Role of PET/CT in patients with unexplained rising alpha fetoprotein post HCC interventional management

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Abstract

Background: Positron emission tomography–computed tomography (PET/CT) is considered a powerful modality in the follow-up of hepatocellular carcinoma (HCC) patients. In this study, PET/CT was done in an evaluation of patients with unexplained rising alpha fetoprotein (AFP) post hepatocellular carcinoma (HCC) interventional management in 40 patients (16 females and 24 males); their age ranged from 25 to 82 years, had undergone interventional management for HCC and underwent PET/CT follow-up within an 8-month duration from their intervention. Whole-body PET/CT was performed after injection of (18)-FDG, and the results were read in a masked manner by two specialists, and diagnostic performance was assessed from the results of consensus masked reading. All the results were evaluated with the Barcelona criteria and biopsy correlation.

Results: During the follow-up PET/CT, 24 patients had complete response and 8 patients showed focal residual while the rest 8 patients showed newly developed lesions.

Conclusion: PET/CT is an excellent method for the evaluation of HCC patients with equivocal results after interventional management.

Keywords: Positron emission tomography, Computed tomography, Alpha fetoprotein, Hepatocellular carcinoma

Background

Hepatocellular carcinoma (HCC) arises in more than 75% of patients with advanced liver cirrhosis. The responsible factor is known in 90% of cases. However, the main risk factors for liver cirrhosis and developing HCC are strongly related to the geographic region [1].

Worldwide, the most important risk factors are viral hepatitis, alcohol, and aflatoxin exposure. Fifty-four percent of all HCCs can be attributed to hepatitis B and 31% to hepatitis C. Interestingly, signs of advanced cirrhosis such as portal hypertension correlate with the development of HCC [2–4].

The widely accepted imaging modalities for staging HCC are dynamic computed tomography (CT) and contrast-enhanced magnetic resonance imaging (MRI) [5–7]. However, CT and MRI have a limited ability to identify distant metastases. Previous studies

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Table 1 Demographic data of the studied patients (no. = 40)

Demographic Data	All studied patients (*n* = 40)	
	No.	%
Gender		
Female	14	35%
Male	26	65%
Age		
Mean ± SD	53 ± 17	
Median (range)	58 (23-80)	

have detected the role of FDG PET/CT in detecting distant metastases in various types of malignancies [8, 9].

Using 18F-FDG PET/CT may be promising in the early evaluation of post-therapy effect and the presence of intrahepatic recurrent or extrahepatic metastatic lesions [10, 11]. However, PET/CT usage in hepatocelluar carcinoma (HCC) remains controversial because of concerns about the relatively low sensitivity, especially for detecting a well-differentiated HCC [12, 13]. Indeed, the diagnostic performance of 18F-FDG PET may strongly depend on biopsy results: one study reported that in patients following transplantation, it detected only 25% of intrahepatic recurrence cases, but 92.9% of extrahepatic metastases larger than 1 cm. In addition, 18F-FDG uptake is increased in inflamed tissue, which can contribute to false positive results [14, 15].

Methods
The current study included 40 cases of HCCs were treated with radiofrequency ablation (RFA), microwave ablation (MWA), transarterial chemoembolization (TACE), and combined technique. Follow-up PET/CT was done for all cases. It was done during the period from July 2016 till January 2017 and was approved by the local research ethical committee at our University. An informed consent was obtained from all patients.

Table 2 Type of hepatitis of all studied patients

Type of hepatitis	All studied patients (*n* = 40)	
	No.	%
HBV	24	60%
HCV	6	15%
Alcoholic liver	10	25%

Table 3 Child–Pugh classification of all studied patients

Child–Pugh classification	All studied patients (*n* = 40)	
	No.	%
A	18	45%
B	14	35%
C	8	20%

Inclusion criteria
Any HCC patient, regarding age and sex, was treated with radiofrequency ablation (RFA), microwave ablation (MWA), transarterial chemoembolization (TACE), and combined technique.

Exclusion criteria
1. Patients with contraindication to contrast: patients with disturbed renal function test (if creatinine > 2), patients with glomerular filtration rate < 30 ml per min per 1.73 m^2 or any acute renal insufficiency related to the hepato-renal syndrome or perioperative liver transplantation
   2. Patients with metastatic HCC
   3. Patients with uncontrolled serum glucose level
   4. Patients who are pregnant

Patient preparation
All patients were asked to fast and rest for a minimum of 6 h before undergoing the examination. Activities including talking, chewing, and walking were restricted. Serum glucose levels were measured 1 h before FDG (fluorodeoxyglucose) injection to ensure that the included patients had a level below 150 mg/dl; the examination was postponed if the level was above 150 mg/dl. No oral contrast agent was administered. In addition, all patients were instructed to void preceding the examination. Patients were placed in a lying down position with raised arms.

PET/CT technique
18F-FDG PET/CT study and image analysis PET studies were performed after various procedures with unexplained elevated alpha fetoprotein for all patients using a dedicated PET scanner (DST PET/CT;

Table 4 TNM staging of HCC in all studied patients

TNM staging	All studied patients (*n* = 40)	
	No.	%
Stage I	21	52.5%
Stage II	8	20%
Stage III	6	15%
Stage IV	5	12.5%

Table 5 Type of treatment of all studied patients

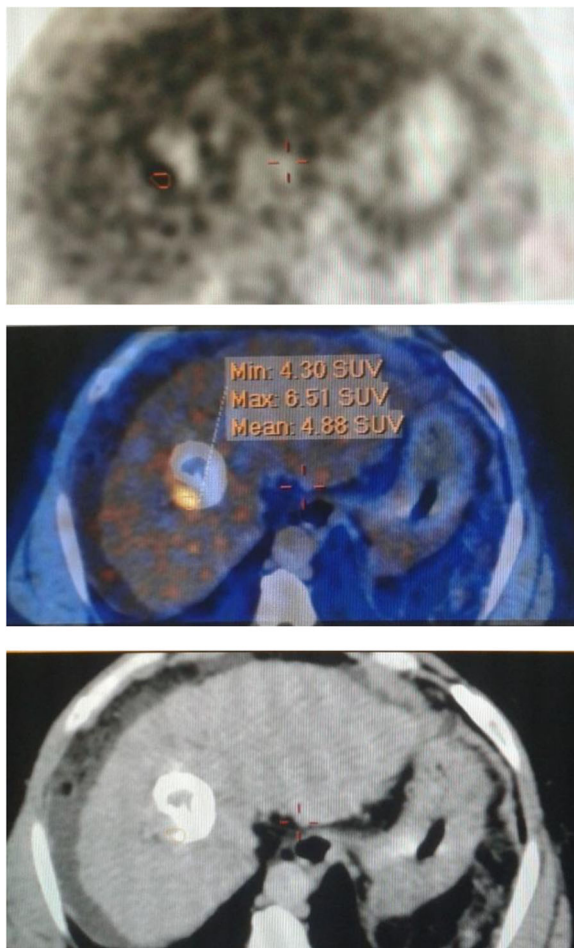| Type of treatment	All studied patients (n = 40)	
	No.	%
RFA	10	25%
MWA	5	12.5%
TACE	15	37.5%
Combined	10	25%

Discovery ST PET-CT, General Electric Medical Systems, Milwaukee, WI, USA). All examinations were carried out using two integrated PET/CT scanners (Ingenuity TF 128; Philips Healthcare, Cleveland, OH, USA) 1 h after intravenous administration of 7–11 mCi of 18F-FDG corresponding to the patient's body weight. The CT scan component of the PET/CT examination included non-contrast CT acquisition of the liver, arterial phase CT of the

Fig. 1 A 57-year-old male underwent TACE for upper segment right lobe HCC with elevated AFP after TACE PET CT revealing focal residual viability related to the posterolateral aspect of the lesion with 6.5 SUVmax

liver, portal venous whole-body CT, and equilibrium phase CT of the liver. For the arterial phase, the contrast agent iopromide (Ultravist) (300 mg of iodine/ml) was used at a dose of 100–120 ml corresponding to the patient's body weight with a 3-ml/s infusion rate, following the administration of 50 ml of a normal saline chaser at a 3-ml/s infusion rate. A 100-HU threshold was set in the region of interest (ROI) at the lower part of the descending thoracic aorta to trigger the start of hepatic arterial phase CT. The portal venous whole-body and equilibrium phases were acquired approximately 65 and 120 s after beginning the contrast medium infusion, respectively. During the portal venous phase, the patients were asked to breathe smoothly. The portal venous whole-body phase images were used for attenuation correction and integration with the PET images.

Image analysis

All CT images, attenuation-corrected PET images, and fused PET/CT images were transferred and viewed centrally on an interactive workstation (IntelliSpace Portal V4.0; Philips Healthcare). The 18F-FDG PET images and contrast-enhanced CT (CECT) images were separated for interpretation (i.e., the 18F-FDG PET image findings were reviewed without knowledge of the CECT findings and vice versa). Two radiologists with 15 and 12 years of experience, respectively, in hepatic CT imaging reviewed all CECT components of the PET/CT scan. Two nuclear medicine physicians with 7 and 5 years of experience, respectively, reviewed all 18F-FDG PET images. All radiologists and nuclear medicine physicians were blinded to any clinical information or the results of the biopsy. Intrahepatic HCC recurrence was noted as newly developed lesions showing hyperenhancement in the arterial phase and washout in the delayed phase of the CECT component. In 18F-FDG PET/CT, disease activity was assessed either qualitatively or semi-quantitatively. Qualitative evaluation was based on the detection of focal 18F-FDG uptake that was higher than the surrounding background and distinct from tracer uptake physiological sites (e.g., bowel and myocardium), whereas semi-quantitative evaluation typically relied on the calculation of the maximum standardized uptake value (SUVmax).

We calculated for each patient the SUVmax of the tumor and the ratio of the tumoral SUVmax to the normal liver SUVmax (TSUVmax/LSUVmax). In order to measure SUVmax for the tumor, we drew a 4×4 pixel square region of interest (ROI) and placed it on the area of the highest activity of the

Table 6 PET/CT, biopsy results, and AFP values per response of all studied patients

	PET/CT		Biopsy		AFP < 100	AFP > 100
	Positive	Negative	Positive	Negative		
Complete response	0	24	2	22	24	0
Partial response	8	0	4	4	5	3
Newly developed lesions	8	0	7	1	4	4

tumor but not covering the entire tumor, with the aid of combined CT and measured SUVmax in the ROI. In the case of multiple tumors, the SUVmax of the tumors was defined as the highest SUVmax of the tumors. To measure SUVmax for normal liver, we drew two 50-pixel circular ROIs and placed one on right lobe and one on liver transplantation (LT) lobe at a location where tumor was not detected on combined CT. The SUVmax of the normal liver was defined as the highest SUVmax of the two ROIs drawn on the normal liver. In this combined protocol, we established the diagnosis based on the combined findings from each modality. A finding was considered positive when it was observed in either the CECT or 18F-FDG PET/CT scan or both. We categorized intrahepatic HCC recurrence as either recurrence adjoining the treated site or at a site further than the original tumor site.

Results

The patients (Table 1) included 26 men and 14 women. The mean age of the enrolled patients was 60 ± 11.7 years (range, 25 – 82 years), and the mean duration of follow-up was 8 months (range, 1 – 59 months). Twenty-four (60%) patients had hepatitis B virus (HBV) infection, six (15%) patients had hepatitis C (HCV) infection, and ten (25%) patients had alcoholic liver disease (Table 2).

The Child–Pugh classification (Table 3) was A in 18 (45 %) patients, B in 14 (35.0%) patients, and C in 8 (20 %) patients.

According to the TNM staging system for HCC (Table 4), 21 (52.5%) patients had stage I disease, 8 (20%) had stage II disease, 6 (15%) had stage III disease, and 5 (12.5%) had stage IV disease.

Ten (25%) patients underwent radiofrequency ablation (RFA), 5 (12.5%) patients underwent microwave ablation (MWA), 13 (37.5%) patients underwent transarterial
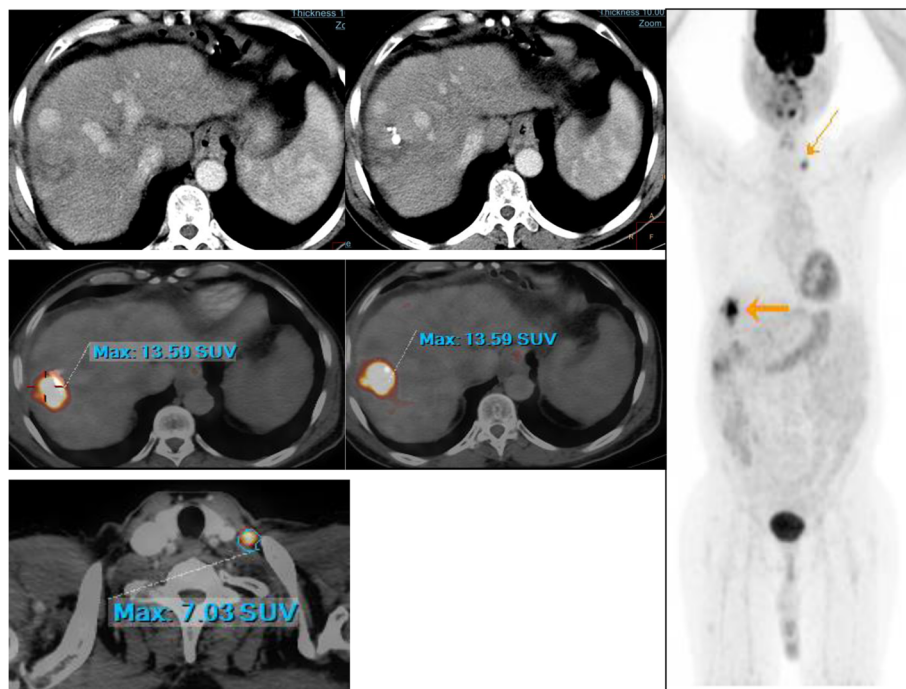
Fig. 2 A 63-year-old male having a history of HCC submitted for TACE 1.5 years ago currently presented with AFP 269. Diagnostic CT was negative, yet persistent rising of AFP PET revealed intense metabolic activity of the whole lesion achieving 13.5 SUVmax with metastatic left supra clavicular LN [7.03 SUVmax]
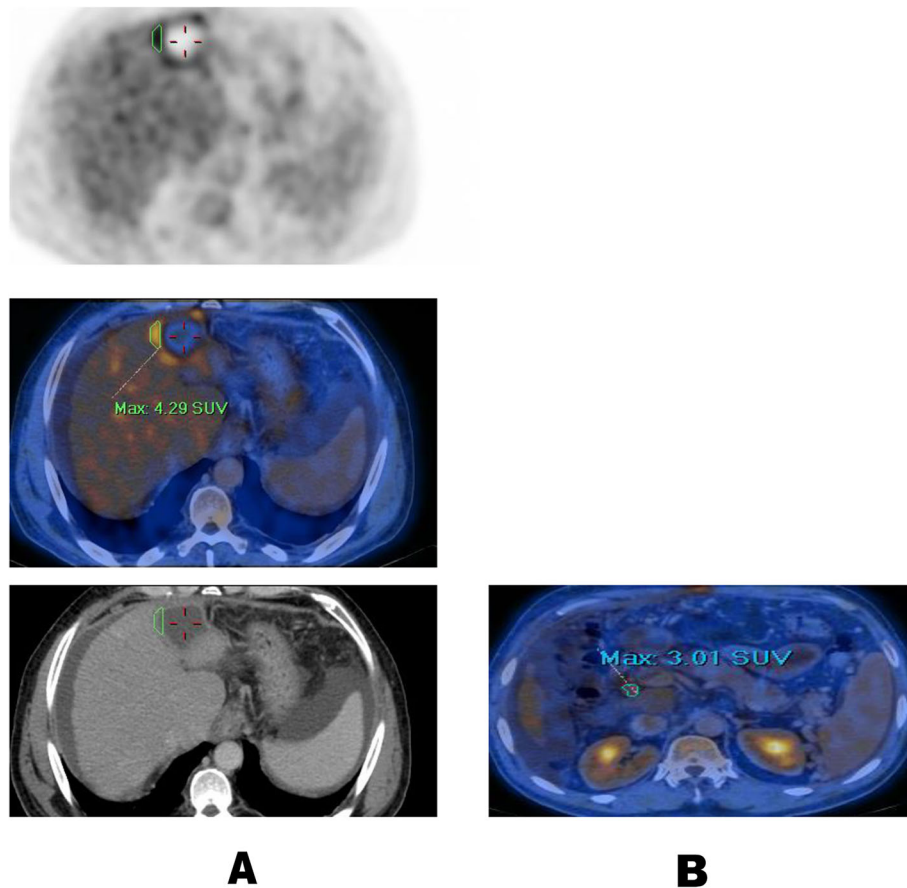
Fig. 3 A 50-year-old with HCC underwent RFA 2 months ago. The AFP was 4603 before the ablation and significantly dropped to 185 after RFA, then elevated again to 3500; PET CT is requested for further evaluation. **a** Clear detection of the marginal activity of the previously ablated lesion with SUVmax 4.2 along its lateral aspect. **b** Increased activity along a small mesenteric lymph node

chemoembolization (TACE), and 10 (25%) patients received combined technique (Table 5).

Twenty-four patients were diagnosed as complete response after management and confirmed by PET/CT. Eight patients showed focal residual/recurrence (Fig. 1), and eight patients showed newly developed lesions (Figs. 2, 3, 4 and 5). A biopsy (Table 6) was taken from the cases, in which biopsy was positive in 13 cases and negative in the other 27 cases. In 16 patients with positive FDG PET scan, alpha fetoprotein (AFP) level was less than 100 ng/ml in 9 patients and more than 100 ng/ml in 7 patients.

Regarding tumor size detected by FDG PET, HCC size was > 5 cm in eight cases and < 5 cm in eight
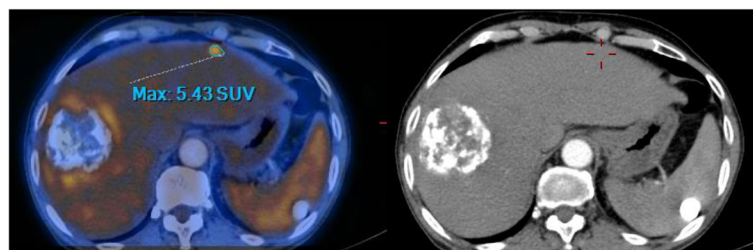
Fig. 4 A 67-year-old male patient, with right lobe hepatic focal lesion, underwent TACE 1 month ago presented now with elevated AFP referred for PET/CT assessment which revealed marginal increased FDG avidity that could represent residual activity or reactive changes, with another metabolically active left lobar subcapsular focus, mostly representing small newly developed HCC
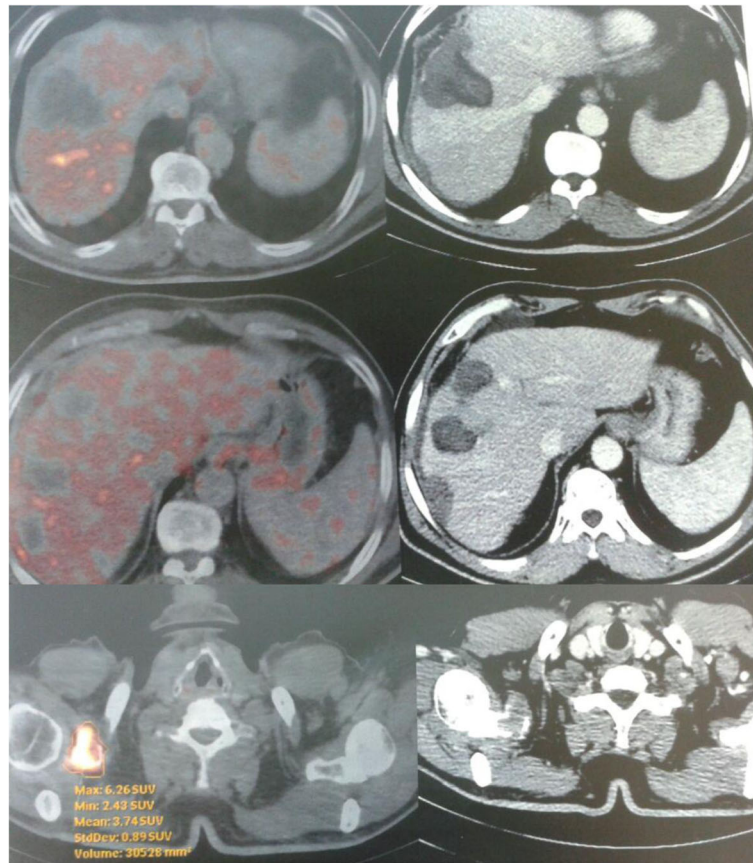
Fig. 5 A 50-year-old male patient with an elevated AFP level despite previous adequate RFA of three focal lesions. PET/CT revealed metastatic focal osteolytic lesion related to the right scapular glenoid notch achieving 6.2 SUVmax denoting metastatic nature

cases. Histologically, there were six well-differentiated, six moderately differentiated, and one poorly differentiated HCCs. FDG PET detected four of the six well- and all the six moderately differentiated HCCs plus the poorly differentiated HCCs. The intensity was evenly distributed between the different histologic grades. There was a strong correlation of FDG uptake with tumor size. In eight HCCs > 5 cm in size, four showed intense uptake on the scan. The other eight HCCs were < or = 5 cm in size, and six were negative for uptake. The sensitivity of FDG PET in detecting HCC < or = 5 cm in size is low and therefore may not be helpful in detecting all of these tumors. For larger tumors, there is a strong correlation of sensitivity and uptake intensity with tumor size and elevated AFP levels. FDG PET sensitivity and uptake intensity did not correlate with histologic grade.

Hence, PET/CT achieved sensitivity = 92.8%, specificity = 88.4%, accuracy = 90%, positive predictive value = 81.25, and negative predictive value = 95.8

Discussion

HCC is the commonest primary hepatic malignancy among adults. Globally, it is the fifth most common cancer and the third most common cause of cancer death [16]. In Egypt, HCC represents 11.75% of the malignancies of GIT and 1.68% of the total malignancies. HCC forms 70% of all hepatic tumors among Egyptians. Both hepatitis B virus (HBV) and hepatitis C virus (HCV) represent a main risk factor for HCC in Egypt other than others causes, e.g., alcoholic liver disease [17].

FDG retention in malignant cells is dependent on intracellular glucose-6-phosphatase enzymatic activity [18]. Healthy liver cells contain high level of glucose-6-phosphatase and a small amount of hexokinase, but this ratio is reversed in the malignant HCC cells. This inconsistency enables FDG to accumulate in HCC but not in normal parenchymal cells [19]. HCCs contain varying levels of this enzyme and therefore reported sensitivity of FDG PET/CT scans in detecting hepatocellular carcinoma ranges between 50 and 70%. Low sensitivity and variation in FDG uptake have been the main reasons for not routinely undergoing FDG PET/CT in HCC work up. Despite accuracy in diagnosing HCC, CT and MRI cannot distinguish a well-differentiated HCC from a poorly

differentiated HCC. Since most HCCs are not biopsied, FDG PET may play a role in predicting tumor characteristics and behavior non-invasively, as the variability of FDG uptake has been related to HCC differentiation and proliferative activity of HCC [20].

In the current study, we evaluated usefulness of FDG PET/CT in predicting prognosis of HCC. In which, we examined 40 known cases of HCC treated by different interventional techniques by using FDG PET/CT. The most important result in this study was that 24 cases showed complete metabolic response (CMR), 8 cases had partial metabolic response (PMR), and the other 8 cases showed newly developed lesions. A biopsy was taken from all cases in which 12 out of 40 were positive. The biopsy results were correlated with PET/CT findings, in which only two cases with CMR, four cases with PMR, and six cases with newly developed lesions had positive biopsies. So, in 40 patients with HCC, PET attained 83% sensitivity, 79 % specificity, and 80% accuracy in the prediction of response.

Chen et al. [21] performed 31 FDG PET studies in 26 patients who had undergone either surgical resection or interventional therapy for HCC. During their follow up, they were noted to have high AFP serum levels. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of FDG PET studies for detecting HCC recurrence were 73.3%, 100%, 74.2%, 100%, and 11.1%, respectively. Thirty patients were included in the study done by Omar et al. [22] in which all patients had history of local treatment of HCC; most of them were treated with TACE or RFA. They had undergone 18F-FDG PET/CT for evaluation of the therapeutic effect after the end of the therapy which showed sensitivity of 18F-FDG PET/CT for detecting HCC recurrence was 96.5% while the specificity was about 83.3%. Current study results agree with Refaat et al. [23] who studied 100 HCC patients who were waiting for LT and who previously underwent locoregional therapy (LRT); they concluded that FDG PET/CT prediction of recurrence had sensitivity of 92.8% and a specificity of 94.1%. Limitations of the current study were mainly a small number of the studied population.

Conclusion
Hepatocellular carcinoma (HCC) represents a common malignancy. PET/CT has an essential role in the follow-up of HCC patients after interventional management (e.g., TACE).

Abbreviations
AFP: Alpha fetoproteinCECTContrast-enhanced computed tomographyCMRComplete metabolic responseFDGFluorodeoxyglucoseHBVHepatitis B virusHCCHepatocellular carcinomaHCVHepatitis C virusLTLiver transplantationMRIMagnetic resonance imagingMWAMicrowave ablationPET/CTPositron emission tomography–computed tomographyPMRPartial metabolic responseRFARadiofrequency ablationROIRegion of interestSUVmaxMaximum standardized uptake valueTACETransarterial chemoembolizationTumor, Node, MetastasisStaging system for cancer

References
1. Janevska D, Chaloska-Ivanova V, Janevski V (2015) Hepatocellular carcinoma: risk factors, diagnosis and treatment. Open Access Maced J Med Sci. 3(4):732–736
2. Sanyal AJ, Yoon SK, Lencioni R (2010) The etiology of hepatocellular carcinoma and consequences for treatment. Oncologist. 15(suppl 4):14–22
3. Venook A, Papandreou C, Furuse J, Ladrón de Guevara L (2010). The incidence and epidemiology of hepatocellular carcinoma: a global and regional perspective the oncologist. 15:5–13.
4. Ferenci P, Fried M, Labrecque D, Bruix J, Sherman M, Omata M et al (2010) World Gastroenterology Organisation guideline. Hepatocellular carcinoma (HCC): a global perspective. J Gastrointestin Liver Dis 19:311–317.7
5. Guo J, Seo Y, Ren S (2016) Diagnostic performance of contrast-enhanced multidetector computed tomography and gadoxetic acid disodium-enhanced magnetic resonance imaging in detecting hepatocellular carcinoma: direct comparison and a meta-analysis. Abdom Radiol 41:1960
6. Choi JY, Lee JM, Sirlin CB (2014) CT and MR imaging diagnosis and staging of hepatocellular carcinoma: part II. Extracellular agents, hepatobiliary agents, and ancillary imaging features. Radiology 273(1):30–50
7. Di Martino M, Marin D, Guerrisi A et al (2010) Intraindividual comparison of gadoxetate disodium-enhanced MR imaging and 64-section multidetector CT in the detection of hepatocellular carcinoma in patients with cirrhosis. Radiology 256(3):806–816
8. Agrawal A, Rangarajan V (2015) Appropriateness criteria of FDG PET/CT in oncology. Indian J Radiol Imaging 25(2):88–101
9. Sharma B, Martin A, Zerizer I (2013) Positron emission tomography-computed tomography in liver imaging. Semin Ultrasound CT MR 34:66–80
10. Liao X, Wei J, Li Y (2018) 18F-FDG PET with or without CT in the diagnosis of extrahepatic metastases or local residual/recurrent hepatocellular carcinoma. Medicine (Baltimore) 97(34):e11970
11. Lin CY, Chen JH, Liang JA et al (2011) 18F-FDG PET or PET/CT for detecting extrahepatic metastases or recurrent hepatocellular carcinoma: a systematic review and meta-analysis. Eur J Radiol 81:2417–2422

12. Park JW, Kim JH, Kim SK (2008) A prospective evaluation of 18F-FDG and 11C-acetate PET/CT for detection of primary and metastatic hepatocellular carcinoma. J Nucl Med 49:1912–1921
13. Sun L, Guan YS, Pan WM et al (2009) Metabolic restaging of hepatocellular carcinoma using whole-body 18F-FDG PET/CT. World J Hepatol 1:90–97
14. Kuehl H, Stattaus J, Hertel S et al (2008) Mid-term outcome of positron emission tomography/computed tomography-assisted radiofrequency ablation in primary and secondary liver tumours - a single-centre experience. Clin Oncol (R Coll Radiol) 20:234–240
15. Kamel IR, Bluemke DA, Eng J et al (2006) The role of functional MR imaging in the assessment of tumor response after chemoembolization in patients with hepatocellular carcinoma. J Vasc Interv Radiol 17:505–512
16. Liao X, Wei J, Li Y et al (2018) 18F-FDG PET with or without CT in the diagnosis of extrahepatic metastases or local residual/recurrent hepatocellular carcinoma. Medicine 97:34
17. Holah NS, El-Azab DS, Aiad HA, Sweed DM (2015) Hepatocellular carcinoma in Egypt: epidemiological and histopathological properties. Menoufia Med J 28:718–724
18. Burt BM, Humm JL, Kooby DA et al (2001) Using positron emission tomography with [(18)F]FDG to predict tumor behavior in experimental colorectal cancer. Neoplasia 3(3):189–195
19. Cho KJ, Choi NK, Shin MH, Chong AR (2017) Clinical usefulness of FDG-PET in patients with hepatocellular carcinoma undergoing surgical resection. Ann Hepatobiliary Pancreat Surg 21(4):194–198
20. Abuodeh Y, Naghavi AO, Ahmed KA et al (2016) Prognostic value of pre-treatment F-18-FDG PET-CT in patients with hepatocellular carcinoma undergoing radioembolization. World J Gastroenterol. 22(47):10406–10414
21. Chen Y, Hsieh D, Liao C, Bai C, Su C, Shen Y, Hsieh J, Liao A, Kao C (2005). Utility of FDG-PET for investigating unexplained serum AFP elevation in patients with suspected hepatocellular carcinoma recurrence. Anticancer Research vol. 25; 6C, 4719-4725.
22. Omar H, Mohamed E, Ayman M, Sherif S (2017) Role of PET/CT in assessment of post therapeutic hepatocellular carcinoma. Egypt J Hospital Med 69(4):2271–2277
23. Refaat R, Basha M, Hassan M (2018) Efficacy of contrast-enhanced FDG PET/CT in patients awaiting liver transplantation with rising alpha-fetoprotein after bridge therapy of hepatocellular carcinoma. Eur Radiol 28:5356

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