

The Contribution of Contrast Enhanced CT to FDG PET on Characterization of Liver Lesions and It's Quantitative Effects

Kontrastlı BT'nin Karaciğer Lezyonlarının Karakterizasyonunda FDG PET'e Katkısı ve Kantitatif Etkileri

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Abstract

Background: The goals of this study was to evaluate the diagnostic capability of enhanced/unenhanced 18F-FDG-PET/CT scans for identifying primary-secondary liver malignancies in terms of size and localization, to decide the quantitative impact of contrast agent on the SUVmax values of liver lesions and normal liver tissue, and to assess the impact in SUVmax metrics following contrast substance administration.

Materials and Methods: This was a prospective research that included patients with suspicious primary and secondary hepatic cancers. Patients had non-enhanced & enhanced regional PET/CT examinations. The dimension, position, densities (HU), visually assessment outcome, and SUVmax values for all pathological lesions were recorded, as well as the HU and SUVmax data of normal hepatic tissue.

Results: There were 97 liver lesions in total. Visually assessment outcome of lesions, the introduction of a contrast substance considerably enhanced the HU and SUVmax measurements for normal hepatic tissue. The HU measurements for lesions bigger than 1cm increased statistically significantly, as did the SUVmax levels of centralized lesions bigger than 1cm. The attenuation adjustment procedures, resulted in an average inaccuracy in computed SUVmax values at the ratio of %5 for normal liver tissue and %6 for all hepatic pathologies following the contrast substance delivery.

Conclusions: The inclusion of contrast substance increases the identification, localization, and characterization of the liver lesions with PET/CT substantially.

Key Words: Contrast material, PET/CT, Liver lesion

Öz

Amaç: Çalışmadaki amaçlarımız, primer-sekonder karaciğer malignitelerinin boyut, lokalizasyon açısından saptanması için kontrastlı/kontrastsız 18F-FDG-PET/BT taramalarının tanısal etkinliğini karşılaştırmak, kontrast maddenin karaciğer lezyonlarının ve normal karaciğer dokusunun SUVmaks değerlerindeki kantitatif etkilerini araştırmak, kontrast madde uygulamasından sonra SUVmaks ölçümlerindeki hata düzeyini belirlemektir.

Materyal ve Metod: Bu çalışma, primer-sekonder karaciğer malignitesi şüphesi olan bireyleri içeren prospektif çalışmadır. Hastalara bölgesel kontrastsız ve kontrastlı PET/BT taramaları yapılmıştır. Malign kabul edilen lezyonların boyutu, lokalizasyonu, dansitesi, görsel derecelendirme skoru, SUVmaks değerleri ile normal karaciğer dokusunun HU, SUVmaks değerleri kaydedilmiştir.

Bulgular: Toplam 97 karaciğer lezyonu tespit edildi. Lezyonların görsel derecelendirme skorları, normal karaciğer dokusu için HU ve SUVmaks değerleri kontrast madde verilmesiyle anlamlı olarak arttı. 1cm'den büyük lezyonların HU değerlerinde ve 1cm'den büyük santral yerleşimli lezyonların SUVmaks değerlerinde istatistiksel anlamlı artış vardı. Atenüasyon düzeltme algoritmaları ile kontrast madde uygulamasından sonra hesaplanan SUVmaks değerlerinde normal karaciğer dokusu için ortalama %5 ve karaciğer lezyonları için %6 hatalı artış vardı.

Sonuç: Kontrast madde kullanımı, PET/BT ile hepatic lezyonların saptanmasını, lokalizasyonunu ve karakterizasyonunu önemli ölçüde iyileştirmektedir.

Anahtar Kelimeler: Kontrast madde, PET/BT, Karaciğer lezyonu

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Introduction

Noninvasive detection of liver malignancies is a crucial step in the decision and also in the application of treatments such as surgery or chemotherapy. For example, it has been demonstrated that surgery may be curable in individuals with colon cancer liver metastasis, particularly when the lesion is localized into the liver and is resectable. As a result, traditional anatomic examinations such as radiography, computerized tomography (CT), and magnetic resonance imaging (MRI) have been utilized to identify the hepatic disease noninvasively (1, 2). When employed alone, nevertheless, these traditional imaging methods may give mediocre findings. Thus, in recent years, standard protocols have been developed for the administration of intravenous (iv.) contrast substances to increase the image quality in CT and MRI practice. With these advances, the sensitivity for the detection of liver tumors via CT and MRI has increased to over 80% (3-6).

The Positron Emission Tomography (PET) imaging is particularly effective at identifying cancer recurrence and metastatic tumors in the preclinical phase, earlier they become visible in traditional diagnostic methods such as CT and MRI. But since PET does not offer anatomical details, it is hard to pinpoint the specific location of any worrisome lesion(s). To overcome this issue, combined PET/CT scanners have been created, which combine a full-ring detection PET scanner and a multidetector column spiral CT scanner. These systems provide both metabolic and anatomical imaging data with a single device in a single session, enabling precise localization of the lesions and areas with increased FDG uptake (7, 8). Previous studies have shown that the use of iv. contrast material in PET/CT yields clinically relevant additional information, aiding the diagnostic and therapeutic approach to these lesions. The greatest benefit of diagnostic PET/CT is arguably the improvements in regard to local tumor staging, which cause significant changes in the clinical management of 21% of cases, often due to the ability to better plan interventions. The determination of the enhancement characteristics with iv. contrast materials also enables the discrimination of benign and malignant liver lesions, further aiding physicians in the diagnosis and treatment of patients (9-11).

In spite of the advantages, non-modifiable administration of contrast agent use protocols for CT and MRI examinations for PET/CT can cause errors, including the masking or mimicking of a number of contrast-related pathologies. Today, there is still no general consensus on the role of iv. contrast agents and their use in the imaging of such lesions and available studies are limited. However, it has also been shown that errors may be prevented by utilizing appropriate techniques (9, 11, 12).

The goal of this research is to assess the diagnostic performance of enhanced and non-enhanced 18F-Fluorodeoxyglucose (FDG) PET/CT imaging for detecting primary and secondary liver cancers in terms of size and location.

Furthermore, we intended examine at the quantitative effects of contrast substances on maximum standardized uptake values (SUVmax) and find any inaccuracies in the SUVmax measures following contrast substance injection.

Materials and Methods

Study group

This study was conducted as a cross-sectional study in patients with primary or secondary liver malignancies (n=23). One patient (case 12) was not included in the statistical evaluation because it was not possible to perform quantitative evaluation of normal liver parenchyma due to the excessive spread of malignant tissue in the liver. Individuals had non-enhanced whole-body PET/CT imaging accompanied by enhanced and non-enhanced localized (the upper abdomen) portal phase PET/CT imaging. Using both enhanced and non-enhanced 18F-FDG PET/CT examinations the size, location, density (HU), visual assessment score, and SUVmax values for every cancerous lesion, in addition to the HU and SUVmax measurements of normal liver tissue, were collected.

Patient Preparation and Imaging Procedures

A hybrid PET/CT scanner (Biograph, Sensation 16 PET/CT system, Siemens AG, Erlangen, Germany) was used for whole-body scanning with the MDCT scan ranged across the head to the mid-thigh. Oral intake was stopped and patients fasted for at least 6 hours prior to PET/CT. Four diabetic patients (cases 6, 14, 19, 21) were administered a low-carbohydrate diet the night before the examination and were instructed not to use insulin for 4 hours before imaging. The maximum blood glucose level was determined to be 180 mg/dl. Only one diabetic patient (case 19) was treated with 10U crystallized insulin within the aforementioned 4-hour duration.

In regard to imaging, patients received an iv. injection of 144 μ Ci/kg FDG. Inspection limits were designated based on pilot images. The non-contrast CT scan was performed from the vertex to the proximal of the thigh with a collimation of 80mA, 110kV and 0.75mm. PET and CT images were reconstructed with a 5 mm slice thickness and axial, sagittal and coronal planes. Late PET/CT imaging with monophasic contrast was performed from the dome of the diaphragm to the lower pole of the liver, without application of contrast material. Whole body PET/CT and late PET/CT imaging times ranged between 31 and 112 minutes (mean 64 minutes). Monophasic contrast-enhanced CT images were obtained in the portal phase after a 70-second delay following the injection of 100 mL of iomeprol. CT parameters in late imaging (without contrast and portal phase contrast) were adjusted accordingly to the parameters of whole body CT scans.

All PET/CT images were evaluated on the same workstation (Siemens Medical Systems). Each liver lesion was evaluated visually and quantitatively using late PET/CT (non-contrast and portal phase contrast) images. Selectivity, localization, size, density (HU) and SUVmax parameters were recorded in all lesions that were determined to be malignant via FDG assessment. The final image qualities were evaluated by using the non-contrast and contrast-enhanced CT images of the lesions, and each image was classified as follows: undistinguishable, moderately selective, and well selective.

In regard to localization, a central lesion was classified as any lesion at least 1 cm away from the liver border, and a subcapsular lesion was defined when the lesion was closer than 1 cm to the liver border. The dimensions of the lesions were measured on CT images and divided into two groups as ≤ 1 cm and >1 cm. The density (HU) and SUVmax values of the lesions were measured by manually placing the ROI ring in the position with maximum FDG uptake in PET images.

Data

Statistical analyses were performed with SPSS (version 20, IBM Corp., Armonk, USA) and SAS computer software (version 9.2, SAS Institute Inc., Cary, NC, USA). The mean attenuation of all CT data sets (HU) and the SUVmean and SUVmax values of all PET reconstructions were summarized by the arithmetic mean

and corresponding standard deviation (SD), and the relative differences of SUVmean and SUVmax were calculated using the Wilcoxon signed-rank test. P values lower or equal to 0.05 were considered to be statistically significant.

Results

We included 22 patients (18 males and 4 females) in our study; the mean age was 59.8 ± 13.2 years. Localization of malignancy was known in 15 patients (8 patients with colorectal carcinoma, 2 with prostate cancer, 3 with lung cancer, 1 with pancreatic cancer, 1 with gastric cancer, 1 hepatocellular carcinoma). Six patients had carcinoma of unknown origin. The baseline characteristics of the patients are shown in Table 1.

Table 1. Baseline Characteristics of Patients

Case	Age	Gender	Diagnosis	Weight(kg)	Injection dose (mCi)	Interval (minutes)
1	72	M	Lung Epidermoid Carcinoma	72	10.86	65
2	35	F	Unknown Malignancy	65	10.9	64
3	57	M	Prostate Adenocarcinoma	64	10.68	62
4	73	M	Unknown Malignancy	80	12.92	31
5	49	M	Prostate Adenocarcinoma	59	10.64	78
6	66	M	Sigmoid Colon Adenocarcinoma	81	13.5	68
7	61	M	Unknown Malignancy	85	12.71	69
8	49	M	Unknown Malignancy	80	11.71	80
9	52	M	Unknown Malignancy	82	12.19	56
10	69	M	Rectum Adenocarcinoma	69	10.85	112
11	61	M	Gastric Adenocarcinoma	51	9.4	60
12	61	M	Unknown Malignancy	65	9.7	41
13	70	M	Small Cell Lung Carcinoma	50	9.83	74
14	75	M	Colon Adenocarcinoma	75	12.57	32
15	43	F	Unknown Malignancy	56	10.57	62
16	59	M	Hepatocellular Carcinoma	60	10.03	42
17	55	M	Sigmoid Colon Adenocarcinoma	76	12.11	53
18	74	M	Lung Epidermoid Carcinoma	80	12.64	100
19	71	M	Pancreas Adenocarcinoma	68	10.63	75
20	27	F	Rectum Adenocarcinoma	68	10.67	75
21	72	M	Rectum Epidermoid Carcinoma	83	13.67	55
22	70	F	Colon Adenocarcinoma	65	10.96	32
23	56	M	Rectum Adenocarcinoma	55	10.57	46

M: Male ; F:Female; Interval: Time from last scan to full-body scans

A total of 97 liver lesions (89 malignant, 8 benign) were detected. The mean size of malignant lesions was 2 ± 1.6 cm (range: 0.6-7.2 cm). Thirty lesions (33.7%) were measured to be ≤ 1 cm in size, while 59 lesions (66.3%) were measured to be >1 cm in size. Fifty-one of the lesions were centrally located and 38 were found to be subcapsular.

The size of 50 lesions could be measured via contrast-enhanced PET/CT, but not via non-contrast images. The borders of 33 lesions were determined to be obscure, but relatively accurate size measurements could be performed in 10 of them. Six lesions were clearly visualized and their dimensions were determined in both contrast-free and contrast-enhanced PET/CT images. The visual selectivity of all lesions increased after iv. contrast agent injection, regardless of size

and location ($p < 0.05$ for all measurements) (Table 2) (Figure 1).

After contrast injection, normal liver parenchyma ($n = 22$), HU and SUVmax values were found to be increased in a statistically significant manner ($p < 0.001$ and $p = 0.004$, respectively). Furthermore, compared to non-contrast images, iv. contrast injection was found to cause a statistically significant increase in HU values in both subcapsular ($n = 17$, $p = 0.028$) and central ($n = 42$, $p < 0.001$) lesions larger than 1 cm (Table 3 and 4). Contrast injection also caused a significant increase in the SUVmax values of central lesions larger than 1 cm ($p < 0.001$), but there was no significant difference in the SUVmax values of subcapsular lesions larger than 1 cm ($p = 0.170$) (Table 4).

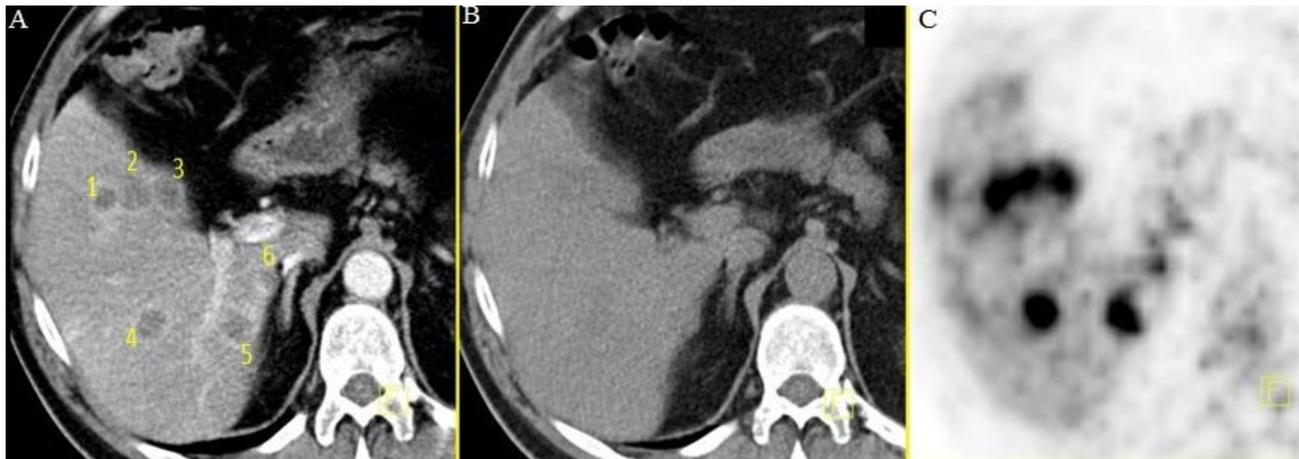


Figure 1. Contrast and non-contrast PET and CT findings of the number, size, and localization of metastatic lesions
 A: Hypodense 6 metastatic lesion in contrast CT
 B: The lesion, which shows a density difference in non-contrast CT, cannot be selected.
 C: Increased pathological metabolic focal activity in metastatic foci in contrast CT

Table 2. Visual Selectability of Malignant Lesions

		Subcapsular		Central	
		≤1cm	>1cm	≤1cm	>1cm
Undistinguishable	Contrast (-) PET / CT	1	1	1	1
	Contrast (+) PET / CT	3	3	3	3
Middle	Contrast (-) PET / CT	1	1	1	2
	Contrast (+) PET / CT	3	3	3	3
Well selected	Contrast (-) PET / CT	2	3	2	3
	Contrast (+) PET / CT	3	3	3	3

Table 3. HU and SUVmax values of normal liver parenchyma

	Normal Liver Parenchyma	
	SUVmax (Mean ± SD)	HU (Mean ± SD)
Contrast (-) PET / CT	2.6±0.6	54.3±5.2
Contrast (+) PET / CT	2.8±0.7	88.7±15.2
p value	0.004	<0.001

A total of eight benign lesions were detected. Two of these lesions were isometabolic with normal liver tissue (2 hemangiomas), whereas six were hypometabolic (5 simple cysts and 1 focal fatty area). A size larger than 1cm was observed in 1 simple cyst (subcapsular), 2 hemangiomas (1 subcapsular, 1 central), and 1 focal fatty area, while 4 simple cysts were measured to be ≤1cm (3 subcapsular, 1 central).

While the visual selectivity of simple cysts and focal fat area did not show a statistically significant difference in contrast-free and contrast-enhanced PET/CT images, the visual selectivity of hemangiomas increased significantly with contrast utilization. The appearance of benign lesions with contrast-enhanced and non-contrast PET/CT are shown in Figure 2.

Table 4. Distribution of HU and SUVmax values in subcapsular and central malignant lesions

	Contrast (-) PET / CT	Contrast (+) PET / CT	p value
HU (Mean ± SD)			
Subcapsular	40.5±6.5	49.5±12.4	0.028
Central	36.5±9.9	46.2±18.2	<0.001
SUV max(Mean ± SD)			
Subcapsular	8.3±2.9	8.7±3.5	0.170
Central	11.5±6	12.3±6.3	<0.001

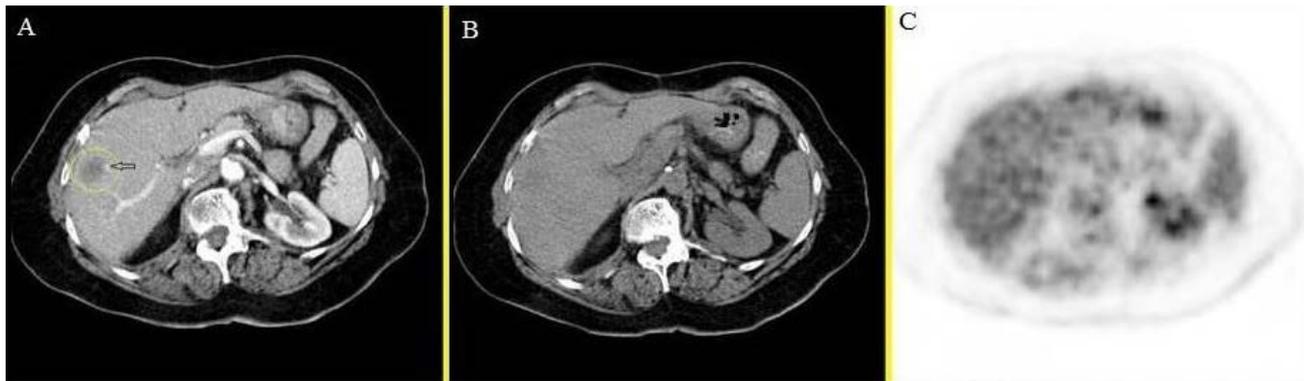


Figure 2. Hemangioma appearance with contrast and non-contrast PET/CT.

A: Typical peripheral nodular contrast area for hypodense lesion (yellow circle) and hemangioma in contrasted CT (arrow)

B: The lesion, which shows a density difference in non-contrast CT, cannot be selected.

C: The distribution of isometabolic activity in the area of hemangioma (SUVmax: 3,21).

Discussion

In the current study, we have found that the visualization of various types of lesions are made simpler with the use of contrast materials. Although contrast injection was also found to increase the HU and SUVmax values of normal tissues, we found that visual selectivity was also increased; a finding that supports the notion that contrast application is beneficial for the accurate assessment of such lesions, with the exception of simple cysts and local fat deposits.

Early diagnosis of primary or metastatic liver malignancies and accurate characterization of these lesions are crucial to achieving the goal of improving the survival of patients who require various therapies for treatment, such as partial hepatic resection, intrahepatic arterial infusion chemotherapy, radiofrequency ablation, laser treatment, cryotherapy, intrahepatic arterial radionuclide infusion and systemic chemotherapy (13–15). CT and MRI are among the most commonly used and accessible imaging modalities in today's medicine. The literature on this topic strongly suggests that the use of contrast agents greatly increases the detection and characterization of lesions (4-6, 16, 17). In patients with cancer, whole-body FDG-PET/CT scans are used to determine disease stage or grade, re-staging, and therapy efficacy. The most important advantage is that, with the 18-F FDG PET/CT modality, the metabolic and anatomical data of lesions are obtained simultaneously, leading to early detection, accurate assessment, and also the determination of prognosis (18, 19).

In this study, we found that the use of contrast agents provides a significant increase in the visual selectivity of various types of lesions. Thus, we can conclude that the localization and dimensions of the lesions can be more clearly defined and more definitive interpretations can be made about the lesion size, which are important for the determination of progression, regression and/or response to treatment. Our findings are similar to those in the international literature. In a retrospective study by Cantwell et al., it was shown that contrast-enhanced PET/CT and MRI were superior to non-

contrast PET/CT in detecting lesions in patients with liver

metastases (11). Similarly, Badiie et al., in another retrospective study, showed that contrast-enhanced PET/CT images were superior to non-contrast PET/CT in the detection of lesions (20).

In our study, when the contrast agent was applied, the SUVmax increase observed in liver tissue was 6.4%, which was a statistically significant increase ($p < 0,01$). Similarly, Berthelsen et al. also reported that the SUVmean value of liver tissue was increased by 5.8%, while SUVmax value was increased by 6.1% (21).

Bunyaviroch et al. examined 2 mediastinal lymph nodes, 2 liver masses, 1 abdominal mass, 1 inguinal mass and 8 abdominal lymph nodes in their study and reported that mean SUV values of these lesions increased by 3.4%. Although they found that this increase was statistically significant, they suggested that this increase was not influential on clinical evaluation (22). Similarly, in our study, the mean SUVmax values of lesions were significantly increased by 5.4% ($p < 0.001$). However, when examined in subgroups according to size and location, there was a statistically significant increase in SUVmax values in only centrally located lesions larger than 1cm (6.5% increase, $p < 0.001$). This result was attributed to the neovascularization or perfusion of pathological tissues which would cause relevant discrepancies in imaging results, and also to the possible increase of errors in attenuation correction caused by higher contrast levels (23, 24).

In a study in which the effects of contrast agent on SUVmax values were investigated, the approximate error rate for SUV was found to be 0.1% for 1 HU (25). In our study, the SUVmax error rate for 100HU was calculated for all lesions and normal liver tissue. We found that a 100 HU increase caused a 5% error in the SUVmax value of normal liver parenchyma and a 6% error in lesions.

Limitations of the study

There are various limitations in our study. Firstly, we did not confirm the histopathological findings of some lesions due to the absence of data, which limited our evaluations to clin-

ical and radiological results. Another limitation is the difference in primary tumor location of the patients included in the study which could have affected the characteristics of lesions significantly. In addition, as we performed manual injection of contrast agent, there may have been uncontrollable but slight differences due to human error in the images.

Conclusion

In conclusion, the use of intravenous contrast substance increases the identification, location, and characterization of liver pathologies using the PET/CT imaging modality. The level of inaccuracy that we have determined in the SUVmax values with contrast material administration does not seem to affect the interpretation of PET/CT images and can feasibly be considered clinically insignificant errors.

Ethical Approval: The study was conducted according to the ethical standards specified in the 1964 Declaration of Helsinki. Written permission was obtained from the Ethics Committee of Ankara Atatürk Training and Research Hospital (İlaç Dışı Klinik Araştırmalar Etik Kurul Koordinatörlüğü /26.12.2012 /B.30.2. YBÜ.006.06.01/125) and the individuals who agreed to participate in the research.

Author Contributions:

Concept: M.K., Ş.T.

Literature Review: M.K., E.Ö., N.Y., Z.K.

Design : M.K.

Data acquisition: M.K.

Analysis and interpretation: M.K.

Writing manuscript: M.K.

Critical revision of manuscript: M.K.

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