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The Role of ^{18}F-FLT PET/CT in Assessing Early Response to Transarterial Radioembolization and Chemoembolization in Patients with Primary and Metastatic Liver Tumors

Primer ve Metastatik Karaciğer Tümörlü Hastalarda Transarteriyel Radyoembolizasyon ve Kemoembolizasyona Erken Yanıtı Değerlendirmede ^{18}F-FLT PET/BT'nin Rolü

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Abstract

Objectives: Metastases and primary malignancies are common in the liver. Local ablative applications such as transarterial chemoembolization (TACE), and transarterial radioembolization (TARE) provide minimally invasive and safe treatment in unresectable liver tumors. Early detection of response to treatment prevents unnecessary toxicity and cost in non-responder patients and provides an earlier use of other options that may be effective. This study aimed to identify the role of ^{18}F-fluorothymidine (FLT) positron emission tomography/computed tomography (PET/CT) in the assessment of early response to TACE and TARE treatments in patients with unresectable primary and metastatic liver tumors.
Methods: This single-center study included 63 patients who underwent ^{18}F-FLT PET/CT for response evaluation after TACE and TARE. After excluding 20 patients whose data were missing 43 TARE-receiving patients were analyzed. The compatibility of change in semi-quantitative values obtained from the ^{18}F-FLT PET/CT images with the treatment responses detected in ^{18}F-fluorodeoxyglucose PET/CT, CT, and MR images and survival was evaluated.
Results: There was no correlation between early metabolic, morphological response, and ^{18}F-FLT uptake pattern, and change in standardized uptake values (SUV) which were ΔSUV_{max}, ΔSUV_{mean}, ΔSUV_{peak}., ΔSUV_{mean}, ΔSUV_{peak} values. There was no significant correlation between ^{18}F-FLT uptake pattern, ΔSUV_{max}, ΔSUV_{mean}, ΔSUV_{peak}, and overall survival, progression-free survival (PFS) for the target lobe PFS for the whole-body. The survival distributions for the patients with >30% change in ΔSUV_{max} and ΔSUV_{peak} values were statistically significantly longer than the patients with <30% change ($p<0.009$ and $p<0.024$, respectively).
Conclusion: There was significant longer PFS for target liver lobe in patients with more than 30% decrease in ^{18}F-FLT SUV_{max} and SUV_{peak} of the liver lesion in primary and metastatic unresectable liver tumors undergoing TARE.

Keywords: ^{18}F-FLT PET/CT, early response, primary, metastatic, chemoembolization, liver tumors, radioembolization, TACE, TARE

Öz

Amaç: Karaciğer hem metastazların hem de primer malignitelerin sık görüldüğü bir organdır. Transarteriyel kemoembolizasyon (TAKE) ve transarteriyel radyoembolizasyon (TARE) gibi lokal ablatif uygulamalar, rezeke edilemeyen karaciğer tümörlerinde minimal invaziv ve güvenli tedavi sağlar. Tedaviye yanıtın erken tespiti, yanıt vermeyen hastalarda gereksiz toksisiteyi ve maliyeti önlerken etkili olabilecek diğer seçeneklerin

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daha erken kullanılmasını sağlar. Bu çalışmada, rezeke edilemeyen primer ve metastatik karaciğer tümörlü hastalarda TAKE ve TARE tedavilerine erken yanıtın değerlendirilmesinde ^{18}F-FLT pozitron emisyon tomografisi/bilgisayarlı tomografinin (PET/BT) rolünün belirlenmesi amaçlanmıştır. **Yöntem:** Tek merkezli bu çalışmaya, TARE ve TAKE tedavileri öncesi ve sonrasında ^{18}F-FLT PET/BT inceleme yapılarak yanıt değerlendirmesi yapılan 63 hasta dahil edilmiştir. Verileri eksik olan 20 hasta dışlanarak 43 TARE alan hasta analiz edilmiştir. ^{18}F-FLT PET/BT görüntülerinden elde edilen semi-kantitatif değerlerdeki değişimin ^{18}F-florodeoksiglukoz PET/BT, BT ve MR görüntülerinde saptanan tedavi yanıtları ile uyumluluğu ve sağkalımlarla ilişkisi araştırılmıştır.

Bulgular: Erken metabolik, morfolojik yanıt ile ^{18}F-FLT tutulum paternindeki değişim, ΔSUV_{maks}, ΔSUV_{mean}, ΔSUV_{peak} olarak ifade edilen SUV değerlerindeki değişim arasında korelasyon saptanmamıştır. ^{18}F-FLT tutulum paterninde değişim, ΔSUV_{maks}, ΔSUV_{mean} ve ΔSUV_{peak} değerleri ile genel sağkalım, tüm vücut ve hedef lob için progresyonsuz sağkalım (PFS) arasında anlamlı ilişki gözlenmemiştir. ΔSUV_{maks} ve ΔSUV_{peak} değerlerinde >%30 değişiklik olan hastaların hedef lob için PFS'leri <%30 değişiklik olanlardan istatistiksel olarak anlamlı düzeyde uzun saptanmıştır (sırasıyla; p<0,009 ve p<0,024). **Sonuç:** TARE uygulanan primer ve metastatik rezektabl olmayan karaciğer tümöründe karaciğer lezyonunun ^{18}F-FLT SUV_{maks} ve SUV_{peak}'inde >%30 azalma olan hastalarda hedef karaciğer lobu için daha uzun PFS saptanmıştır.

Anahtar kelimeler: ^{18}F-FLT PET/BT, erken yanıt, primer, metastatik, kemoembolizasyon, karaciğer tümörleri, radyoembolizasyon, TAKE, TARE

Introduction

Both metastases and primary malignancies, such as hepatocellular carcinoma (HCC) and cholangiocellular cancer, are common in the liver. Metastases are the most common liver malignancy, and leading tumors metastasize to the liver are colorectal cancer, neuroendocrine tumors, other gastrointestinal cancers, and breast cancer. HCC is the sixth common cause of cancer and the third common cause of cancer-related deaths worldwide (1,2). Since the liver involvement is effective on survival, curative surgical applications are the first-line therapy, either with adjuvant chemotherapy or alone, providing the most significant survival advantage. However, surgery cannot be applied to most patients at diagnosis or tumor recurrence due to advanced-stage disease or inappropriate clinical status (1,3). Local ablative applications such as radiofrequency, microwave, and cryo-ablation, irreversible electroporation (IRE), endovascular transarterial chemoembolization (TACE), and transarterial radioembolization (TARE) provide minimally invasive and safe treatment (4,5,6,7,8). It has been reported that TARE and TACE provide long-term survival advantage and low toxicity, especially in patients with good performance and low tumor burden (5,7,8,9,10,11).

The prediction or early detection of response to therapy prevents unnecessary toxicity and cost that may be life-threatening in non-responder patients and provides an earlier use of other treatment options that may be effective. The morphological response evaluation with computed tomography (CT) and magnetic resonance (MR) requires a relatively long period and tumor shrinkage. Positron emission tomography (PET)/CT or PET/MR hybrid imaging, based on metabolic processes, provides earlier response assessment and concurrent anatomical information. ^{18}F-fluorodeoxyglucose (FDG) is the most commonly used agent in PET imaging (12,13,14,15,16). However, since tumors with low-glucose metabolism and low cellularity, small-sized and well-differentiated tumors show low ^{18}F-FDG uptake, alternative agents such as thymidine analog 3'-deoksy-(F-18)-3´-fluorotimidin (^{18}F-FLT), which reflects the proliferation of cells, ^{11}C-acetate, which reflects hypoxia, C11-choline or ^{18}F-choline, which reflects aerobic metabolism (fatty acid synthesis) are being investigated (15,17,18,19,20,21,22,23).

^{18}F-FLT, an analog of thymidine, is phosphorylated with thymidine kinase-1 (TK1) and is converted to ^{18}F-FLT-monophosphate, which cannot penetrate DNA and is trapped in the cytosol. ^{18}F-FLT is a TK1-specific substrate that increases in proliferating cells while not found in silent cells and correlates with a proliferation marker Ki-67 index (24,25). Imaging with ^{18}F-FLT has advantages such as non-invasive quantitation of cell proliferation, three-dimensional tumor imaging, and evaluating the whole tumor proliferation heterogeneity in multiple tumor areas simultaneously. Studies show that tumor proliferation changes can be detected early with ^{18}F-FLT PET/CT after radiotherapy (1,2,3). Knowing that TARE is an internal radiotherapy method, this study aimed to describe the role of ^{18}F-FLT PET/CT in assessing the early response to TARE and TACE in patients with primary and metastatic liver tumors.

Materials and Methods

Ankara University Faculty of Medicine Human Research Ethics Committee Approval (İ3-117-19) was obtained for this single-center study with prospective and retrospective components and was performed under the Helsinki Directive and Good Clinical Practices Guidelines. Informed consent was obtained from all volunteers included in the study.

Patients

The inclusion criteria of this study were TACE or TARE therapy for histologically/cytologically or radiologically diagnosed

primary (HCC, cholangiocellular carcinoma) or metastatic liver tumor; staged with CT/MR, ^{18}F-FDG PET/CT, or PET/MR; Eastern Cooperative Oncology Group performance score ≤2; over 18 years of age; follow-up more than three months; available data. Patients with claustrophobia and pain that prevent imaging and patients who did not want to participate in the study were excluded. There was no intervention in the treatment selection or management of the patients. According to the standard evaluations, the relevant specialist (medical oncology, gastroenterology specialist, or general surgeon) chose the treatment.

^{18}F-FLT and ^{18}F-FDG PET/CT Imaging

The presence or history of systemic or local ablative therapy, chronic disease, etc., can affect the evaluation was questioned and noted. To reduce the total body radiation dose and increase the image quality, oral hydration and emptying of the bladder before imaging was provided. Approximately 60 min after the ^{18}F-FDG and ^{18}F-FLT were given intravenously, the whole-body PET/CT imaging was performed starting 60 min after injection. Following at least 6 hours of fasting, when blood glucose level was <150 mg/dL, ~4-5 MBq/kg ^{18}F-FDG was administered. Approximately 60 min after the administration of radiopharmaceutical, whole-body PET/CT images were obtained. FLT was synthesized in-house according to standard procedures (25). After administration of 3.4-9.3 mCi ^{18}F-FLT intravenously, the whole-body PET/CT imaging was performed starting 60 min after injection (26,27,28,29,30). Following CT for attenuation correction, and anatomical correlation, whole-body PET images were obtained, in the supine position, from the vertex to the middle thigh, and 3 min per bed. PET/CT Discovery ST (GE Healthcare Waukesha, Wisconsin, USA) was used for PET/CT hybrid imaging. After assessing maximum intensity projection, cross-sectional and fusion images, areas with high, mixed (heterogeneous), equal and low uptake from adjacent liver parenchyma were noted. The same parameters and assessments were used for ^{18}F-FDG and ^{18}F-FLT imaging, which were performed twice, before the treatment as baseline and for response evaluation after therapy.

The target lesion was defined as sole or the largest lesion in the target lobe. Standardized uptake values (SUV): SUV_{max}, SUV_{mean}, SUV_{peak} were calculated automatically for hypermetabolic and heterogeneous (mixed) target lesions on a workstation by using PET software (GE Healthcare). A 2 cm region of interest was manually defined for isometabolic, and hypometabolic target lesions on the summed images by using the same software. Since the reference (non-tumoral) liver parenchymal SUV values of the patients showed a significant difference both between the patients and the baseline and post-treatment images of the same patient, the target background ratio (TBR) of the target lesions were calculated by proportioning the SUV values of the target lesion to reference values and were evaluated separately. Reference SUV values were calculated by manually placing a 2 cm region of interest in the liver in a tumor-free area to measure background liver activity (26,28,29,30). Patients were divided into groups with and without the change of SUV values calculated from the difference between the target lesion's post-treatment and pre-treatment SUV values, which were calculated and referred to as delta (Δ) SUV values.

Statistical Analysis

The changes between baseline and post-treatment ^{18}F-FLT PET/CT images were compared to the responses detected with ^{18}F-FDG PET/CT and CT/MRI, evaluated according to the PERCIST and RECIST 1.1 criteria, respectively, and progression-free survival (PFS) and overall survival (OS). All statistical analyses were performed using IBM SPSS for Windows, version 25.0 (SPSS, Armonk, NY: IBM Corp.). Kolmogorov-Smirnov test was used to assess the assumption of normality. The continuous variables that did not have a normal distribution were expressed as medians (minimum-maximum). For non-normally-distributed continuous variables, differences between groups were tested using Mann-Whitney U test and Kruskal-Wallis test. Lastly, Pearson chi-square analysis and Fisher's Exact test determined associations between categorical variables, while Pearson and Spearman correlation analysis determined associations between continuous variables. The survival times of groups were obtained using Kaplan-Meier analysis and the difference in survival times between groups were compared with the Log Rank test. A two-sided p value <0.05 was considered as statistically significant.

Results

Patients

Sixty-three consecutive patients were included in the study between December 2018 and January 2020, who underwent pre- and post-treatment ^{18}F-FLT PET/CT to evaluate their response to TARE and TACE treatments. Although all patients underwent baseline imaging, 4 of the TACE-receiving patients and 16 of the TARE-receiving patients could not undergo ^{18}F-FLT PET/CT or other imaging for response evaluation either due to decreased performance status that hindered further procedure or death. Since the patients who received TACE did not

undergo PET/CT or CT/MRI to evaluate the response to treatment, and most of their data were missing TACE-receiving patients were excluded from the analysis. Forty-three TARE-receiving patients were analyzed to have a homogenous population and statistical analysis. Detailed patient characteristics are listed in Table 1.

^{18}F-FLT, ^{18}F-FDG PET/CT and CT/MRI

Other than one patient who did not undergo ^{18}F-FDG PET/CT scanning for response evaluation because of the tumor's ^{18}F-FDG non-avidity at the baseline, all remaining patients underwent ^{18}F-FLT PET/CT, ^{18}F-FDG PET/CT, and CT/MR before and after TARE. The morphological response evaluation was performed with contrast-enhanced CT for 2 patients and with contrast-enhanced MR for 41 patients. Imaging characteristics of ^{18}F-FLT PET/CT are given in Tables 2, 3; characteristics of ^{18}F-FDG PET/CT and CT/MRI are given in Table 2. ^{18}F-FLT PET/CT, ^{18}F-FDG PET/CT, and contrast-enhanced liver MR of a patient with ^{18}F-FDG non-avid, persistent ^{18}F-FLT avid lesions and progressive disease are presented in Figure 1.

Correlation between the diagnosis, longest diameter of the target lesion, volume and percentage of tumors in the target lobe, age, the number of lesions in the target lobe, early metabolic, morphological response and ^{18}F-FLT visual change, ΔSUV_{max}, ΔSUV_{mean}, ΔSUV_{peak}, $\Delta SUV_{max}TBR$, $\Delta SUV_{mean}TBR$, and $\Delta SUV_{peak}TBR$ values were not significant. Calculated p values from statistical analyses are presented in Table 4.

Survival

During 18.4 months follow-up, 22 patients died. OS was median 7.0 (3.3-17.4) months, PFS was median 3.4 (1.3-17.4) months for the target lobe; and median 3.2 (1.3-17.4) months for whole-body. There was no significant correlation between ^{18}F-FLT visual change, ΔSUV_{max}, ΔSUV_{mean}, ΔSUV_{peak}, $\Delta SUV_{max}TBR$, $\Delta SUV_{mean}TBR$, and $\Delta SUV_{peak}TBR$ and OS, PFS for target lobes, and PFS for whole-body (Table 4). A log-rank test was run to determine whether there were differences in the target lobe's PFS distribution for the ΔSUV_{max} and ΔSUV_{peak} groups when the cut-off >30% change was applied. The target lobe's PFS for the patients with a >30% decrease in SUV_{max} was significantly longer than those without [350±57 days 95% confidence interval (CI) 238-463 vs. (130±21 days 95% CI 90-171 (χ^2 (1): 6.774) p=0.009]. The target lobe's PFS for the patients with more than 30% change in SUV_{peak} was statistically significantly longer than the patients with <30% change [338±59 days 95% CI 222-453 vs. 1730±38 days 95% CI 98-247 χ^2 (1): 5.095, p=0.024]. Estimated survival chance at 209th day was 0.549±0.129 for 17 patients with no change in SUV_{max}, while the estimated survival chance at 92nd day was 0.500±0.098 in patients with more than 30%

Table 1. Patient characteristics

Characteristics	Median (minimum-maximum)	n=43	%
Gender			
Male	-	30	70
Female	-	13	30
Age	63 (38-79) years	-	-
Underlying liver disease			
Yes	-	15	35
No	-	28	65
Previous treatments			
Surgery	-	5	12
RFA	-	3	7
TACE	-	4	9
TARE	-	1	2
Chemotherapy alone	-	14	36
Chemotherapy + LRT	-	4	9
None	-	12	-
Microsphere			
Resine	0.65 (0.6-1.3) GBq	6	14
Glass	6.5 (3-18) GBq	37	86
Target lobe			
Right	-	34	79
Left	-	8	19
Transplanted liver	-	1	2
Primary tumor			
HCC	-	17	40
Klatskin	-	7	16
Colon	-	14	32.5
Gastric	-	2	4.6
Breast	-	2	4.6
Pancreas	-	1	2.3
Presence of primary tumor for liver metastasis			
Yes	-	3	16
No	-	16	37
Extrahepatic metastases			
Yes	-	20	47
No	-	23	54
The largest diameter of target lesion			
Pre-treatment	49.7 (8-190) mm	-	-
Post-treatment	60.3 (9-190) mm	-	-
Number of lesions on target lobe			
1	-	11	26

Table 1. Continued			
1-5	-	11	26
5-10	-	7	16
>10	-	14	32
Tumor volume percent on target lobe	14 (1-100) %	-	-
Event after TARE			
Alive-disease progression	-	13	30
Alive-partial response or stable disease	-	8	19
Died due to disease progression/other causes	-	14	32
Died due to liver failure	-	8	19

HCC: Hepatocellular carcinoma, LRT: Locoregional therapy, RFA: Radiofrequency ablation, TACE: Transarterial chemoembolization, TARE: Transarterial radioembolization

decrease in SUV_{max}. Estimated survival proportion at 209th days were 0.514±0.134 in 16 patients without change in SUV_{peak} value; while this proportion was 0.519±0.096 at 90th day for the patients with more than 30% decrease in SUV_{peak} value (Figure 2, Table 4).

Discussion

This study assessed the role of PET/CT with ^{18}F-FLT, a radiopharmaceutical reflecting cell proliferation, in response evaluation after TARE and found significant longer PFS for the target liver lobe in patients with more than 30% decrease in ^{18}F-FLT SUV_{max} and SUV_{peak} of the target liver lesion. There was no significant relationship between SUV values and treatment response.

Although there are metabolic and morphological techniques used for assessing treatment response, there is no standard response evaluation and follow-up protocol for TARE. Response evaluation after TARE is performed at different times with PET/CT, CT, or MR depending on the center's practice. Since response assessment with CT and MRI takes a longer time and has their limitations, PET/CT and PET/MR, functional, molecular and anatomical imaging techniques, are used for early response evaluation with agents that reflect tumor-specific metabolism (13,14,15,16,18,21,22,23). ^{18}F-FDG PET/CT is the most common metabolic imaging method due to increased glucose metabolism in many types of cancer. ^{18}F-FDG PET/CT can be used to assess treatment response in poorly differentiated and high-grade tumors. However, since small and well-differentiated tumors (such as HCC, NET) show low or no ^{18}F-FDG uptake due to low glucose metabolism and cellularity, imaging with new-tumor-specific agents is needed (13,16,21,22,23). PET/CT imaging with ^{18}F-FLT, which reflects cell proliferation, is a non-invasive imaging

Table 2. ^{18}F-FLT PET/CT, ^{18}F-FDG PET/CT and CT/MRI characteristics

Characteristics	Median (minimum-maximum	n=43	%
Time from pretreatment ^{18}F-FLT PET/CT to TARE	8 (1-63) days	-	-
Administered activity for pretreatment ^{18}F-FLT PET/CT	6.4 (4.6-10.4) mCi	-	-
Pretreatment ^{18}F-FLT PET/CT	-	**43**	-
Hypermetabolic lesions	-	6	14
Mixed uptake pattern	-	5	12
Isometabolic	-	13	30
Hypometabolic	-	19	44
Time from TARE to post-treatment ^{18}F-FLT PET/CT	48 (33-73) days	-	-
Administered activity for post-treatment ^{18}F-FLT PET/CT	6.4 (3.4- 9.3) mCi	-	-
Post-treatment ^{18}F-FLT PET/CT	-	**43**	-
Hypermetabolic lesions	-	2	5
Mixed uptake pattern	-	2	5
Isometabolic	-	12	28
Hypometabolic	-	27	62
Visual change of target lesions on ^{18}F-FLT PET/CT			
Yes	-	24	56
No	-	19	44
Persistant hypermetabolic	-	2	5
Hypermetabolic mixed uptake	-	1	2
Hypermetabolic isometabolic	-	1	2
Hypermetabolic hypometabolic	-	2	5
Persistant mixed uptake	-	1	2
Mixed uptake hypometabolic	-	4	10
Persistant isometabolic	-	12	28
Isometabolic hypometabolic	-	1	2
Persistant hypometabolic	-	19	44
Time from pretreatment ^{18}F-FDG PET/CT to TARE	15 (1-64) days	**43**	-
Time from TARE to post-treatment ^{18}F-FDG PET/CT	47 (34-72) days	**42**	-
Post-treatment ^{18}F-FDG PET/CT response assessment on target lobe			
Complete response	-	5	12
Partial response	-	13	
Stable disease	-	14	
Progressive disease	-	10	
Time from pretreatment CT/MR to TARE	13 (1-79) days	43	
Time from TARE to post-treatment CT/MR	97 (46-171) days	43	
Post-treatment CT/MR response assessment on target lobe			
Complete response	-	2	4
Partial response	-	7	16
Stable disease	-	17	40
Progressive disease	-	17	40

CT: Computed tomography, FLT: Fluorothymidine, ^{18}F-FDG: ^{18}F-fluorodeoxyglucose, MRI: Magnetic resonance imaging, PET/CT: Positron emission tomography/computed tomography, TARE: Transarterial radioembolization

Table 3. ^{18}F-FLT PET/CT values	
SUV value	**Median (minimum-maximum)**
Pre-treatment ^{18}F-FLT PET/CT	
SUV_{max}	6.7 (2.7-22) g/mL
SUV_{mean}	4.4 (1.1-12.4) g/mL
SUV_{peak}	4.9 (1-18.2) g/mL
SUV_{max}TBR	0.9 (0.3-3.0)
SUV_{mean}TBR	0.8 (0.2-2.4)
SUV_{peak}TBR	0.9 (0.1-3.2)
Post-treatment ^{18}F-FLT PET/CT	
SUV_{max}	5.9 (2.5-31.9) g/mL
SUV_{mean}	3.6 (0.9-14.9) g/mL
SUV_{peak}	4.9 (1-26.5) g/mL
SUV_{max}TBR	0.7 (0.3-3.8)
SUV_{mean}TBR	0.6 (0.1-3.3)
SUV_{peak}TBR	0.7 (0.1-4.1)
Difference between pre- and post-treatment ^{18}F-FLT values	
ΔSUV_{max}	-2.0 (-9.3-25.2)
ΔSUV_{mean}	0.9 (-8.1-17.1)
ΔSUV_{peak}	-2.0 (-8.2 -21.2)
ΔSUV_{max}TBR	-1.0 (-1.3-0.8)
ΔSUV_{mean}TBR	0 (-1.5-0.9)
ΔSUV_{peak}TBR	0 (-1.4-1.0)

FLT: Fluorothymidine, SUV_{max}: Maximum standard uptake value, SUV_{mean}: Mean standard uptake value, SUV_{peak}: Peak standard uptake value, TBR: Tumor background rate, PET/CT: Positron emission tomography/computed tomography

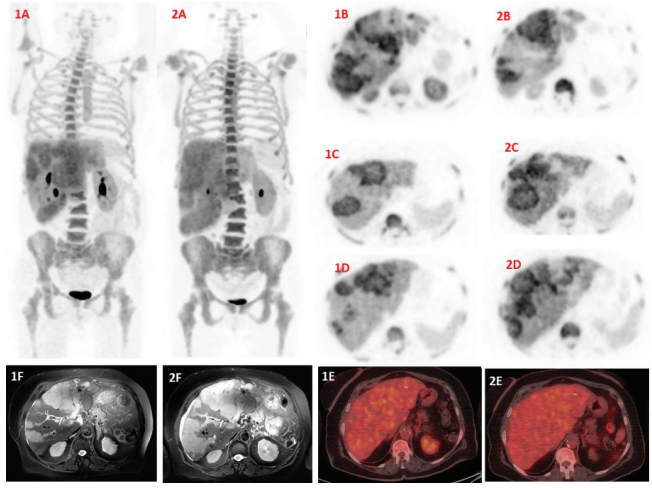

Figure 1. ^{18}F-FLT PET MIP images before (1A) and after (2A) TARE therapy of a 70 years old female patient with HCC. Axial ^{18}F-FLT PET images revealed hypermetabolic liver lesions (SUV_{max}: 16.1) before embolization (1B, 1C, 1D); post-therapy images revealed decreased activity on the left liver lobe, but most of the lesions were still hypermetabolic (SUV_{max}: 16.4) (2B, 2C, 2D). Pretreatment MR revealed multiple contrast-enhanced tumoral foci; after treatment, there were new lesions and progression on all lesions. T2-weighted MR shows multiple foci on both lobes before (1F) and after (2F) therapy. Tumoral foci were ^{18}F-FDG non-avid (1E) and non-avidity did not change after TARE (2E)
FLT: Fluorothymidine, MIP: Maximum intensity projection, PET: Positron emission tomography, TARE: Transarterial radioembolization, SUV_{max}: Maximum standard uptake value, MR: Magnetic resonance

method and has been used for the response evaluation (24,25,26,27). In addition to complex and competing factors in the FLT uptake mechanism, there are notable differences between patient preparation, imaging time after injection, protocol, amount of injected activity, reconstruction method, analysis techniques, timing before and after treatment, patient numbers, and disease groups in studies with F-^{18}FLT PET/CT (24,25,26,27,28,29,30,31,32).

As far as it is known, this is the first study to investigate the role of ^{18}F-FLT PET/CT in the early response evaluation after TARE. There are few studies investigating the role of FLT PET/CT in evaluating the liver-specific treatment response, considering high background liver uptake especially in HCC patients that hamper the detection of liver/lesions. Studies evaluated therapy of TACE-receiving HCC patients and systemic chemotherapy-receiving liver metastatic colorectal cancer patients (28,29,32).

Sharma et al. (32) investigated the role of ^{18}F-FLT PET/CT in assessing treatment response to TACE in HCC patients. They used temporal-intensity voxel clustering [kinetic spatial filtering (KSF)] in lesion detection to overcome high background liver signal and thus ^{18}F-FLT uptake but they could not achieve improvement in lesion detection by applying it. They reported 73% detection rate for pretreatment ^{18}F-FLT PET, and 30% reduction in mean ^{18}F-FLT PET uptake after TACE. In the current study, KSF could not be used due to unavailability, target lesion based detection rate for pretreatment ^{18}F-FLT PET/CT was 53% (9/17) for HCC patients. In our study, although the change in ^{18}F-FLT SUV_{max}, SUV_{mean} and SUV_{peak} values (Table 3) had no significant relationship with treatment response; patients with more than 30% decrease in ^{18}F-FLT SUV_{max} and SUV_{peak} of the target lesion had significant longer PFS for target liver lobe after TARE.

Mogensen et al. (29) investigated the role of ^{18}F-FLT PET/CT in patients with at least one measurable colorectal cancer liver metastasis and received first-line chemotherapy. They reported a reduction in ^{18}F-FLT uptake in 85% patients, whereas there was no relationship between the early change in measured ^{18}F-FLT SUV_{max}, and RECIST 1.1 based response. In this study, similar to their study, there was no relationship between the change in SUV values (ΔSUV_{max}, ΔSUV_{mean}, and ΔSUV_{peak}) and RECIST 1.1 and PERCIST-based responses. Contractor et al. (28) investigated the role of ^{18}F-FLT PET/CT in evaluating the

Table 4. Statistical analysis of ^{18}F-FLT PET/CT values	
Parameter	**p value**
Visual change-early response	0.930[a]
Visual change-anatomical response	0.710[a]
^{18}F-FLT SUV values-early response	
ΔSUV_{max}	0.290[a]
ΔSUV_{mean}	0.100[b]
ΔSUV_{peak}	0.430[a]
ΔSUV_{max}TBR	0.600[a]
ΔSUV_{mean}TBR	0.270[a]
ΔSUV_{peak}TBR	0.280[a]
^{18}F-FLT SUV values-anatomical response	
ΔSUV_{max}	0.450[b]
ΔSUV_{mean}	0.660[c]
ΔSUV_{peak}	0.450[b]
ΔSUV_{max}TBR	0.400[b]
ΔSUV_{mean}TBR	0.400[b]
ΔSUV_{peak}TBR	0.400[a]
Overall survival-SUV values, visual change	
ΔSUV_{max}	0.630[c]
ΔSUV_{mean}	0.160[c]
ΔSUV_{peak}	0.870[c]
ΔSUV_{max}TBR	0.210[c]
ΔSUV_{mean}TBR	0.260[c]
ΔSUV_{peak}TBR	0.590[c]
Visual change	0.690[c]
Progression free survival for target lobe	
ΔSUV_{max} [§]	0.009[c]
ΔSUV_{mean} [§]	0.190[c]
ΔSUV_{peak} [§]	0.024[c]

[a]Pearson chi-Square, [b]Fisher's Exact test, [c]Log Rank(Mantel-Cox), [§]if >30% percent change accepted as significant, FLT: Fluorothymidine, SUV_{max}: Maximum standard uptake value, SUV_{mean}: Mean standard uptake value, SUV_{peak}: Peak standard uptake value, TBR: Tumor background rate, PET/CT: Positron emission tomography/computed tomography

treatment response of breast and colorectal cancer liver metastases. They reported that SUV_{ave} and SUV_{max} showed a significant decrease in responders two weeks after the first-line chemotherapy, and the change in FLT uptake can distinguish those who responded to the treatment from non-responders. In our study, ^{18}F-FLT PET/CT was evaluated for the treatment response after TARE, an locoregional therapy (LRT), not a systemic treatment and there was no significant difference in the change in SUV_{max}, SUV_{mean}, and SUV_{peak} values among responder and non-responders.

The key point in the early evaluation of the treatment response is to distinguish non-responder to discontinue unnecessary treatment, thus avoid toxicity and cost. It is critical to distinguish the resectable disease from those who require more aggressive treatment. Patients with shrinkage of tumors up to 30% are considered to have stable disease, according to RECIST 1.1, and are unresponsive to treatment (12,13,15,16). In this study, tumor sizes of patients with stable disease decreased, reflecting the beneficial effect of the treatment. However, since this decrease in size remained below the RECIST 1.1 response criteria, it was accepted as a stable disease and unresponsive to treatment. It should be recognized that patients with stable disease, especially with colon cancer, are accepted as responders and continue to receive systemic treatment in clinical practice (33). Generally, chemotherapy-refractory liver metastases are referred for LRTs such as TARE. Thus, even defined stable disease can provide longer survival and can be accepted as responsive. If patients with stable disease are accepted as responders to therapy, statistical analysis can be found significantly in long-term follow-up results. Because liver resection was not performed on any patient after radioembolization, except for the transplantation patient, post-treatment histopathological tumor changes, background of persistent ^{18}F-FLT hypometabolism and correlation of histopathology with ^{18}F-FLT values could not be evaluated.

It can be argued that the timing of the ^{18}F-FLT was not right. But, TARE is an internal radiotherapy procedure, and response to radiotherapy is generally evaluated later than chemotherapy/selective systemic therapies (27,30). ^{18}F-FDG PET/CT and ^{18}F-FLT PET/CT imaging were done approksimately ≥4 weeks after the procedure. Studies evaluating radiotherapy response revealed a significant relationship between ^{18}F-FLT PET/CT and response or survival in patients with head-neck, esophageal, breast, lung, rectal, etc., cancer (30). This study distinguished real responders from non-responders who were grouped based on post-radiotherapy response assessment techniques ^{18}F-FDG PET/CT and CT or MR. No correlation was found between the semi-quantitative values such as ΔSUV_{max}, ΔSUV_{mean}, ΔSUV_{peak}, SUV_{max}TBR, SUV_{mean}TBR, and SUV_{peak}TBR values calculated from ^{18}F-FLT PET/CT images. There was a significant relationship with PFS for target liver lobe and >30% decrease in ^{18}F-FLT SUV_{max} and SUV_{peak} of the target lesion.

Study Limitations

The most significant limitations of this study are the small sample size, consequent heterogeneous patient population, and the small number of patients who responded to the therapy. Therefore, in statistical analysis, results reaching

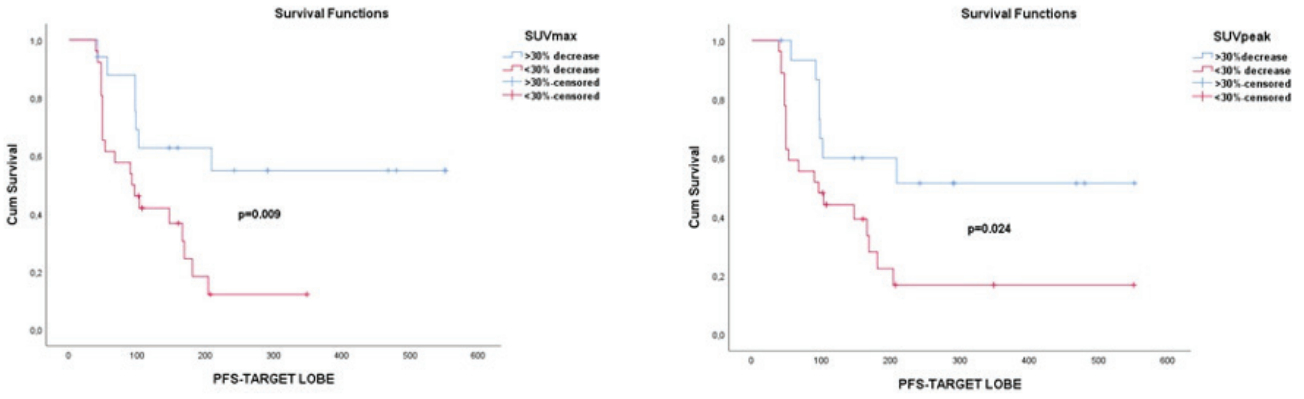

Figure 2. Kaplan-Meier method with log-rank test results revealing a significant difference in progression free survival distribution of target lobe for the patients with and without >30% change in SUV_{max} (p=0.009) and SUV_{peak} (p=0.024)
SUV_{max}: Maximum standard uptake value, SUV_{peak}: Peak standard uptake value, PFS: Progression free survival

a significant degree could not be obtained for SUV parameters. TARE candidate patients have different clinical scenarios, such as highly variable liver lesion number and size, disease stage, history of single or multi-step systemic treatment, liver resection, transplant, and LRT's. Also, since there is a clear difference in disease etiologies, clinical and radiological status, it was not possible to standardize the patient group. Reproducible and re-applicable clinical data from a larger and standardized patient population are required to assess the role of [18]F-FLT PET/CT in the evaluation of response to TARE treatment.

Conclusion

This study found significantly longer PFS for the target liver lobe in patients with more than 30% decrease in [18]F-FLT SUV_{max} and SUV_{peak} of the liver lesion in patients with primary and metastatic unresectable liver tumors undergoing TARE. The changes in [18]F-FLT PET/CT SUV_{max}, SUV_{mean}, SUV_{peak}, SUV_{max}TBR, SUV_{mean}TBR, and SUV_{peak}TBR values had no significant relationship with response in [18]F-FDG PET/CT or in contrast-enhanced CT/MR after TARE. [18]F-FLT PET/CT can be used as an alternative/complementary imaging method to [18]F-FDG PET/CT in the early evaluation of the treatment response in patients undergoing TARE for primary or secondary liver tumor.

Ethics

Ethics Committee Approval: Ankara University Faculty of Medicine Human Research Ethics Committee Approval (İ3-117-19).

Informed Consent: Informed consent was obtained from the volunteers included in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.S.B., E.C.Ç., D.N., Concept: D.N., N.Ö.K., M.S.B., E.C.Ç., Design: D.N., N.Ö.K., Data Collection or Processing: D.N., Analysis or Interpretation: S.H., D.N., Literature Search: D.N., N.Ö.K., Writing: D.N., N.Ö.K., K.M.K.

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