FDG-PET-based Selective De-escalation of Radiotherapy for HPV-Related Oropharynx Cancer: Results from a Phase II Trial

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Introduction:
Treatment de-escalation in HPV-related oropharyngeal squamous cell carcinoma (OPSCC) aims to minimize toxicity without compromising oncologic outcomes. We conducted a prospective phase II nonrandomized trial using FDG-PET imaging biomarkers to selectively de-escalate chemoradiotherapy (CRT). We hypothesized this would maintain locoregional control in all patients while decreasing toxicity in the de-escalated cohort.

Methods:
Eligible patients had stage I-II p16+ or HPV+ OPSCC with baseline tumor FDG-PET-avidity. All were planned to receive 70 Gy to gross disease and 56 Gy to elective nodal regions in 35 fractions with concurrent weekly carboplatin/paclitaxel. Mid-treatment PET was performed at fraction 10. If metabolic tumor volume was reduced by ≥50%, CRT was completed at 54 Gy in 27 fractions.

The primary objective was to demonstrate non-inferiority of 24-month locoregional recurrence (LRR) overall by comparing the upper 90% confidence interval (CI) to 25%. Secondary objectives were failure patterns, survival, ctDNA trends, mpMRI, and toxicity. Toxicity measures included patient-reported outcomes (UWQOL-RTOG, FACT-HN, XQ). Kaplan-Meier analyses were used for survival outcomes.

Results:
Eligible patients (n = 84) were enrolled from 2018 - 2023; 90% male, 75% stage I, and 48% never-smokers. De-escalation criteria were met in 42% (n = 35). The 54 Gy cohort had fewer patients with T3 tumors (3% vs 20%, p = 0.02) and lower median baseline weight (188 vs. 207 lbs, p = 0.015); no other differences in distribution of baseline factors nor initial RT plans were found.

Median follow up at this analysis was 28.9 mo overall, 31.6 mo for 54 Gy and 25.9 mo for 70 Gy patients. LRR at 24 mo was 7% (90% CI: 2% - 12.1%) in the entire cohort, 5% (90% CI: 0% – 10.5%) with 70 Gy, and 10% (90% CI: 1% - 18.2%) with 54 Gy. There were 5 LRR and 3 distant recurrences overall. Of 4 patients with only LRR, 3 were salvaged surgically without systemic therapy and have no evidence of disease, and 1 (70 Gy cohort) declined surgery. There was 1 cancer-related death after a distant-only recurrence in the 70 Gy cohort.

Median weight loss from baseline in the 54 Gy cohort was significantly less at 1 mo (6.5% vs. 10.6%, p <0.001) and 3 mo (6% vs. 12.6%, p <0.001) post-RT. Use of feeding tube during RT or ≤1 mo post-RT was numerically better in 54 Gy patients (11% vs. 16%, p = 0.5). The 70 Gy cohort had one grade 4 (G4) carotid artery injury and one likely treatment-related death. The 54 Gy cohort had no G4+ toxicities, with less decrement from baseline in median UWQOL-RTOG scores for pain subscale at 1 mo (5 vs 10, p = 0.01) and mucus subscale at 12 mo (0 vs. 5, p = 0.2) post-RT. Remaining PRO instrument analyses are ongoing and will be presented.

Conclusion:
Mid-treatment FDG-PET may be a reliable biomarker to selectively de-escalate radiation dose in early-stage HPV+ OPSCC to improve toxicity while preserving oncologic outcomes.