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Research Article / Araştırma Makalesi

The value of late phase imaging with FDG-PET/CT in liver metastases of colorectal carcinoma

Kolorektal kanserli hastalarda metastatik karaciğer lezyonlarının geç faz FDG-PET/BT görüntülemesinin değerlendirilmesi

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ABSTRACT

Aim: Our aim was to investigate the role of late-phase imaging with FDG-PET/CT in colorectal carcinoma patients with liver metastases.

Material and Method: Dual-phase FDG-PET/CT scan was retrospectively evaluated in colorectal carcinoma patients with liver metastases. Late phase imaging was acquired 92-253 minutes (mean 158.53±35.7 minutes) after the FDG injection. Sixty-eight metastatic lesions were determined in 37 patients. Mean lesion SUVmax and lesion-to non-tumorous liver tissue ratio was calculated and results of routine FDG-PET imaging were compared with late-phase imaging.

Results: Metastatic lesion sizes were 9 to 230 mm (mean 3.71±3.7 cm). SUVmax values of the metastasis and non-tumorous liver SUVmax for routine and late-phase imaging were as follows respectively; 7.19±3.8, 10.3±5.4; 2.98±0.7, 2.41±0.6. In the late phase imaging metastatic liver lesions SUVmax values were increased ($p< 0.01$) and non-tumorous liver SUVmax values were decreased ($p< 0.01$). Compared to routine imaging, in late phase, lesion to non-tumorous liver tissue was increased ($p< 0.001$). Lesion retention index was increased by 45.74±31.8% and the non-tumorous liver index was decreased by 18.63±10.4%.

Conclusion: The results of this study indicate that normal liver FDG uptake decreases in time and late-phase imaging improves the tumor to normal tissue ratio and enables differentiation of metastatic liver lesions from normal liver.

Keywords: Dual-Phase, FDG-PET, liver metastases, colorectal carcinoma

ÖZ

Amaç: Amacımız, karaciğer metastazı olan kolorektal karsinom hastalarında FDG-PET/BT ile geç faz görüntülemenin rolünü araştırmaktır.

Gereç ve Yöntem: Karaciğer metastazı olan kolorektal karsinomlu hastalarda çift fazlı FDG-PET/BT taraması retrospektif olarak incelendi. FDG enjeksiyonundan 92-253 dakika (ortalama 158,53±35,7 dakika) sonra geç faz görüntüleme alındı. Otuz yedi hastada 68 metastatik lezyon saptandı. Ortalama lezyon SUVmax ve lezyon/tümor olmayan karaciğer doku oranı hesaplandı ve rutin FDG-PET görüntüleme sonuçları geç faz görüntüleme sonuçları ile karşılaştırıldı.

Bulgular: Metastatik lezyon boyutları 9-230 mm bulundu (ortalama 3,71±3,7 cm). Rutin ve geç evre görüntüleme için metastaz ve tümörsüz karaciğer SUVmax değerleri SUVmax olarak sırasıyla; 7,19±3,8, 10,3±5,4 ve 2.98±0.7, 2,41±0,6 olarak hesaplandı. Geç evre görüntülemede metastatik karaciğer lezyonlarında, SUVmax değerleri artmış ($p<0.01$) ve tümör içermeyen karaciğer dokusunda SUVmax değerleri azalmıştır ($p<0.01$). Rutin görüntülemeye kıyasla geç faz görüntülerinde lezyon/ tümörsüz karaciğer dokusu oranı artmıştır ($p=0.001$). Karaciğer metastatik lezyon retansiyon indeksi %45,74±31,8 oranında artmış ve tümör içermeyen karaciğerde ise retansiyon indeksi %18,63±10,4 oranında azalmıştır.

Sonuç: Bu çalışmanın sonucu olarak, normal karaciğer dokusunda FDG tutulumunun zamanla azaldığını, geç faz görüntüleme ile de lezyon/tümörsüz karaciğer dokusu oranının belirginleştirdiği ve metastatik karaciğer lezyonlarının normal karaciğerden daha kolay ayırt edilmesini sağladığını göstermektedir.

Anahtar Kelimeler: Geç faz, FDG-PET, karaciğer metastazı, kolorektal karsinom

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INTRODUCTION

In colorectal cancers, the liver is one of the most common regions of metastases in hematogenous spread of disease (1). On the course of cancer, depending on the primary tumor type liver metastasis can be found in 25% of all cases. The detection of liver metastasis not only results in the spread of the disease but also effects the treatment approaches from local treatment surgical approaches to systemic chemotherapies. However, surgical removal of liver metastases can provide cure especially in colorectal cancers and increase the 5-year survival rate by 58-61% (2).

For the detection of liver lesions, PET (positron emission tomography) is a functional imaging method based on the metabolic information of increased glucose utilization in cancer cells (3). A meta-analysis comparing imaging modalities found that FDG (Fluorine-18 labeled fluoro-2-deoxy-glucose)-PET has sensitivity of 93.8% and specificity of 98.7% per patient basis in detecting liver metastasis of colorectal carcinomas (4).

FDG accumulation is usually expressed in Standard Uptake Value (SUV) which is calculated by dividing the ratio of tissue activity (mCi/mL) to the patient's body weight (5). However, though SUV over 2.5 or over in many literatures is usually accepted as malignant (6) there is no specific limit for SUV values and especially in tissues with high physiological uptake and there is no definite limit in the malignant benign distinction for SUV values. Apart from the SUV, the retention index can be used for quantification. The retention index of the lesion is calculated by the difference of SUV between the images. Retention index=SUV2-SUV1/SUV1x100% (7).

Besides, by calculating the ratio of acquired counts from the region of interest of the lesion to the non-tumorous surrounding tissue (L/B) can be used for quantification. In general, unlike other tissues, liver tissue FDG uptake is physiologically heterogeneous. Nevertheless, the physiologically intense and heterogeneous FDG uptake observed in liver leads to difficulty in the evaluation of liver lesions. The FDG-PET sensitivity is lower than many other malignant tumors due to the variable levels of glucose-6-phosphatase depending on the type of lesion for liver lesions. The value of late-phase imaging in various cancers such as lung, pancreas, head and neck, breast and cervical cancers has been emphasized in differentiating benign lesions from malignant lesions (8–12).

Although the FDG-PET imaging procedure is recommended to be performed after 45 minutes, at the 60th minute on average, various differences are observed in the literature in this regard. A study performed late imaging study to differentiate the malignancy from inflammatory lesions by Zhuang et al. (13) showed that in malignant tissues FDG uptake continues to accumulate over time.

In a study with advanced or recurrent cervical cancer, they found that late phase FDG-PET images caused changes in the treatment of 31% of patients (14). A study with head and neck cancer compared the ratio of the tumor SUV value to the contralateral the tissue SUV value in acquisitions between 47-112 min and 77-142 min, and they found that the ratio was increased by 23±29% and this rate has increased even more in late-phase images taken after 30 minutes (15).

Regarding the discussed literature above in performing late phase imaging, we hypothesized that the sensitivity may be higher in late-phase acquisition which may facilitate the separation of metastatic liver lesions from the liver and provide an accurate interpretation. We have evaluated the diagnostic efficiency of late-phase FDG-PET/CT in patients with a liver metastasis in addition to the routinely acquired images.

MATERIAL AND METHOD

All the patients underwent a 6 to 8-hour fasting and diabetic patients using insulin were not included in this study to minimize the level of glucose competing with FDG in the blood to avoid increased liver uptake. All patients were advised to be hydrated and not to exercise on the day and the day before the PET/CT scan. There were 37 patients in total, (14 female, 23 male) and all the 68 lesions were suspected of liver metastases. The patients' ages were between 23 to 80 years and mean patient age was 55.51±11.7 years. All the patients were injected FDG dose once and both of the acquisitions were acquired by the same FDG dose. Intravenous FDG of 0.2 mCi/kg was given through an antecubital catheter and patients were kept immobile and silent in a dimly lighted room for around 20 minutes prior to and after injection. FDG-PET/CT images were acquired at a 4 sliced multidetector helical CT scanner and a bismuth germanate crystal equipped Discovery ST PET/CT (GE Healthcare, Milwaukee, WI, USA). Emission data were acquired starting from calvarium base till mid-thigh. The transmission time required for each bed position was 3 minutes. Mean PET/CT acquisition time was 22 minutes and mean number of required bed positions was 5 to 7 beds. CT images were utilized to obtain attenuation maps for the attenuation correction of PET images. Furthermore, CT images were fused to PET images automatically to determine the exact anatomical location. The CT transmission scan was acquired with 140 kVp and 110 mA and 3.5 mm slice thickness.

Both the routine and the late phase F18-FDG PET/CT images were evaluated both visually and semi-quantitatively by two nuclear medicine physicians.

For each lesion, the maximum standard uptake value (SUVmax) was calculated automatically. Both in the routine and the late phase image evaluation, CT images were utilized to obtain the anatomical position of the lesions. At the late phase images, CT images acquired during the routine FDG-PET/ CT were utilized for attenuation correction and these images were fused to late-phase images. Non-tumorous liver tissue SUVmax value was calculated by drawing multiple regions of interest (ROI) and mean SUVmax was calculated by getting the average value of

those ROIs. The ratio of the routine FDG-PET/CT image to the late phase FDG-PET/CT was calculated for each lesion and also for the non-tumorous liver tissue. It has been demonstrated that other SUV, the retention index can be utilized for quantification. Lyshchik et al. (7) have calculated the retention index by subtracting the routine FDG-PET/CT SUVmax value from the late phase FDG-PET/CT image SUVmax value, divided by the routine FDG-PET/CT SUVmax value. According to this formula retention index was calculated for each lesion.

Statistical Analysis

The data were analyzed with Statistical Package for Social Sciences for Windows software (SPSS version 23.0, SPSS Inc., Chicago, Illinois, USA). The Mann–Whitney U tests were used for statistical evaluation of the difference between the two imaging sessions both in liver metastases and in non-tumorous liver tissue. To evaluate the relation between the acquisition times and the metastatic lesion and the non-tumorous liver tissue the Pearson correlation test was used. A value of $p < 0.05$ was accepted as statistically significant.

Ethical Declaration

Retrospectively, all the patients with colorectal carcinoma who were referred to FDG-PET/CT due to staging, re-staging, response to therapy with a liver lesion were included in this study. The procedures were followed according to the regulations established by the Clinical Research and Ethics Committee (Ankara Training and Research Hospital, Date 22/03/2011, number 0120, decision 2541) and to the Helsinki Declaration of the World Medical Association. All the patients were given signed informed consent.

RESULTS

The routine FDG-PET/CT images were acquired between 46-91 minutes after the FDG injection. The mean acquisition time for the routine FDG-PET/CT images were 63.88±12.3 minutes. The late phase FDG-PET/CT images were acquired between 92-253 minutes (mean: 158.53±35.7) after the routine FDG-PET/CT injection for 1 or 2-bed position, covering the liver area. The range of the metastatic lesion size varied between 0.9 to 23 cm (mean lesion size: 3.71±3.7). Three lesions were smaller than or equal to 1 cm. The calculated mean SUVmax of the non-tumorous liver tissue in routine FDG-PET/CT images was 2.98±0.7, however, in the late-phase the calculated mean SUVmax of the non-tumorous liver tissue was decreased to 2.42±0.6. The difference in the non-tumorous liver tissue between the routine F18-FDG-PET/CT images and the late phase FDG-PET/CT images were statistically significant ($p<0.01$) (**Table 1**).

A patient example was demonstrated in **Figure 1.**

The visual evaluation revealed that all the lesions demonstrated increased FDG uptake. The calculated SUVmax in the liver metastases in routine FDG-PET/CT images was 7.19±3.8, the calculated mean SUVmax of the late phase was increased to 10.30±5.4. The difference in the liver

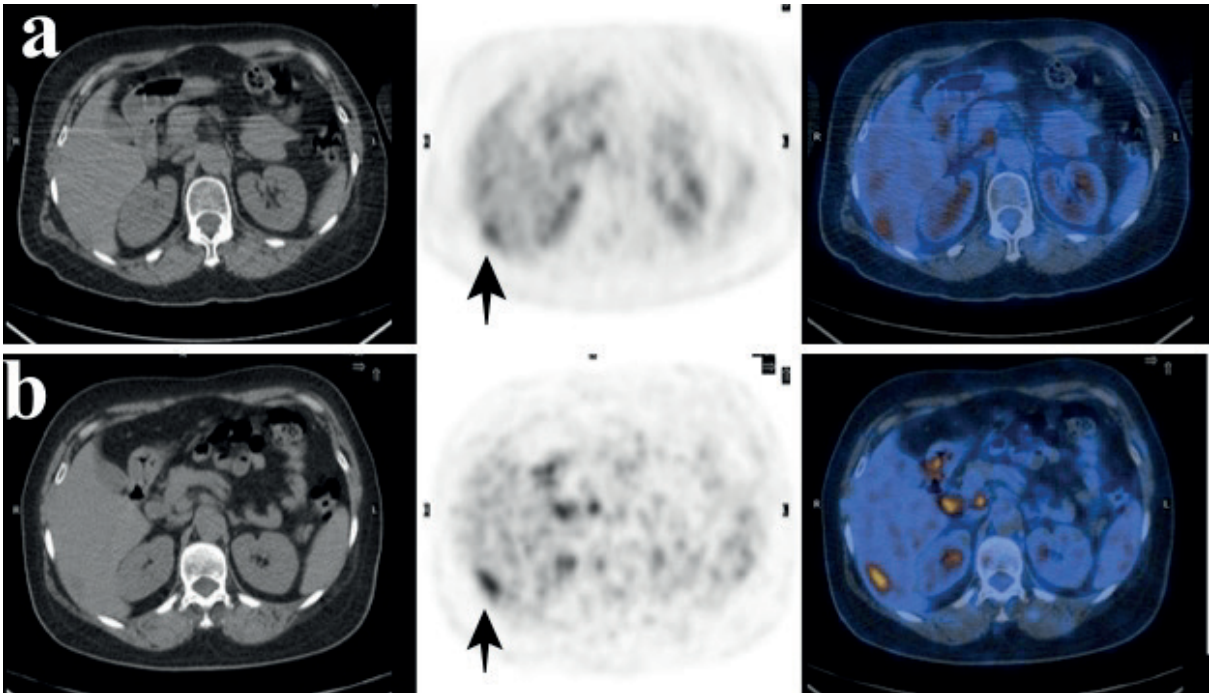

Figure 1. 53 year-old female colorectal carcinoma was referred to PET/CT for the evaluation of a liver mass. The routine FDG-PET images were presented in row a). CT, FDG-PET and fused FDG-PET/CT images respectively presented a lesion with SUVmax: 4.37 and non-tumorous liver SUVmax:3.2. The late phase FDG-PET images in row b) CT, FDG-PET and fused FDG-PET/CT images respectively, the mass shown with black arrow has shown a much higher SUVmax: 7.04 compared to routine FDG-PET images and non-tumorous liver has shown a decreased SUVmax:2.9. The calculated retention index was 97%.

Table 1. Liver metastatic lesions and Non-tumorous liver SUVmax values

	Routine Imaging SUVmax	Late Phase Imaging SUVmax	p values
Liver metastases	7.19±3.8	10.30±5.4	< 0.01
Non-tumorous Liver	2.98±0.7	2.41±0.6	< 0.01

metastases between the routine FDG-PET/CT images and the late phase FDG-PET/CT images was statistically significant (p<0.01) (**Table 1**).

The routine FDG-PET/CT mean lesion L/B ratio was 2.48±1.2 and the late phase FDG-PET/CT was 4.38±2.1 and the difference between L/B ratios was statistically significant (p<0.001) (**Table 2**).

Table 2. Lesion-to non-tumorous liver tissue SUVmax values

	Routine Imaging	Late Phase Imaging	p values
Lesion-to non-tumorous liver tissue (L/B)	2.48±1.2	4.38±2.1	< 0.001

There was moderate positive correlation between the time of acquisition and L/B ratio (p<0.05, r:0.56). And there was moderate positive correlation between the time of acquisition and the SUVmax decrease of the non-tumorous tissue (p< 0.001, r: 0.472). Nevertheless, there was no correlation between the time of acquisition and SUVmax of the metastatic lesion (p>0.05, r<0.2), or the time of acquisition and the size of the metastatic lesions and (p>0.05, r<0.2), or between the time of acquisition and the patient age (p>0.05, r<0.2).

The mean RI was calculated for lesions was 45.74±31.8% (range 1.10-193.75) and the decrease of mean RI of non-tumorous liver was 18.63± 10.4% (range 4.43-40.83) (**Table 3**).

Table 3. Liver metastases and lesion-to non-tumorous liver tissue SUVmax values

	Retention Index
Non-tumorous liver tissue	-18.63± 10.4%
Liver metastases	45.74±31.8%
p value	< 0.001

Furthermore, in 3 patients with colorectal carcinoma, referred due to elevated CEA levels, in total 4 new liver metastatic foci were identified which were not apparent in the routine FDG-PET/CT images. One of those patients are presented in **Figure 2** and **Figure 3**.

193.75%.

DISCUSSION

Liver is considered as the most common region of metastasis in many cancers including colorectal cancers (2). Liver metastasis affects the course of the primary disease, life span, mode of treatment, and operability. It has been shown that the life span is prolonged after surgery in the presence of liver metastasis before the disease becomes widespread (16).

The heterogeneous FDG uptake is thought to be due to the hexokinase enzyme that converts FDG into FDG-6P

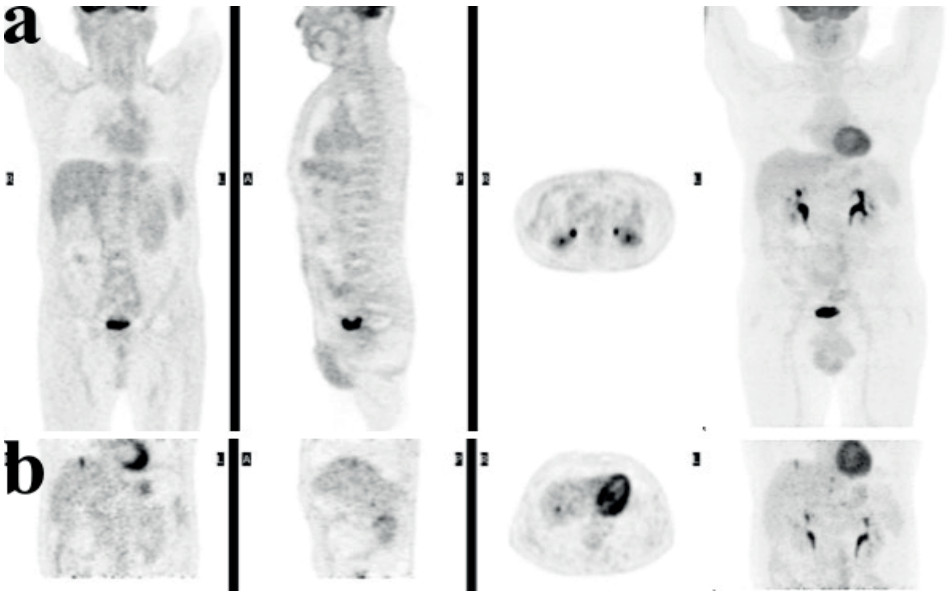

Figure 2. 50 year-old male rectum carcinoma was referred due the increase in CEA levels. The routine FDG-PET images were presented in row a) Coronal, sagittal, transaxial and maximum intensity projection images respectively did not presented any lesion and non-tumorous liver SUVmax:3.26. The late phase FDG-PET images in row b) Coronal, sagittal, transaxial and maximum intensity projection images images respectively, has shown a focal FDG uptake with an SUVmax: 7.99 and non-tumorous liver SUVmax was decreased to 2.95. The calculated retention index was from the same region was

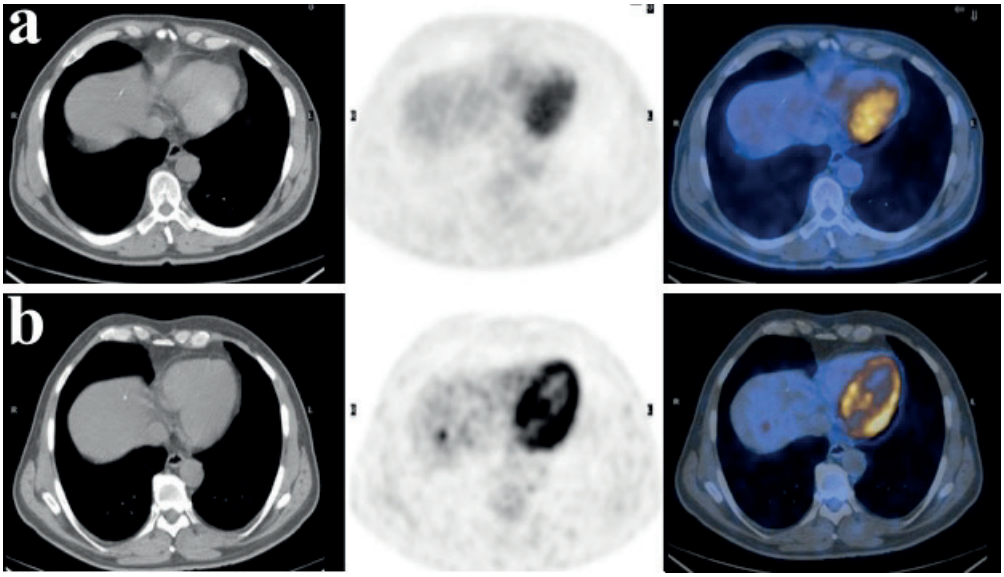

Figure 3. a). Respectively, CT, FDG-PET and fused FDG-PET/CT images acquired at routine FDG-PET/CT of the patient presented in **Figure 2. b)** CT, FDG-PET and fused FDG-PET/CT images respectively, at late phase FDG-PET/CT.

as well as the glucokinase enzyme specific to the liver. Although this situation causes more FDG uptake in the first phase of the FDG uptake, the FDG uptake in the liver decreases over time as in the other tissues. The glucose-6-phosphatase enzyme (G6Pase), which converts FDG-6P to FDG, is quite high in normal liver tissue, it is almost zero in metastatic liver tumors and variable in primary liver tumors (17).

A study with pancreatic cancer patients found that FDG PET has a sensitivity of 68% in liver lesions, whereas, in metastatic liver lesions larger than 1 cm, the specificity of FDG-PET was found to be 97% and in metastatic lesions less than or equal to 1 cm, the FDG-PET sensitivity was 43% (18). In a study with liver metastases of colorectal tumors smaller than 1 cm, the false negativity of FDG-PET was reported as 5% (19). Through the literature, it has been suggested that specificity may increase even in lesions smaller than 1 cm as a result of decrease in FDG accumulation in time and decrease in metastatic liver lesions (20,21). In our study, the lesions sizes range from 14 to 230 mm and the average size of the lesions was 3.71±3.7 centimeters and we had 3 lesions equal to 1 cm or under 1 cm. All those 3 lesions were clearly visible.

In colorectal cancer studies for staging of liver, the sensitivity of FDG-PET was around 90-97%, while the specificity was 88-100% (4,15,22). In these studies, lesion imaging was routinely performed between 45 and 70 minutes. A study in patients with suspected liver metastases reported that 11.1% of the liver lesions were present only at late PET images (23). In our study, in all 37 patients and 68 lesions in late images liver lesions were detected. Compared to late-phase imaging, the routine FDG-PET images localized 64 of the 68 lesions and the sensitivity of late-phase imaging to detect liver lesions on lesion basis was calculated as 94.11%. On patient basis, in 3 of 37 patients with metastatic liver lesions, routine images could not detect all the liver lesions that late-phase imaging has detected and the sensitivity to detect liver metastatic lesions was calculated as 91.89%.

In a study consisting of primary liver tumors and metastatic liver lesions, reported that late phase images are useful in distinguishing liver lesions, more prominent in metastatic tumors (24). A study evaluate liver metastasis in patients with pancreatic carcinoma found that rather than the images acquired at 1 hour or 3 hours, the images acquired at 2 hours were thought to be more useful to rule out the presence of liver metastasis (25). Regarding this, we also evaluating the metastatic lesion by the time of acquisition. In our study, the mean time difference was 94.65±38.2 minutes in all patients (range between 14-178 minutes) and we grouped the patients according to the time differences of acquisitions, we had 3 groups. The first group had their late phase imaging within an hour, consisting of 34 patients; the second group had their late phase imaging between an hour and 2 hours, consisted of 14 patients; the third group had their late phase imaging after 2 hours, consisted of 20 patients. However, we did not find any differences between groups in terms of retention index of the metastatic lesions.

A dual time point study evaluating liver metastases in colorectal carcinoma, confirmed the metastatic lesions by histopathology and found that a delayed scan is more favorable (26). One of the main limitations of our study is, we did not confirm the lesions by histopathology, however other than the patients with known liver metastasis, all the other patients liver masses were confirmed by conventional imaging methods. We had 4 additional lesions in 3 patients' that were identified in late-phase imaging which were not localized in the early study. All of the 4 lesions were larger than 1 cm, the lowest SUVmax of those lesions in routine images was 2.72 and the lowest late-phase imaging SUVmax was 4.88. However, due to the heterogenous

liver background, it was not possible to identify the lesions in the routine FDG-PET imaging.

Delbeke D et al. (22) reported that in a group of patients liver masses including liver metastases, cholangiocellular carcinoma, primary liver tumors, and liver abscesses, FDG-PET showed high sensitivity in metastatic liver tumors. They also found that lesion/ non-tumorous liver ratio was higher than 2 and SUV values were greater than 3.5 in all malignant tumors and lesion/ non-tumorous liver ratio was less than 2 and the SUVmax values were less than 3.5 in benign lesions. In our study the mean lesion/ non-tumorous liver ratio was higher than 2 (2.48±1.2) in the routine FDG-PET/CT imaging and much higher in late-phase imaging (4.38±2.1) (**Table 2**) and in all lesions SUVmax was higher than 2, however, in 31 lesions the mean lesion/ non-tumorous liver ratio was less than 2 which suggested that the threshold of 2 for the lesion/non-tumorous liver was not as reliable as SUVmax in the quantitative evaluation of metastatic liver lesions for our study.

In the study of Condrad et al. (27) in thoracic malignancies with the same method, they accepted a 5% increase in the images taken 30 minutes after the first acquisition and emphasized that late-phase is important for malignant benign distinction. In our study, mean retention index in liver lesions calculated in this study was found 45.73±31.8% (**Table 3**). Our results support that quantification values such as the retention index used alongside the SUV are useful when evaluated together with visual evaluation.

Concordant with the literature (28), in our study, we found that the presence of heterogeneous non-tumorous liver, decreases by time and late-phase imaging may help us to find new metastatic foci in liver. The non-tumorous liver tissue SUVmax decrease is correlated by time of acquisition. The late acquired images increase the reliability of detection of metastatic liver lesions by the separation of the lesion from the non-tumorous liver tissue, thanks to the utilization of FDG, decreasing over time from the liver parenchyma.

CONCLUSION

Our results support that the FDG-PET sensitivity of detecting metastatic liver lesions in colorectal carcinoma patients may be increased by acquiring late-phase images. Besides late-phase images can facilitate the identification of suspicious metastatic lesions from the non-tumorous liver tissue and facilitate accurate interpretation.

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Conflict of Interest: The authors declare that there is no conflict of interest.

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