Original Article
Mol Imaging Radionucl Ther 2021;30:79-85 DOI:10.4274/mirt.galenos.2021.92053

^{68}Ga-PSMA PET/CT Versus ^{18}F-FDG PET/CT for Imaging of Hepatocellular Carcinoma

Hepatoselüler Karsinomun Görüntülenmesinde ^{18}F-FDG PET/BT'ye Karşı ^{68}Ga-PSMA PET/BT

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Abstract

Objectives: This study aimed to compare the metabolic parameters obtained from ^{18}fluorine-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) and gallium-68 (^{68}Ga)-prostate-specific membrane antigen (PSMA) PET/CT and investigate the relationship between serum alpha-fetoprotein and PET scan parameters in patients with hepatocellular carcinoma.

Methods: Fourteen patients were recruited after dynamic magnetic resonance imaging (MRI) of the upper abdomen, and ^{18}F-FDG and ^{68}Ga-PSMA PET/CT imaging studies were conducted. Regions of interest (ROIs) were drawn from lesion-free liver tissue, abdominal aorta (A), and right medial gluteal muscle (G) for the background activity. Maximum standard uptake value (SUV_{max}) of these regions were compared with the SUV_{max} of primary tumor (T).

Results: On visual assessment, five patients (36%) experienced low ^{18}F-FDG uptake in the primary lesion, three patients (21%) experienced moderate uptake, and six patients (43%) experienced high uptake. However, only one patient (7%) showed low ^{68}Ga-PSMA uptake, two patients (14%) showed moderate uptake, and 11 patients (79%) showed high uptake. Four patients with a low ^{18}F-FDG uptake showed high ^{68}Ga-PSMA uptake, while one patient exhibited low uptake with both ^{18}F-FDG and ^{68}Ga-PSMA. The number of lesions on ^{68}Ga-PSMA PET/CT and MRI was significantly higher than ^{18}F-FDG PET/CT (p=0.042 and 0.026, respectively). T/A and T/G values were significantly higher in ^{68}Ga-PSMA than ^{18}F-FDG (p=0.002 and 0.002, respectively).

Conclusion: ^{68}Ga-PSMA PET/CT is superior to ^{18}F-FDG PET/CT in the staging of hepatocellular carcinoma. High ^{68}Ga-PSMA uptake could be promising for PSMA-targeted radionuclide treatments.

Keywords: Hepatocellular cancer, ^{68}Ga-PSMA, ^{18}F-FDG, PET/CT, AFP

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Received: 11.01.2021 **Accepted:** 13.02.2021

Öz

Amaç: Bu çalışmanın amacı, ^{18}flor-florodeoksiglukoz (^{18}F-FDG) pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) ve galyum-68 (^{68}Ga)-prostat spesifik membran antijen (PSMA) PET/BT'den elde edilen metabolik parametreleri karşılaştırmak ve hepatosellüler karsinomlu hastalarda serum alfa-fetoprotein ve PET parametreleri arasındaki ilişkiyi araştırmaktı.

Yöntem: Çalışmaya üst karın bölgesinden dinamik manyetik rezonans görüntüleme (MRG) görüntülemesi olan 14 hasta alındı ve ^{18}F-FDG ve ^{68}Ga-PSMA PET/BT görüntülemeleri yapıldı. Arka plan aktivitesi için lezyonsuz karaciğer dokusundan, abdominal aortadan (A) ve sağ medial gluteal kastan (G) ilgi alanları (ROI) çizildi ve bu bölgelerin maksimum standardize uptake değerini (SUV_{maks}) primer tümörün (T) SUV_{maks}'ı ile karşılaştırıldı.

Bulgular: Görsel değerlendirmede, ^{18}F-FDG PET/BT'de 5 hastada (%36) primer lezyonda düşük ^{18}F-FDG tutulumu, 3 hastada (%21) orta düzeyde ve 6 hastada (%43) yüksek düzeyde tutulum vardı. Öte yandan, ^{68}Ga-PSMA PET/BT'de sadece 1 hastada (%7) düşük PSMA tutulumu varken, 2 hastada (%14) orta düzeyde ve 11 hastada (%79) yüksek düzeyde tutulum vardı. Düşük FDG tutulumu gösteren dört hasta yüksek PSMA tutulumu gösterirken, 1 hasta hem düşük ^{18}F-FDG, hem de düşük PSMA tutulumu göstermiştir. ^{68}Ga-PSMA PET/BT ve MRG'deki lezyon sayısı ^{18}F-FDG PET/BT'den anlamlı derecede yüksekti (sırasıyla p=0,042 ve 0,026). ^{68}Ga-PSMA'da T/A ve T/G değerleri ^{18}F-FDG'den anlamlı olarak yüksekti (sırasıyla p=0,002 ve 0,002).

Sonuç: ^{68}Ga-PSMA PET/BT, hepatoselüler karsinomun evrelendirilmesinde ^{18}F-FDG PET/BT'den üstün bulunmuştur. Yüksek ^{68}Ga-PSMA tutulumu, PSMA hedefli radyonüklid tedavileri için umut verici olabilir.

Anahtar kelimeler: Hepatosellüler kanser, ^{68}Ga-PSMA, ^{18}F-FDG, PET/BT, AFP

Introduction

Liver cancer is the 6th most frequent malignancy and the 4th most common cause of cancer-related deaths worldwide. Hepatocellular carcinoma (HCC), which develops due to major risk factors such as hepatitis B virus, hepatitis C virus, aflatoxin-containing foods, and non-alcoholic steatohepatitis, accounts for 75%-85% of primary liver cancers (1). Conventional dynamic contrast-enhanced imaging methods, including computed tomography (CT) and magnetic resonance imaging (MRI), are routinely used in the diagnosis of HCC, with 62%-82% sensitivity and over 90% specificity. Nodules larger than 1 cm show high contrast enhancement in the arterial phase of CT and MRI and wash out in venous and late phases (2). Alpha-fetoprotein (AFP), a serum biomarker, is one of the most commonly used markers in HCC screening and diagnosis. However, its sensitivity and specificity are unsatisfactory, especially in early-stage HCCs (3). The histopathological examination of the tumor tissue is the gold standard in the definitive diagnosis of HCC, but it may cause tissue damage and seeding along the biopsy tract (4).

^{18}Flourine-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography(PET)/CT is associated with the aggressiveness of HCC; moderately and well-differentiated HCCs exhibit a low ^{18}F-FDG uptake, while poorly differentiated HCCs show high uptake (5,6). ^{18}F-FDG PET/CT shows a high sensitivity in detecting lymph nodes and extrahepatic metastases, which are poor prognostic factors for HCC, but show a low sensitivity in detecting primary HCC lesions (7,8).

Prostate-specific membrane antigen (PSMA) is a type 2 transmembrane protein and is overexpressed in prostate cancer (PCa). ^{68}Ga-PSMA PET/CT is widely used in staging, evaluating the treatment response, and assessing relapse in PCa (9). However, in many solid tumors, including HCCs, high PSMA uptake indicates neoangiogenesis (10,11).

In this prospective study, we compared the metabolic parameters obtained from ^{18}F-FDG PET/CT and ^{68}Ga-PSMA-11 PET/CT and investigated the association between PET parameters and serum AFP in patients with HCC.

Material and Methods

Patient Characteristics

Fourteen patients [13 males; 1 female; mean age: 63.8±6.0 years (58-76)] were included in this study. Twelve patients had a Child-Pugh (CP) score "A" cirrhosis, and two patients had a CP-B cirrhosis. Twelve patients had a newly diagnosed HCC, one patient had a history of transarterial chemoembolization (TACE), and one had radiofrequency ablation + TACE for HCC. While six patients had a histopathological confirmation, eight patients were diagnosed with HCC based on radiological findings and serum AFP levels. Patients were recruited after dynamic MRI of the upper abdomen, and ^{18}F-FDG and ^{68}Ga-PSMA-11 PET/CT imaging studies were conducted in the same week. AFP and routine laboratory tests and ^{18}F-FDG PET/CT were performed for all patients on the same day. Patients who previously received chemotherapy or had a history of hepatic tumor surgery were excluded from the study. This study was conducted in concordance with the local good clinical practice guidelines and current laws. The Local Ethics Committee of İstanbul Training and Research Hospital approved this study under the decision number: 2018/1297. Written informed consent was obtained from all patients.

PET/CT Scan and Evaluation

Whole-body PET/CT imaging was performed 60 min after intravenous injection of ^{18}F-FDG (3.5-5.5 MBq/kg) and ^{68}Ga-PSMA-11 (2-2.5 MBq/kg) in a PET/CT scanner [mCT 20 ultra HD LSO PET/CT (Siemens molecular imaging, Hoffmann Estates, Illinois, USA)] on different days. CT imaging was performed in the craniocaudal direction with a 5 mm slice thickness and rotation time of 0.5 sec [80-140 kV, 20-266 mAs, 0.8 pitch, and 512x512 matrix (personalized settings determined by the automatic exposure control system; automatically defined by the software used by the manufacturer, depending on the patient)]. Then, PET imaging was performed in the same range through the craniocaudal direction for 2 min for each PET bed; ultra HD images were acquired using the time of flight + true X algorithm at iteration two and subset 16 values for reconstruction.

^{18}F-FDG and ^{68}Ga-PSMA-11 PET/CT images were both evaluated by two nuclear medicine physicians with at least 10 years of experience in PET/CT, and decisions were made with consensus. Both PET/CT studies were scored visually. 1: Low uptake (equal or less than liver), 2: Moderate uptake (slightly higher than liver), 3: High uptake (markedly higher than liver). SUV_{max} of primary lesions were acquired by drawing a volume of interest to include the lesion in all three planes in ^{18}F-FDG and ^{68}Ga-PSMA-11 PET/CT. Moreover, regions of interest of 1 cm diameter were drawn from lesion-free liver tissue (L), abdominal aorta (A), and right medial gluteal muscle (M) for background maximum standard uptake value (SUV_{max}). Using these three background SUV_{max}, tumor to normal liver parenchyma (T/L), tumor to abdominal aorta (T/A), and tumor to gluteal muscle (T/G) parameters were calculated separately.

Statistical Analysis

SPSS version 21.0 software (IBM Corporation, Armonk, New York, USA) was used for statistical analyses of the variables. The normality of one-variable data was tested with the Shapiro-Francia test, while variance homogeneity was evaluated using Levene's test. Mann-Whitney U test was used to compare independent and non-normally distributed variables, while the Wilcoxon signed-rank test was used to compare dependent and normally distributed variables. Pearson and Spearman's rho tests were used to analyze the correlation of variables. The variables had a 95% confidence interval, and a p value less than 0.05 was considered significant.

Results

Six patients exhibited a bilobar involvement, while eight patients had a lobar involvement. On MRI, nine patients showed a mosaic enhancement pattern, and five patients showed a homogeneous enhancement pattern. The median size of primary tumors on MRI is 80.5 mm (20 mm-140 mm). The smallest lesion detected on ^{68}Ga-PSMA PET had a diameter of 8 mm, and the lesion had been described on MRI.

On the visual evaluation, five patients (36%) showed a low ^{18}F-FDG uptake in the primary lesion, three patients (21%) showed a moderate ^{18}F-FDG uptake, and six patients (43%) showed a high ^{18}F-FDG uptake. In contrast, one patient (7%) showed low ^{68}Ga-PSMA uptake, two patients (14%) showed moderate ^{68}Ga-PSMA uptake, and 11 patients (79%) showed high ^{68}Ga-PSMA uptake. Four patients with low ^{18}F-FDG uptake showed high ^{68}Ga-PSMA uptake (Figure 1), while one patient exhibited low uptake with both ^{18}F-FDG and ^{68}Ga-PSMA (Figure 2). Two patients with moderate ^{18}F-FDG uptake showed higher ^{68}Ga-PSMA uptake (Figure 3). In contrast, one patient with moderate ^{68}Ga-PSMA uptake showed higher ^{18}F-FDG uptake (Table 1).

The total number of liver lesions on ^{68}Ga-PSMA PET/CT, MRI, and ^{18}F-FDG PET/CT are 61, 57, and 30, respectively. The number of liver lesions on ^{68}Ga-PSMA PET/CT and MRI were significantly higher than ^{18}F-FDG PET/CT (p=0.042 and 0.026, respectively). There was no statistically significant difference between the number of liver lesions on MRI and ^{68}Ga-PSMA PET/CT (p=0.593) (Table 2).

^{68}Ga-PSMA PET/CT revealed a pathologically increased radiotracer uptake in the abdominal lymph nodes of four patients. Of these four patients, one patient had no ^{18}F-FDG uptake. Two patients had ^{18}F-FDG and ^{68}Ga-PSMA-

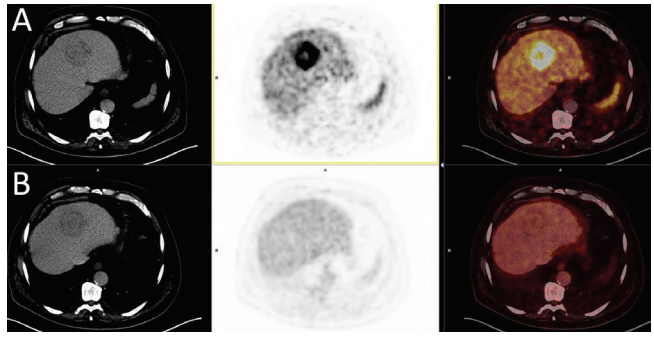

Figure 1. A 69-year-old male diagnosed with hepatocellular carcinoma (AFP: 4.5 ng/mL) by magnetic resonance imaging. The left lobe mass showed (A) an intense ^{68}Ga-PSMA (T/L: 4.49), while it showed no significant ^{18}F-FDG (B) uptake (T/L: 1.01)

AFP: Alpha-fetoprotein, ^{68}Ga: Gallium-68, ^{18}F-FDG: ^{18}Fluorine-fluorodeoxyglucose, T: Tumor uptake, L: Normal liver parenchyma uptake, PSMA: Prostate-specific membrane antigen

positive mediastinal lymph nodes, while the remaining patient, who was later histopathologically diagnosed with anthracosis, had only ^{18}F-FDG uptake. One patient had focally increased radiotracer accumulation in the prostate gland on both ^{18}F-FDG and ^{68}Ga-PSMA PET/CT, consistent with a synchronous tumor in the prostate.

The median SUV_{max} of primary lesions in ^{18}F-FDG and ^{68}Ga-PSMA PET/CT were 6.45 (range: 3.7-21.3) and 16.7 (range: 9.3-48.9), respectively. When median T/L, T/A, and T/G ratios were compared, T/L ratio had no statistically significant difference between ^{18}F-FDG and ^{68}Ga-PSMA (p=0.331), whereas T/A and T/G were significantly higher in ^{68}Ga-PSMA than ^{18}F-FDG (p=0.002 and 0.002, respectively).

Of our six patients with histopathology results, one was reported as having poorly differentiated HCC, two, as well-

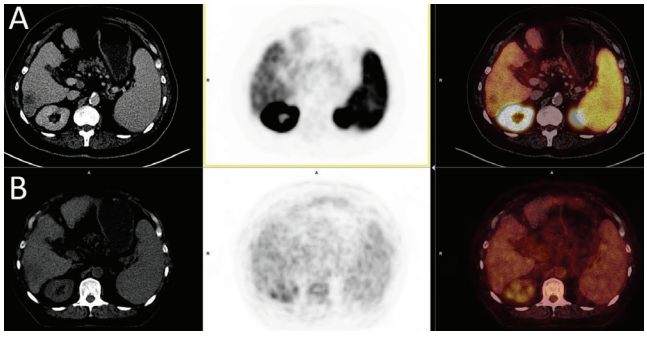

Figure 2. A 62-year-old male with alcohol-induced cirrhosis. Magnetic resonance imaging revealed a mass compatible with hepatocellular carcinoma, showing a typical contrast enhancement pattern (not shown). AFP: 1.648 ng/mL. ^{68}Ga-PSMA: (A) SUV_{max}: 9.3; T/L 0.93. ^{18}F-FDG: (B) SUV_{max}: 4.5; T/L 0.85

AFP: Alpha-fetoprotein, ^{18}F-FDG: ^{18}Fluorine-fluorodeoxyglucose, SUV_{max}: Maximum standard uptake value, PSMA: Prostate-specific membrane antigen, T: Tumor uptake, L: Normal liver parenchyma uptake

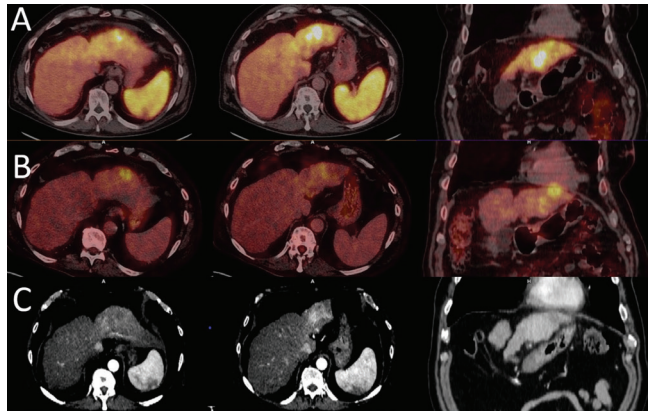

Figure 3. A 67-year-old cirrhotic male with hepatocellular carcinoma in the left lobe of the liver. ^{68}Ga-PSMA: (A) SUV_{max}: 28.1; T/L: 3.95; T/G: 31.2. ^{18}F-FDG: (B) SUV_{max}: 10.1; T/L: 2.76; T/G: 7. In arterial phase CT images (C), it is seen that PSMA uptake is higher in the hyperenhancement areas and ^{18}F-FDG uptake is higher in the non-enhancing areas of the tumor

T: Tumor uptake, L: Normal liver parenchyma uptake, G: Gluteus medius muscle uptake, ^{68}Ga: Gallium-68, ^{18}F-FDG: ^{18}Fluorine-fluorodeoxyglucose, PSMA: Prostate-specific membrane antigen, SUV_{max}: Maximum standard uptake value, CT: Computed tomography

Table 1. ^{18}F-FDG and ^{68}Ga-PSMA PET/CT findings of patients

Patient no	AFP (µg/L)	^{18}F-FDG LN	PSMA LN	^{18}F-FDG uptake	PSMA uptake	^{18}F-FDG T/L	PSMA T/L	^{18}F-FDG T/A	PSMA T/A	^{18}F-FDG T/G	PSMA T/G
1	351	1	6	Moderate	High	1.36	3.84	1.33	8.75	3.42	21.65
2	1643	2	2	Moderate	High	1.39	2.16	1.78	4.62	3.88	12.64
3	4.7	1	1	High	High	5.54	1.88	4.5	6.06	10.38	5.73
4	7.8	1	1	Low	High	0.86	2.11	0.93	7.27	1.63	20.75
5	4.5	1	1	Low	High	1.01	4.49	1.19	10.4	2.69	22.23
6	1648	1	1	Low	Low	0.85	0.93	1.4	4.94	4.44	11.33
7	17.3	1	1	Moderate	Moderate	1.48	1.44	1.84	4.86	5	9.47
8	60473	1	2	High	Moderate	4.62	1.37	6.01	3.31	15.22	16.71
9	205	4	>20	High	High	4.36	1.87	4.36	4.45	9.21	17.09
10	1042	12	>20	High	High	3.86	10.1	4.47	16.82	11.22	47.89
11	15195	1	2	High	High	2.91	2.81	3.73	5.07	7.68	20.63
12	10	1	1	Low	High	1.11	2.74	1.39	8.31	4.84	21.55
13	91	2	2	High	High	2.76	3.95	2.4	8.74	6.99	31.16
14	24.7	1	1	Low	High	1.11	3.98	2.4	7.33	3.28	41.22

AFP: Alpha-fetoprotein, A: Aorta, LN: Lesion number, L: Liver, T: Tumor, G: Medial gluteal muscle, ^{18}F-FDG: ^{18}Fluorine-fluorodeoxyglucose, ^{68}Ga: Gallium-68, PSMA: Prostate-specific membrane antigen, PET/CT: Positron emission tomography/computed tomography

Table 2. Comparison of ^{18}F-FDG and ^{68}Ga-PSMA PET/CT uptake ratios (SUV_{max})

	Mean	Median	SD	Minimum	Maximum	p
^{18}F-FDG SUV_{max}	8.99	6.45	5.30	3.72	21.3	**0.006^{w}**
PSMA SUV_{max}	20.88	16.69	11.76	9.29	48.9	
T/L ^{18}F-FDG	2.36	1.42	1.63	0.850	5.54	0.331^{w}
T/L PSMA	3.12	2.45	2.30	0.930	10.1	
T/G ^{18}F-FDG	6.42	4.92	3.89	1.63	5.73	**0.002^{w}**
T/G PSMA	21.43	20.69	11.76	15.2	47.9	
T/A ^{18}F-FDG	2.62	1.81	1.65	0.932	6.01	**0.002^{w}**
T/A PSMA	7.21	6.67	3.45	3.31	16.8	

^{w}Wilcoxon signed-rank, T: Tumor; L: Liver, A: Aorta, G: Medial gluteal muscle, ^{18}Fluorine-fluorodeoxyglucose, ^{68}Ga: Gallium-68, PSMA: Prostate-specific membrane antigen, PET/CT: Positron emission tomography/computed tomography, SUV_{max}: Maximum standard uptake value

differentiated HCC, and three, as HCC without specifying differentiation levels. ^{18}F-FDG (T/B: 1.48) and PSMA (T/B: 1.44) uptake in the patient with poorly differentiated HCC were similar, and a moderate radiopharmaceutical uptake was observed in both studies. The primary tumors in the two patients with well-differentiated HCC showed a low level of radiopharmaceutical uptake (T/B: 1.11 and 1.12) in ^{18}F-FDG PET/CT and intense radiopharmaceutical uptake (T/B: 2.74 and 3.96) in PSMA PET/CT. Two of the three patients whose differentiation level was not specified showed intense ^{18}F-FDG (T/B: 3.86 to 2.76) and PSMA (T/B:10.1 to 3.98) uptake, while one patient showed low ^{18}F-FDG (T/B: 0.86) and intense PSMA (T/B: 2.1) uptake.

When the relationship between the laboratory results and PET parameters was examined, serum AFP levels showed a statistically significant positive correlation with ^{18}F-FDG T/A ratio only (r=0.641 p=0.007). However, there was no correlation between ^{68}Ga-PSMA parameters and serum AFP (p>0.05).

Discussion

In this prospective study, we investigated the contribution of ^{68}Ga-PSMA PET/CT to the evaluation of HCCs. The most important findings in this study were primary tumors showing higher ^{68}Ga-PSMA uptake on visual assessment and the ability of ^{68}Ga-PSMA to detect more primary and metastatic lesions compared with ^{18}F-FDG. Conventional imaging methods, such as MRI, are routinely used as the first choice in the diagnosis of HCC due to the typical enhancement pattern with hyperenhancement in the arterial phase and wash out in the portal and late venous phases (12). Although MRI is generally sufficient for diagnosis, it cannot provide information about the biological behavior of HCC. PET radiopharmaceuticals, especially ^{18}F-FDG, are helpful in this context. ^{18}F-FDG PET/CT appears as an important non-invasive diagnostic tool, especially in terms of detecting metastatic lesions in HCC. It is known that ^{18}F-FDG PET/CT findings constitute a stronger prognostic factor than the nodule's size and number, as described in Milan criteria. Because ^{18}F-FDG avidity may predict the risk of relapse in patients who are planned to undergo liver transplantation, resection, or ablation, it may have a direct effect on the transplantation and ablation outcome (13,14). However, ^{18}F-FDG PET/CT has a low sensitivity in HCC due to overexpression of multidrug resistance protein and increased glucose-6-phosphatase activity in HCC cells, and its use in routine clinical practice is limited (15,16). Therefore, different radiopharmaceuticals have been investigated for the evaluation of primary and extrahepatic metastases of HCCs. Agents with high sensitivity, including ^{18}F-fluorocholine and ^{11}C-acetate, have a relatively poorer availability and, therefore, a limited use (17,18).

Non-prostate solid tumors may exhibit a wide endothelial PSMA expression, associated with neoangiogenesis and vascular growth factor regulation (19,20,21). Recent studies have shown that HCC shows a higher ^{68}Ga-PSMA uptake compared with ^{18}F-FDG (11,22). In our study, ^{68}Ga-PSMA PET/CT revealed more lesions than ^{18}F-FDG PET/CT, and the lesions showed a higher PSMA uptake compared with ^{18}F-FDG.

A recent study has reported that peritumoral/vascular expression of PSMA is greatly associated with grade 3 HCC (5/6, 83.3%) but can also be observed in grade 2 HCC (10/15, 66.7%). This was associated with the clinicopathological characteristics of HCC. Fibrolamellar HCC, normal hepatic tissue, and non-neoplastic cirrhotic tissue are reported to not overexpress PSMA. HCCs, arising in the setting of cirrhosis (9/10, 90.0%), show a significantly increased peritumoral/vascular PSMA

expression compared with non-cirrhotic HCCs (6/12, 50%) ($p<0.05$) (23).

In a study that evaluates seven patients and 37 lesions, Kesler et al. (11) demonstrated ^{68}Ga-PSMA uptake to be much higher than the background hepatic activity in 36/37 lesions. Twenty-eight lesions with no ^{18}F-FDG uptake showed high ^{68}Ga-PSMA uptake, while eight lesions showed both ^{18}F-FDG and ^{68}Ga-PSMA uptake. In their study involving 19 patients, Kuyumcu et al. (22) reported that ^{68}Ga-PSMA uptake was higher than ^{18}F-FDG uptake in nine patients. Four patients had a higher ^{18}F-FDG uptake compared with ^{68}Ga-PSMA, while two patients showed no uptake (22). In our study, 13 patients had an increased ^{68}Ga-PSMA uptake, while nine patients had an increased ^{18}F-FDG uptake. Four patients with no ^{18}F-FDG uptake had a high ^{68}Ga-PSMA uptake, however, one patient showed neither ^{18}F-FDG nor ^{68}Ga-PSMA uptake. One patient with moderate ^{68}Ga-PSMA uptake exhibited a higher ^{18}F-FDG uptake. Because of these results, the staging and treatment strategy can be changed through using ^{68}Ga-PSMA PET/CT instead of ^{18}F-FDG PET/CT for metabolic imaging in patients with HCC.

Kesler et al. (11) reported extrahepatic involvement in two of seven patients, while Kuyumcu et al. (22) reported extrahepatic involvement in one patient. In our study, four patients had extrahepatic involvement on ^{68}Ga-PSMA PET/CT, whereas ^{18}F-FDG PET/CT failed to reveal the involvement in one of these patients. One patient with ^{68}Ga-PSMA-negative mediastinal lymph nodes, which was later evidenced to be anthracosis by histopathological examination, showed false positivity in ^{18}F-FDG PET/CT. This supports the deduction that ^{68}Ga-PSMA PET/CT may provide more accurate staging than ^{18}F-FDG PET/CT.

Kuyumcu et al. (22) found no statistically significant difference between the mean SUV_{max} of primary tumor in ^{18}F-FDG and ^{68}Ga-PSMA PET/CT and T/L ratios. The researchers only evaluated T/L ratio but did not analyze T/A and T/G ratios (22). Because it has recently been reported that T/A ratios have a prognostic significance in rectal cancer (24), we analyzed T/A and T/G ratios in our study as well. We observed no statistical significance in terms of T/L ratios between ^{18}F-FDG and ^{68}Ga-PSMA PET/CT, while we found significantly higher T/A and T/G ratios and SUV_{max} in ^{68}Ga-PSMA PET/CT.

Since patients with histopathology results are few in our study, it will be difficult to make a clear evaluation of the relationship between HCC differentiation and PSMA involvement. However, PSMA uptake was significantly higher than ^{18}F-FDG uptake in our patients with well-differentiated HCC. In our patient with less differentiated HCC, ^{18}F-FDG, and PSMA uptakes were found to be similar compared with the background activity. Low ^{18}F-FDG uptake is an expected finding in patients with well-differentiated and moderately differentiated HCC, and our findings on the relationship between HCC differentiation and ^{18}F-FDG involvement are consistent with the literature (25). Since there are no studies in the literature, no correlation could be made between PSMA PET/CT and HCC differentiation.

In this preliminary study, no relationship was found between ^{68}Ga-PSMA tumor uptake and serum AFP level, suggesting that tumor angiogenesis and AFP production are independent parameters in HCC.

Study Limitations

First limitation of the current study is the relatively small number of patients, although our population is similar to other prospective studies in the literature. Second, not all patients had a histopathologically confirmed diagnosis, and some patients were diagnosed according to typical radiological findings.

Conclusion

^{68}Ga-PSMA PET/CT is superior to ^{18}F-FDG PET/CT in the diagnosis and staging of HCC. These preliminary findings show that ^{68}Ga-PSMA PET/CT has a supportive role for MRI in T staging, especially in demonstrating multicentric tumors, and it can be superior to MRI in demonstrating extrahepatic involvement. High PSMA uptake is promising for PSMA-targeted radionuclide treatments in metastatic HCC, which responds poorly to standard chemotherapy regimens. ^{68}Ga-PSMA PET/CT may also be helpful in evaluating treatment response, warranting further prospective studies in this area.

Ethics

Ethics Committee Approval: The Local Ethics Committee of İstanbul Training and Research Hospital approved this study under the decision number: 2018/1297.

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.G., Concept: N.E., C.G., Design: C.G., T.F.Ç., Ö.K., Data Collection or Processing: R.U.G., M.S.Ç., C.G., T.A., Analysis or Interpretation: C.G.,Ö.K., N.E., M.S.Ç., Literature Search: R.U.G., T.A., Writing: C.G., T.F.Ç.

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

Financial Disclosure: The authors declared that this study has received no financial support.

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