Correlations between DW-MRI and \(^{18}\)F-FDG PET/CT parameters in head and neck squamous cell carcinoma following definitive chemo-radiotherapy

Steve Connor\(^{1,2,3}\) | Cherry Sit\(^{3}\) | Mustafa Anjari\(^{3}\) | Teresa Szyszko\(^{4}\) | Joel Dunn\(^{4}\) | Irumee Pai\(^{1,5}\) | Gary Cook\(^{1,4}\) | Vicky Goh\(^{1,3}\)

\(^{1}\)School of Biomedical Engineering and Imaging Sciences, St Thomas’ Hospital, King’s College, London, UK
\(^{2}\)Department of Neuroradiology, King’s College Hospital NHS Foundation Trust, London, UK
\(^{3}\)Department of Radiology, Guy’s and St Thomas’ NHS Foundation Trust, London, UK
\(^{4}\)King’s College London & Guy’s and St. Thomas’ PET Centre, London, UK
\(^{5}\)Department of Otolaryngology, Guy’s and St Thomas’ NHS Foundation Trust, London, UK

Correspondence
Steve Connor, Neuroradiology Department, Ruskin Wing, Kings College Hospital, Denmark Hill, London SE5 9RS, UK.
Email: steve.connor@kcl.ac.uk

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Abstract

Background: Posttreatment diffusion-weighted magnetic resonance imaging (DW-MRI) and \(^{18}\)F-fluorodeoxyglucose (\(^{18}\)F-FDG) positron emission tomography (PET) with computed tomography (PET/CT) have potential prognostic value following chemo-radiotherapy (CRT) for head and neck squamous cell carcinoma (HNSCC). Correlations between these PET/CT (standardized uptake value or SUV) and DW-MRI (apparent diffusion coefficient or ADC) parameters have only been previously explored in the pretreatment setting.

Aim: To evaluate stage III and IV HNSCC at 12-weeks post-CRT for the correlation between SUV\(_{\text{max}}\) and ADC values and their interval changes from pretreatment imaging.

Methods: Fifty-six patients (45 male, 11 female, mean age 59.9 ± 7.38) with stage 3 and 4 HNSCC patients underwent 12-week posttreatment DW-MRI and \(^{18}\)F-FDG PET/CT studies in this prospective study. There were 41/56 patients in the cohort with human papilloma virus-related oropharyngeal cancer (HPV OPC). DW-MRI (ADC\(_{\text{max}}\) and ADC\(_{\text{min}}\)) and \(^{18}\)F-FDG PET/CT (SUV\(_{\text{max}}\) and SUV\(_{\text{max}}\) ratio to liver) parameters were measured at the site of primary tumors (n = 48) and the largest lymph nodes (n = 52). Kendall’s tau evaluated the correlation between DW-MRI and \(^{18}\)F-FDG PET/CT parameters. Mann-Whitney test compared the post-CRT PET/CT and DW-MRI parameters between those participants with and without 2-year disease-free survival (DFS).

Results: There was no correlation between DW-MRI and \(^{18}\)F-FDG PET/CT parameters on 12-week posttreatment imaging (\(P = .455-.794\); tau = −0.075-0.25) or their interval changes from pretreatment to 12-week posttreatment imaging (\(P = .1-.946\); tau = −0.194-0.044). The primary tumor ADC\(_{\text{mean}}\) (\(P = .03\)) and the interval change in nodal ADC\(_{\text{min}}\) (\(P = .05\)) predicted 2-year DFS but none of the \(^{18}\)F-FDG PET/CT parameters were associated with 2-year DFS.
Conclusions: There is no correlation between the quantitative DWI-MRI and $^{18}$F-FDG PET/CT parameters derived from 12-week post-CRT studies. These parameters may be independent biomarkers however in this HPV OPC dominant cohort, only selected ADC parameters demonstrated prognostic significance. Study was prospectively registered at http://www.controlled-trials.com/ISRCTN58327080

KEYWORDS
carcinoma, squamous cell, chemo-radiotherapy, diffusion-weighted magnetic resonance imaging, head and neck cancer, positron emission tomography, posttreatment

1 | BACKGROUND

Head and neck squamous cell carcinoma (HNSCC) is the seventh most common cancer worldwide. Patients with advanced loco-regional disease can be treated with radiotherapy, or combined chemoradiotherapy (CRT), but 25% to 50% will have residual disease that requires further intervention. Early posttreatment detection of residual tumor is required in order to optimize the outcomes of salvage surgery. Unfortunately, clinical assessment and structural imaging are limited in their ability to detect loco-regional residual or recurrent disease due to treatment-related soft tissue distortion.

In order to overcome the shortcomings of structural imaging in this clinical scenario, metabolic imaging with $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET) in combination with computed tomography (PET/CT) has become widely utilized. $^{18}$F-FDG PET/CT is reported to be a highly sensitive technique for detection of HNSCC in the post-CRT setting. Semiquantitative analysis of maximum standardized uptake value (SUV$_{max}$) with $^{18}$F-FDG PET-CT has been shown to have prognostic significance, with increased SUV$_{max}$ being associated with treatment failure.

Quantitative diffusion-weighted magnetic resonance imaging (DW-MRI) with measurement of the apparent diffusion coefficient (ADC) is another functional imaging technique, which may be used to help distinguish tumor from posttreatment changes and has been applied to the early posttreatment assessment of HNSCC. The majority of studies have found that an increased posttreatment ADC or greater rise in ADC from the pretreatment to the intratreatment or posttreatment studies is a predictor of treatment success. It is still unclear whether $^{18}$F-FDG and ADC values provide similar information with regard to viable tumor cells, or whether the two are entirely unrelated biomarkers. Both ADC values and SUV$_{max}$ have shown significant correlation with different histopathological parameters although this may depend on tumor grade.

It is still unclear whether $^{18}$F-FDG and ADC parameter values may be independent biomarkers, which are complementary in stratifying the probability of residual disease, should also be explored.

Our hypothesis was that there would be a significant negative linear relationship between ADC and SUV values on 12-week post-CRT studies in patients with stage III and IV HNSCC. Thus, our primary objective was to determine any correlation between ADC and SUV$_{max}$ values on 12-week post-CRT studies, and between their interval changes from pretreatment to 12-week post-CRT studies. Our secondary objective was to evaluate these posttreatment ADC and SUV$_{max}$ Values and their interval changes for their ability to predict 2-year DFS outcomes.

2 | METHOD

2.1 | Participants

Participants were recruited for a prospective single center cohort observational study (http://www.controlled-trials.com/ISRCTN58327080) following Research Ethics Committee approval (REC reference 13/LO/1876) and informed consent.

Participants were eligible if: (a) there was a histologically confirmed stage III and IV primary SCC of the head and neck without distant metastatic disease, (b) a 1-cm$^2$ area of measurable primary tumor and/or nodal tumor on the basis of standard clinico-radiological staging, and (c) curative CRT was planned. Exclusion criteria included prior CRT, an Eastern Cooperative Oncology Group (ECOG) performance status >2, inability to provide informed consent, known allergy to gadolinium-based contrast medium and eGFR<30 mL/min.

2.2 | Treatment and HPV status

Intensity-modulated radiotherapy (IMRT) was delivered as per the standard of care which was 7-Gy in 35 fractions; 2Gy per fraction delivered once daily, 5 days a week. Concomitant intravenous cisplatin at a dose of 35 mg/m$^2$ every 7 days, starting on day 1 of radiotherapy, was used for all patients with adequate GFR and no contraindications to cisplatin (n = 47) with carboplatin being used if...
measured GFR < 50 or if patient had a history of hearing impairment (n = 16). Two patients received radiotherapy alone. HPV status was analyzed for all oropharyngeal and 1/13 other cancers. This involved p16 testing using an immune-stain or high-risk HPV DNA testing using in situ hybridization.

### 2.3 Imaging

Participants underwent MRI prior to commencement of CRT, while MRI and $^{18}$F-FDG PET/CT were performed at 12 weeks after completion of treatment. Although pretreatment $^{18}$F-FDG PET/CT imaging was not mandated as a component of the study, it was performed in selected patients according to the institutional protocol.

### 2.4 Magnetic resonance imaging

#### 2.4.1 Protocol and technique

Participants underwent full standard institutional head and neck soft tissue protocol MRI on a 1.5 Tesla Siemens Magnetom Aera system (Siemion Medical Systems GmbH, Erlangen, Germany) using a surface-phased array neck coil (Table 1). In addition, an echo planar diffusion-weighted sequence was acquired including matched images in the axial plane with multiple b-values (0, 50, 100, 800, and 1500 s/mm$^2$) and the following scan parameters: repetition time 5900 ms, echo time 60 ms, two signal averages, FOV 240 mm $\times$ 240 mm, slice thickness 4 mm with a 0.5 mm slice gap. ADC maps were calculated from the $b = 100$ and $b = 800$ values.

#### 2.4.2 MRI processing and analysis

Processing and analysis of diffusion imaging was performed offline. Data from our institutional Picture Archiving and Communication System (PACS) database were transferred to OsirIX v8.0.2, open-source Mac-based medical image processing software. The regions of interest (ROIs) were placed by a radiologist with 3 years of experience under the supervision of a radiologist with 21 years of experience, who provided training in five cases and ongoing review of a further five cases. Free hand ROIs were placed on the assessable primary tumor and/or largest lymph node using the OsirIX Draw tool with the images magnified to a standard 300%. They were defined on the diffusion-weighted imaging (DWI) $b = 800$ map as a focus of increased signal relative to background, but with access to the other MRI sequences. Areas of necrosis (non-enhancement and high B0 map signal) and peri-tumoral oedema (avid enhancement and high B0 map signal) were avoided.

ROIs were placed on the baseline and 12-week posttreatment MRI studies in sequence. If there was no longer a 6 mm short axis focus of DWI signal on the posttreatment studies at the location of the initial lesion, a standardized 6 mm diameter circular ROI was placed at its original location by reference to the other sequences and these ROIs were termed “nonmeasurable.” All ROIs were then translated directly to a calculated ADC map generated from the $b100$ and $b800$ images using the OsirIX ADCmap v1.9 plugin (https://web.stanford.edu/~bah/software/ADCmap/). ADC$_{\text{mean}}$ and SD were recorded with ADC$_{\text{mean}}$ calculated as $\text{ADC}_{\text{mean}}$ – one SD (rather than absolute $\text{ADC}_{\text{min}}$).

### 2.5 $^{18}$F-FDG PET/CT

#### 2.5.1 Protocol and technique

The $^{18}$F-FDG PET/CT was performed as per institutional clinical practice. Participants were fasted for at least 6 hours prior to administration of 350-400 MBq $^{18}$F-FDG. PET/CT scans were acquired 90 minutes after injection from the upper thigh to the base of skull (arms up) with additional local views of the head and neck (arms down) on one of two PET/CT scanners (Siemens mCT Flow VST or GE Discovery DST 710). Images were acquired in 3D time-of-flight (TOF) acquisitions, according to local protocols. A low-dose CT scan ($140$ kV, $10$ mA, 0.5 second rotation time, and 40 mm collimation) was performed at the start in order to provide attenuation correction. Images were reconstructed using ordered subset expectation maximization (OSEM) method. For GE Discovery 710, the parameters were: Algorithm: “VPFX”, OSEM, time-of-flight, 2 iterations 24 subsets; Matrix size: $256 \times 256 \times 47$; Pixel Spacing: $2.73 \times 2.73 \times 3.27$; Post-

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**Table 1 MRI protocol**

| Plane | Slice thickness/gap | TR/TE | Field of view | Number of averages | Pixel Bandwidth | Flip angle | Acquisition matrix |
|-------|---------------------|-------|---------------|-------------------|-----------------|------------|-------------------|
| T1w   | Axial               | 4/0   | 549/11        | 220 $\times$ 220  | 1               | 200        | 160               | 384/269          |
| T2w   | Axial               | 4/0   | 5830/102      | 220 $\times$ 220  | 1               | 190        | 150               | 384/346          |
| T1w fat saturated-DIXON postgadolinium | Axial | 4/0 | 566/11 | 220 $\times$ 220 | 1 | 330 | 145 | 320 $\times$ 224 |
| STIR  | Coronal             | 3/0.3 | 3000/35 Ti 140 | 260 $\times$ 260  | 1               | 220        | 160               | 320 $\times$ 224 |
| T1w fat sat-DIXON postgadolinium  | Coronal | 3/0.3 | 708/10 | 280 $\times$ 280  | 1               | 340        | 145               | 320 $\times$ 320 |
filter: Gaussian 6.4 mm FWHM. For the Siemens mCT Flow, the parameters were: Algorithm: OSEM, time-of-flight, 2 iterations 21 subsets; Matrix size: 200 × 200 × 46; Pixel Spacing 3.07 × 4.07 × 2; Post-filter: Gaussian 5.0 mm FWHM.

2.5.2 18F-FDG PET/CT data processing and analysis

On pretreatment 18F-FDG PET/CT imaging, a 6 mm diameter volume of interest (VOI) was placed at the site of most intense FDG uptake at the site of either the primary lesion and/or the largest lymph node, which was matched to the ROI placed for the MRI analysis. The SUVmax was calculated with semiautomated software on a Hermes workstation (Hermes Gold 3, Stockholm). The VOIs were placed by a radiologist with 3 years’ experience, under the supervision of a radiologist with 16 years’ experience who provided training in five cases and review of further five cases.

The same method for VOI measurement was applied on 12-week posttreatment 18F-FDG PET/CT imaging and SUVmax was recorded. The VOIs were chosen with MRI guidance, and always correlated with areas of increased tracer uptake on the pretreatment images. If there was reduced or no uptake on the posttreatment images relative to background, the posttreatment MRI images were referenced and a 6 mm VOI was placed at the same site as the MRI ROI. If necrosis was identified within a lesion, the area of necrosis was excluded as much as possible, and VOI was placed in the area of most intense tracer uptake. Areas of normal physiological uptake were avoided.

A freehand region of interest (ROI) was placed over the right lobe of the liver, at approximately its largest diameter, to record background liver SUVmax. This was performed in order to calculate the SUVmax ratio to liver parameter.

2.6 Treatment outcome

Outcome evaluation comprised clinical assessment at 1 year and 2 years following completion of treatment. A 12-week posttreatment positron emission tomography computed tomography (PET CT) study was standard of care and was used to guide clinical management. Treatment failure was determined by cytological or histological confirmation (biopsy or resection) or by serial progression on imaging follow-up. The 2-year DFS was recorded according to status at 2 years following completion of treatment.

2.7 Statistical analysis

The Shapiro-Wilks normality test determined a proportion of the ADCmean and liver SUVmax data to show a significant deviation from normal (with a multiple comparison corrected threshold). Therefore, the primary descriptive statistics focused on the nonparametric median ± interquartile range and the primary correlation was performed with the nonparametric Kendall’s Tau method.

The correlation between ADCmean and SUVmax at the tumor and nodal sites on the 12-week post-CRT studies, and the interval change from pretreatment imaging to 12-week posttreatment studies was analyzed. The threshold for statistical significance was set at $P < .05$. This study provided 95% power to detect a true “moderate” correlation of $\tau = 0.34$ at this threshold.

The same statistical approach was used to extend the comparison to alternative parameters (ADCmin, SUVmax ratio to liver) on the 12-week posttreatment studies, as well as the interval change from pretreatment imaging to 12-week posttreatment studies. The subgroup of patients with measurable disease as defined by a clear focus of DWI signal on the 12-week posttreatment DW-MRI was also analyzed separately.

Scatter plots of 18F-FDG PET/CT and MRI measures were produced to demonstrate any correlation with 95% confidence intervals. The Mann-Whitney test was used for a univariate analysis comparing tumor and nodal ADC and SUVmax parameters with the dichotomized 2-year DFS.

3 RESULTS

3.1 Participants

The participant flowchart is summarized in Figure 1.

There were 70 participants initially enrolled in the study. However, five patients were subsequently withdrawn and a further nine participants did not attend for one of the posttreatment studies (Figure 1). Therefore, 12-week post-CRT 18F-FDG PET-CT and DW-MRI were analyzed for 56 patients (45 male, 11 female, mean age 59.9 + 7.38). Since the ROIs were only placed on 1 cm2 areas of measurable primary tumor and/or nodal tumor, the measurements were performed at the primary site alone (no measurable pathological lymph nodes, n = 4), the largest lymph node alone (no measurable primary tumor, n = 8) or both sites (n = 44). The tumor site, subsite, and HPV status are documented in Table 2. There was a majority of human papilloma virus-associated oropharyngeal cancer (HPV OPC) participants in this prospectively recruited cohort.

Since pretreatment 18F-FDG PET/CT was performed according to the institutional protocol rather than under the research protocol, it was only available for 43 patients. There were 36/43 patients who also had 12-week post-CRT 18F-FDG PET-CT and DW-MRI available. Therefore, the interval changes from pretreatment to 12-week posttreatment studies could be analyzed in 36 patients with ROIs placed at the largest lymph node alone (n = 6) or both sites (n = 30).

At 2-year follow-up, there were three participants with isolated nodal recurrence, one participant with isolated primary recurrence and two participants with distal metastases alone. The participants with nodal recurrence underwent salvage neck dissection. There were therefore 50/56 patients with 2-year DFS.
Enrolled
n=70

Withdrawn due to incomplete treatment
(n= 2)
Baseline imaging severely degraded (n=2)
Revised histological diagnosis (n=1)

Pre-treatment PET-CT performed outside study protocol
n=43
Primary tumour n=35
Lymph node n=41

Did not attend 12 week post-treatment DW-MRI or PET-CT
n=9

Allocation and pre-treatment DW-MRI
n=65
Primary tumour n=57
Lymph node n=59

Analysis: for change between pre- and 12 week post- treatment DW-MRI and PET CT
n=36
Primary tumour n=30
Lymph node n=36

Analysis: for 12 week post treatment
DW-MRI and PET CT
n=56
Primary tumour n=48
Lymph node n=52

12 week post-treatment DW-MRI and PET CT both performed
n=56

12 week post-treatment DW-MRI and PET CT both performed
n=36

Measurable disease on post-treatment DW-MRI
Primary tumour n=0/48
Lymph node n=19/52
(11/52 lymph nodes with pre-treatment DW-MRI and PET CT)

Analysis: for 12 week post treatment
DW-MRI and PET CT
n=56
Primary tumour n=48
Lymph node n=52

12 week post-treatment DW-MRI and PET CT both performed
n=36

Analysis: for change between pre- and 12 week post- treatment DW-MRI and PET CT
n=36
Primary tumour n=30
Lymph node n=36

Pre-treatment PET-CT performed outside study protocol
n=43
Primary tumour n=35
Lymph node n=41

FIGURE 1 Participant flow chart
3.1.1 | Associations between post-CRT DW-MRI and PET/CT parameters

The descriptive statistics for the tumor and nodal ADC<sub>mean</sub>, ADC<sub>min</sub>, SUV<sub>max</sub>, SUV<sub>max</sub> lesion: liver at 12-week posttreatment imaging, together with interval changes from pretreatment imaging are shown in Table 3.

No significant negative correlations were demonstrated between ADC<sub>mean</sub> and SUV<sub>max</sub> at the tumor and nodal sites on the 12-week post-CRT studies (\( P = .455-.794; \) tau = −0.075-0.25), or their interval changes from pretreatment to 12-week posttreatment studies (\( P = .1-.946; \) tau = −0.194-0.044). Scatter plots of the correlation are demonstrated in Figure 2. There was also no correlation between any of the other DW-MRI (ADC<sub>min</sub>) and 18F-FDG PET/CT (SUV<sub>max</sub> lesion: liver) parameters with respect to the 12-week posttreatment studies or pretreatment to 12-week posttreatment interval changes (Figures 3 and 4). Table 4 demonstrates the correlation of MRI parameters and PET/CT parameters, with Table 5 demonstrating the same correlation but restricted to patients with measurable disease (n = 19/52 lymph nodes) at 12-weeks posttreatment.

3.1.2 | Prediction of 2 year DFS with post-CRT DW-MRI and PET/CT parameters

The comparison of ADC and SUV<sub>max</sub> parameters in participants with and without 2 year DFS is demonstrated in Table 6. The primary tumor ADC<sub>mean</sub> at 12-weeks post-CRT DW-MRI (\( P = .03 \)) and the interval change in nodal ADC<sub>min</sub> from pretreatment to 12-weeks post-CRT DW-MRI (\( P = .05 \)) were associated with 2-year DFS. None of the other ADC parameters and no SUV<sub>max</sub> parameters were able to predict 2-year DFS.

4 | DISCUSSION

This study provides novel data comparing post-CRT diffusion quantitative DW-MRI and 18F-FDG PET/CT parameters in HNSCC. No

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### Table 2

| Oropharynx | n = 43 | HPV +ve | HPV −ve | Not tested |
|---|---|---|---|---|
| Tongue base | 26 | 41 | 2 |
| Tonsil | 16 | 2 |
| Soft Palate | 1 | |

| Larynx | n = 8 | HPV +ve | HPV −ve | Not tested |
|---|---|---|---|---|
| Supraglottic | 6 | 0 |
| Transglottic | 2 | 1 |

| Hypopharynx | n = 5 | HPV +ve | HPV −ve | Not tested |
|---|---|---|---|---|
| PIRiform Fossa | 5 | 0 |

### Table 3

| Node ADC<sub>min</sub> at 12 weeks | n | Mean | SD | LQ | Median | UQ |
|---|---|---|---|---|---|---|
| 52 | 1028.70 | 245.04 | 888.25 | | 1030.00 | 1163.73 |
| 48 | 1373.79 | 282.27 | 1181.00 | | 1369.46 | 1583.78 |
| Change in node ADC<sub>min</sub> pre-12 weeks | 52 | 338.07 | 343.62 | 159.75 | | 337.00 | 470.71 |
| Change in tumor ADC<sub>min</sub> pre-12 weeks | 48 | 732.17 | 333.37 | 461.62 | | 780.00 | 971.00 |
| Node ADC<sub>mean</sub> at 12 weeks | 52 | 1462.88 | 250.71 | 1326.14 | | 1458.28 | 1573.10 |
| Tumor ADC<sub>mean</sub> at 12 weeks | 48 | 1830.08 | 270.71 | 1614.87 | | 1821.60 | 1984.39 |
| Change in node ADC<sub>mean</sub> pre-12 weeks | 52 | 1462.88 | 250.71 | 1326.14 | | 1458.28 | 1573.10 |
| Change in tumor ADC<sub>mean</sub> pre-12 weeks | 48 | 1830.08 | 270.71 | 1614.87 | | 1821.60 | 1984.39 |

| Node SUV<sub>max</sub> at 12 weeks | n | Mean | SD | LQ | Median | UQ |
|---|---|---|---|---|---|---|
| 52 | 1.89 | 0.55 | 1.52 | | 1.83 | 2.33 |
| 48 | 3.00 | 0.88 | 2.32 | | 2.96 | 3.62 |
| Change in node SUV<sub>max</sub> pre-12 weeks | 36 | −7.11 | 4.43 | −9.95 | | −6.39 | −4.25 |
| Change in tumor SUV<sub>max</sub> pre-12 weeks | 30 | −10.24 | 6.78 | −13.73 | | −10.31 | −5.15 |
| Liver: node SUV<sub>max</sub> at 12 weeks | 52 | 0.72 | 0.20 | 0.56 | | 0.71 | 0.88 |
| Liver: tumor SUV<sub>max</sub> at 12 weeks | 48 | 1.17 | 0.35 | 0.91 | | 1.09 | 1.36 |
| Change in liver: node SUV<sub>max</sub> pre-12 weeks | 36 | −2.57 | 1.75 | −3.58 | | −2.33 | −1.75 |
| Change in liver: tumor SUV<sub>max</sub> pre-12 weeks | 30 | −3.74 | 2.67 | −5.01 | | −3.48 | −1.65 |

Abbreviations: LQ, lower quartiles; UQ, upper quartiles.
correlation was demonstrated between ADCmean and SUVmax on 12-week post-CRT studies, or between the interval change in ADCmean and SUVmax from pretreatment to 12-week posttreatment for (C) primary tumor and (D) lymph node. PET measures (y-axes) and MRI measures (x-axes). Line of best fit (blue) with 95% confidence intervals shown overlaid (grey).

Posttreatment 18F-FDG PET/CT is an established technique for the evaluation of post-CRT advanced HNSCC. Since treatment-induced inflammation in the very early posttreatment period may lead to false positive studies, 18F-FDG PET/CT is usually delayed until 12 weeks following the completion of CRT in order to increase the specificity. Semiquantitative analysis demonstrating increased posttreatment SUVmax values and lack of significant reduction in SUVmax values within loco-regional tumor has been shown to indicate treatment failure. Similarly, quantitative DW-MRI has been investigated in the posttreatment setting, with a higher ADC, or a greater interval increase from pre- to intra- or posttreatment ADC being associated with loco-regional treatment success.

It would therefore be useful to establish whether the posttreatment DW-MRI and 18F-FDG PET/CT-based parameters are correlated with each other. While treatment failure is associated with interval changes in both posttreatment SUVmax and ADC, they may still have a complementary role in evaluating treatment response if they are demonstrated to be independent variables. This would inform on appropriate early posttreatment protocols and the applicability of new technologies such as PET-MRI, which would measure both parameters simultaneously.

Previous reports comparing SUV and ADC parameters in HNSCC are restricted to the pretreatment scenario and these have demonstrated disparate results. Choi et al (n = 31) and Nakajo et al (n = 26) reported significant negative correlations between pretreatment ADC and SUV. It was argued that the glycolytic activity evaluated with 18F-FDG PET-CT is therefore significantly related with the microstructural environment evaluated by DW-MRI in patients with HNSCC. In contrast, Varoqaux et al (n = 33) and Freuhwald-Wallamar et al (n = 46) showed no statistical relationship, and hence identified pretreatment SUV and ADC as potentially independent biomarkers in HNSCC. One study has compared quantitative DW-MRI and 18F-FDG PET/CT parameters in the posttreatment setting at another tumor site, with ADCmin and SUVmax found not to be significantly correlated in recurrent cervical (gynecological) cancer.

Alternative 18F-FDG PET/CT and ADC parameters were also evaluated. First, although SUV is the more commonly used parameter...
FIGURE 3  Pretreatment MRI and FDG PET/CT study in a 64-year-old male patient with T2N2b left oropharynx tumor. T2W, \( b = 800 \) DWI and ADC map (\( b = 100-800 \)) MRI images (A and C) and CT, PET, PET/CT fused images (B and D) indicating the left glosso-tonsilar sulcus tumor (arrows in A and B) and left level 2 lymph node (arrows in C and D). The ROIs on the MRI study include areas of increased DWI signal corresponding to intermediate T2w signal in the cores of the primary and nodal tumor as indicated (ovals in A and C). The 6 mm VOI on the PET-CT study is seen within the central portion of the primary and nodal tumor (circles in B and D).
FIGURE 4  12-week post-chemo-radiotherapy MRI and PET/CT study in the same patient. T2w, $b = 800$ DWI and ADC map ($b = 100-800$) MRI images (A and C) and CT, PET, PET/CT fused image (B and D) indicating the site of the previous left glosso-tonsillar sulcus tumor, which is now nonmeasurable and left level 2 lymph node, which has markedly reduced in size (arrows in C and D). The 6 mm ROIs on the MRI study are placed at the site of the previous primary tumor (circle in A) and at the residual nodal tumor as indicated (circle in B). The corresponding 6 mm VOI on the PET-CT study is seen within the central portion of the primary and nodal tumor (circles in B and D).
in the assessment of HNSCC treatment response,\textsuperscript{13-18} the role of absolute SUV values in the posttreatment evaluation of HNSCC with \textsuperscript{18}F-FDG PET/CT has been questioned.\textsuperscript{10,52} As an alternative, \textsuperscript{18}F-FDG uptake may be measured relative to normal tissue/background tissue, and quantitative interpretative criteria such as the Porceddu, Hopkins, and Deauville scoring systems are based on this approach.\textsuperscript{53-55} Zhong et al evaluated these scoring systems and found that they demonstrated high specificity, PPV, and NPV.\textsuperscript{56} Tumor uptake exceeding liver tracer uptake is indicative of disease in all these criteria, and hence we decided to include tumor SUV to liver ratio as another \textsuperscript{18}F-FDG PET/CT parameter. Some previous studies have demonstrated total lesion glycolysis (TLG) to be a superior predictor of HNSCC treatment outcomes\textsuperscript{57}; however, this requires an assessment of metabolic tumor volume, which was not possible in many of the posttreatment cases, where there was no definable FDG uptake and a standardized small VOI was placed. Second, with respect to the DW-MRI parameters, both ADC\textsubscript{mean} and ADC\textsubscript{min} were evaluated in this study since each has previously been applied to previous comparisons of quantitative DW-MRI with \textsuperscript{18}F-FDG PET/CT on pretreatment imaging.\textsuperscript{35,36}

It is of note that while selected ADC parameters were able to predict treatment outcomes in this study, none of the SUV\textsubscript{max} parameters proved prognostically useful in this study. Some previous studies have shown that posttreatment SUV\textsubscript{max} is a less accurate predictor of outcome in HPV OPC cohorts.\textsuperscript{58,59} In addition, the unexpectedly high rate of HPV-OPC participant recruitment also resulted in low rate of treatment failure such that it was suboptimally powered for the comparison of quantitative DW-MRI and \textsuperscript{18}F-FDG PET/CT parameters with 2-year DFS.

There are potential shortcomings with the study methodology. First, there are greater challenges with the accurate placement and measurement of ADC and SUV in the posttreatment setting. For

### TABLE 4

| MRI (X) | PET (Y) | n  | tau  | P-value |
|---------|---------|----|------|---------|
| Node ADC\textsubscript{mean} at 12 weeks | Node SUV\textsubscript{max} at 12 weeks | 52 | −0.061 | .528 |
| Node ADC\textsubscript{mean} at 12 weeks | Node SUV\textsubscript{max} at 12 weeks | 52 | −0.025 | .794 |
| Tumor ADC\textsubscript{mean} at 12 weeks | Tumor SUV\textsubscript{max} at 12 weeks | 48 | −0.075 | .455 |
| Tumor ADC\textsubscript{mean} at 12 weeks | Tumor SUV\textsubscript{max} at 12 weeks | 48 | −0.042 | .676 |
| Node ADC\textsubscript{min} at 12 weeks | SUV\textsubscript{max} liver: node at 12 weeks | 52 | −0.027 | .776 |
| Node ADC\textsubscript{min} at 12 weeks | SUV\textsubscript{max} liver: node at 12 weeks | 52 | −0.034 | .723 |
| Tumor ADC\textsubscript{min} at 12 weeks | SUV\textsubscript{max} liver: tumor at 12 weeks | 48 | −0.048 | .639 |
| Tumor ADC\textsubscript{min} at 12 weeks | SUV\textsubscript{max} liver: tumor at 12 weeks | 48 | −0.059 | .551 |
| Node ADC\textsubscript{mean} change pre-12 weeks | Node SUV\textsubscript{max} change pre-12 weeks | 36 | −0.194 | .100 |
| Node ADC\textsubscript{min} change pre-12 weeks | Node SUV\textsubscript{max} change pre-12 weeks | 36 | −0.101 | .946 |
| Tumor ADC\textsubscript{mean} change pre-12 weeks | Tumor SUV\textsubscript{max} change pre-12 weeks | 30 | 0.030 | .832 |
| Tumor ADC\textsubscript{min} change pre-12 weeks | Tumor SUV\textsubscript{max} change pre-12 weeks | 30 | 0.039 | .762 |
| Node ADC\textsubscript{mean} change pre-12 weeks | SUV\textsubscript{max} liver: node change pre-12 weeks | 36 | −0.175 | .138 |
| Node ADC\textsubscript{min} change pre-12 weeks | SUV\textsubscript{max} liver: node change pre-12 weeks | 36 | 0.022 | .860 |
| Tumor ADC\textsubscript{mean} change pre-12 weeks | SUV\textsubscript{max} liver: tumor change pre-12 weeks | 30 | 0.025 | .860 |
| Tumor ADC\textsubscript{min} change pre-12 weeks | SUV\textsubscript{max} liver: tumor change pre-12 weeks | 30 | 0.044 | .735 |

### TABLE 5

| MRI (X) | PET (Y) | n  | tau  | P-value |
|---------|---------|----|------|---------|
| Node ADC\textsubscript{mean} at 12 weeks | Node SUV\textsubscript{max} at 12 weeks | 19 | −0.035 | .834 |
| Node ADC\textsubscript{min} at 12 weeks | Node SUV\textsubscript{max} at 12 weeks | 19 | −0.199 | .234 |
| Node ADC\textsubscript{mean} at 12 weeks | SUV\textsubscript{max} liver: node at 12 weeks | 19 | 0.006 | 1.000 |
| Node ADC\textsubscript{min} at 12 weeks | SUV\textsubscript{max} liver: node at 12 weeks | 19 | −0.158 | .368 |
| Node ADC\textsubscript{mean} change pre-12 weeks | Node SUV\textsubscript{max} change pre-12 weeks | 11 | −0.236 | .359 |
| Node ADC\textsubscript{min} change pre-12 weeks | Node SUV\textsubscript{max} change pre-12 weeks | 11 | −0.055 | .879 |
| Node ADC\textsubscript{mean} change pre-12 weeks | SUV\textsubscript{max} liver: node change pre-12 weeks | 11 | −0.236 | .359 |
| Node ADC\textsubscript{min} change pre-12 weeks | SUV\textsubscript{max} liver: node change pre-12 weeks | 11 | −0.055 | .879 |
instance, there is a reduction in conspicuity of any anatomical tumor target on MRI and the qualitative assessment of the tumor site may not detect FDG tracer greater than background on 18F-FDG PET/CT. This resulted in there being only one third of nodal sites and no primary tumor sites which demonstrated a clear DWI focus to guide the ROI placement on the 12-week posttreatment DW-MRI studies. In addition, the DW-MRI and 18F-PET/CT measurements should ideally have been colocalized, but no fusion of the MRI and 18F-PET/CT data sets was feasible. Second, we do not present interobserver agreement statistics as part of this study and this would be particularly pertinent to the posttreatment analysis. Varoquaz et al has previously evaluated reproducibility of pretreatment ADC and SUV measurements with ICC > 0.9 for both. Third, the HPV-OPC dominant cohort is a potential confounding factor in this study with its unique histopathological characteristics and differing tumor metabolism. It is recognized that pretreatment ADC values are lower and over a wider range in HPV OPC, which may influence posttreatment ADC values or their interval change.

5 | CONCLUSION

We provide the first direct comparison of posttreatment DW-MRI and 18F-FDG PET/CT variables and their interval change from pretreatment values in patients with stage III and IV HNSCC. There was no significant negative linear relationship between ADC and SUV values on 12-week post-CRT studies or their interval changes in this HPV OPC dominant cohort. None of the SUV max parameters and only selected ADC parameters were associated with 2-year disease-free outcome. Since both the relationship between ADC and SUV values and the prognosis is influenced by HPV OPC status, further studies should focus on HPV negative HNSCC to determine whether DW-MRI and 18F-FDG PET/CT provide independent biomarkers in the post-CRT setting.

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AUTHOR CONTRIBUTIONS

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization, SC, VG; Methodology, SC, VG, GC, TS; Investigation, SC, CS, MA; Formal Analysis, SC, JD: Data Curation, MA, SC; Writing—Original Draft, SC; Writing—Review & Editing, SC, VG, GC, TS, IP; Visualization, JD, SC, CS; Supervision, SC, VG; Project Administration, SC; Funding Acquisition, SC.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.
ETHICAL STATEMENT
Institutional approval from the Research Ethics Committee (REC reference 13/LO/1876) and informed consent were obtained from all participants. The study conforms to recognized standards of the Declaration of Helsinki.

ORCID
Steve Connor https://orcid.org/0000-0001-5502-4972

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