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Pre-treatment PET/MRI based FDG and DWI imaging parameters for predicting HPV status and tumor response to chemoradiotherapy in primary oropharyngeal squamous cell carcinoma (OPSCC)

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ABSTRACT

Objectives: To determine the feasibility of pre-treatment primary tumor FDG-PET and DWI-MR imaging parameters in predicting HPV status and the second aim was to assess the feasibility of those imaging parameters to predict response to therapy.

Material and Methods: We retrospectively analyzed primary tumors in 33 patients with proven OPSCC. PET/MRI was performed before and 6 months after chemo-radiotherapy for assessing treatment response. PET Standardized uptake value (SUVmax), total lesion glycolysis (TLG), metabolic tumor volume (MTV), and apparent diffusion coefficient (ADC) from pre-treatment measurements were assessed and compared to the clinicopathological characteristics (T stages, N stages, tumor grades, HPV and post-treatment follow up). HPV was correlated to the clinicopathological characteristics.

Results: ADCmean was significantly lower in patients with HPV^{+ve} than HPV^{-ev}, ($P = 0.001$), cut off value of ($800 \pm 0.44*10^{-3}mm^2/s$) with 76.9% sensitivity, and 72.2% specificity is able to differentiate between the two groups. No significant differences were found between FDG parameters (SUVmax, TLG, and MTV), and HPV status, ($P = 0.873$, $P = 0.958$, and $P = 0.817$), respectively. Comparison between CR and NCR groups; ADCmean, TLG, and MTV were predictive parameters of treatment response, ($P = 0.017$, $P = 0.013$, and $P = 0.014$), respectively. HPV^{+ve} group shows a higher probability of lymph nodes involvement, ($P = 0.006$)

Conclusion: Our study found that pretreatment ADC of the primary tumor can predict HPV status and treatment response. On the other hand, metabolic PET parameters (TLG, and MTV) were able to predict primary tumor response to therapy.

Introduction

There is an increasing incidence worldwide for reporting aggressive OPSCC [1]. Alcohol and tobacco are the most etiological factors of developing OPCCS [2,3]. It has been also found that high-risk sexual behavior is a growing factor for increasing HPV-positive especially among young people [4]. There are several biological, clinical, and epidemiological to distinguish HPV-positive from HPV-negative entities [5]. Previous studies have demonstrated that patients with positive HPV have been shown better response to therapy and better survival

Abbreviations: PET/MRI, Positron Emission Tomography/Magnetic Resonance Imaging; SUV, Standardized Uptake Value; MTV, Metabolic Tumor Volume; TLG, Total Lesion Glycolysis; CRT, Chemo-Radiotherapy; HCC, Head and Neck Cancer; FDG, Fluorodeoxyglucose; AJCC, American Joint Committee on Cancer; OPSCC, oropharyngeal squamous cell carcinoma; EORTC, European Organization for Research and Treatment of Cancer; DWI, Diffusion-Weighted Imaging; ADC, Apparent Diffusion Coefficient.

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compared to negative HPV [6–8].

Diffusion-weighted imaging-magnetic resonance imaging (DWI-MRI) as a non-invasive technique is a widely used technology to assess the motion of water molecules (Brownian motion) as a non-invasive diagnosis technology of tissue biology [9], by taking apart the texture of a biologic tissue based on the water molecules motion at a microscopic level [10]. Several studies have reported the feasibility of DWI represented as apparent diffusion coefficient (ADC) in clinical uses ranging from interpretation microstructures of the tumors to the assessment of treatment response to therapy [11,12]. Moreover, DWI weighted imaging has shown promising results for HPV status assessment in patients with OPSCC [13–15].

The combined PET/MRI imaging modality used nowadays offers wider imaging parameters to assess tissue microstructure. In addition to DWI, it provides information from the metabolic parameters which assess the tumor metabolism, as such, maximum standardized uptake value (SUVmax), which represents maximum FDG uptake in the tumor, was found to provide prognostic information in HNSCC, although, the information gathered was controversial [16–18]. Volumetric FDG parameters such as total lesion glycolysis (TLG) and metabolic tumor volume (MTV) have also widely studied [19] TLG and MTV derived from F-18FDG-PET have shown to have prognostic significance in HNSCC, including HPV-associated OPSCCs. [20–23] As well as several studies have demonstrated the ability of MTV and TLG to predict treatment outcomes in OPSCC. [16,17,24–26]

The purpose of our study was to assess and compare the prognostic value of the FDG PET (SUVmax, TLG, and MTV) and DWI imaging parameters in predicting HPV status and prognostic value after 6 months of treatment.

Table1
Patients demographics.

Number of patients	*33*
Mean Age (y)	*(61.4 ± 0.7)*
Men	*23 (69.7%)*
Women	*10 (30.3%)*
Histologic Grade	
Well-differentiated	*4 (12.1%)*
Moderately-differentiated	*14 (42.4%)*
Poorly- differentiated	*15 (45.5%)*
Primary tumor	
Palatine tonsil	*7 (21.2%)*
Tongue root	*15 (45.5%)*
Soft palate	*2 (64.1%)*
Pharyngeal wall	*9 (27.3%)*
T category	
T1	*2 (6.1%)*
T2	*13 (39.%)*
T3	*12 (36.4%)*
T4	*6 (18.2%)*
N category	
N0	*3 (9.1%)*
N1	*6 (18.2%)*
N2	*16 (48.5%)*
N3	*8 (24.2%)*
M Category	
M0	*32 (97.0%)*
M1	*1 (3.0%)*
HPV STATUS	
HPV+	*16 (48.5%)*
HPV -	*17 (51.5%)*
Treatment response	
CR	*21 (63.6%)*
NCR	*12(36.4%)*

Materials and methods

A retrospective study was approved by the Clinical Center, Regional and Local Research Ethics Committee (CCRLREC), Doctoral School of Health Sciences, University of Pecs, and Somogy County Mór Kaposi Teaching Hospital, Kaposvar, Hungary. The requirements of the informed consent were waived and confirmed by the (CCRLREC) due to the retrospective nature, all methods were carried out following the relevant guidelines and regulations (Declaration of Helsinki). From May 2016 to June 2019, 46 patients with proven OPSCC underwent ^{18}F-FDG PET/MRI for staging, restaging, and assessment of the disease, and post-therapy follow-up (5–6 months on average). The inclusion criteria were (1) proved non-treated primary OPSCC, (2) patients underwent PET/MRI including DWI sequence (3) HPV test was performed. Exclusion criteria were: (1) patients who had non-measurable ADC (2) patients with motion artifact or suboptimal image quality including motion artifacts, and patients who did not underwent post-therapy follow up. Finally, a total of 33 patients were included in our study. Table1. Final confirmation of malignancy was done after biopsy of the primary tumor and metastatic lymph nodes.

PET/MRI imaging

The examinations were carried out in a dedicated PET/MRI (3 T) unit (Biograph mMR, Siemens AG, Erlangen, Germany) following PET/CT whole-body examinations. Patients were asked to fast for at least 6 h before receiving the 18F-FDG injection and their blood glucose levels were tested to ensure euglycemia before receiving the tracer injection. 18F-FDG with an adapted bodyweight dosage (4 MBq/kg, range 163–403 MBq) Intravenously injected; acquisition began within 75 min (60 ± 10 min after the uptake period) after the FDG tracer injection [27]. On average (15 ± 5 min), PET/MRI was performed after PET/CT. Images were collected using Head and Neck coils in the supine position. Included were PET/MRI parameters (ADC, SUV, TLG, and MTV) [27].

MRI sequences were T2-weighted TSE turbo inversion recovery magnitude (TIRM) (TR/TE/TI 3300/37/220 ms, FOV: 240 mm, slice thickness: 3 mm, 224 × 320) coronal plan, T1-weighted turbo spin-echo (TSE) (TR/TE 800/12 ms, FOV: 200 mm, slice thickness: 4 mm, 224 × 320) and T1-weighted TSE Dixon fat suppression (FS) (TR/TE 6500/85 ms, FOV: 200 mm, slice thickness: 4 mm, 256 × 320) transversal and were acquired without an intravenous contrast agent. Magnetic resonance-based attenuation correction (MRAC) series was used for PET attenuation correction for the PET data set, and the wide range bed position PET emission scan with a fixed FOV range (20 cm) and matrix (172x172) without bed movement was acquired for 900 s as well. An iterative ordered subset expectation maximization (3D OP-OSEM) PET image reconstruction algorithm was used with 3 iterations and 21 subsets, and 4 mm Gaussian filtering settings. The PET data were corrected for scattering, random coincidences, and attenuation using the MR data [27].

Diffusion-weighted Imaging (DWI) was obtained by using an axial echo-planar imaging (EPI) sequence with b-values of 0 and 800 and 1,000 s/mm^2 (FoV 315 mm, repetition time TR/TE: 9900/75 ms, 5 mm slice thickness and voxel size 2.3 × 2.3 × 5 mm and slice gap 10 mm). Furthermore, an axial Dixon FS T1-weighted TSE sequence and a coronal TSE Dixon FS sequence were conducted after injection of contrast material (Gadovist© Bayer Healthcare, Leverkusen, Germany) at 0.1 mmol per kg of bodyweight [27,28].

Image analysis

PET SUVmax, TLG, MTV parameters were measured in each patient using Siemens Syngo Via (20VB) application, which provided an automated delineated volumetric analysis based on the SUV. Using the VOI Sphere tool, the metabolic volumetric contours were segmented. VOIs have been assessed blindly to the histopathological characteristics. SUVmax represented the single voxel activity concentration of a specific tumor with the highest SUV [27]. A fixed 2.5 threshold of SUV was used for MTV and TLG calculations proposed by *Pak et al.* [29]. The volume above the given VOI represents MTV while TLG represents the VOI of the average SUVmean multiplied by the MTV [27].

The ADC map was automatically generated and analyzed on the implemented eRAD picture archive and communicating system (PACS) software. On the ADC map, DWI images were analyzed by drawing a round or oval region of interest (ROI) manually, covering the largest tumor diameter [30], on a single DWI slice [31] in the most homogenous part within the center of the tumor, the area which represents the lowest ADC or the highest SUV blindly to the histopathological characteristics after excluding or/and avoiding the necrotic and cystic areas. We didn't use the whole tumor volume technique for calculating ADC value while this method is more reproducible than those obtained from the measurements of a single slice or small ROI, the explanation is that there was no significant difference between the tumor ADCs obtained using whole-volume measurements and the single-slice approach.[32] Thus, we chose the single-slice approach because it's simpler, quicker, and as a result, more favored in clinical practice than the whole volume ROIs protocol which is time-consuming and more complicated. By summing all voxels ADC values on the drawn ROI for the selected slice, the average ADC values determined by the software automatically were referred to as ADCmean. We evaluated ADCmean values only, which was previously proposed as a more reliable indicator of tumor cellularity since the entire lesion is taken into account.[33] Besides, ADCmean minimizes the effect of tumor heterogeneity and its higher reliability to distinguish different entities in the same image [34]. We used the average ADC of the overall area included in the ROI which is calculated automatically by the software, where "Avg" represents the average ADC values for all voxels within the ROI and "Dev" Represents the standard deviation.

Clinical evaluation

To evaluate the treatment results of the primary tumor based on pre and post-therapy PET/CT and PET/MRI data, we used the European Organization for Research and Treatment of Cancer (EORTC) system [35]. To evaluate the predictive value of the pre-treatment imaging parameters we created two patient groups based on the PET/MRI therapeutic response and clinical follow-up. The two groups represent complete remission (CR) that includes only patients with complete remission and non-complete remission (NCR) which include patients with partial response, stable disease, and progressive disease patients.

Analysis of the HPV status

Immunohistochemistry of p16 protein overexpression from tumor blocks (Ventana Medical System - p16 protocol, Roche p16 cintec histology assay antibody 1: 5 dilution) was performed by the pathology department of Csolnoky Ferenc hospital from the primary tumor to detect the presence of high-risk HPV infection. We identified cases as positive, in which we observed so-called "block positivity", meani g both the nucleus and the plasma show strong staining in the tumor cells. Additional staining patterns (e.g., cytoplasmic only) were assessed as negative.

Statistical analysis

Statistical analysis was performed by using SPSS 25 (IBM SPSS Statistics, Armonk, New York, USA). The data collected were evaluated using descriptive statistics (mean ± standard deviation), for variables with normal distribution, median, and interquartile range for variables with non-normal distribution. The normality of the measured FDG and DWI was assessed by Shapiro-Wilks test. We used the Spearman correlation coefficient to assess the correlation between FDG and DWI parameters with T stages, N stages, and graders. Mann Whitney test, Wilcoxon's rank-sum test for group comparison with variables not normally distributed; TLG, and MTV ($P < 0.001$). ADCmean and SUVmax due to normally distributed were analyzed with independent sample *t* test for group comparison (HPV status and post-therapy results) and ANOVA test between ADC values and grades of the primary tumor. A Chi-square test was used to assess the association between categorical variables, (HPV, T stages, N stages, grades and post-therapy results). Variables for which $P < 0.1$ in univariate analysis were subjected to multiple linear regression analysis to determine those that were independently associated with the imaging parameters by integrating statistical differences in the univariate analysis into the multivariate linear regression model. ROC curve was used to determine the best cut off value to differentiate between HPV + and HPV-. A p-value < 0.05 was indicated as a statistically significant result.

Results

A total of 33 patients were enrolled in the study. The SUVmax, TLG, MTV and ADCmean measured from the primary tumors were 12.61 ± 0.5 (range, 3.4–23.5); 139 ± 0.87 (range, 5.79–883.46), 15 ± 0.14 (range, 1.91–88.83) and 0.820 ± $1.12*10^{-3}mm^2/s$ (range, 0.610–1.050 ± $1.12*10^{-3}mm^2/s$), respectively.

Correlation between HPV with FDG and DWI parameters

Based on the baseline measurements, 16 patients were positive, and 17 were negative for HPV. Independent sample *t*-test indicates that the ADCmean values of HPV^+ (0.758 ± $0.70*10^{-3}mm^2/s$) were significantly lower than HPV^- (0.905 ± $0.74*10^{-3}mm^2/s$), ($P = 0.001$), (Table 2), (Figure 1). Additionally, Spearman correlation coefficient indicates a significant inverse correlation between ADC and primary tumor grades (well, moderately and poorly differentiated tumors), ($r = -0.378$, $P = 0.030$), (Table 2). On the other hand, no significant differences were found between SUVmax, TLG, and MTV with HPV status, ($P = 0.873$, $P = 0.958$, and $P = 0.817$), respectively, (Table 2), (Figure 1). Moreover, SUVmax was significantly higher in patients with a higher N stage ($r = 0.366$, $P = 0.036$). Higher TLG and MTV were observed with a higher T stage, ($r = 0.361$, $P = 0.039$ and $r = 0.368$, $P = 0.035$), respectively. (Table 2).

To investigate which factors were independently influencing change in the ADC of the primary tumor (due to the significant results with HPV and primary tumor degree of differentiation), a multiple regression model was applied on HPV status and grade of the primary tumor, the results show that only HPV was an independent factor influencing change in ADC, ($P = 0.001$), while the effect of the degree of differentiation was not significant, ($P = 0.138$).

ROC curve was used to calculate the best cut-off value of ADC to differentiate between HPV + and HPV- groups. The result shows that at a value of (800 ± $0.44*10^{-3}mm^2/s$), the area under the curve (AUC) was 69.7% with 76.9% sensitivity and 73.3% specificity Fig 2.

Correlation between HPV and histopathological characteristics

Chi-square test used to assess the association between the categorical

Table 2
Clinicopathological comparison with FDG and DWI imaging parameters.

Grouping	SUVmax	TLG	MTV	ADC
T stages *	r = 0.51	***r = 0.361***	***r = 0.368***	r = 0.171
	P = 0.780	***P = 0.039***	***P = 0.035***	P = 0.341
N stages *	***r = 0.366***	r = 0.132	r = 0.127	r = − 0.276
	P = 0.036	P = 0.466	P = 0.485	P = 0.101
Grades *	r = 0.081	r = 0.000	r = − 0.007	***r = − 0.378***
	P = 0.656	P = 1.000	P = 1.000	***P = 0.030***
HPV status	P = 0.873	P = 0.958	P = 0.817	***P = 0.001***

*Spearman rho test was used to assess the correlation between ADC, SUVmax, TLG and MTV imaging parameters with T stages, N stages and Grades of the primary tumor. Mann-Whitney test for two categorical variables (HPV) with TLG and MTV parameters, Independent sample *t* test with ADC, and SUVmax values. A significant result at a level of $p < 0.05$ was highlighted in Bold

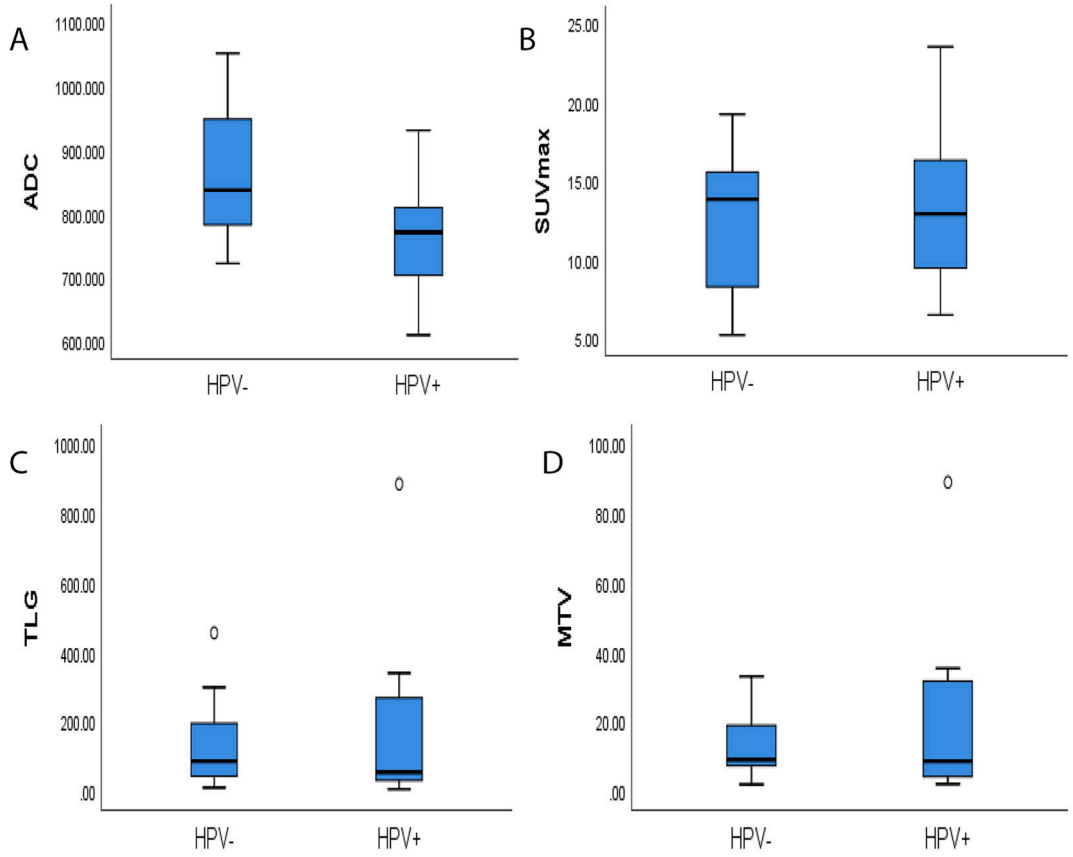

Fig. 1. Boxplots displaying the distribution of ADC, TLG, MTV, and SUVmax (A, B, C, and D) according to HPV status. (A) ADCmean values of HPV+ev tumors were significantly lower than those of HPV-ev tumors (P = 0.001). (B) SUVmax shows no significant difference, (P = 0.873). (C) TLG shows no significant difference, (P = 0.958), and finally, (D) MTV shows no significant difference, (P = 0.817).

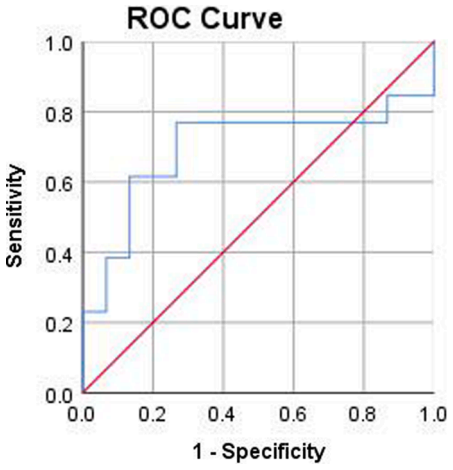

Fig. 2. Receiver operating characteristic (ROC) curve analysis of HPV according to primary tumor ADC, (ROC) curve with AUC (69.7%), 95% confidence interval was ranged between 0.478 and 0.917, best cut off value was (800 ± 0.00 * 10^{-3} mm^2/s) to distinguish between HPV+ from HPV- with a sensitivity of 76.9% and specificity of 73.3%.

variables. Details of the TNM staging summarized in (supplementary 1). No significant correlations were found between HPV groups and T stages; HPV+ (T1 = 2, T2 = 7, T3 = 4, and T4 = 3), HPV- (T1 = 0, T2 = 6, T3 = 8, and T4 = 3), (P = 0.336), no significant association between HPV status and N stages, HPV+ (N0 = 1, N1 = 1, N2 = 8 and N3 = 6), HPV- (N0 = 2, N1 = 5, N2 = 8 and N3 = 3), (P = 0.174)., or with primary tumor degree of differentiation; HPV+ (well differentiated = 0, moderately differentiated = 7, and poorly differentiated = 9), HPV- (well differentiated = 4, moderately differentiated = 7, and poorly differentiated = 6), (P = 0.102).

Predicting treatment response

According to the independent sample *t*-test, a statistically significant difference was found between CR (n = 21) vs NCR (n = 12) with pre-treatment ADC values (0.801 vs 0.893*$10^{-3}$$mm^2$/s, P = 0.017), respectively. Wilcoxon rank test demonstrates a significant difference between CR and NCR with pre-treatment TLG (76.77 vs 224.80, P = 0.013) and MTV (9.088 vs 23.27, P = 0.014), (Figure 3). CR and NCR were illustrated in (Figure 4) and (Figure 5), respectively. No statistically significant difference was found between the two groups and SUVmax, (P = 0.664). (Figure 3). Moreover, according to Chi-square test, HPV+ (CR = 14, NCR = 2) and HPV- (CR = 7, NCR = 10) were significantly associated, (P = 0.006) between CR and NCR patients.

Discussion

We analyzed the efficacy of combined PET/MRI imaging parameters to predict HPV status and local response of OPSCC treated by CRT with curative intent. We found that HPV + lesions are associated with lower ADC values than HPV- lesions, which might be useful as a non-invasive technique to evaluate HPV status. With a value of (809 ± 0.37*$10^{-3}$$mm^2$/s), the area under the curve (AUC) was 80.0% with 73.7% sensitivity, and 73.3% specificity can differentiate between HPV groups. In contrast, FDG parameters did not show any statistical significance between HPV groups, which means that FDG might not be useful for

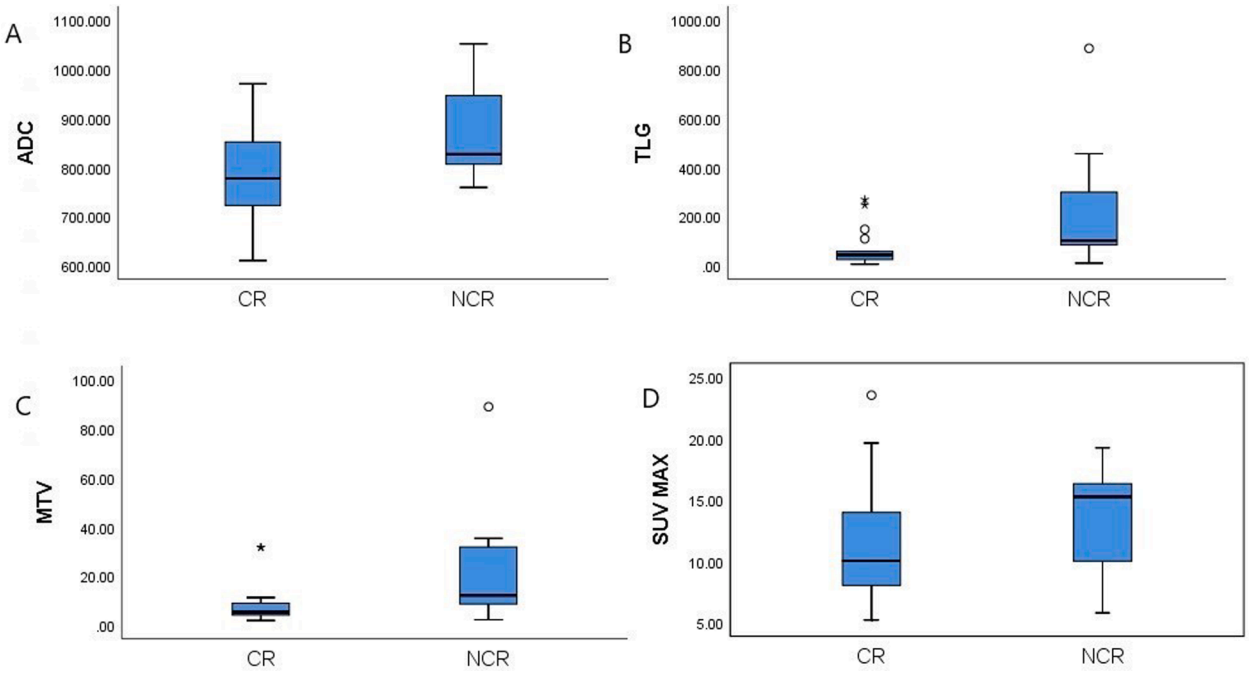

Fig. 3. Boxplots displaying the distribution of ADC, TLG, MTV, and SUVmax (A, B, C, and D) according to treatment results. (A) pretreatment ADC values of CR tumors were statistically significant lower than those of NCR tumors (P = 0.017). (B) pre-treatment TLG shows a statistically significant higher in NCR than CR tumors, (P = 0.013). (C) pre-treatment MTV shows a statistically significant higher in NCR than CR tumors, (P = 0.014), and (D) pre-treatment SUVmax didn't differ significantly between both groups, (P = 0.664).

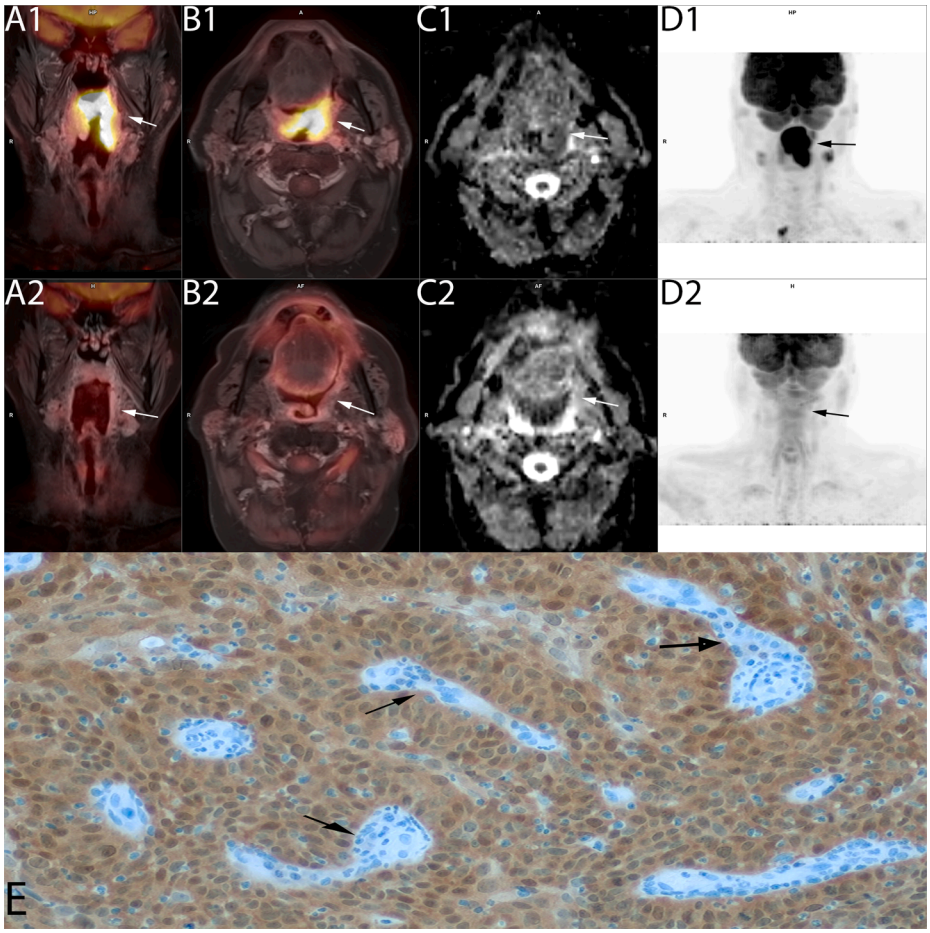

Fig. 4. Complete remission (CR) for HPV+ patient: pre-treatment coronal (A_1), axial (B_1) PET/MRI images, axial (C_1) MR-diffusion weighted imaging (DWI) apparent diffusion coefficient (ADC) map of the tumor, and (D_1) PET imaging show oropharyngeal tumor spread over the soft palate, palatine tonsil and posterior wall of the pharynx, pretreatment maximum standardized uptake value (SUV max): 19.61, total lesion glycolysis (TLG): 147.81, metabolic tumor volume (MTV): 11.28 cm^3, mean ADC (ADC mean): $0.610 \pm 0.52 \times 10^{-6}$ s/mm^2. Post-treatment coronal PET (A_2), axial (B_2) PET/MR, axial DWI ADC (C_2), (D_2) images show complete remission (CR); without any pathologic FDG accumulation, and diffusion restriction on the observed volume, and (E) Representative immunohistochemical staining showing examples of P16 expression levels in HPV+.

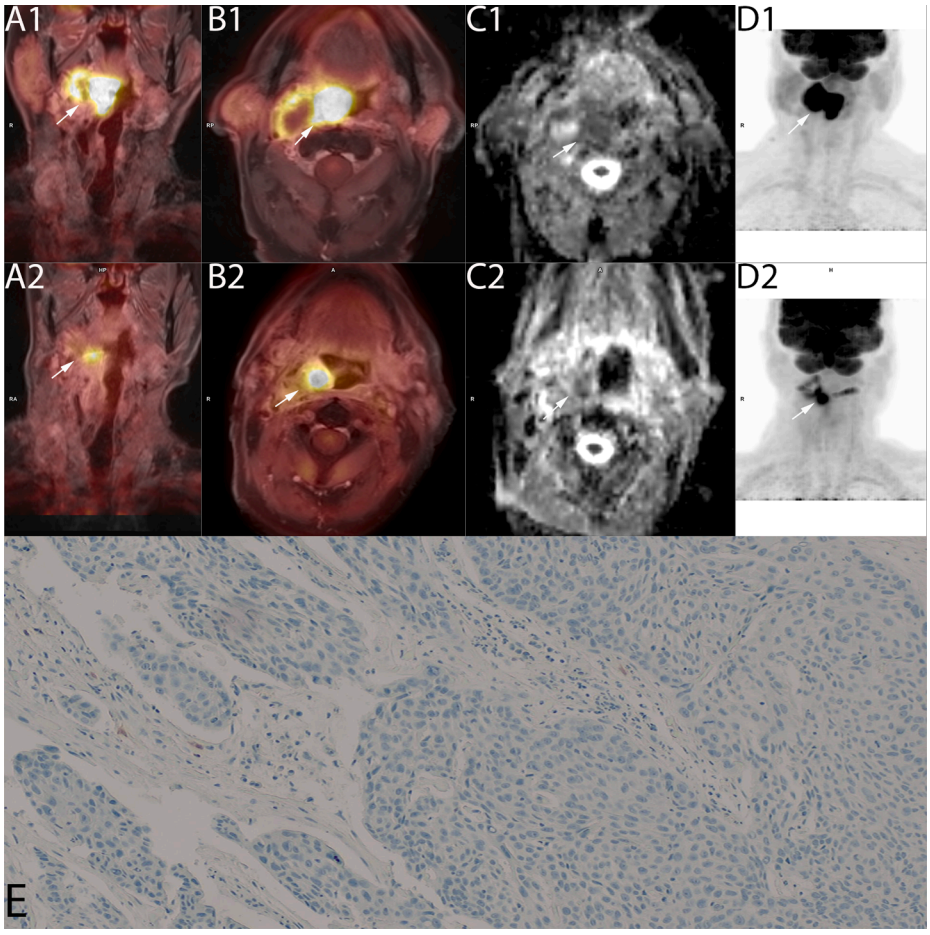

Fig. 5. Non-complete remission (NCR) for HPV- patient: coronal (A_1), axial (B_1) PET/MRI images, axial (C_1) MR-diffusion weighted imaging (DWI) apparent diffusion coefficient (ADC) map of the tumor, and (D_1) PET imaging show right palatine tonsil tumor spreading into tongue root, pretreatment maximum standardized uptake value (SUV max): 15.24, total lesion glycolysis (TLG): 99.72, metabolic tumor volume (MTV): 9.16 cm^3, mean ADC (ADC mean): 1.050 ± 0.680 × 10^{-6} s/mm^2. Post-treatment coronal PET (A_2), axial (B_2) PET/MR, axial DWI ADC (C_2), (D_2) PET image show non-complete remission (CR); with pathologic FDG accumulation, and diffusion restriction on the observed volume, and (E) Representative immunohistochemical staining showing examples of P16 expression levels in HPV-.

predicting HPV status. Our study has also demonstrated that DWI, FDG volumetric metabolism parameters (TLG and MTV) are useful predictor biomarkers to assess the response before treatment in OPSCC, while SUVmax may not. Besides, the HPV + patients group have shown a better response to therapy than HPV- patients.

In head and neck squamous cell carcinoma (HNSCC), OPSCCs are the most associated HPV-related tumors; they tend to respond well to therapy and carry a favorable prognosis [36]. HPV status has been previously studied and investigated in OPSCC based on morphology [37,38], or molecular biology [39–41]. Imaging parameters have been also used to predict HPV infection as a non-invasive technique, DWI was proposed to have the ability to differentiate between HPV-positive and HPV-negative. Several studies found that HPV + has lower ADC than HPV- OPSCC's [13–15,42,43]. This might be attributed to the positive correlation between ADC and total percentage area of stroma, and an inverse correlation with the cell density in tumors [44]. Our result was similar to previous reports, which suppose the hypothesis of the association between ADC and HPV infection. A value of (809 ± 0.37*$10^{-3}$$mm^2$/s) was able to differentiate between the two groups, which was parallel with previous studies [13,14]. The significance of this result is since that tumors with low pretreatment ADC values respond better to chemo/radiotherapy than tumors with low ADC values [14].

The diagnosis of primary and metastatic (HNSCC) has been increasingly studied by FDG-PET, which due to its accuracy and sensitivity has been recognized as a standard of reference nowadays, as well as being used for post-treatment surveillance. Some studies have investigated the role of FDG PET imaging parameters in predicting HPV infection. However, previous studies show a controversial result, some reports found that the FDG parameter (SUVmax) is helpful to differentiate between HPV + and HPV- [45–48], while others didn't [47,49,50]. It has also been proposed that volumetric metabolism parameters (TLG, MTV) could provide more details for tumor metabolism. Previous studies have demonstrated that TLG and MTV have superior prognostic values than SUVmax since they reported that larger tumor volume correlates with the overall survival and inferior local control [18,21,23], this, in turn, might be reflected on patients with HPV + since it shows a higher percentage of loco-regional response and longer free survival. However, our study found no significant difference between FDG imaging parameters and HPV infection, which in turn, might limit the prospective use of these imaging parameters in clinical use. Similar results were reported by other authors [47,50,51]. The reason of our results might be attributed to the lack of a significant correlation between T stages and HPV status, since previous reports were found that HPV- tumors have higher T stages than HPV+, which as a results affect the tumor metabolism, since higher FDG uptake was observed in higher T stages, this might explain why HPV- tumors have higher FDG values (SUVmax, TLG, and MTV), in our study there was no significant difference between HPV + and HPV- because there was no difference in T stages between the two groups [23,52]. Thus, we suppose that the significant correlation between HPV status and FDG parameters, if reported, is attributed to the size difference between HPV + and HPV- [52]. However, most of the previous studies have heterogeneous primary tumor localization (oral, laryngeal, nasopharyngeal, pharyngeal), as a result, the concluded results might have limited accuracy. Thus, to investigate more efficient results of PET parameters role in OPSCC, this should be investigated separately

New hybrid imaging modalities such as PET/CT or PET/MRI have emerged as useful technologies to assess HNSCC tumors in terms of prognosis and follow up. Overall, HNC's as proposed previously, have a possibility of locoregional recurrence in the first two years after therapy

up to 50–60% of the patients [53]. Several imaging parameters have been used for the Propose of predicting response to therapy, DWI represented by ADC, and metabolic parameters (SUVmax, TLG, and MTV), different results have been reported, while some studies found some of them are feasible while other didn't. There is a need in clinical practice to assess accurately the tumor response to therapy, this is due to the high mortality in patients with HNSCC'S, therefor, all available tools to assess cancer should be combined to allow the physicians to select the most appropriate treatment protocols, especially to assess the prognosis of the patient, so it's highly important to identify potential predictive biomarkers to have better treatment strategies.

In this study, we found that DWI and metabolic imaging parameters TLG and MTV can provide more accurate information for treatment prediction since we found that higher TLG and MTV before therapy lead to a higher probability of recurrence and lower rates of response [19,54], these findings do not eliminate the role of the basic FDG parameter (SUVmax) for prediction, although, in our study, we found no significant correlation between SUVmax and response. Overall, in OPSCC, it has been reported that TLG and MTV have better results in the prediction of overall survival and disease-free survival [55]. In regard to ADC, our results revealed that ADC might be useful for predicting response after therapy, although we have lost data for 5 patients in post-treatment examinations. According to Sae et al. there is a trend that DWI can predict tumor response to therapy in HNSCC, several studies have reported higher ADC after therapy, but still of the major limitations of the previous studies is the heterogeneity of the tumors, as well as the number of studies, are small [56]. PET imaging parameters also provide very important information regarding tumor microstructures. Our study compared to the previous published in HNS has more homogenous primary tumor localization (OPSCC), it also one of the fewest papers which compare the role of the combined biomarkers derived from PET/MRI combined technique. However, since we didn't find a significant correlation between PET parameters and HPV status, PET parameters seem to be less important to add a significant diagnostic role during OPSCC related HPV lesions assessment [55]. Finally, our study emphasize that HPV + tumors tend to have better response to therapy than HPV- tumors [57].

As a limitation of the current study, small sample size, retrospective design, single institute approach, and using the conventional FDG and DWI parameters which do not include texture analysis should be noted. Although moderate sample size, we only included OPSCC patients from the HNC group to ensure a homogeneous population that may increase the reliability of our results.

In conclusion, this study found that pre-treatment ADC was a predictor of HPV status and post-therapy results. On the other side, FDG parameters were able to predict tumor response to therapy, but they don't show a feasible role in predicting HPV status. Based on the reported results, both DWI and FDG parameters are important to assess patients with OPSCC and their role might be complementary to each other.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available under a reasonable request. This study is a part of a project in the clinical trials repository, [**ID:** NCT04360993].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2021.105239.

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