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

| Demographic Data | All studied patients (n = 40) |
|------------------|-----------------------------|
| Gender           |                             |
| Female           | 14                          | 35%                      |
| Male             | 26                          | 65%                      |
| Age              |                             |
| Mean ± SD        | 53 ± 17                     |
| Median (range)   | 58 (23-80)                  |

### 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 m² 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;
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 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 5

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

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.
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

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

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

**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 supraclavicular LN [7.03 SUVmax]
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
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 fetoprotein
CECT: Contrast-enhanced computed tomography
CMR: Complete metabolic response
FDG: Fluorodeoxyglucose
HBV: Hepatitis B virus
HCC: Hepatocellular carcinoma
HCV: Hepatitis C virus
LT: Liver transplantation
MR: Magnetic resonance imaging
MWA: Microwave ablation
PET/CT: Positron emission tomography–computed tomography
PMR: Partial metabolic response
RFA: Radiofrequency ablation
ROI: Region of interest
SUV: Standardized uptake value
TACE: Transarterial chemoembolization
Tumor, Node, Metastasis: Staging system for cancer

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Authors’ contributions

AM, MM, and OA conceived and designed the analysis. SR collected the data, performed the analysis, and wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the ethical committee of Ain Shams University on June 2016 (no reference number was given at that time). All patients included in this study gave written informed consent to participate in this research by the patients themselves or by primary degree relatives.

Consent for publication

Patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests

The authors declare that they have no competing interests.

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