

Association Between Diffusion Weighted-Imaging (DWI) and Simultaneous ¹⁸F-FDG-PET/MRI Parameters with a Comparison of their Diagnostical Role in Head and Neck Squamous Cell Carcinoma (HNSCC)

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Abstract

Background: Hybrid PET/MRI is an emerging imaging technology proved to be useful for better understanding of the tumor metabolism and cellularity, it also plays a very important in staging, assessment and post-therapy follow up. PET/MRI can be used to better understand how tumors act, especially prior to therapy. Our aim in this study is to assess the association of ^{18}F -Fluorodeoxyglucose positron-emission-tomography (18F-FDG/PET) and DWI imaging parameters and multi-clinical factors correlations and comparing their diagnostical performance to predict tumor aggressiveness in HNSCC.

Results: No significant correlations were found between DWI and any of ^{18}F -FDG parameters SUVmax, TLG and MTV, ($r = -0.184$, $P=0.125$, $r = -0.182$, $P=0.248$, and $r = -0.037$, $P=0.756$), respectively. As SUVmax and TLG of the primary tumor increase, the tumor aggressiveness to involve more lymph nodes increase, ($r = 0.321$, $P=0.006$ and $r = 0.332$, $P=0.005$), respectively. Comparison between patients with positive (N+) and negative (N-) lymph node groups show that SUVmax and ADC can predict lymph nodes metastasis, ($P=0.004$ and $P=0.012$), respectively. SUVmax best cut-off value of (6.8 ± 0.8), had higher accuracy than ADC, best cut-off value of ($0.981 \pm 0.97 \times 10^{-3} \text{mm}^2/\text{s}$), (sensitivity: 83.6%, 70.0% and specificity: 80.0%, 78.7%), respectively. Additionally, TLG and MTV were positively correlated with T-stages ($P=0.024$ and $P=0.001$), respectively. ADC was inversely correlated with tumor grades ($P=0.030$).

Conclusions: Our results revealed a non-significant correlation between the FDG-PET and DWI-MR parameters. The FDG-PET-based glucose metabolic and DWI-MR derived cellularity data may represent different biological aspects of HNSCC. SUVmax was superior to DWI in predicting lymph nodes metastasis.

Background:

Worldwide; Head and neck cancer is the sixth most common malignancy; approximately 6% of all cancer cases, accountable for an estimated 1–2% of all cancer deaths.[1] H&N cancers are a heterogeneous group of cancers that existed anatomically close to each other, but different in terms of etiology, histology, diagnostic and treatment approaches.[2] About 91% of all H&N cancer are squamous cell carcinomas, 2% are sarcomas and the other 7% are adenocarcinomas, melanomas and not well-specified tumors.[3]

Recently, ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET)/magnetic resonance imaging (MRI) has emerged as an effective and accurate imaging modality in oncology.[4] The PET/MRI is expected to be more valuable than PET or CT alone or combined because the PET/MRI involves better contrast in soft tissues and a lower radiation dose from the MRI system.[4] The superior role of the PET/MRI over other imaging modalities is the ability to perform many functional imaging techniques.[5] This includes DWI which is a widely used technology to assess the motion of water molecules (Brownian motion) as a noninvasive diagnosis technology of tissue biology, [6] by taking apart the texture of a biologic tissue based on the water molecules motion at a microscopic level.[7] ADC represents DWI in

determining the tumor's cellularity.[8], [9] The higher cellular tumor resulted in more restriction to water molecule motion which, as a result, gives lower ADC values and vice versa.[10] This means that the water molecule's motion is reflecting the signal loss on DWI due to different water permeability through the structures.[11] Previous studies have proved the inversely proportional correlation between ADC and tumor cellularity.[12], [13] ADC also was found to be effective in primary tumor assessment, differentiating between benign and malignant neoplasms, staging and monitoring post-treatment follow-up.[14], [15] Moreover, ADC was found to be useful for predicting treatment response in HNSCC.[16]

The FDG uptake values measured from PET imaging has an important role in head and neck imaging due to its ability to measure the glucose metabolism in the tumors,[17]–[19] which may also reflect the tumor's aggressiveness and the risk of the metastasis to spread to the adjacent structures.[20], [21] SUV is the most common parameter used to estimate glucose metabolism, and it has shown promising results in predicting the presence of lymph nodes metastatic during the primary assessment as well as a predictor of survival and recurrence.[22] Recently; new metabolic parameters, TLG and MTV have emerged as new parameters that can measure the glucose metabolism activity of tumors and have been founded to be more effective than SUV because tumor contour is considered when using MTV and TLG. [23] Since SUVmax doesn't reflect the metabolic activity of the entire lesion but it measures the highest glucose metabolism in the target ROI.[24] While MTV represents the volume of the ^{18}F -FDG activity in the lesion and TLG represents the sum of the SUV within the lesion. Furthermore, the glucose metabolic activity is positively correlated to the tumor cellularity.[25], [26]

Previous studies suggest that tumor cellularity and metabolism might be correlated. However, previous results were discordant; *Varoquax et al.* found, in their study of SCC, that there was no significant correlation between the tumor cellularity represented by ADC and the tumor metabolic activity represented by SUV.[27] *Fruehwald et al.* reported that there was no correlation between SUV and ADC either in the DWIBS or EPI.[28] Similar findings have been reported by other authors.[29]–[31] In contrast, *Nunez et al.* reported in their study of HNSCC that the metabolic activity was strongly correlated to the tumor cellularity; there was an inverse significant correlation between the ADC and SUV.[32] *Nakajo et al.* found that the tumor metabolic activity (SUV) was correlated inversely with the tumor cellularity represented by ADC.[21] It's not clear yet why some authors have found strong correlations while others have not, and whether there is a correlation between tumor cellularity and metabolic activity.

^{18}F -FDG imaging parameters and DWI/ADC are a commonly used parameter in PET/MRI. These imaging parameters show a promising results to measure activity level of tissue metabolism, cellularity and proliferation. [9], [33] The use of these imaging parameters were also expanded to study the differences between benign and malignant in the microstructure level, prediction of treatment response, survival analysis and their correlation with the clinical and pathological information of the tumors.[14], [22], [34]

Therefore, our study was aimed to investigate the correlation between FDG parameters and ADC values, which has focused, in-depth, on finding out if there is a correlation between tumor metabolic activity and

cellularity represented by ADC and SUVmax, TLG and MTV, as well as assessing the ability of these imaging parameters to determine tumor aggressiveness by predicting lymph nodes involvement.

Materials And Methods:

Patients and demographics:

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 Megyei Kaposi Mor Educational Hospital, Pecs, Hungary. Approval number (IG/00686-000/2020). Requirement of the informed consent was waived and confirmed by the (CCRLREC) due to the retrospective nature, and all methods were carried out in accordance with the relevant guidelines and regulations (Declaration of Helsinki). From May 2016 to June 2019, 109 patients with proven HNC underwent ¹⁸F-FDG PET/MRI for staging and restaging, assessment of the disease and post-therapy follow up. The inclusion and exclusion criteria were (1) proved non-treated primary HNC, (2) patients underwent PET/CT and PET/MRI including DWI sequence (3) single tracer injection session. Exclusion criteria (1) patients who had non-measurable ADC, or FDG parameters (2) patients with motion artifact or bad image quality. Finally, a total of 71 patients were included in our study. *Table (1)*. Final confirmation of malignancy was done after PET/MRI examination the primary tumor and metastatic lymph nodes combined with biopsy.

Table 1
patients demographics

Number of patients	71
Mean Age (y)	<i>(61.6 ± 0.8)</i>
Men	<i>49 (69.0%)</i>
Women	<i>22 (31.0%)</i>
Histologic Grade	
Grade 1	<i>12 (16.9%)</i>
Grade 2	<i>41 (57.7%)</i>
Grade 3	<i>18 (20.4%)</i>
Localization	
Pharyngeal	<i>32 (45.1%)</i>
Laryngeal	<i>15 (21.1%)</i>
Oral	<i>22 (33.8%)</i>
T category	
T1	<i>4 (5.6%)</i>
T2	<i>19 (26.8%)</i>
T3	<i>26 (36.6%)</i>
T4	<i>22 (31.0%)</i>
N category	
N0	<i>10 (14.1%)</i>
N1	<i>9 (12.7%)</i>
N2	<i>45(63.4%)</i>
N3	<i>7 (9.9%)</i>
M Category	
M0	<i>63 (88.7%)</i>
M1	<i>8 (11.3%)</i>
N groups	
N+	<i>61(85.9%)</i>
N -	<i>10 (14.1%)</i>

PET/MRI imaging:

Examinations were performed in a dedicated PET/MRI (3T) unit (Biograph mMR, Siemens AG, Erlangen, Germany) after PET/CT examinations (single tracer injection). Patients were requested to fast for at least 6 hours before ^{18}F -FDG injection and their Blood glucose levels were checked before they received the tracer injection to ensure euglycemia. Intravenous ^{18}F -FDG with a bodyweight adapted dose (4 MBq/kg, range 163–403 MBq) was intravenously injected; after the FDG tracer injection, the acquisition was started within 142 minutes (average 225 minutes). Images were obtained in the supine position using Head and Neck coils. 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. For the PET data collection, a magnetic resonance-based attenuation correction (MRAC) sequence was used for PET attenuation correction, and the wide range bed position PET Emission scan was acquired for 900 seconds with a fixed FOV range (20 cm) and matrix (172×172) without bed movement as well. An iterative ordered subset expectation maximization (3D OP-OSEM) PET image reconstruction algorithm was used with 3 iterations and 8 subsets, and 4 mm Gaussian filtering settings. The PET data were corrected for scattering, random coincidences and attenuation using the MR data. The DWI was obtained by using an axial echo-planar imaging (EPI) sequence with b-values of 0 and 800 s/mm^2 (FoV 315 mm, repetition time TR/TE: 9900/75 ms, 5 mm slice thickness and voxel size $2.3 \times 2.3 \times 5 \text{ mm}$ 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.

Image analysis:

In each patient, the SUVmax, TLG, MTV were measured from the PET imaging; Siemens (Syngo Via 10VB) was used, which provided an automatized delineated SUV-based volumetric analysis. The metabolic volumetric contours were segmented by using the Syngo Via (VOI) Sphere tool. The single voxel activity concentration of a particular tumor with the highest SUV was represented by SUVmax while SULpeak represented the hottest point in the tumor foci, where the lean body mass normalized as the average SUV was measured at 1 cm^3 in a spherical ROI. A fixed 2.5 threshold of SUV was used for tumor SUVmax for both MTV and TLG proposed by *Pak et al.*[35] The volume above the given VOI was represented the MTV while the TLG represented the VOI of the average SUVmean or SULmean multiplied by the MTV. The ADC map was automatically generated and analyzed on the implemented eRAD software. DWI images were analyzed by drawing round or oval region of interest (ROI) manually on the ADC map covering the largest tumor diameter, [18] on single DWI slice [28] within the center of the lesion in the most homogenous part which were the lowest ADC or the highest SUV reported after excluding or/and avoiding the necrotic and cystic areas. We did not use whole tumor volumes ADC measurements approach although it has been found to be more reproducible than those obtained from single slice or small ROI's measurements.

However, there was no significant difference between the tumor ADCs obtained using whole-volume measurements and the single-slice approach.[36] Thus, we have chosen the single-slice method because it's easier, faster and as a result more preferred in clinical practice than the whole volume ROIs protocol which is time consuming and more complicated. Average ADC values calculated by the software automatically was referred to as ADCmean by summing all voxels ADC values on the drawn ROI for the chosen slice. We assessed only ADCmean values, which as previously proposed as a more reliable indicator of tumor cellularity since the entire lesion is taken into account.[37] ADCmin, on the other hand, was suggested to reflect the most proliferative portion of a tumor or highest tumor cell density, due to the effects of lesion heterogeneity or artifacts the use of ADCmin is likely to result in more errors.[38] In addition, ADCmean minimizes the effect of tumor heterogeneity and its higher reliability to distinguish different entities in the same image. [39] 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. Figures (1).

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 \pm standard deviation), for variables with normal distribution and median and interquartile range for variables with non-normal distribution. The Spearman rank correlation (r) was used to estimate the association between ^{18}F -FDG parameters and DWI values as well as tumor size, T stages, N stages and tumor grades. ANOVA or Kruskal–Wallis test were performed with primary tumor localization. Independent sample t or Mann-Whitney test were applied to compare imaging parameters values with Sex, M stages. 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 statistically differences in the univariate analysis into the multivariate linear regression model, we used transforming function to convert variables with non-normal distribution into normal distribution. Mann-Whitney test and independent sample T-test were applied on the imaging parameters after the patients were grouped based on lymph nodes involvement into positive (N+) and negative lymph nodes (N-). Receiver operating characteristics (ROC) was recruited to identify sensitivity, specificity and area under curve (AUC), The cutoff values was selected according to the sensitivity and specificity of each tangency point. A p-value < 0.05 was indicated as a statistically significant result.

Results:

Spearman's correlation coefficient was applied on ^{18}F -FDG parameters and ADC values; the results show that ^{18}F -FDG parameters (SUVmax, TLG and, MTV) were not correlated with ADC values ($r = -0.184$, $P = 0.125$, $r = -0.182$, $P = 0.248$, and $r = -0.037$, $P = 0.756$), respectively. A summary of correlations is shown in *Table (2)*. Figure 2 (A, B and C).

Table 2
summary of correlations between FDG and DWI imaging parameters

<i>Parameter</i>		<i>ADCmean</i>	<i>SUVmax</i>	<i>TLG</i>	<i>MTV</i>
<i>ADCmean</i>	<i>Spearman (rho)</i>		-.184	-.182	-.037
	<i>Sig. (2-tailed)</i>		.125	.129	.756
<i>SUVmax</i>	<i>Spearman (rho)</i>			.558**	.261*
	<i>Sig. (2-tailed)</i>			.000	.028
<i>TLG</i>	<i>Spearman (rho)</i>				.861**
	<i>Sig. (2-tailed)</i>				.000
<i>MTV</i>	<i>Spearman (rho)</i>				
	<i>Sig. (2-tailed)</i>				
<i>*significant at level of 0.05</i>					
<i>** significant at level of 0.01</i>					

For clinipathological comparison, we compared primary tumor FDG parameters (SUVmax, MTV, and TLG) and ADC with sex, tumor size (measured as the maximum diameter of the tumor in pathologic results, mean size was 49.8 ± 2.5 mm), T stages, N stages, M stages (7th Edition American Joint Committee on Cancer pathological staging criteria), [40] localization and the degree of differentiation (grades). The results show that SUVmax was correlated positively with tumor size and N stages, ($P = 0.001$ and $P = 0.006$), respectively. TLG was positively correlated with tumor size, T stages and N stages ($P = 0.000$, $P = 0.024$ and $P = 0.005$), respectively. MTV was positively correlated with tumor size and T stages, ($P = 0.000$ and $P = 0.001$), respectively. ADC, in the other side, was found to be inversely correlated with the degree of differentiation ($P = 0.030$) and a tendency to correlate with N stages, ($P = 0.089$). No other significant correlations observed, ($P > 0.05$) for all parameters. *Table (3)*.

Table 3
Clinicopathological correlations with FDG and DWI imaging parameters

Grouping	SUVmax	TLG	MTV	ADC
T stages	r = 0.051 P = 0.671	r = 0.268 P = 0.024	r = 0.389 P = 0.001	r = 0.079 P = 0.510
N stages	r = 0.321 P = 0.006	r = 0.332 P = 0.005	r = 0.145 P = 0.228	r = -0.204 P = 0.089
Grades	r = 0.055 P = 0.648	r = -0.070 P = 0.563	r = -0.047 P = 0.699	r = -0.258 P = 0.030
Tumor size	r = 0.374 P = 0.001	r = 0.679 P = 0.000	r = 0.635 P = 0.000	r = -0.139 P = 0.248
Localizations	P = 0.389	P = 0.128	P = 0.367	P = 0.270
SEX	P = 0.314	P = 0.522	P = 0.784	P = 0.897
M stages	P = 0.283	P = 0.785	P = 0.913	P = 0.347
<p>. Spearman correlation coefficient was applied for (T stages, N stages, Grades and Tumor size)</p> <p>Kruskal-Wallis was used to compare the FDG imaging parameters with primary tumor localization and ANOVA with ADC values. Mann-Whitney test for two category variables (sex, M stages) with FDG parameters, Independent sample t test with ADC values.</p> <p>. Significant result was highlighted in Bold</p>				

Multiple regression analysis was recruited for factors that shown correlation ($P < 0.1$) in univariate analysis to investigate the factors that influence the change in SUVmax, TLG, MTV and ADC. The results show that tumor size and N stages were independent factors influencing SUVmax, ($P = 0.020$ and $P = 0.024$), respectively. Tumor size and N stages were independent factors influencing TLG, ($P = 0.000$ and $P = 0.044$), respectively. T stages and tumor size were independent factors influencing MTV ($P = 0.004$ and $P = 0.000$), respectively. Tumor grade was found to be independent factor influencing ADC ($P = 0.032$). *Table (4)*.

Table 4
Multiple Regression Analysis Showing the Effects
of Prognostic Factors on 18f-FDG parameters

Prognostic factors	B	T	P value
SUVmax			
Tumor size	.409	3.333	.020*
T stages	N/A	N/A	N/A
N stages	.227	1.995	.024*
TLG			
Tumor size	.767	8.988	.000*
T stages	- .050	- .598	.552
N stages	.115	2.050	.044*
MTV			
Tumor size	.662	6.857	.000*
T stages	.149	3.010	.004*
N stages	N/A	N/A	N/A
ADC			
N stages	- .012	1.299	.198
Tumor grades	- .026	-2.188	.032*
*Significant result			
N/A: Not assessed			

When excluding the effect of the tumor size from the regression model, we found that N stages were independent factor influencing SUVmax ($P = 0.011$), but not T stages ($P = 0.838$). Both T stages and N stages were independent factors influencing TLG, ($P = 0.018$ and $P = 0.034$), and T stages were found to be independent factor influencing MTV, ($P = 0.001$).

To investigate the ability of FDG and ADC parameters to predict tumor aggressiveness, we classified the patients based on lymph nodes involvement into Negative and Positive groups (N- and N+) and compared with these parameters. PET/MRI was the reference to define the two groups. Our results show that SUVmax, TLG and ADC revealed a statistically significant differences ($P = 0.004$, $P = 0.033$ and $P = 0.012$), respectively. MTV did not ($P > 0.05$). Figure 3 (A, B and C and D).

The ROC curve was used to analyze the diagnostic efficacy of ADC and SUVmax (due to widely use in daily practice) in predicting lymph node metastasis in HNC. For ADC; AUC was 73.1%, 95% confidence interval was ranged between 0.550 and 0.912, best cut off value was (0.981 ± 0.97) to predict lymph node metastasis with sensitivity of 70.0% and specificity of 78.7%, *Fig. 4 (A)*. SUVmax best cut off value to predict lymph node metastasis was (6.8 ± 0.8) , AUC was 80.8%, 95% confidence interval was ranged between 0.633 and 0.984. Sensitivity and specificity were 83.6% and 80.0%, respectively. Figure 4 (B).

Discussion:

The present study demonstrated that PET/MR provides valuable imaging data for HNC patients. Various pathological factors were associated with PET/MR results and may serve a role in the evaluation of the prognosis of patients with HNC. As for emerging technology, PET/MRI offers different imaging data to study tumor microstructure environment, we started our study by correlating these imaging to each other. Previous data demonstrated an inverse correlation between ADC value, derived from DWI, with cellularity. [8]–[10] FDG imaging parameters, on the other hand, were found to be positively correlated with cellularity.[25], [26], [41] Although glucose metabolism and cellularity of tissue are two different biological biomarkers of a tumor, an inverse correlation between 18F-FDG and DWI parameters has been suggested. [42] this hypothesis was proposed because both 18F-FDG and ADC were correlated with tumor cellularity. [37] Our results showed that FDG uptake parameters (SUVmax, TLG, and MTV) were not significantly correlated with the ADCmean value. Similar results were observed; *Min et al.*, in their study of HNSCC, reported that there was no significant correlation between ADCmean with SUVmax and SUVmean, also no significant correlation was found between ADCmean and both MTV and TLG.[30] *Surov et al.*, in a recent study, reported no significant correlation between ADCmean and SUVmax or SUVmean ($r = -0.255$, $P = 0.450$ and $r = -0.318$, $P = 0.340$), respectively.[31]

Controversially to our results, *Nunez et al.* observed, in their study of HNSCC, an inverse significant correlation between the mean SUV and the mean ADC ($r = -0.67$, $P = 0.01$).[32] *Nakajo et al.* also observed that the SUVmax was correlated inversely with the ADCmean ($r = -0.566$, $P = 0.005$).[21] *Nakamatsu et al.*, in their study of metastasis in lymph nodes from HNSCC, found strong negative correlations between SUVmax and ADCmean values ($P > 0.001$), their results showed that the metabolic activity was influenced strongly by the tumor cellularity.[43] *Han et al.* reported, in their study of HNSCC, that there was a slightly significant inverse correlation between SUV and ADC ($r = -0.333$, $P = 0.054$). They also found a negative significant correlation between ADC and TLG ($r = -0.347$, $P = 0.044$).[44]

Our explanation for the lack of correlation is the fact that both imaging parameters explain different tissue microstructures characteristics, DWI assess the water molecule motion in the tissue and affected by the cellularity, proliferation rate and cell counts which in clinical use affected by ROI size placement and interobserver variability.[36] While metabolic activity was independent of tumor size and shape because tumor is segmented by adaptive thresholding.[37]

The present study correlated FDG and DWI imaging parameters with clinopathological characteristics to explore their effect on the imaging parameters values. Our results reveal that FDG metabolic parameters have reported different correlations; it has shown that primary tumor SUVmax and TLG were significantly correlated with tumor size and N stages; the larger tumor size means more cancer cells, thus, more active overall hyperplasia, in other words, greater glucose metabolic activity to tolerate the biological activity, differentiation and proliferation of the cancer cell.[45] Metastatic lymph node, in the other hand, is one of the most important influencing factors in the prediction of cancer surgery. [1] It's well known that higher degree of malignancy means more infiltration and thus the possibility of lymph nodes metastasis is high. [46] According to El-naaj et al. when there is no noticeable lymph node metastasis in the clinical and imaging examinations, the incidence of occult metastasis was high (20–34)%. [47] Thus, it's important to predict the possibility of lymph node metastasis occurrence. This study was found that the AUC was 0.808, which means that SUVmax is useful to predict lymph node metastasis. According to *Zheng et al.* there was a positive significant correlation between lymph nodes status and SUVmax, higher SUVmax, resulted in more lymph nodes metastasis, which means that SUVmax has a promising predictive role in lymph node diagnosis.[45] *Micco et al* reported a significant correlation between lymph node occurrence with SUVmax and TLG.[18] *Morand et al.* have observed similar results, higher lymph nodes involvement was found in patients with higher primary tumor SUVmax.[48] In the same study, the authors reported that TLG did not correlate with lymph node status [48]. Furthermore, in our study, no significant correlation observed between MTV and the lymph node status. A similar result reported by *Morand et al.* [48] and Chan et al. [49] In contrast to *Micco et al.* who reported a significant association between MTV and lymph nodes occurrence.[18] SUVmax might be promising imaging biomarker to predict tumor aggressiveness.

ADC, on the other hand, show significant correlation with tumor grades, which reflect the degree of water motion within the tumor cells, this is from the fact that higher grade tumors (G3) show more restriction to water molecules motion (lower cellularity) which as result affect ADC. On the other side, ADC did not show significant correlations with T stages, N stages or Tumor size, although there was a slightly inverse correlation with N stages ($P = 0.089$). In other words, as the ADC tend to be lower (poorly differentiated tumors), the lymph nodes involvement increase, but this result was not statistically significant. Although, when dividing the patients to two groups (N + and N-) the ADC show significant difference, which means that ADC has the ability to predict lymph node metastasis. *Abdel Razek et al.* in their study of Nasopharyngeal carcinoma have reported a statistically significant difference between primary tumor ADC and nodal involvement, ($P = 0.003$), [50] this mean that patients without lymph nodes involvement showed higher ADC value than those patients who have confirmed lymph nodes enlargement. In the other hand, *Nakajo et al.* have reported in their study of primary HNSCC similar results, there was no significant difference in the ADC between N-positive and N-negative groups ($p = 0.74$), [21] similar results were also reported by other authors.[51], [52] The explanation of their result was attributed that those patients with poorly or undifferentiated malignancy are usually reporting metastatic lymph nodes.[50]

None of the previous studies have compared the efficacy of PET/MRI system different imaging biomarkers in HNC tumor aggressiveness prediction. Thus, to our knowledge, this is the first study to

compare PET/MRI system derived imaging parameters in lymph nodes involvement in HNSCC. Our results show that SUVmax and ADC were found to have the ability to differentiate between the two lymph nodes groups (N+ and N-) based on the primary tumor measurements, which as a result might help to predict tumor development and prognosis. Our study shows that SUVmax had higher diagnostic performance, higher sensitivity and better specificity than ADC, as well as the presence of significant correlation with N stages which has not been found in ADC. Nevertheless, ADC can predict tumor aggressiveness and lymph nodes involvement prediction but with limited efficacy. The importance of successful prediction of tumor aggressiveness and lymph nodes involvement might help in practice to increase the aggressiveness of the therapy.

Based on our study results and findings, there were several correlations between PET/MRI imaging parameters and clinical tumor characteristics, we suggest that glucose metabolism assessed by 18F-FDG and cellularity assessed by ADC have different roles in cancer evaluation, so we recommend PET/MRI as a combined examination rather than PET or MRI alone.

As for this study's limitations, First, the heterogeneity of the tumor localization. Second, our study focused on the search of correlation between 18F-FDG, ADC and histopathological features only in HNSCC. Third, associations with other functional tumor parameters, such as apoptosis factors and were not analyzed. Fourth, design of the study was retrospective.

Conclusion:

Our results revealed no linear correlation between the FDG PET and DWI-MR parameters. The FDG PET-based glucose metabolic and DWI MR derived cellularity data may represent different biological aspects of HNSCC tumors and simultaneous PET/MR imaging could provide complementary diagnostic information. SUVmax, have shown higher accuracy in predicting tumor aggressiveness than ADC.

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. *(G): Grade.

Declarations

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that greatly assisted the research, although they may not agree with all of the interpretations of this paper.

The Authors' Contributions:

OF designed the study, OF and PT collected and processed the data. DS and AK segmented FDG measurements and generated the figures. OF conducted data collection and processing, statistical analysis and wrote the paper. TZ review the draft. AK, ZS, and IR discussed the results and contributed to the final form of the article.

Competing interest:

All authors declare no competing interests.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the clinical trials repository, [ID: NCT04360993].

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Figures

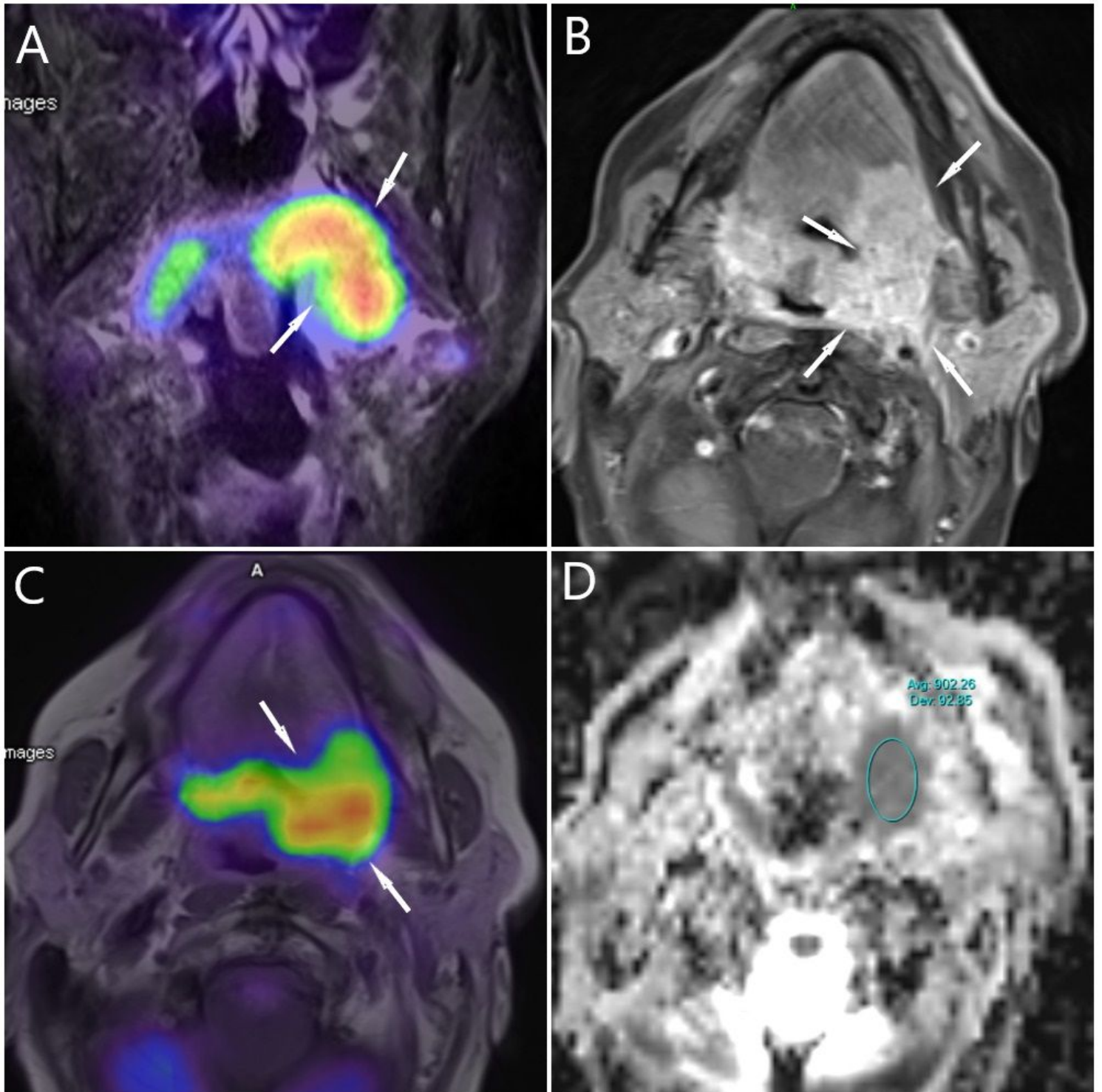


Figure 1

ADC and 18F-FDG measurements of 67 male patient with Oropharyngeal carcinoma. (A) T2-PET_tirm coronal MRI show the intensive FDG accumulation (arrow). (B) T1-tse-sagittal show the horizontal spreading of the tumor (arrows). (C) T1-PET fused image show the ROI within the tumor (arrows), and (D) DWI/ADC map showing the average and standard deviation of ADC value.

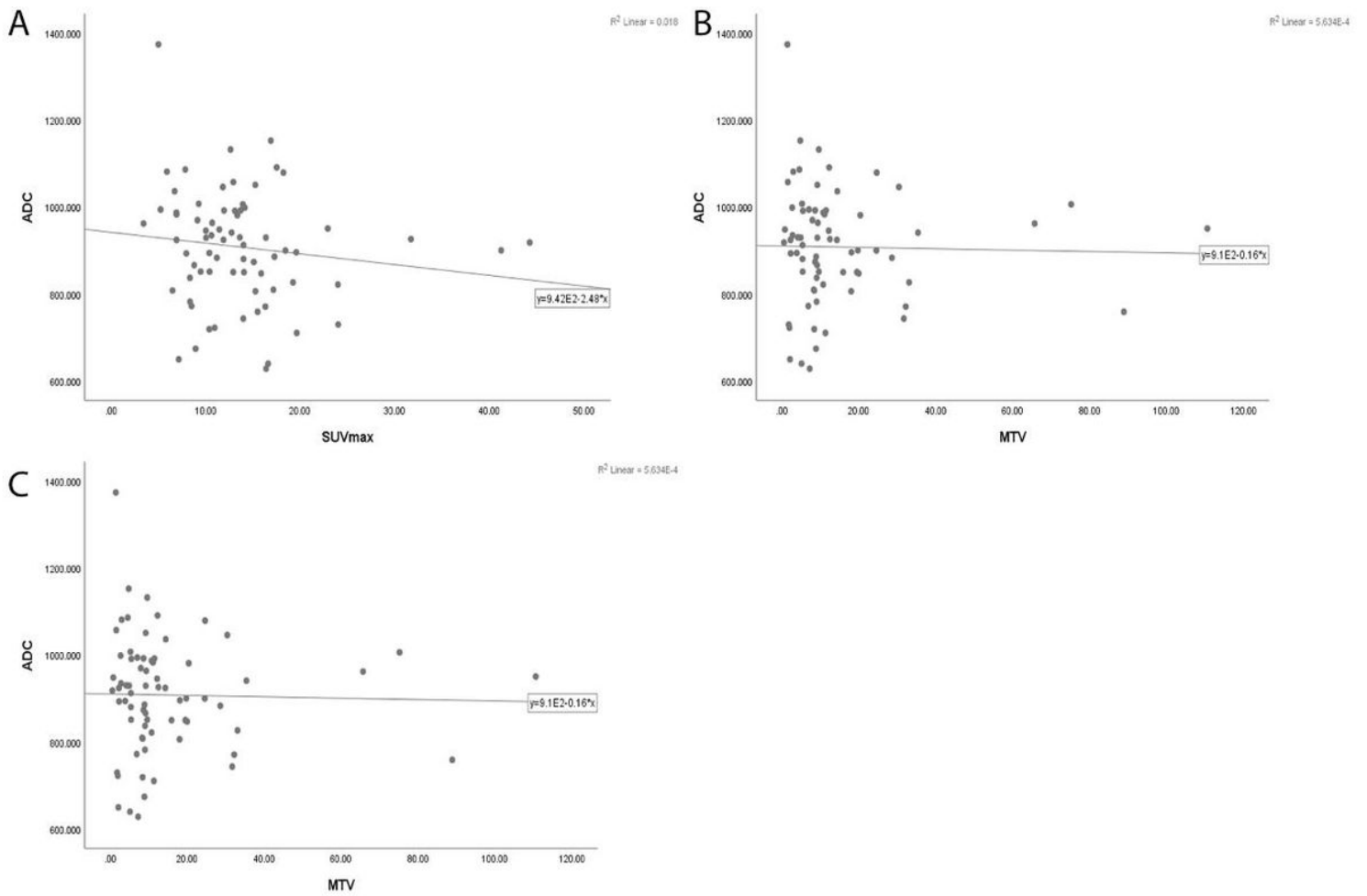


Figure 2

Scatter diagram showing the correlation between the ADCmean and (A) SUVmax, (B) TLG and (C) MTV. No significant linear correlation observed between ADCmean and any of 18F-FDG parameters, $P > 0.05$.

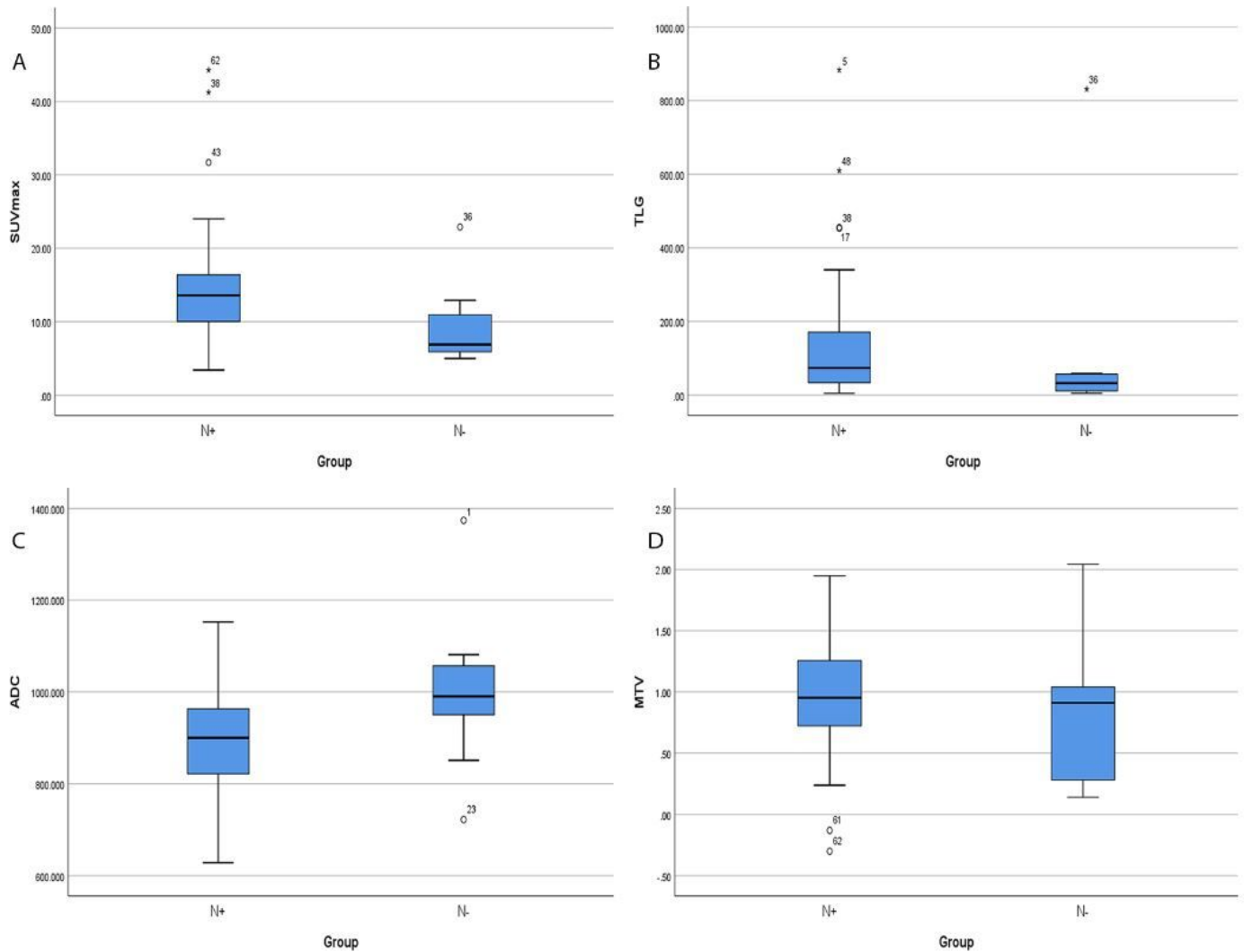


Figure 3

Boxplots displaying the distribution of SUVmax, TLG, ADC and MTV (A, B, C and D) according to lymph nodes status. (A) SUVmax values of positive lymph nodes tumors were significantly higher than those lymph nodes negative tumors ($P=0.004$). (B) TLG show no significant difference between positive and negative lymph node ($P=0.134$). (C) ADC values of positive lymph nodes tumors were significantly lower than those lymph nodes negative tumors ($P=0.012$) and finally, (D) MTV positive lymph nodes tumors and negative lymph nodes tumors were not statistically significant difference ($P=0.342$).

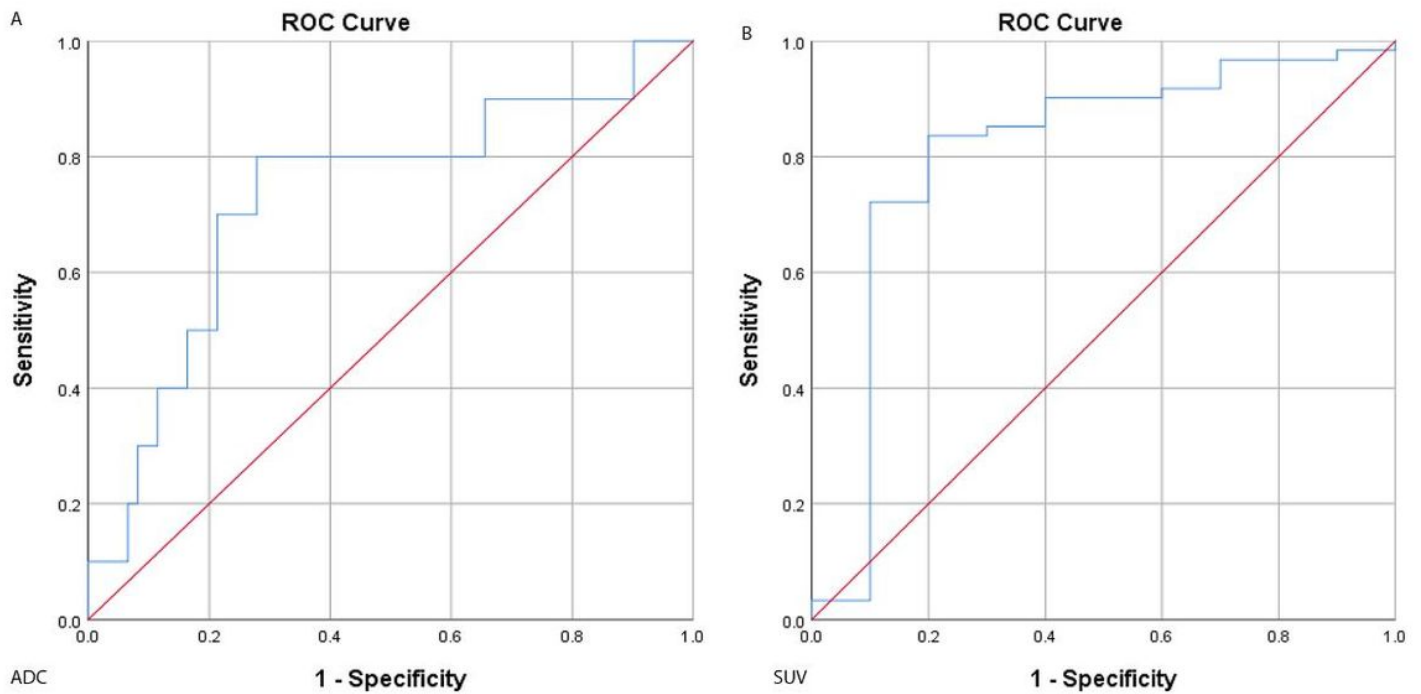


Figure 4

Receiver operating characteristic (ROC) curve analysis of lymph nodes prediction according to ADC and SUVmax of primary tumor. (A) ADC (ROC) curve with AUC (73.1%), 95% confidence interval was ranged between 0.550 and 0.912, best cut off value was $(0.981 \pm 0.97 \times 10^{-3} \text{mm}^2/\text{s})$ to diagnose lymph node metastasis with sensitivity of 70.0% and specificity of 78.7%. (B) SUVmax (ROC) curve with AUC was 80.8%, 95% confidence interval was ranged between 0.633 and 0.984, best cut off value to diagnose lymph node metastasis was (6.8 ± 0.8) with sensitivity (83.6%) and specificity 80.0%.