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Mapping Clinically Relevant Dose×LET Differences for Skin Sparing with Spot Delete in Head and Neck Proton Therapy

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Key Finding: Skin rind Spot Delete produces a statistically significant reduction in high-LET skin volume at clinically relevant doses, not detectable with DVHs but isolated using voxelwise Dose×LET analysis.

INTRODUCTION

Spot Delete[1] removes Bragg Peaks from the 5mm skin rind and has been clinically shown to reduce dermatitis time-to-onset and severity[2]. However, classic DVH analysis did not identify a significant decrease in dose to the skin using this technique. **The purpose of this study was to identify the Dose×LET region in skin that explains reduced dermatitis with Spot Delete.**

DLVHs are a novel method to identify correlations between adverse effects, dose, and LET. Rather than preselecting arbitrary Dose×LET cutoffs, this work uses voxelwise Dose×LET difference mapping with multiple-comparison control, then extracts a single contiguous, interpretable region that best represents clinically meaningful DLVH change. Voxelwise significance maps across Dose×LET bins can be spatially extensive; combining FDR-adjusted significance (q), effect size (Cohen's d), directionality (negative ΔVolume), and cluster contiguity yields a planning-relevant region.

METHODS AND MATERIALS

- 15 HN patients were retrospectively planned with Spot Delete (SD) in the 5mm skin rind and without (Ref).
- Skin DLVH difference maps were analyzed per bin:
$$\Delta V(D,L) = V_{SD}(D,L) - V_{Ref}(D,L)$$
- Group-level maps of mean $\Delta V(D,L)$ were computed (Figure 1).
- Voxelwise paired comparisons across patients were performed using the Wilcoxon signed-rank test.
- Multiple comparisons were controlled using Benjamini–Hochberg false discovery rate (FDR) correction, yielding q-values (threshold $q \le 0.05$).
- Effect sizes were calculated using Cohen's d:
$$d = \frac{\text{mean}(\Delta V)}{\text{standard deviation}(\Delta V)}$$
- To obtain a clinically interpretable summary, a binary mask was defined using combined criteria:
  •LET ≥ 3.0 keV/µm •Dose ≥ 10 Gy •$\Delta V(D,L) < 0$
  •$q \le 0.05$ •Cohen's $d \le -0.8$
- From the binary mask, the largest 4-connected contiguous component in Dose×LET space was retained.

REFERENCES

1. Hedrick, Samantha G., et al. "Scripted spot removal in PBS proton therapy planning." *Journal of Applied Clinical Medical Physics* 23.2 (2022): e13491
2. Hedrick, Samantha G., et al. "Reducing Radiation Dermatitis for PBS Proton Therapy Breast Cancer Patients Using SpotDelete." *International Journal of Particle Therapy* 13 (2024): 100628..

RESULTS

- $\Delta V(D,L)$ maps show a consistent negative signal localized to high-LET, moderate-to-high dose bins. This region is not separable in standard DVHs (Figure 1).
- Single dominant contiguous cluster in LET ≥ 3 keV/µm & Dose ≥ 10 Gy was spatially stable across patients.
- Region-summed $\Delta V < 0$ in all/most patients and Wilcoxon signed-rank (region metric): $q \approx 2 \times 10^{-4}$ (FDR corrected).
- These support a systematic reduction of high-LET skin volume in SD plans (Figure 2).
- This result provides a mechanistic explanation for reduced dermatitis risk despite minimal conventional DVH separation: the principal plan difference concentrates in high-LET skin exposure at clinically relevant dose.
- We provide a directly testable, LET-aware planning strategy aligned with the observed DLVH change associated with Spot Delete skin sparing.
- Clinically actionable objective - minimize skin volume receiving high LET at clinically relevant doses. Either:
  - minimize summed ΔV within the extracted Dose×LET region (as a QA/benchmark metric) or
  - minimize a corresponding Dose×LET overlap metric in prospective planning.

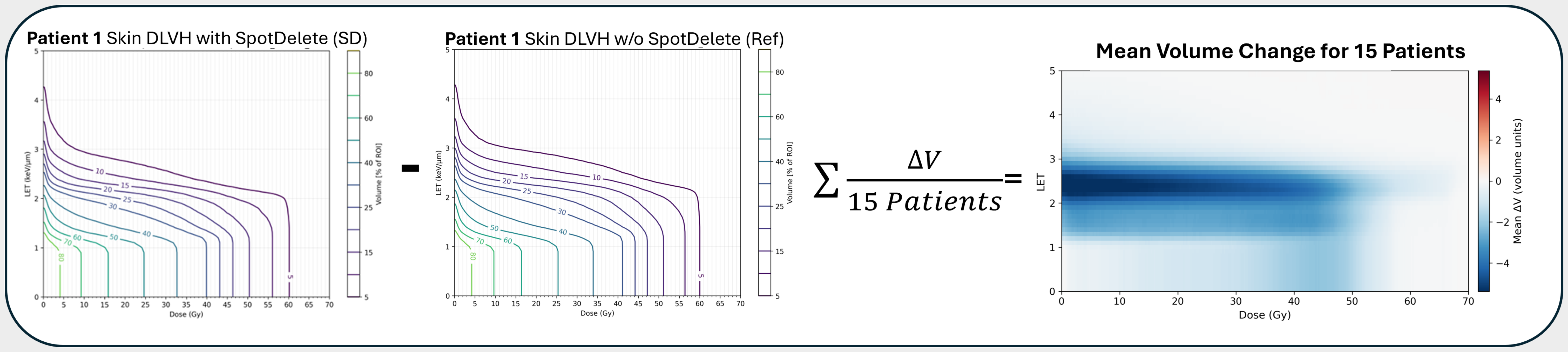

Figure 1. Patient-level skin DLVHs with Spot Delete (**left**) and without Spot Delete (**middle**) illustrate redistribution in Dose×LET space. The mean ΔV(Dose,LET) map across 15 patients (**right**) summarizes systematic changes, where $\Delta V = V_{SD} - V_{Ref}$ and negative ΔV (blue) represents reduced skin volume receiving the specified dose and LET with Spot Delete.

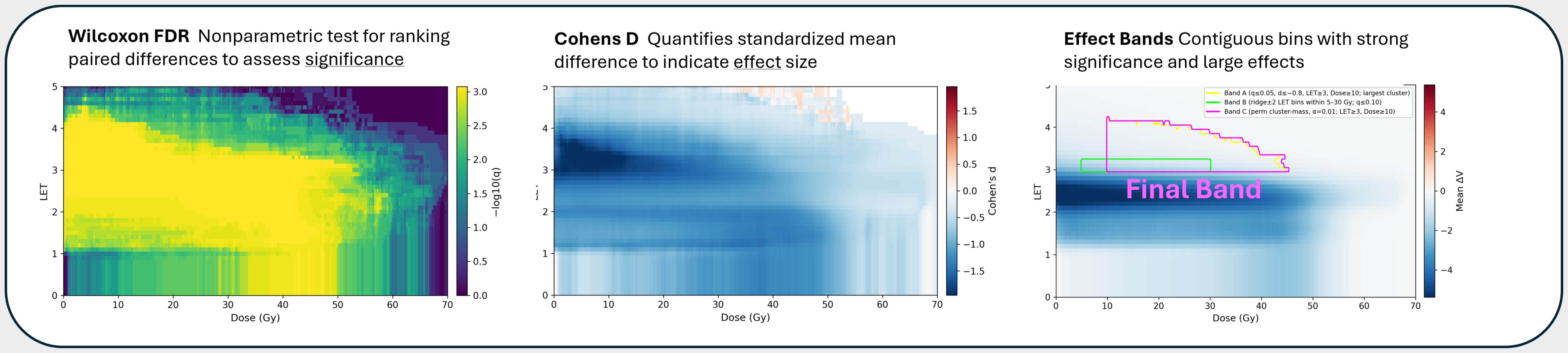

Figure 2. Identification of the dominant skin Dose×LET region altered by Spot Delete. **Left**: voxelwise significance across Dose×LET bins displayed as −log10(q) from Wilcoxon signed-rank testing with Benjamini–Hochberg FDR correction. **Middle**: voxelwise effect size (Cohen's d) for $\Delta V(D,L) = V_{SD}(D,L) - V_{Ref}(D,L)$. **Right**: overlay of candidate region masks and the final selected contiguous region emphasizing high LET, negative ΔV, strong FDR significance, large effect size, and connectivity.

CONCLUSIONS

Dose×LET difference mapping with FDR-controlled inference, effect-size gating, and contiguity filtering isolates an interpretable high-LET/high-dose region capturing the dominant DLVH difference associated with Spot Delete skin sparing in HN, supporting LET-aware skin planning objectives.

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