Combined Dose and Linear Energy Transfer Effects on Capsular Contracture in Proton Postmastectomy Radiation: A Matched Case-Control Study

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Purpose: Pencil beam scanning (PBS) proton therapy enables highly conformal dose distributions and is increasingly used for postmastectomy radiation therapy (PMRT) to reduce cardiopulmonary exposure. However, implant-based reconstruction (IBR) in the setting of PMRT remains susceptible to capsular contracture, and the potential contribution of elevated linear energy transfer (LET) in PBS has not been well characterized. This study aimed to investigate the combined effects of dose and dose-averaged linear energy transfer (LET_d) on capsular contracture after proton PMRT and to derive preliminary, clinically interpretable *dose–LET volume constraints (DLVCs)*.

Methods: We conducted a retrospective case-control study of consecutive breast cancer patients who underwent mastectomy followed by implant-based reconstruction and conventionally fractionated proton PMRT (50 Gy in 25 fractions) between 2015 and 2021. Patients who developed Baker grade III–IV capsular contracture were identified and matched 1:2 with controls using nearest-neighbor matching based on clinical and pathological variables. *Dose-LET volume histograms (DLVHs)* were calculated for peri-implant tissue (5-mm shell around the implant). Generalized linear mixed-effects regression (GLMER) was employed to identify DLVH indices significantly associated with capsular contracture. Redundant indices were removed using Spearman correlation analysis. DLVCs were derived from receiver operating characteristic (ROC) analysis and evaluated using a support vector machine (SVM)-based normal tissue complication probability (NTCP) model with leave-one-out cross-validation

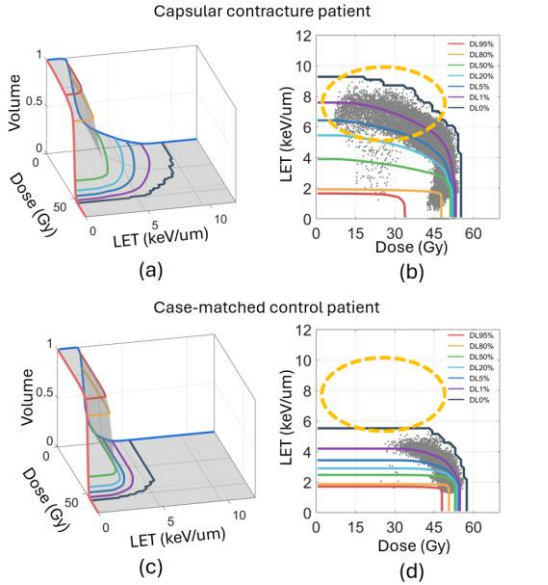

Figure 1. 3D surface plot and iso-volume contour plot of Dose-LET volume histogram (DLVH) of surrounding implant for one AE patient and one case-matched control patient. Iso-volume lines of DL0%, 1%, 5%, 20%, 50%, 80%, and 95% were plotted. The DLVH index, V(d, l), was defined as V(% for normalized volume) of the structure with a dose of at least d Gy[RBE] and an LET_d of at least l keV/µm. The gray dots in the iso-volume contour plot. The dark shaded grey in 3D plot indicates the DLVH surface.
The yellow dashed circles in iso-volume contour plot highlight the difference of DLVHs between capsular contracture patient and control patient.

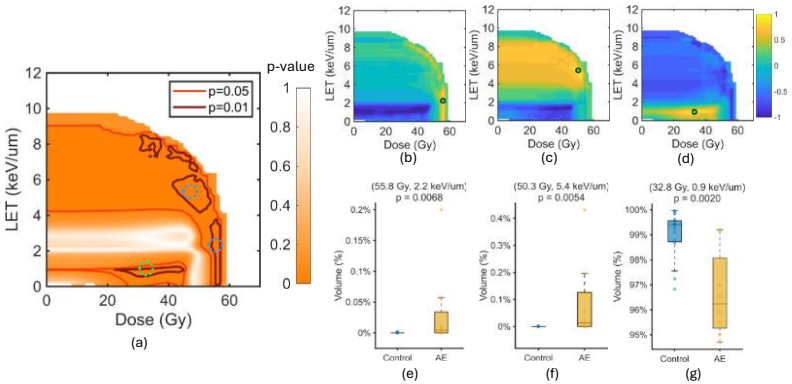

Figure 2. (a) p-value map of generalized linear mixed-effects regression (glmer) models for all DLVH indices. Iso-p-value lines of 0.01and 0.05 were contoured in the map. The index correlated with capsular contracture are a larger V(55.8 Gy, 2.2 keV/µm) and V(50.3 Gy, 5.4 keV/µm) of the capsular contracture (blue circles) and smaller V(32.8 Gy, 0.9 keV/um) of the capsular contracture (green circles). (b-d) Spearman's coefficient map of the DLVH indices, which were indicated by green dots. V(55.8 Gy, 2.2 keV/µm) and V(50.3 Gy, 5.4 keV/µm) show relatively low correlation. But they both have negative correlation to V(32.8 Gy, 0.9 keV/um). Spearman's coefficient map of other two redundant DLVH indices are present in SI. (e-g) Box plot of 3 significant DLVH indices, with p=0.0068, 0.0054 and 0.0020.

Results: Among 145 consecutive patients, 8 developed capsular contracture and were matched to 16 controls. Three independent DLVH indices were significantly associated with capsular contracture ($p<0.01$): V(55.8 Gy[RBE=1.1], 2.2keV/µm), V(50.3 Gy[RBE=1.1], 5.4keV/µm), and V(32.8Gy[RBE=1.1], 0.9keV/µm). After Benjamini–Hochberg (BH) false discovery rate correction across all 4,096 DLVH indices, all three remained significant (q_{BH} = 0.052). The corresponding DLVCs were: V(55.8 Gy[RBE=1.1], 2.2keV/µm) < 0.0033%, V(50.3 Gy[RBE=1.1], 5.4keV/µm) < 0.0017%, and V(32.8 Gy[RBE=1.1], 0.9keV/µm) > 96.98%. The SVM-based NTCP model achieved an area under the ROC curve (AUROC) of 0.867, with accuracy of 91.7%, sensitivity of 87.5%, and specificity of 93.8%.

Conclusion: Capsular contracture following proton PMRT is significantly associated with the combined effects of dose and LET_d in peri-implant tissue. The derived DLVCs represent candidate dosimetric constraints that warrant further investigation and prospective validation in breast cancer patients undergoing proton PMRT with implant-based reconstruction.

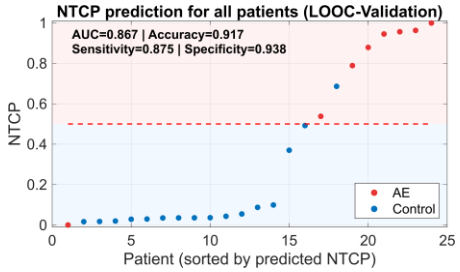

Figure 3. NTCP prediction for all patients for the LOOC-validation.

Chen, J., Ma, Z., Cao, M., Gao, R. W., Yang, Y., Ding, Y., ... Robert, M& Liu, W. (2026). Dose-LET Interactions Predict Capsular Contracture After Proton Postmastectomy Radiation Therapy. *arXiv preprint arXiv:2601.11731*.

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