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Correlation of ^{18}F-FDG/PET SUV_{max}, SUV_{mean}, MTV, and TLG with HIF-1α in Patients with Colorectal Cancer

Kolorektal Kanserli Hastalarda ^{18}F-FDG/PET SUV_{maks}, $SUV_{ortalama}$, MTV, TLG ile HIF-1α'nın Korelasyonu

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Abstract

Objectives: Post-hypoxia hypoxia-inducible factor (HIF)-1α activation plays a vital role in colorectal cancer (CRC) angiogenesis. Although glucose metabolism is induced in some cancer types via HIF-1α, the prognostic significance of HIF-1α in CRC and its correlation with ^{18}fluorine-fluorodeoxyglucose (^{18}F-FDG) uptake in positron emission tomography (PET) remain controversial. This study aims to investigate the association between ^{18}F-FDG/PET parameters and HIF-1α expression in CRC.

Methods: Thirty-six histopathologically confirmed patients with CRC who had ^{18}F-FDG/PET scans before surgery were enrolled in the study. The correlations between the maximum standardized uptake value (SUV_{max}), SUV_{mean}, metabolic tumor volume (MTV), total lesion glycolysis, HIF-1α overexpression, and histopathological features were evaluated.

Results: The tumor location, tumor diameter, perineural invasion, lymphovascular invasion, T and N stage were not significantly correlated with HIF-1α overexpression. In contrast, the tumor differentiation was negatively correlated with HIF-1α expression (r=-0.332, p=0.048). None of the ^{18}F-FDG/PET parameters was significantly correlated with HIF-1α overexpression. A significant relationship was found between tumor differentiation, tumor necrosis percentage, and MTV (p=0.030, p=0.020).

Conclusion: The expected association between HIF-1α overexpression and ^{18}F-FDG/PET parameters was not found in this study. However, there was a relationship between MTV, tumor differentiation, and tumor necrosis percentage. Hence, further studies are required to predict the pathological and prognostic courses of CRC using a diagnostic ^{18}F-FDG/PET evaluation.

Keywords: Hypoxia-inducible factor-1α, colorectal cancer, ^{18}F-FDG/PET/CT, MTV, TLG

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Öz

Amaç: Dokuda hipoksi sonrası hipoksi ile indüklenebilir faktör (HIF)-1α aktivasyonu, kolorektal kanser (KRK) anjiyogenezinde önemli bir rol oynar. Glikoz metabolizmasının bazı kanser türlerinde HIF-1α yoluyla indüklendiği bilinmesine rağmen; KRK'de HIF-1α'nın prognostik önemi ve pozitron emisyon tomografisinde (PET) ^{18}flor-florodeoksiglukoz (^{18}F-FDG) tutulumu ile korelasyonu önceki çalışmalarda tartışmalı konulardır. KRK olgularında ^{18}F-FDG/PET parametreleri ile HIF-1α ekspresyonu arasındaki ilişkiyi araştırmaktır.

Yöntem: Cerrahi öncesi ^{18}F-FDG/PET taramaları mevcut olan histopatolojik olarak tanı almış 36 KRK hastası çalışmaya alındı. Maksimum standardize uptake değeri (SUV_{maks}), $SUV_{ortalama}$, metabolik tümör hacmi (MTV), total lezyon glikolizis ve HIF-1α aşırı ekspresyonu ile histopatolojik özellikler arasındaki korelasyonlar değerlendirildi.

Bulgular: Tümör lokasyonu, tümör çapı, perinöral invazyon, lenfovasküler invazyon, T ve N evresi, HIF-1α aşırı ekspresyonu ile istatistiksel olarak anlamlı korelasyon göstermezken, tümör derecesi HIF-1α ekspresyonu ile negatif korelasyon gösterdi (r=-0,332, p=0,048). ^{18}F-FDG/PET parametrelerinin hiçbiri, HIF-1α aşırı ekspresyonu il e istatistiksel olarak anlamlı korele bulunmadı. Tümör derecesi ve tümör nekroz oranı ile MTV arasında anlamlı bir ilişki bulundu (p=0,030, 0,020).

Sonuç: HIF-1α aşırı ekspresyonu ile ^{18}F-FDG/PET parametreleri arasında beklenen ilişki bu çalışmada ortaya konamamıştır, ancak MTV ile tümör farklılaşması ve tümör nekroz oranı arasında bir ilişki mevcuttur. Bu nedenle, tanısal ^{18}F-FDG/PET değerlendirmesi ile KRK'nin patolojik ve prognostik seyrini tahmin etmek için daha fazla çalışmaya ihtiyaç vardır.

Anahtar kelimeler: Hipoksi ile indüklenebilir faktör-1α, kolorektal kanser, ^{18}F-FDG/PET/BT, MTV, TLG

Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide (1). In all types of carcinoma, including CRC, the formation of new blood vessels is essential for tumor growth and distant metastasis (2,3). Many angiogenic growth factors have been described in the literature. The hypoxia-inducible factor (HIF)-1α gene family is one of these growth factors. In addition, HIFs are considered the main factors that initiate gene expression required for angiogenesis. HIF, a heterodimer, is a helix-loop-helix Per-ARNT-Sim transcription factor. It has three homologs identified as HIF-1α, HIF-2α, and HIF-3α. HIF-1α and HIF-2α play an essential role in tumor vascularization (4). In parallel with this, HIF-1α and HIF-2 HIF-2α are expressed in many types of cancer and can be used as prognostic factors in some cancers (5,6,7,8,9). HIF-1α expression is not affected by the hypoxic state of the cells and is already constitutively expressed. The accumulation of the subunit of HIF-1α in the cell in a short time occurs by preventing the naturally existing proteasomal degradation due to hypoxia. In hypoxia, the subunit that accumulates in the cell is HIF-1α (10,11,12). It is claimed that the expression of HIF-1α and HIF-2α in neoplastic cells has a predictive value on the survival of patients with CRC (13).

Positron emission tomography (PET), which is based on the high glucose uptake of neoplastic tissues, traces ^{18}fluorine-fluorodeoxyglucose (^{18}F-FDG) and enables the detection of tumoral activities in the whole body and thereby facilitates staging of the disease. By making a semiquantitative glucose measurement with ^{18}F-FDG/PET, the standardized uptake value (SUV) of the tumoral tissue is calculated (14). PET/computed tomography (CT) has been widely used in clinical practice to characterize and stage tumors non-invasively. The SUV, a semiquantitative index in PET/CT, has been popularly accepted by nuclear physicians in daily use to demonstrate the uptake of glucose in tumors/normal tissues. However, it remains questionable because of several reasons. First, the semiquantitative SUV_{max} is a sensitive indicator of metabolic activity and tumor proliferation; however, it is the SUV on the highest image pixel, reflecting a single-pixel value of the maximum intensity of ^{18}F-FDG activity in the tumor, ignoring the extent of metabolic abnormality and changes in the distribution of a tracer within the whole tumor mass (15,16). Second, SUV is calculated based on the whole-body weight metric (17). Third, studies have reported that many factors might influence SUV, and SUV_{max} is unreliable and recommendable because of its poor reproducibility (3%±11%). Researchers recommended volume-based variables such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) to reflect the metabolic activities within the whole tumor mass to overcome these controversies. Instead of whole-body weight, the administered dose should be based on volume-based parameters corrected by lean body mass (18).

By examining the correlation between HIF-1α expression and ^{18}F-FDG/PET parameters (SUV_{max}, SUV_{mean}, MTV, and TLG) in patients with CRC, the possibility of predicting the pathological and prognostic course of CRC by diagnostic ^{18}F-FDG/PET is investigated in the present study. In addition, the link between microscopic tumor diameter, lymphovascular invasion (LVI), perineural invasion (PNI), tumor necrosis percentage, tumor differentiation, and ^{18}F-FDG uptake was also evaluated.

Materials and Methods

Patients

The electronic database of patients diagnosed with colorectal adenocarcinoma by endoscopic biopsy between January 2018 and July 2019 in the department of surgical oncology of our institute was retrospectively reviewed. The ones scanned by ^{18}F-FDG/PET/CT for staging before surgery and undergoing curative surgical intent were included in the study. The patients who did not have a PET scan before primary surgery or had a PET scan but did not undergo primary surgery at our center were excluded. In addition, the patients who received neoadjuvant therapy for rectal cancer were not considered suitable for the pathological re-analysis and were excluded. The data of 36 patients who met the criteria were enrolled in the current study. ^{18}F-FDG/PET scans were performed on all patients between January 2018 and August 2019, at least 15 days after the endoscopic biopsy. If no distant metastases were defined on ^{18}F-FDG/PET images, patients were considered suitable for curative surgery.

The study was approved by the Scientific Research Ethics Committee of the Medical Faculty of University Süleyman Demirel (protocol code, 13.02.2020/51). All procedures applied were performed in accordance with the ethical standards of the institutional research committee in alliance with the 1964 Helsinki declaration and its later amendments. Informed consent was waived owing to the retrospective nature of the study.

Pathological Evaluation and Immunohistochemistry

The surgical materials were prepared for hematoxylin and eosin staining by paraffin blocking after slicing the primary tumor and resecting the lymph nodes. The slides were evaluated by an experienced pathologist from the department of pathology of our institute. Microscopic tumor diameter, LVI, PNI, tumor necrosis percentage, and differentiation were documented in the pathological evaluation. A tumor-node-metastasis (TNM) stage was defined for each patient according to the American Joint Committee on Cancer TNM staging classification (8th edition). The pathologist identified the most convenient paraffin-embedded block in the surgical specimen to perform the immunohistochemistry. Monoclonal rabbit anti-human HIF-1α antibodies (clone, EP1215Y; dilution, 1:100; Abcam, Cambridge, MA, USA) were used to evaluate the HIF-1α expression. A biotinylated goat anti-polyvalent secondary antibody (TP-125-BN; Thermo Fisher Scientific, Inc., Waltham, MA, USA) experiment was performed in parallel as a negative control, and human ovarian carcinoma was used as a positive control. The avidin-biotin-peroxidase complex accomplished the immunostaining process. The grade of staining was defined via a light microscope. Cytoplasmic and nuclear immunoreactivity in tumor cells was considered positive when evaluating immunostaining (Figure 1). The cut-off value to differentiate positive and negative immunoreactivity was determined as at least 10% (19).

^{18}F-FDG/PET Imaging Procedure

Whole-body ^{18}F-FDG/PET scans of patients diagnosed with CRC were performed with a Philips Gemini TF PET/CT scanner (Philips Medical Systems B. V., Eindhoven, Holland) in the nuclear medicine department of our institute. The procedure was initiated by checking that the patient's serum glucose level was under 150 mg/dL after six hours of fasting. Patients were administered ^{18}F-FDG intravenously (Monrol Eczacibasi, Istanbul, Turkey) calculated as 3.7 MBq (0.1 mCi/kg) per kilogram, and 60 minutes after injection, PET/CT scans were performed. Post-CT, a three-dimensional emission scan was recorded for two minutes per location.

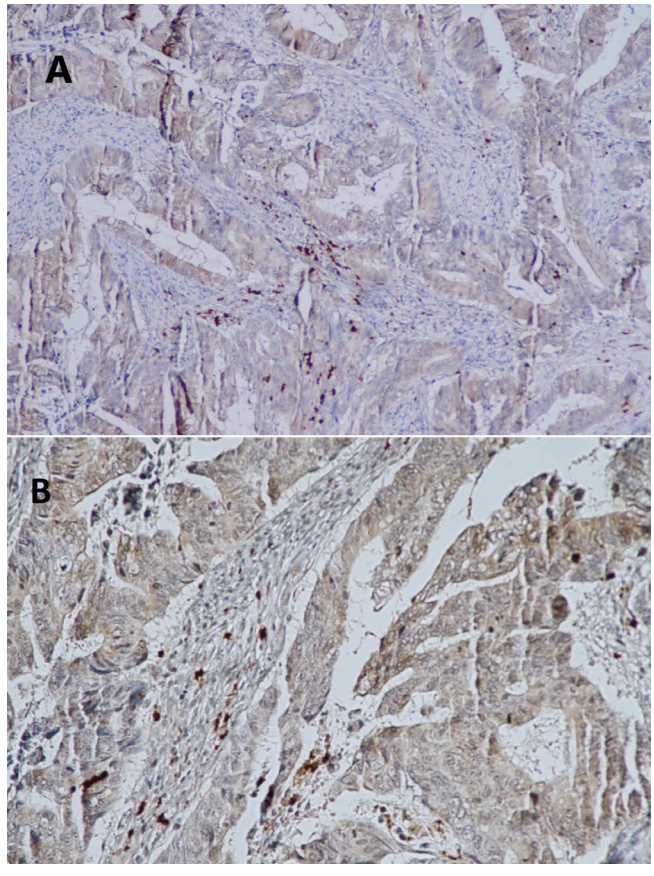


Figure 1. (A) Diffuse cytoplasmic and mild nuclear staining of HIF-1α in tumor cells (x100). (B) Diffuse-moderate cytoplasmic and mild nuclear staining of HIF-1α in tumor cells (x200)

HIF-1α: Hypoxia-inducible factor-1α

Images obtained from the PET and CT were examined in cross-sectional planes and rotational maximum intensity projection. The ^{18}F-FDG uptake in the primary tumor was measured semi-quantified by the SUV_{max} and the SUV_{mean}. The volume-based parameter MTV (mL) was determined using PET VCAR, the semiquantitative software embedded in the Philips workstation (the estimated threshold for discrimination of tumors was decided to be equal to or more than 42% of SUV_{max}. TLG was calculated based on the formula: $TLG=MTV\times SUV_{mean}$ (Figure 2).

Statistical Analysis

All values presented in the tables are expressed as medians (minimum-maximum) due to the non-parametric distribution of the variables. The clinicopathological features of the HIF-1α positive and negative groups were compared using the chi-square test. The medians of PET/CT parameters and tumor diameters of the HIF-1α groups were compared with the Mann-Whitney U test. Correlations between pathological findings, HIF-1α overexpression, and PET/CT parameters were analyzed by the Spearman correlation test. All analyses were two-sided, and $p<0.05$ was considered statistically significant. Statistical analyses were conducted via SPSS, version 21.0 (SPSS Inc. Chicago, IL, USA).

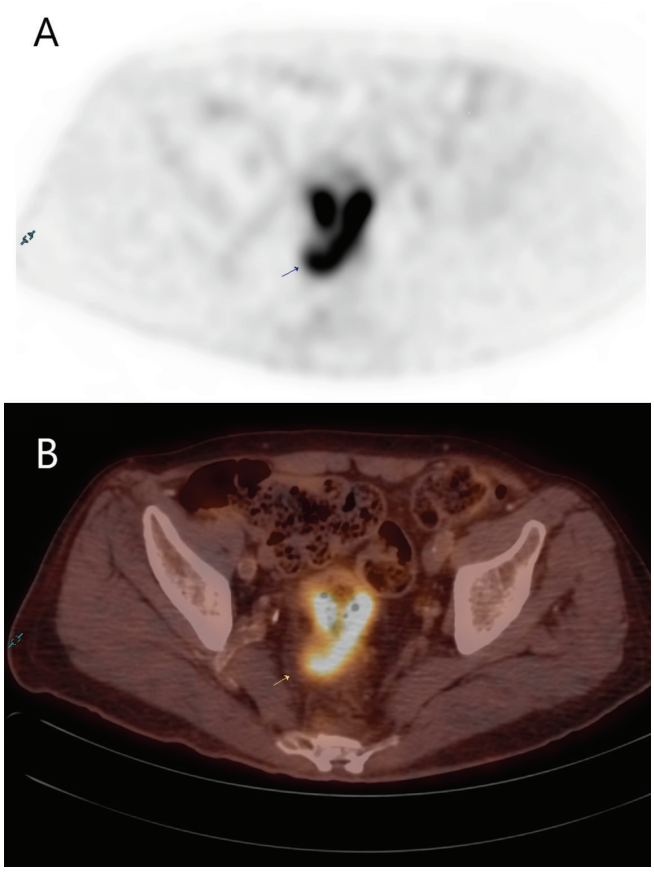


Figure 2. (A) ^{18}F-FDG/PET and (B) hybrid PET/computed axial tomography images demonstrating a rectosigmoid colorectal adenocarcinoma with conspicuously increased ^{18}F-FDG uptake (maximum standardized uptake value: 20.36, metabolic tumor volume: 98.05, total lesion glycolysis: 684:37) in a 74-year-old man. Histopathological features of the tumor were as follows: pT3 (5.7 cm), N0, well-differentiated, and HIF-1α overexpressed

^{18}F-FDG: ^{18}Fluorine-fluorodeoxyglucose, PET: Positron emission tomography, HIF-1α: Hypoxia-inducible factor-1α

Results

Patient Characteristics

Thirteen (36.1%) female and 23 (63.9%) male patients were enrolled in the study. The median age was 64 (37-88) years. The primary tumor locations were the colon in seven (19.4%) patients, the sigmoid colon in four (11.1%) patients, the rectosigmoid in five (13.9%) patients, and the rectum in 20 (55.6%) patients. Seventeen (47.22%) patients were HIF-1α negative, and 19 (52.78%) were positive. The difference between HIF-1α positive and negative groups regarding gender, age, tumor location, TN stage, PNI, LVI, tumor differentiation, tumor necrosis percentage, or tumor diameter (p=0.083-0.879) were not statistically significant. Moreover, SUV_{max}, SUV_{mean}, MTV (mL), and TLG were also not significantly different in the HIF-1α groups (p=0.090-0.318). Table 1 shows all the clinicopathological features and PET/CT parameters of HIF-1α groups and patients.

HIF-1α, Pathological, and PET/CT Parameters

The correlations between HIF-1α expression, pathological features, and FDG-PET parameters were evaluated by Spearman's rank test. As a result, only tumor differentiation was weakly negatively correlated with HIF-1α expression (r=-0.332, p=0.048) (Table 2). There were no statistically significant correlations between HIF-1α expression and ^{18}F-FDG/PET parameters. Tumor diameter was positively correlated with MTV (mL) and TLG as predicted from the calculation formulas of MTV (mL) and TLG ($p<0.001$). The only significant correlations were between tumor differentiation, tumor necrosis percentage, and MTV (mL) (p=0.030 and p=0.020, respectively) in the correlation tests of pathological features with ^{18}F-FDG/PET parameters (Table 3).

Discussion

Hypoxia is known as a factor that adversely affects the treatment response in solid cancers. Hypoxia is associated with poor survival in many types of cancer, such as breast, bladder, gynecological, and pancreatic

cancers (5,6,7,8,20,21). HIFS occurs as a transcriptional response to hypoxic stress. Post-hypoxia HIF-1α activation plays a vital role in CRC angiogenesis. HIF binds to the vascular endothelial growth factor (VEGF) promoter region, allowing VEGF transcription to form new blood vessels. Therefore, HIF-1α is used as a poor prognostic marker (22). The overexpression of both HIF-1α and HIF-2α is associated with a poor prognosis in colorectal cancer. In addition, a correlation was found between HIF-1α overexpression and clinicopathological features, such as stage, depth of invasion, lymph node involvement, and metastasis (23). In the present study, HIF-1α positive and negative group patients were compared for T and N stages, LVI, PNI, tumor differentiation, tumor necrosis percentage, and tumor size., However, no significant difference was found between them (p=0.879-0.083).

Clavo et al. (24) researched ^{18}F-FDG uptake status changes under different oxygen levels in various tumor cells *in vitro*. It was considered that hypoxia regulates the ^{18}F-FDG uptake according to the increased ^{18}F-FDG levels after mild hypoxic treatment (24,25). Toba et al. (26) investigated the relation of HIF-1α, GLUT-1, VEGF, and ^{18}F-FDG uptake in thymic epithelial tumors. Tumor size was the most significant parameter that correlated with SUV_{max} (r=0.60,

Table 1. The clinicopathological features and ^{18}F-FDG/PET parameters of HIF-1α negative and positive groups and all patients

	Total (n=36)	HIF-1α negative (n=17)	HIF-1α positive (n=19)	p
Gender				
Female	13 (36.1%)	8 (47.1%)	5 (26.3%)	0.172
Male	23 (63.9%)	9 (52.9%)	14 (73.7%)	
Age				
<65	22 (61.1%)	10 (58.8%)	12 (63.2%)	0.530
≥65	14 (36.8%)	7 (41.2%)	7 (36.8%)	
Tumor location				
Colon	7 (19.4%)	4 (23.5%)	3 (15.8%)	0.385
Sigmoid	4 (11.1%)	3 (17.6%)	1 (5.3%)	
Rectosigmoid	5 (13.9%)	1 (5.9%)	4 (21.1%)	
Rectum	20 (55.6%)	9 (52.9%)	11 (57.9%)	
T stage				
T1	3 (8.3%)	1 (5.9%)	2 (10.5%)	0.879
T2	4 (11.1%)	2 (11.8%)	2 (10.5%)	
T3	29 (80.6%)	14 (82.4%)	15 (78.9%)	
N stage				
N0	19 (52.8%)	10 (58.8%)	9 (47.4%)	0.683
N1	11 (30.6%)	4 (23.5%)	7 (36.8%)	
N2	6 (16.7%)	3 (17.6%)	3 (15.8%)	
PNI				
Yes	17 (47.2%)	9 (52.9%)	8 (42.1%)	0.376
No	19 (52.8%)	8 (47.1%)	11 (57.9%)	
LVI				
Yes	16 (44.4%)	7 (41.2%)	9 (47.4%)	0.485
No	20 (55.6%)	10 (58.8%)	10 (52.6%)	
Tumor differentiation				
Well-differentiated	18 (50%)	6 (35.3%)	12 (63.2%)	0.083
Moderately differentiated	15 (41.7%)	8 (47.1%)	7 (36.8%)	
Poorly differentiated	3 (8.3%)	3 (17.6%)	0	
Tumor necrosis percentage*	10% (0%-45%)	15% (0%-45%)	8% (0%-35%)	0.232
Tumor diameter (cm)*	5.5 (1-12.5)	6 (3-12.5)	5.5 (1-7)	0.193
SUV_{max}*	17.31 (7.9-36.79)	19.29 (8.07-35.09)	17.21 (7.9-36.79)	0.159
SUV_{mean}*	7.56 (4.23-13.86)	7.63 (4.23-13.86)	7.51 (4.31-12.65)	0.318
MTV (mL)*	83.5 (6.27-435.84)	119.29 (10.49-341.25)	46.59 (6.27-435.84)	0.117
TLG*	596.32 (27.03-3756.94)	1030.18 (68.01-2639.73)	363.41 (27.03-3756.94)	0.090

*The median values and minimum-maximum ranges are denoted for the numerical data. ^{18}F-FDG: ^{18}Fluorine-fluorodeoxyglucose, PET: Positron emission tomography, HIF-1α: Hypoxia-inducible factor-1α, PNI: Perineural invasion, LVI: Lymphovascular invasion, SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis

p<0.001), and the expression of HIF-1α showed a moderate association, but the expression of GLUT-1 showed no correlation with SUV_{max}. Moreover, Rajendran et al. (27) studied the association between hypoxia proportional to ^{18}F-fluoromisonidazole (FMISO) uptake and glycolysis evaluated by ^{18}F-FDG uptake on PET images in soft-tissue sarcomas, glioblastoma multiforme, breast cancers, and patients with head and neck cancer. When the four tumor types were analyzed separately, a correlation between ^{18}F-FDG and FMISO was significant in only head and neck tumors (27).

CRC presenting with large necrotic and hypoxic lesions tend to be resistant to chemoradiotherapy. Although CRC with HIF-1α overexpression has been indicated to have a worse prognosis (23,28,29,30), there are conflicting opinions in the literature regarding the prognostic importance of HIF-1α for CRC. In the present study, the prognostic value of HIF-1α was not investigated because the study population was heterogeneous for tumor localization (seven colon, four sigmoid colon, five rectosigmoid, and 20 rectum), which have different treatment modalities and different prognoses.

The primary aim of the present study was to evaluate the link between HIF-1α overexpression and the PET/CT parameters in CRC. No statistically significant correlation was found between HIF-1α, SUV_{max}, SUV_{mean}, MTV, or TLG. Glucose uptake, a hallmark of cancers, increases with malignancy through the up-regulation of membrane glucose transporters and improves hexokinase activity. It is usually evaluated on ^{18}F-FDG/PET by calculating SUV in the tumor. In addition, SUV_{max} is the most commonly used parameter in clinical trials.

Nevertheless, the tumor metabolic burden regarding MTV and TLG can comprehensively reflect glucose uptake within the whole tumor rather than a single-pixel value of ^{18}F-FDG activity (SUV_{max}). They were adopted as the optimal parameters for the therapeutic evaluation by PET Response Criteria in Solid Tumors (31). Also, MTV and TLG are more accurate biomarkers for T and M stage predictions than SUV_{max} (32). The significant correlation found in the present study between MTV, TLG, and tumor diameter was due to the calculation methods of MTV and TLG. Besides, the statistically significant correlations between MTV, TLG, tumor differentiation, and tumor necrosis percentage are

Table 2. Correlation results of HIF-1α overexpression and clinicopathological features of patients

	Correlation coefficient	p value
Tumor location	0.171	0.319
T stage	-0.050	0.770
N stage	0.083	0.631
PNI	-0.108	0.529
LVI	0.062	0.719
Tumor differentiation	**-0.332**	**0.048**
Tumor necrosis percentage	-0.204	0.233
Tumor diameter	-0.220	0.197

The statistically significant results are in bold. HIF-1α: Hypoxia-inducible factor-1α, PNI: Perineural invasion, LVI: Lymphovascular invasion

Table 3. Correlation results of HIF-1α, pathological findings, and TN stage with ^{18}F-FDG/PET parameters

		SUV_{max}	SUV_{mean}	MTV	TLG
HIF-1α	Correlation coefficient p value	-0.238 0.162	-0.169 0.325	-0.265 0.118	-0.287 0.090
Tumor diameter	Correlation coefficient p value	0.136 0.429	0.145 0.398	**0.672** **<0.001**	**0.616** **<0.001**
Tumor differentiation	Correlation coefficient p value	-0.126 0.465	-0.163 0.342	**0.362** **0.030**	0.281 0.097
Tumor necrosis percentage	Correlation coefficient p value	-0.152 0.376	-0.223 0.191	**0.386** **0.020**	0.300 0.076
PNI	Correlation coefficient p value	0.185 0.281	-0.040 0.816	0.032 0.852	-0.008 0.963
LVI	Correlation coefficient p value	-0.156 0.363	-0.108 0.532	0.110 0.522	0.065 0.708
T stage	Correlation coefficient p value	-0.077 0.654	-0.105 0.541	0.328 0.051	0.237 0.164
N stage	Correlation coefficient p value	-0.176 0.305	-0.115 0.506	0.052 0.763	0.003 0.988

The statistically significant results are in bold. HIF-1α: Hypoxia-inducible factor-1α, TN: Tumor-node, ^{8}F-FDG: ^{18}Fluorine-fluorodeoxyglucose, PET: Positron emission tomography, PNI: Perineural invasion, LVI: Lymphovascular invasion, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, SUV_{max}: Maximum standardized uptake value

remarkable. Poor tumor differentiation is related to a worse prognosis in CRC (33).

Study Limitations

This study has some limitations because of its retrospective design and small sample size. The sample size was limited because ^{18}F-FDG/PET is not routinely indicated in the staging of CRC. Therefore, a heterogeneous group of tumor locations was enrolled in the study to compose the sample size.

Conclusion

The prognostic significance of HIF-1α in CRC and its correlation with PET/CT parameters were controversial issues in previous studies. We found no significant relationship between HIF-1α and clinicopathological features or PET/CT parameters. However, there was a relationship between MTV, TLG, and tumor differentiation, and tumor necrosis percentage. Hence, further studies are required to predict the pathological and prognostic courses of CRC using a diagnostic ^{18}F-FDG/PET evaluation.

Ethics

Ethics Committee Approval: The study was approved by the Scientific Research Ethics Committee of the Medical Faculty of University Süleyman Demirel (protocol code, 13.02.2020/51).

Informed Consent: Informed consent was waived owing to the retrospective nature of the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.S.Ş., N.K., M.E., İ.Z., Concept: S.S.Ş., Z.A.K., E.E., Design: S.S.Ş., Z.A.K., Data Collection or Processing: S.S.Ş., N.K., Z.A.K., M.E., Analysis or Interpretation: Z.A.K., Literature Search: Z.A.K., E.E., S.S.Ş., Writing: Z.A.K.

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