Original Article

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The Effect of GLUT-1-XbaI G>T and HaeIII T>C Polymorphisms on ^{18}F-FDG Uptake Rates

GLUT-1-XbaI G>T ve HaeIII T>C Polimorfizmlerinin ^{18}F-FDG Alım Oranları Üzerindeki Etkisi

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Abstract

Objectives: To investigate the effects of glut polymorphisms on ^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) uptake rates.

Methods: The ^{18}F-FDG positron emission tomography/computed tomography images and mass lesion metabolism standard uptake value maximum (SUV_{max}) results of the patients were evaluated. Glucose transporter protein-1 (GLUT-1)-XbaI G>T (rs2754218) and HaeIII T>C (rs1385129) polymorphisms and their effects on ^{18}F-FDG uptake rates were investigated using DNA obtained from peripheral blood.

Results: When the XbaI G>T genotype distribution of the patients was examined, the XbaI G/G genotype was found to be 87%, the XbaI G/T genotype 12%. The XbaI T/T phenotype was detected in only one patient (1%). In the HaeIII T>C genotype distribution, the HaeIII C/C genotype was found as 54%, the HaeIII T/C genotype as 31%, and the HaeIII T/T genotype as 15%. When the XbaI and HaeIII genotypes were examined together, the number of polymorphic genotypes was significantly higher in the lung and bronchial tumor groups compared to other cancer types.

Conclusion: The presence of polymorphism in at least one of the two gene regions, in the lung-bronchial tumor group and the high SUV_{max} value in this patient group, may indicate a change in the involvement rates.

Keywords: Glucose transporter protein-1 polymorphism, ^{18}Fluorine-fluorodeoxyglucose, positron emission tomography imaging, glucose transporter protein-1-XbaI G>T (rs2754218), HaeIII T>C (rs1385129)

Öz

Amaç: Glut polimorfizmlerinin ^{18}Flor-florodeoksiglukoz (^{18}F-FDG) alım oranları üzerindeki etkisinin araştırılmasıdır.

Yöntem: Hastaların pozitron emisyon tomografisi/bilgisayarlı tomografi görüntüleri ve kitle lezyon metabolizması standart alım değeri maksimum (SUV_{maks}) sonuçları değerlendirildi. Periferik kandan alınan DNA ile hastalarda glikoz taşıyıcı protein-1 (GLUT-1)-XbaI G>T (rs2754218) ve HaeIII T>C (rs1385129) polimorfizmleri ve ^{18}F-FDG tutulum oranlarına etkileri araştırıldı.

Bulgular: Hastaların XbaI G>T genotip dağılımına bakıldığında, XbaI G/G genotipi %87; XbaI G/T genotipi %12 olarak bulundu. XbaI T/T fenotipi sadece 1 hastada (%1) tespit edildi. HaeIII T>C genotip dağılımında, HaeIII C/C genotipi %54; HaeIII T/C genotipi %31; HaeIII T/T genotipi %15 olarak bulundu. XbaI ve HaeIII genotipleri birlikte incelendiğinde, polimorfik genotip sayısının akciğer ve bronşiyal tümör gruplarında diğer kanser tiplerine göre anlamlı derecede yüksek olduğu görülmüştür.

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Öz

Sonuç: Akciğer-bronşiyal tümör grubunda hastalardaki iki gen bölgesinden en az birinde polimorfizmin olması ve bu hasta grubunda SUV_{maks} değerinin yüksek olması tutulum oranlarında bir değişikliğe işaret edebilir.

Anahtar kelimeler: Glikoz taşıyıcı protein-1, ^{18}Flor-florodeoksiglukoz, pozitron emisyon tomografisi görüntüleme, glikoz taşıyıcı protein-1-XbaI G>T (rs2754218), HaeIII T>C (rs1385129)

Introduction

Glucose transporter protein-1 (GLUT-1) is the most widely distributed GLUT isoform in the human body. It is expressed on the surface of almost all types of cells. Glucose transport via GLUT-1 is driven by a gradient across the cell membrane. Glucose transporters comprise a family of facilitative transporters that are divided into three classes. GLUT-1 is a member of class 1 and is highly expressed in glomeruli, mesangial cells, endothelial cells, and podocytes. It is also insulin-independent (1).

The *GLUT-1* gene (SLC2A1) (rs841853) is located on chromosome 1p34.2 and contains 10 exons and 9 introns. Single nucleotide polymorphisms are variations in DNA sequence that occur when a single nucleotide in the genome differs between members of a species. This small variance in DNA sequence can affect the development of certain diseases or the response to pathogens, drugs, or other agents. Accordingly, single nucleotide polymorphisms of the *GLUT-1* gene, located on chromosome 1p35-p31.3, are known to have potential functional effects on diabetic nephropathy, vascular calcifications, renal carcinoma risk, and the uptake of 2-(^{18}F) ^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) related to cancer risk (2).

Positron emission tomography/computed tomography (PET/CT) imaging, which detects the glucose analog ^{18}F-FDG, provides the opportunity to obtain both anatomical and metabolic information about a tumor. ^{18}F-FDG accumulates in tumor cells because rapidly growing cancer cells have the ability to increase glucose metabolism. A positive correlation has been shown between tumor ^{18}F-FDG uptake and tumor aggressiveness (3).

GLUT-1 is a key rate-limiting molecule in the transport and metabolism of glucose in cancer cells. It is also expressed in several human carcinomas. The upregulation of GLUT-1 suggests that it plays a crucial role in tumor biology. Therefore, it is hypothesized that increased expression of GLUT-1 in human carcinomas indicates improved metabolism and energy utilization, as well as more aggressive behavior. High protein expression of GLUT-1 has been observed in most urothelial carcinomas, which is related to tumor stages and grades, as well as poor tumor differentiation prognosis (4). The uptake mechanism and biochemical pathway of ^{18}F-FDG have been extensively studied both *in vitro* and *in vivo*. The transport of ^{18}F-FDG across the cell membrane via glucose transport proteins and intracellular phosphorylation by hexokinase has been identified as key steps (5).

^{18}F-FDG PET/CT is an imaging modality capable of detecting functional tumor tissue. This is made possible by the increased glucose metabolism characteristic of tumors. Images obtained through this method are superimposed with CT images, allowing for both visual and quantitative assessment, thus providing anatomical and metabolic information about the tumor.

The standardized uptake value (SUV) in tumor tissue is adjusted for the given dose and the patient's weight, reflecting the average activity. ^{18}F-FDG enters the cell via facilitated diffusion with the help of GLUT transporters (6). It is then phosphorylated by the enzyme hexokinase into ^{18}F-FDG-6-phosphate, leading to its accumulation within the cell. Cancer cells exhibit increased GLUT-1 expression. Polymorphisms can influence gene expression and protein function (7). This study aimed to investigate the impact of GLUT-1-XbaI G>T (rs2754218) and HaeIII T>C polymorphisms on ^{18}F-FDG uptake.

Materials and Methods

Data Sampling

Our study included patients who applied to Pamukkale University Faculty of Medicine, Department of Nuclear Medicine, PET/CT unit for ^{18}F-FDG oncological whole-body PET/CT due to malignancy investigation. These patients had a preliminary diagnosis or were diagnosed with cancer, had not received any treatment, and were going to undergo ^{18}F-FDG PET for the first time. Patients with a definite pathological diagnosis of cancer constituted the study group. The control group will consist of those reported as normal on the ^{18}F-FDG PET/CT study or those reported as benign by pathology, even if there are abnormal uptake findings.

This study included 100 patients and 100 healthy individuals in the control group. PET/CT images of the patients were evaluated to assess mass lesion metabolism and the presence of metastatic foci. This was a prospective case-control study, and its protocol was approved by the Pamukkale University Non-Interventional Clinical Research

Ethics Committee (number: E-60116787-020-5047, date: 05.01.2021). All procedures carried out on patients were in accordance with the Helsinki Declaration.

^{18}F-FDG PET/CT Procedure

All patients were instructed to fast for 4 hours prior to the intravenous administration of ^{18}F-FDG. Before ^{18}F-FDG injection, the blood glucose levels of all patients are checked, and 3.7 MBq/kg ^{18}F-FDG is administered intravenously to patients with blood glucose levels below 160 mg/dL. Whole-body PET/CT scans were acquired approximately 45-60 minutes after injection using a PET/CT unit (Gemini TF TOF PET/CT; Philips, Cleveland, OH, USA). The system consists of a full-ring dedicated PET scanner and a 2-slice spiral CT scanner.

The imaging protocol involved patient preparation with 1,500 mL of water-based oral contrast agent, and intravenous injection of 140 mL of contrast medium (Ultravist 300; Schering AG). A CT scan (100 mA at 130 kV) was acquired first, followed by a PET scan (3 dimensions, emission time, 4-6 min/bed position depending on body weight). A pulmonary gating technique in both PET and CT scans was used to avoid artifacts caused by breathing. Standardized uptake value was determined in tumor tissue as a measure of ^{18}F-FDG uptake using a region of interest technique. PET images, non-contrast low-dose CT images, and PET/CT fusion images are examined with visual and semiquantitative SUV_{max} values.

GLUT-1 Genotyping

DNA samples were isolated from the peripheral blood of the patients immediately before the PET/CT scan and stored at -20 °C. GLUT-1-XbaI G>T (rs2754218) and HaeIII T>C (rs1385129) polymorphisms were determined from the extracted genomic DNA using the standard phenol-chloroform method. The primers used in both polymerase chain reaction amplification and DNA sequencing are listed in Table 1 (4,8).

Statistical Analysis

This study utilized a power analysis to determine the required sample size, aiming for a medium-high effect size (f=0.4), with 95% confidence and 90% power. As a result of the analysis, it was found that at least 84 participants were needed for the patient group. To account for a possible 15% loss of data, 100 patients were included in the study, while the control group was also formed with 100 patients. Data analysis was performed using SPSS 25 software. Continuous variables were presented as mean ± standard deviation, while categorical variables were presented as counts and percentages. Genotype data frequency analysis was employed to determine the distribution of patient genotypes. One-way ANOVA was used to compare differences among more than two independent groups when the assumptions for parametric tests were met. The Mann-Whitney U test was used for group comparisons when parametric assumptions were not met. Spearman correlation analysis was used to examine the relationships between continuous variables. Fisher's exact test was used to assess differences between categorical variables. A p-value of less than 0.05 was considered statistically significant for all analyses.

Results

The DNA sequence analysis results of the GLUT-1 XbaI G>T(rs2754218) polymorphism are shown in Figure 1.

The DNA sequence analysis result of the GLUT-1 HaeIII T>C (rs1385129) polymorphism is shown in Figure 2.

When the XbaI G>T genotype distribution was examined, the XbaI G/G genotype was seen at a rate of 87%, and the XbaI G/T genotype was seen at a rate of 12%. The XbaI T/T genotype was detected in only 1 patient (1%). In the HaeIII T/C genotype distribution, C/C genotype was detected at 54%, T/C genotype at 31%, and T/T genotype at 15% (Table 2).

SUV_{max} Primer values were determined as 11.65±12.7 in the melanoma group, 11.09±5.48 in the lung-bronchial tumors group, 10.73±3 in the urogenital tumors group, 2.15±4.8 in the gastrointestinal system (GIS) tumors group, and 5.26±2.19 in the breast cancer group. PET/CT images and SUV_{max} values of the patients with lung-bronchial cancer diagnosis are shown in Figure 3 (Table 3).

When the cancer types were examined according to the system in which the cancer was seen, the patient group was divided into subgroups as melanoma, lung-bronchial

Table 1. PCR and DNA sequencing primers

	Primers	PCR product
GLUT-1 G>T (rs2754218)	**F:** 5'-TGC AAC CCA TGA GCT AAC AA-3' **R:** 5'-GAA CCC AGC ACT CTG TAG CC-3'	305 bp
GLUT-1 T>C (rs1385129)	**F:** 5'-CTC CCA GAC ACG CCT ATA ACA GT-3' **R:** 5'-GGC TGG TGT CCA TAA GCC AAC G-3'	173 bp

PCR: Polymerase chain reaction, GLUT-1: Glucose transporter protein-1

tumors, urogenital tumors, GIS tumors, breast cancer and other. While the XbaI G/G genotype was found in all patients with melanoma, urogenital tumors, GIS tumors, breast cancer, and other cancer subgroups, the XbaI G/G, G/T, and T/T genotypes were seen in lung-bronchial tumors. In melanoma and urogenital tumors, the HaeIII C/C genotype was seen, while in other tumor types, all genotypes were detected (Table 4).

In addition, XbaI and HaeIII genotypes were evaluated together, and the relationship between cancer types and both genotypes was examined. It was shown that the number of polymorphic genotypes was significantly higher, especially in the lung and bronchial tumor group, compared to other cancer types.

The relationship between XbaI and HaeIII genotypes, and SUV is shown in Table 5. The genotypes with the highest SUV_{max} values were identified to be XbaI G/G and HaeIII C/C and XbaI G/T and HaeIII T/T.

Finally, Table 6 demonstrates the age distribution of the patients, revealing a mean age of 57.8 years with a range between 20 and 87 years. Table 7 presents the gender

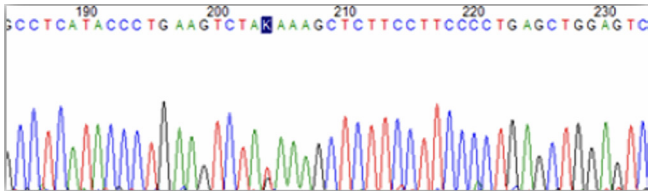

Figure 1. K indicates that the G>T nucleotide change in the sequence analysis is inherited in heterozygous form

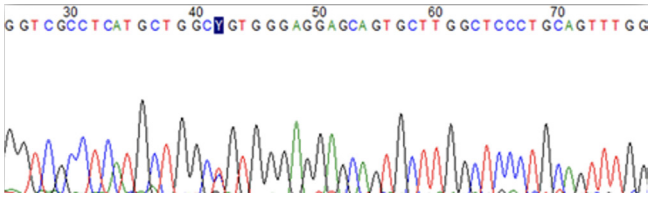

Figure 2. Y indicates that the C>T nucleotide change in the sequence analysis was inherited in a heterozygous form

Table 2. Genotype distributions of patient and control groups

	Patients genotype n (%)	Control genotype n (%)
GLUT-1 XbaI G>T (rs2754218)	**G/G** 87 (87%) **G/T** 12 (12%) **T/T** 1 (1%)	**G/G** 87 (87%) **G/T** 13 (13%)
GLUT-1 HaeIII T>C (rs1385129)	**C/C** 54 (54%) **T/C** 31 (31%) **T/T** 15 (15%)	**C/C** 48 (48%) **T/C** 42 (42%) **T/T** 10 (10%)

GLUT-1: Glucose transporter protein-1

Table 3. Cancer types and SUV_{max} results of PRIMARY tumor

Type of cancer	SUV_{max} (mean ± standard deviation)
Melanoma	11.65±12.7
Lung-bronchial tumors	11.09±5.48
Urogenital tumors	10.73±3
GIS tumors	2.15±4.8
Breast cancer	5.26±2.19
Other	9.75±5.38

SUV_{max}: Maximum standardized uptake value, GIS: Gastrointestinal system

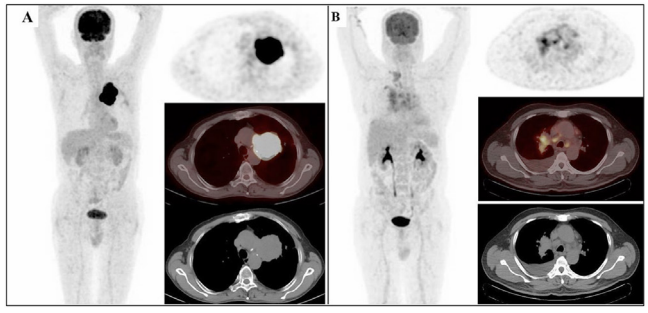

Figure 3. PET/CT images of patients with lung-bronchial cancer
PET/CT images of a 70-year-old male showing the left lung. SUV_{max}: 7.56. (XbaI G>T genotype: G/G; HaeIII T>C genotype: C/C)
B: PET/CT images of a 53-year-old male on the right lung. SUV_{max}: 10.37. (XbaI G>T genotype: G/T; HaeIII T>C genotype: T/C)
PET/CT: Positron emission tomography/computed tomography, SUV_{max}: Maximum standardized uptake value

Table 4. Cancer types and GLUT-1 genotype result

	GLUT-1 XbaI G>T (rs2754218) genotype n (%)	GLUT-1 HaeIII T>C (rs1385129) genotype n (%)
Melanoma	**G/G** 4 (100%) **G/T** **T/T**	**C/C** 4 (100%) **T/C** **T/T**
Lung-bronchial tumors	**G/G** 24 (64,86%) **G/T** 12 (32,43%) **T/T** 1 (2,70%)	**C/C** 10 (27,77%) **T/C** 15 (41,66%) **T/T**
Urogenital tumors	**G/G** 17 (100%) **G/T** **T/T**	**C/C** 17 (100%) **T/C** **T/T**
GIS tumors	**G/G** 15 (100%) **G/T** **T/T**	**C/C** 11 (73,33%) **T/C** 4 (26,67%) **T/T**
Breast cancer	**G/G** 16 (100%) **G/T** **T/T**	**C/C** 8 (34,78%) **T/C** 6 (26,09%) **T/T** 9 (39,13%)
Other	**G/G** 11 (100%) **G/T** **T/T**	**C/C** 4 (25%) **T/C** 6 (37,5%) **T/T** 6 (37,5%)

distribution, indicating that 46% of the patients were female and 54% were male. Table 8 summarizes the distribution of patients' diagnoses based on International Classification of Diseases codes, with lung-related abnormalities (R91) being the most common diagnosis (22%).

Discussion

PET/CT, a non-invasive imaging technique widely accepted worldwide, provides exceptional benefits in oncology patient follow-up, helping to reduce mortality and morbidity in cancer patients. The level of ^{18}F-FDG uptake, which generally reflects tumor aggressiveness, indicates viable tumor tissue and increased glucose metabolism. The accumulation of ^{18}F-FDG in tumors demonstrates the known natural behavior of tumors.

The most commonly used radiopharmaceutical in PET/CT is ^{18}F-FDG, a glucose derivative. ^{18}F-FDG, a glucose analog, is taken up by living cells in the first step of the normal glucose pathway. It is used in cancer diagnosis due to the increased glycolytic activity in neoplastic cells. The rate of glucose metabolism is consistent with the rate of ^{18}F-FDG uptake.

Glucose transporters, chiefly GLUT-1, play critical roles in the import and metabolism of glucose and auxiliary substrates (9,10,11). and are significantly overexpressed in many cancers, including brain, breast, cervical, colorectal, cutaneous, endometrial, esophageal, hepatic, lung, oral, ovarian, pancreatic, prostate, and renal cancers. The cellular uptake mechanism of ^{18}F-FDG has been studied both *in vitro* and *in vivo*. Studies have shown that polymorphisms in the GLUT-1 transporter protein affect the cellular uptake of ^{18}F-FDG. These polymorphisms have been identified as GLUT-1-XbaI G>T (rs2754218), HpyCH4V A>T (rs710218), and HaeIII T>C (rs1385129). Polymorphisms in the *GLUT-1* gene have been associated with increased ^{18}F-FDG uptake, accelerated tumor growth, and breast cancer.

Numerous studies have investigated the influence of the GLUT-1-XbaI G>T polymorphism (rs2754218) on ^{18}F-FDG uptake, with a primary focus on various cancer types. Relevant studies have reported the association between

Table 5. Association between XbaI and HaeIII genotypes and SUV_{max} values of PRIMARY tumor

Genotype	SUV_{max} mean ± standard deviation
XbaI G/G & HaeIII C/C	10.89±5.85
XbaI G/T & HaeIII T/T	10.65±6.75
XbaI G/T & HaeIII T/C	9.54±5.02
XbaI T/T & HaeIII T/T	
XbaI G/G & HaeIII T/T	4.28±3.48
XbaI G/G & HaeIII T/C	6.81±2.67

SUV_{max}: Maximum standardized uptake value

Table 6. Characteristic analysis of the patient (age)

	n	Mean	SD	Min.	Max.
Age	100	57.8	13.37	20	87

SD: Standard deviation, Min.: Minimum, Max.: Maximum, n: Number

Table 7. Characteristic analysis of the patient (gender)

Gender	n	%
Female	46	46%
Male	54	54%

Table 8. Patients' diagnosis statement

ICD code	Diagnosis description	n	%
C04	Base of tongue CA	1	1.00
C09	Tonsil CA	1	1.00
C15	Esophagus CA	1	1.00
C16	Stomach CA	1	1.00
C18	Colon CA	4	4.00
C21	Anus and anal canal CA	1	1.00
C22	Liver and intrahepatic bile duct CA	1	1.00
C25	Pancreas CA	4	4.00
C32	Larynx CA	7	7.00
C34	Bronchus and lung CA	8	8.00
C38	Heart, mediastinum and pleura CA	1	1.00
C43	Skin malignant melanoma	4	4.00
C45	Mesothelioma	1	1.00
C49	Connective and soft tissue CA	1	1.00
C50	Breast CA	16	16.00
C53	Cervix uteri CA	3	3.00
C54.1	Endometrium CA	1	1.00
C56	Ovary CA	1	1.00
C61	Prostate CA	1	1.00
C62	Testis CA	1	1.00
C64	Kidney CA (excluding renal pelvis)	7	7.00
C67	Bladder CA	2	2.00
C80	Malignant neoplasm, unspecified site	7	7.00
D37.4	Colon, uncertain behavior neoplasm	1	1.00
K62	Other diseases of anus and rectum	1	1.00
M79	Other soft tissue disorders	1	1.00
R91	Lung, diagnostic A.B	22	22.00

ICD: International Classification of Disease, CA: Cancer

the societal T allele and high ^{18}F-FDG in ethnic studies, claiming that this allele could increase the capability for glucose transport and hence increased tumor activity. Conversely, the investigations on GLUT-1 HaeIII T>C polymorphism have not been exhaustive, and some studies have speculated that the C allele may be related to lower ^{18}F-FDG uptake (9,11,12).

In our study, the XbaI G/G genotype was observed in 87% of the patients, while the XbaI G/T genotype was found in 12%. Only one patient (1%) had the XbaI T/T genotype. For the HaeIII T>C genotype distribution, the HaeIII C/C genotype was detected in 54%, HaeIII T/C genotype in 31%, and HaeIII T/T genotype in 15%.

The genotype distributions in both gene regions varied according to cancer types (p=0.0001). There was no statistically significant difference in SUV_{max} values between the XbaI and HaeIII genotypes (p-values: p=0.89 and p=0.541, respectively). Cancer types were categorized based on the affected system, the patient group was divided into subgroups: melanoma, lung and bronchial tumors, urogenital tumors, GIS tumors, breast cancer, and others. All patients in the melanoma, urogenital tumors, GIS tumors, breast cancer, and other cancer subgroups had the XbaI G/G genotype. However, in lung-bronchial tumors, the XbaI G/T genotype was observed at a rate of 32.43%.

XbaI and HaeIII genotypes were evaluated together to examine their relationship with cancer types was observed that the number of polymorphic genotypes was significantly higher in the lung-bronchial tumor group compared to other cancer types. Particularly, patients in the lung-bronchial tumor group had mutations in at least one of the two gene regions.

However, ^{18}F-FDG uptake intensity varies depending on tumor histopathology. While epidermal and adenocarcinomas, such as small cell lung cancer, show a high degree of uptake, tumors like bronchoalveolar and carcinoid tumors, which have dense mucinous content or are slow-growing, may not show pathological levels of ^{18}F-FDG uptake.

This study investigated the relationship between GLUT-1 polymorphisms (specifically GLUT-1-XbaI G>T and HaeIII T>C), ^{18}F-FDG uptake rates, and cancer types. Here's a breakdown of the findings:

Genotype Distribution Varies by Cancer Type: The distribution of GLUT-1-XbaI G>T and HaeIII T>C genotypes differed significantly among various cancer types. Notably, the XbaI G/T genotype was more prevalent in lung-bronchial tumors compared to other cancer types.

No Significant Difference in SUV_{max} values Based on Genotype Alone: No statistically significant difference was found in SUV_{max} values when comparing groups based solely on XbaI or HaeIII genotypes.

High Prevalence of Polymorphisms in Lung and Bronchial Tumors: A significantly higher number of patients with lung-bronchial tumors exhibited polymorphisms in at least one of the two *GLUT-1* gene regions compared to other cancer types.

Conclusion

Though the study has failed to establish a proper correlation between specific genotypes and SUV_{max} values, a high prevalence of GLUT-1 polymorphisms in lung-bronchial tumor patients with high SUV_{max} values may highlight a possible relation, requiring further research. There is a complex relationship between genetic variation, glucose metabolism, and uptake of ^{18}F-FDG in cancer.

Potential Consequences: Further studies will be needed to unravel the consequences of such results. If, in the near future, more associations between GLUT-1 variations and ^{18}F-FDG uptake in specific cancers are developed, then this would imply the following: a) Personalized medicine: Treatment strategies could be developed with a focus on the unique properties of each individual's genome. b) Diagnostic precision: It could allow for more accurate interpretation of ^{18}F-FDG PET/CT scans for certain malignancies. c) Drug development: Interference with GLUT-1 may also represent a potential therapeutic approach for drugs under development.

Ethics

Ethics Committee Approval: The protocol was approved by the Pamukkale University Non-Interventional Clinical Research Ethics Committee (number: E-60116787-020-5047, date: 05.01.2021).

Informed Consent: This was a prospective case-control study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.K., D.Y., Concept: D.Y., A.K., Design: D.Y., A.K., Data Collection or Processing: V.K.A., D.Y., A.K., Analysis or Interpretation: M.K., V.K.A., Y.B., D.Y., A.K., Literature Search: Y.A., D.Y., A.K., Writing: Y.A., Y.B., A.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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