Longitudinal FDG PET as a Surrogate for FMISO-Defined Hypoxia in HPV-Positive Oropharyngeal Cancer

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ABSTRACT

Purpose: Tumor hypoxia drives radio-resistance in head and neck cancer (HNC) and can guide radiation dose de-escalation. Tumor hypoxia can be imaged using 18F-fluoromisonidazole (FMISO PET; non-standard-of-care). Because hypoxia drives glycolysis, we assessed correlations between 18F-fluorodeoxyglucose (FDG PET; standard-of-care) and FMISO-defined hypoxia.

Methods: We retrospectively analyzed 13 HPV-positive oropharyngeal cancer patients who underwent baseline FDG PET (pre-RT), repeat FDG PET (week 2), and FMISO PET 2 weeks into radiotherapy as part of a prospective phase II trial (NCT03323463).

Hypoxic tumor subvolumes (HSV) were defined using an FMISO tumor-to-background (floor-of-mouth) ratio ≥ 1.2. Tumor volume (TV), FDG SUVmax, FDG SUVmean, metabolic tumor volume (MTV50%), and MTV50% SUVmean were extracted from FDG PET. Pearson correlations compared pre-RT FDG, week 2 FDG, and ΔFDG metrics with FMISO SUVmean, FMISO SUVmax, HSV SUVmean, and HSV volume. Associations with clinical dose de-escalation decisions were also assessed. Primary and nodal disease were analyzed separately.

Results: In nodal disease, FMISO SUVmean strongly correlated with baseline tumor volume ($r = 0.751$, $p < 0.01$) and MTV50% ($r = 0.711$, $p < 0.01$), as well as week 2 tumor volume ($r = 0.779$, $p < 0.01$) and MTV50% ($r = 0.702$, $p < 0.01$). MTV50% also strongly correlated with HSV volume (pre-RT: $r = 0.723$, $p < 0.001$; week 2: $r = 0.592$, $p < 0.05$).

In primary disease, tumor volume, FDG SUVmean, and FDG SUVmax at both time points strongly correlated with FMISO SUVmax ($r = 0.694$–0.811, $p < 0.001$). FDG SUVmax, FDG SUVmean, and MTV50% SUVmean also strongly correlated with HSV volume ($r = 0.712$–0.862, $p < 0.001$). ΔFDG metrics for both GTV and MTV showed no significant correlation with hypoxia. Baseline FDG SUVmax and FDG SUVmean in primary disease were the only metrics significantly lower in the two patients eligible for dose de-escalation ($p = 0.026$).

Conclusions: FDG-PET metrics were associated with FMISO-defined hypoxia, with distinct patterns for primary versus nodal GTV. Volumetric parameters best reflected nodal hypoxic burden, while FDG uptake, particularly SUVmax, predominated in primary tumors. Baseline GTVp FDG uptake correlated most strongly with mid-treatment FMISO. Surprisingly, correlations were weaker for week-2 FDG metrics and dynamic percent-change measures were not correlated. Further work with a larger cohort of patients is needed to assess the utility of using FDG instead of FMISO response to select patients for de-escalation

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INTRODUCTION

- Tumor hypoxia is a key prognostic and predictive factor for radiotherapy (RT) treatment response in Head and Neck Squamous Cell Carcinoma (HNSCC) and is an important metric in dose de-escalation techniques.
- Direct hypoxia imaging using 18F-fluoromisonidazole (FMISO) PET is being explored for hypoxia-guided adapted therapy (e.g., Phase III trial NCT06563479). However, FMISO remains an investigational tracer that requires specialized on-site production facilities, limiting its deployment outside major academic infrastructure.
- Conversely, 18F-fluorodeoxyglucose (FDG) PET is standard-of-care, ubiquitous, and routinely acquired. Because hypoxia upregulates glucose metabolism via HIF-1α (the Pasteur effect), standard FDG metrics could offer an accessible, surrogate method to map hypoxic tumor volumes.
- Prior studies have reported only modest correlation between FDG and FMISO, with discordant findings between primary and nodal disease.

OBJECTIVE

To assess correlations between standard of care FDG PET metrics at baseline and mid-treatment (Week 2) and FMISO-defined hypoxia in primary and nodal disease in HPV-positive OPC.

METHODS AND MATERIALS

Cohort: 13 patients with HPV-positive oropharyngeal cancer enrolled in a prospective Phase II trial (NCT03323463).
Protocol Workflow:

- Baseline FDG PET before starting radiotherapy (Pre-RT)
- Repeat FDG PET & FMISO PET at approximately Week 2 of RT
- Longitudinal change in metabolic tumor burden (dFDG) and tumor volume.

Analysis: Primary tumors (GTVp) and nodal disease (GTVn) were delineated and analyzed independently using multi-parametric correlation matrices.

- FMISO metrics: SUVmax, SUVmean, Hypoxic subvolume (HSV)
- FDG metrics: SUVmax, SUVmean, Volume, MTV50%, MTV50% SUVmean

RESULTS

- **Nodal Disease Matrix:** Nodal hypoxia (GTVn) was predominantly associated with volumetric FDG-PET parameters, with tumor volume and metabolic tumor volume showing strong correlations with normalized FMISO SUVmean and HSV volume (r up to 0.779, $p<0.001$ and 0.723, $p<0.01$ respectively; *Table 1*).
- **Primary Disease Matrix:** In primary disease, FDG-PET uptake metrics at both time points correlated strongly to FMISO-PET SUVmax and HSV. Pre-RT FDG SUVmax provides the strongest correlation to FMISO SUVmax ($r=0.811$, $p<0.001$), while mid-treatment SUVmean provided the strongest correlation to HSV ($r=0.862$, $p<0.001$) *(Table 2).*
- **Interval Changes (ΔFDG):** Longitudinal changes of both FDG-PET uptake and volumetric metrics exhibited no correlation with underlying FMISO hypoxia metrics.
- **De-escalation Substratification:** Pre-RT FDG SUVmax and SUVmean within the primary tumor were the only FDG-based metrics found to be significantly lower in patients eligible for dose de-escalation ($p = 0.026$, *Figure 1*).

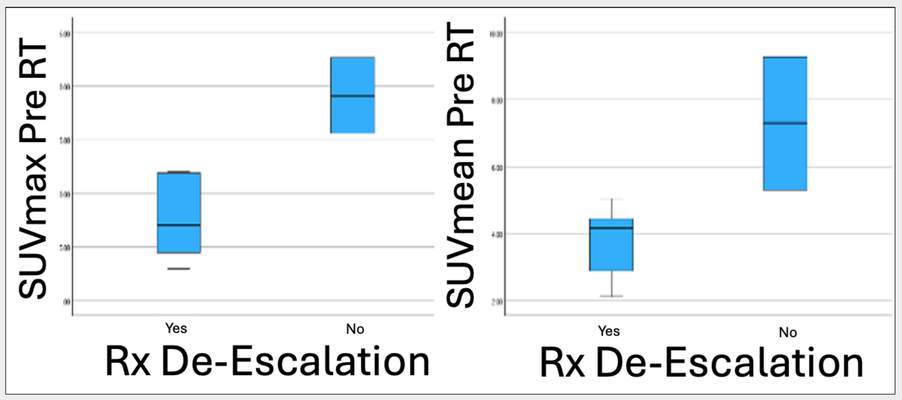
Table 1. *Pearson r coefficients tracking FDG-PET parameters against FMISO-PET in Nodal Disease (*p<0.05, **p<0.01, ***p<0.001).*

	FMISO_SUVmax	FMISO_SUVmean	HSV_SUVmax	HSV_SUVmean	HSV_Vol
SUVmax_Pre-RT	0.52	0.585*	0.459	0.459	0.194
SUVmean_Pre-RT	0.416	0.394	0.493	0.517	0.215
Vol_Pre-RT	0.199	0.751**	0.442	0.373	0.49
SUVmax_Week2	0.308	0.603*	0.472	0.448	0.393
SUVmean_Week2	0.739**	0.641*	0.597*	0.61*	0.456
Vol_Week2	0.201	0.779***	0.545*	0.476	0.592*
ΔFDG_mean	0.134	0.147	0.268	0.289	0.01
ΔFDG_max	0.355	0.24	0.213	0.231	-0.05
ΔFDG_vol	0.094	0.079	-0.469	-0.491	-0.457
MTV_SUVmean_Pre-RT	0.505	0.569*	0.433	0.433	0.161
MTV_Vol_Pre-RT	0.335	0.711**	0.363	0.297	0.723**
MTV_SUVmean_Week2	0.377	0.614*	0.496	0.473	0.406
MTV_Vol_Week2	0.587*	0.702**	0.275	0.226	0.592*
ΔMTV	0.376	0.237	0.172	0.188	-0.091

Table 2. *Pearson r coefficients tracking FDG-PET parameters against FMISO-PET in Primary Disease (*p<0.05, **p<0.01, ***p<0.001).*

	FMISO_SUVmax	FMISO_SUVmean	HSV_SUVmax	HSV_SUVmean	HSV_Vol
SUVmax_Pre-RT	0.811***	-0.469	0.619*	0.573*	0.712**
SUVmean_Pre-RT	0.694**	-0.323	0.542	0.483	0.8***
Vol_Pre-RT	0.694**	-0.403	0.366	0.328	0.505
SUVmax_Week2	0.763**	-0.441	0.489	0.423	0.831***
SUVmean_Week2	0.641*	-0.299	0.436	0.365	0.862***
Vol_Week2	0.81***	-0.53	0.6*	0.568*	0.562*
ΔFDG_mean	0.341	-0.156	0.412	0.423	0.112
ΔFDG_max	0.081	-0.048	0.282	0.33	-0.307
ΔFDG_vol	0.17	-0.034	-0.114	-0.137	0.165
MTV_SUVmean_Pre-RT	0.409	-0.145	0.371	0.31	0.778*
MTV_Vol_Pre-RT	0.49	-0.214	0.327	0.274	0.618
MTV_SUVmean_Week2	0.747**	-0.409	0.484	0.416	0.847***
MTV_Vol_Week2	0.173	0.154	0.369	0.362	0.243
ΔMTV	-0.626*	0.481	-0.219	-0.203	-0.155

Figure 1. Baseline FDG-PET GTV_p SUV_{max} and SUV_{mean} stratified by treatment cohort (70 Gy vs. de-escalation, $p = 0.026$).



DISCUSSION

- **GTV-Specific Behavior**
  - Primary tumor hypoxia was associated with absolute $SUV_{max, mean}$, whereas nodal hypoxia correlated with volumetric metrics (TV and MTV).
- **Longitudinal FDG behavior**
  - Baseline FDG-PET outperformed mid-treatment uptake values in predicting tumor hypoxia
  - Relative changes in FDG uptake (ΔFDG) were not correlated with mid-treatment hypoxia.
  - Standard-of-care FDG-PET at baseline is a potential surrogate for assessing tumor hypoxia.

CONCLUSIONS

- FDG-PET metrics correlated with tumor hypoxia as defined by FMISO PET
- Primary tumor hypoxia was most strongly associated with FDG uptake (SUV), whereas nodal hypoxia was most strongly associated with volumetric FDG metrics.
- Baseline FDG-PET showed higher value in predicting FMISO-defined tumor hypoxia than repeat mid-treatment or the change between the two measurements (ΔFDG).

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