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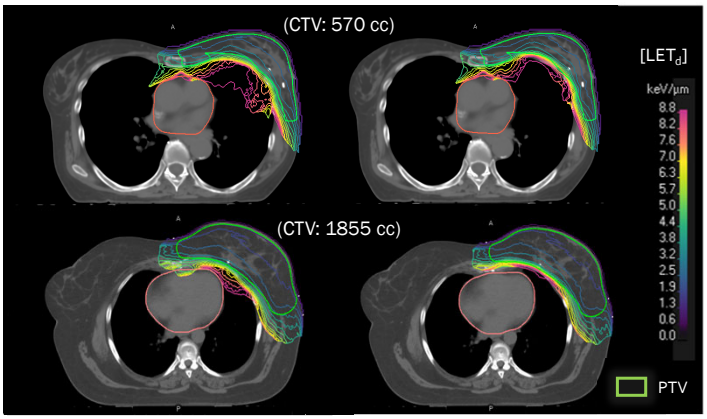
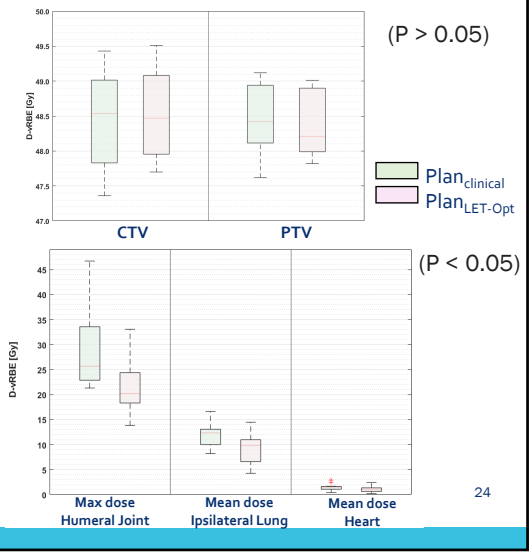
OAR Sparing in PBS Proton Left Breast

- LETd Comparison: Clinical Plan vs. LET Optimized Plan[18]

$Plan_{clinical}$ $Plan_{LET\text{-}opt}$





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3. Determine if LET optimization functions have a positive impact on OAR dose sparing with left breast proton treatment plans.

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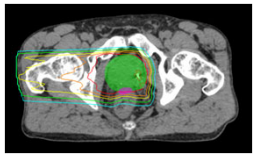
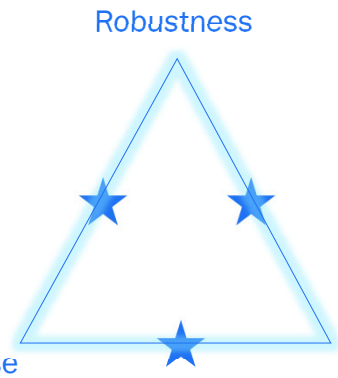
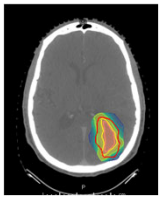
Challenges and Controversies in LET Optimization

- **LET Optimization Trilemma: Balancing Competing Objectives[19]**
  - Simultaneous optimization of superior target coverage, OAR dose sparing with LET optimization, and robustness - not always achievable
  - Competing objectives require clinical priority-based compromise



- Prostate PBS with SFO
  - Robustness↑, Uniform Dose↑
  - LET optimization ■





- High LET optimized into the tumor
  - LET optimization ■, RBE benefits ↑
  - Robustness ↓

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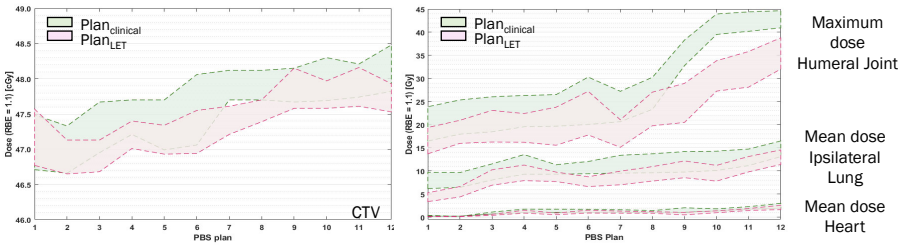
Challenges and Controversies in LET Optimization

- **Remaining Challenges in Variable RBE Model Application[19,20]**
  - Risk factors of uncertainties of LET, LETd, RBE models to TCP and NTCP
  - LET_d averages the LET spectrum within a voxel — high and low LET contributions are combined, potentially masking true biological effects of high LET components
  - Challenges in Isolating True High LET Effects from Dose-Dependent LETd Variation

Dose Band Width Across Robustness Evaluation Scenarios



  - Biological and clinical uncertainties: Patient-specific genetic and DNA repair profiles are not currently incorporated into LET-based RBE models
  - Combined medium-to-high dose and high LET regions may carry clinically significant biological effects — thresholds remain under active investigation

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Conclusions

1. Relationship between LET & RBE Within Proton Plans

- Fixed RBE of 1.1 remains the current clinical standard, supported by experimental and clinical outcome data
- Phenomenological variable RBE models estimate LET effects, more sensitively for low α/β tumors and OAR at the distal end and tumors

2. OAR for High LET Effects in PBS Proton Left Breast Treatment

- Informed by reported clinical complications following PBS proton breast treatment, vRBE doses for ipsilateral lung, heart, and humeral joint were spared through high LET reduction
- LET optimized two-field PBS plans were feasible in reducing OAR vRBE doses while maintaining target coverage with acceptable robustness

3. Impact of LET Optimization on OAR Dose Sparing in Left Breast Proton Plans

- LETd limitations in capturing the true LET spectrum and biological uncertainties in isolating genuine high LET effects highlight the need for further investigation
- Simultaneously achieving LET reduction for OAR dose sparing and superior target coverage with acceptable robustness remains a key challenge for clinical implementation

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Acknowledgments

- The author would like to thank the dosimetry and physics teams at the University of Florida Health Proton Therapy Institute and Moffitt Cancer Center for their invaluable support and contributions to this study.

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