

# Role Of PET/CT in Assessment of Post Interventional Treatment of Hepatocellular Carcinoma

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**Abstract:**

**Purpose:** to highlight the role of PET/CT in evaluation of post interventional treatment (radiofrequency ablation & TACE) of hepatocellular carcinoma. **Background:** Hepatocellular carcinoma (HCC) is one of the major causes of mortality among patients with cirrhosis. It represents about 11.85% of the malignancies of all GIT organs and 1.78% of the total malignancies among Egyptians. **Patients and methods:** From February 2018 to November 2019, twenty five patients (20 males and 5 females, their age ranged from 44 to 75 years with mean age of  $60.60 \pm 7.35$  years) were referred to the radiology unit with hepatocellular carcinoma and had underwent TACE ( 2 patients had history of combined TACE and RFA procedures ). <sup>18</sup>F-FDG PET/CT and triphasic CT examinations were conducted in a private radiology center in Cairo for all patients using combined PET-CT machine (Philips intgenuity TF PET/CT 128 slices). **Results:** PET/CT showed true positive results in 20 patients, true negative results in 3 patients, false negative results at one patient and false positive results at one patient. In our study, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of <sup>18</sup>F -FDG PET/CT were 95.24%, 75%, 95.24%, 75% and 92% respectively. **Conclusion:** PET/CT showed higher accuracy in assessment of the intervention bed without affection by lipiodol artifact as well as detection of extra hepatic spread of HCC in single whole body examination which is crucial for patients preparing for liver transplantation and differentiation between benign and malignant portal vein thrombosis.

**Key words:** 18F-FDG PET/CT, HCC, TACE, AFP



## Abbreviations:

|             |  |
|-------------|--|
| <b>AFP</b>  | Alpha-fetoprotein                          |
| <b>CECT</b> | Contrast enhanced computed tomography      |
| <b>PET</b>  | Positron Emission Tomography               |
| <b>CT</b>   | Computed tomography.                       |
| <b>CTAC</b> | Computed tomography attenuation correction |
| <b>FDG</b>  | Fluorodeoxyglucose                         |

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## Introduction

Hepatocellular carcinoma (HCC) represents the commonest primary hepatic tumor of adults. It is the 6th most common tumor in the world and the third commonest cause of cancer related deaths (1).

Based on their gene expression profiles HCCs with high  $^{18}\text{F}$ -FDG uptake are reported to be more aggressive than HCCs with low  $^{18}\text{F}$ -FDG uptake. Moreover, baseline PET/CT has great prognostic value for HCC patients who are treated with radiofrequency ablation and TACE (2, 3).

Interventional treatment has been applied to patients with inoperable HCC. Despite initial remission of HCC after interventional treatment, recurrence is common.

Since patients with recurrent HCC may be amenable to potentially curative resection, early detection of intrahepatic recurrence and /or extra hepatic metastases is extremely important and can facilitate successful retreatment at an early stage (4)

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## Aim of the Work

The aim of this study is to highlight the role

of PET/CT in evaluation of post interventional treatment (radiofrequency ablation & TACE) of hepatocellular carcinoma, hence guiding the clinician to proper management strategy

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## Patients and Methods

### Patients

The study was prospectively on twenty five patients (20 males and 5 females) during the period from February 2018 to November 2019, their age ranged from 44 to 75 years with mean age of  $60.60 \pm 7.35$  years) were referred to the radiology unit with hepatocellular carcinoma and had underwent TACE ( 2 patients had history of combined TACE and RFA procedures ).  $^{18}\text{F}$ -FDG PET/CT and triphasic CT examinations were conducted in a private radiology center in Cairo for all patients using combined PET-CT machine (Philips intgenuity TF PET/CT 128 slices). The study was approved by the institutional ethics committee.

### Inclusion criteria:

- Patients of any age who underwent TACE for HCC.
- One patient had submitted to TACE on transplanted liver was included .
- Both sexes were included.

### Exclusion criteria:

- Patients with past history of contrast

allergy.

- Patients with blood glucose level >300 mg/dl at the time of the study.
- High serum creatinine > 2 mg / dl.
- Small lesions < 10 mm

### **Technique of examination:**

#### **Patient preparation:**

##### ➤ **2 days prior to examination:**

- Refrain from all strenuous activity.

##### ➤ **1 day prior to examination:**

- Limitation of carbohydrate diet for the previous 24 hours before the date of examination.
- High water intake was allowed.

##### ➤ **12 hours prior to examination:**

- Nothing to eat or drink, except water, for 6 hours before the examination. Drinking water as much as possible was needed until arrival.
- Serum creatinine level measurement.
- For diabetic patients:
  - ❖ Patients on oral hypoglycemics must be fasting for at least 6 hours prior to the examination with administration of the routine oral medical regimen.
  - ❖ Patients on insulin regimen should control blood glucose level to be less than 200 mg/dl for at least 2 days prior to the examination, then patients had breakfast at the early morning with

administration of the regular insulin regimen followed by total fasting, with exception of water intake.

##### ➤ **On the day of study:**

- Patient must be present 15-30 minutes before PET scan.

- A consent form was signed by the patient (or his guardian) after the detail of the procedure was explained.

- Remove metallic items and jewelry and the patient was given a gown to wear.

- Assessment of patient's body weight.

- Serum glucose level was measured in the center just before 18F-FDG injection, and it must be less than 200 mg/dl.

☒ In case of diabetic patients with blood glucose level above 200 mg/dl, subcutaneous insulin injection was administered with monitoring of the blood glucose level until reaching the accepted level (100-200 mg/dl) then the study was started.

- Fixation of intravenous cannula.
- Detailed explanation of the procedure, including strict instructions to keep

calm and avoid muscular activity prior to the examination.

- FDG was administered and must circulate for approximately 50- 60 minutes prior to the scan, during this period; patient must be in quite resting position.
- The scan took 20 minutes at the machine.

### **1- 18 FDG Dose:**

- 1 mCi /10Kg of 18FDG was administered to each patient 60 minutes before the examination.

### **2- Examination time:**

The whole study took approximately 80 minutes (60 minutes in waiting room after FDG injection then 20 minutes at the PET /CT machine.

The examination was performed starting by low dose non enhanced CT scan for attenuation correction, then a whole body PET study followed by Triphasic CT.

### **3- Patient position:**

- ✓ The patient was asked to empty the bladder before entering the PET/CT machine.
- ✓ The patient was introduced to the PET-CT machine, lying in supine position with head fixation and arms elevated up.

### **4- PET Technique:**

PET was performed following the attenuation correction CT study without moving the patient. Approximately 9 to 11 bed positions were planned in the three-dimensional acquisition mode for scanning the entire patient in one and half minute for image acquisition at each bed position.

### **5- PET/CT Fusion:**

For each of these sets of PET and CT images, corresponding “fusion” images, combining the two types of data, were processed by special software to produce functional and anatomical image simultaneously.

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## **Results**

Twenty five patients (20 males and 5 females) were included in this study. Their age ranged from 44 to 75 years with mean age of  $60.60 \pm 7.35$  years. All patients had history of local treatment of HCC by trans-arterial chemoembolization (2 patients had history of combined TACE and RFA)

The diameter of the lesions ranged between 1cm and 8.5 cm with mean diameter of  $4.2 \text{ cm} \pm 1.79$ .

The hepatic segmental distribution of the chemo-mobilized lesions was as following:

segment II ( 1 patient) , segment III ( 2 patients ), segment IV ( 2 patients), segment V ( 3 patients ) ,segment VI ( 3 patients ) , segment VII ( 7 patients ) , segment VIII ( 6 patients ) and one patient on top of transplanted liver (1 patient ) as described in table 1.

|                 |                    | Total no. = 30 |
|-----------------|--------------------|----------------|
| Site of lesions | II                 | 1 (4%)         |
|                 | III                | 2 (8%)         |
|                 | IV                 | 2 (8%)         |
|                 | V                  | 3 (12%)        |
|                 | VI                 | 3 (12%)        |
|                 | VII                | 7 (28%)        |
|                 | VIII               | 6 (24%)        |
|                 | Transplanted liver | 1 (4%)         |
| Size of lesion  | Mean ± SD          | 4.20 ± 1.79    |
|                 | Range              | 1 – 8.5        |

To determine the accuracy of the results, our standard included laboratory serial AFP level monitoring, follow up by different imaging modalities and histopathological results of the resected liver in case of transplantation .

Serial AFP monitoring of the 25 patients were as following; 23 patients had persistent elevated AFP levels and the remaining 2 patients had normal levels of AFP and were preparing for liver transplantation. Out of the 23 patients with elevated AFP levels, triphasic CT study was positive for viable tumoral tissue in only 18 patients and showed no enhancement in 5 patients, among these CT negative patients, PET /CT showed positive nodular FDG uptake at intervention bed in 2 patients and the other 3

patients showed extra hepatic metastatic spread in spite of successful local chemo-embolization. While PET/CT was positive in 22patients out of the 23 patients with elevated AFP levels, this leaved a single fore mentioned patient by PET/CT showed characteristic enhancement pattern of viable HCC at triphasic CT.

The other 2 patients with normal AFP level showed no abnormal findings on CT, yet on PET/CT there was a single false positive case due to regional hyperemia causing increased FDG uptake. This case of regional hyperemia underwent liver transplantation and histopathological results of the resected liver revealed complete necrosis with no malignant cells.

Among the patients with positive extra hepatic metastasis detected by PET/CT; one patient showed local recurrence at the intervention bed with metastatic abdominal lymph nodes and 2 patients were positive for extra hepatic metastasis in spite of successful local treatment ( one patient was positive for osseous deposits and the other one for supra renal metastasis).

PET/CT showed true positive results in 20 patients, true negative results in 3 patients, false negative results at one patient and false positive results at one patient.

In our study, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of <sup>18</sup>F-FDG PET/CT were 95.24%, 75%, 95.24%, 75% and 92% respectively as described in table 2.

| PET | Sensitivity | Specificity | PPV    | NPV | Accuracy |
|-----|-------------|-------------|--------|-----|----------|
|     | 95.24%      | 75%         | 95.24% | 75% | 92%      |

PPV positive predictive value.  
NPV negative predictive value

## Discussion

Hepatocellular carcinoma is one of the most common malignant tumors worldwide. Early detection and treatment of recurrent HCC after loco regional interventional treatment are important for patient survival (2).

Percutaneous techniques such as TACE are now available to manage HCC. Assessment of tumor response after TACE is important to determine whether the tumor is completely eradicated or needs additional treatment (2).

CT and MRI are the most widely used tools to assess patients underwent loco-regional intervention procedures such as TACE based on reduction in size or changes in the internal structure as well as enhancement pattern (2).

The evaluation of treatment response using

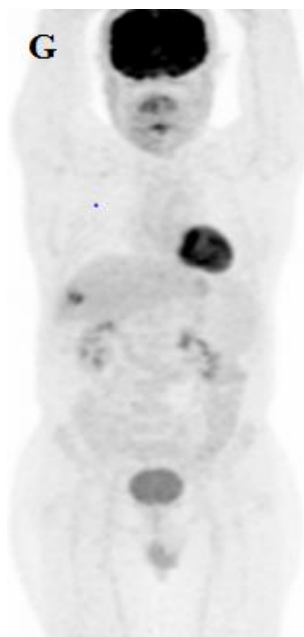
size criteria, based on the Response Evaluation Criteria in Solid Tumors (RECIST), does not apply well post chemoembolization of HCC. So, most investigators have depended on the presence or absence of contrast enhancement for determination of therapeutic response (2).

The European Association for the Study of the Liver (EASL) criteria and the modified Response Evaluation Criteria in Solid Tumors (mRECIST) have been widely used for post TACE assessment however evaluation of the lesions based on enhancement criteria might not be in agreement with the actual biological assessment(5).

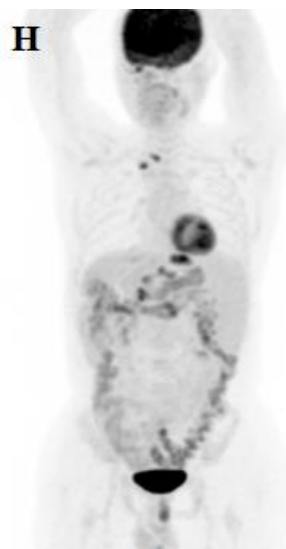
The beam-hardening artifact of high-attenuation lipiodol on CT masks the intra-lesional viable tumor detection, in addition after TACE the feeding arteries of the residual tumor are significantly thinner; these changes may affect the degree of enhancement of the tumor (4).

The complete and homogenous intra-lesional deposition of lipiodol would indicate a high degree of necrosis within the lesion: however, it is difficult to discriminate correctly the viability and necrosis of the tumors in case of dispersed deposition of lipiodol, because lipiodol-negative areas do not correspond to viable

areas of the tumors. On the contrary, whole-body 18F-FDG PET/CT scan may represent a valuable imaging tool to detect residual viable tissue based on metabolic activity without affection by lipiodol artifact (4) as described in figure1.



PET/CT is a unique combination of the cross-sectional anatomic data provided by CT and the metabolic data provided by PET. It has the advantage of local therapy assessment as well as detection of extra hepatic spread of HCC which is crucial for planning of liver transplantation. In contrast to the morphological image diagnosis, FDG-PET evaluates viability based on glucose metabolism and it is not influenced by tumor morphology or lipiodol deposition (6) as described in figure2.



The avidity of FDG uptake was defined in our study as maximum standardized uptake value (SUV max). Positive FDG uptake is considered when the lesion uptake is higher than the physiological background activity of normal liver tissue which was also adopted by the study done by (7).

In our study the median value of Tumor-SUVmax in the positive cases was 7.4 (ranged from 3.5 to 24), most of them were poorly differentiated HCCs, yet a single case measuring about 1.4 SUVmax was a well differentiated HCC type. In the study done previously (8) the median value of Tumor-SUVmax 4.3 (ranged from 2.0 to 11.6).

The median value of TSUV max / LSUV max in our study is 2.9 (range from 1.06 to 7.27) considering the cut off value 1.06 which is correlated to the study done before



(9), where the TSUV max/LSUV max cut off value was 1.65.

The false positive interpretations in PET/CT are due to physiological uptake, infection and recent chemotherapy whereas false negative results may be found with well differentiated HCC and the small lesions below the scanner resolution (< 10 mm) (6). Therefore in our study the examination was done at least 6 weeks after TACE for the most accurate characterization of loco-regional response after chemoembolization.

Small lesions < 10 mm that are below the scanner resolution might be missed unless they show avid FDG uptake on top of normal liver tissue background activity so lesions less than 10 mm were excluded from our study.

The diameter of the lesions in our work ranged between 1cm and 8.5 cm (with mean diameter of 4.2 cm) which is comparable to the study done by (8) where the diameter of the lesions ranged between 2.5 and 10.5 cm (with mean diameter of 5.5 cm).

Although PET-CT has been found to show suboptimal sensitivity in detection of well differentiated HCC where the lesion FDG uptake is similar to the surrounding normal liver activity, it is useful in the detection of extra hepatic spread of HCC with superior

accuracy in comparison with CT and MRI. According to (10), <sup>18</sup>F-FDG PET has been used in many institutes to assess extra hepatic metastasis before liver transplantation for HCC.

The higher sensitivity of PET for detecting extra hepatic metastases of HCC as compared with primary lesions could be explained by an increased likelihood for metastasis to occur in poorly differentiated type of HCC, which tends to have a higher level of FDG uptake (11).

Our study demonstrated higher sensitivity of PET/CT in detection of local viable tumoral tissue following TACE which may be masked by lipiodol artifact in addition to its ability to detect extra hepatic metastasis of HCC in a single whole body examination which may be crucial for patients preparing for liver transplantation hence influencing patient selection.

In our study PET/CT showed sensitivity, specificity and accuracy of 95.24%, 75% and 92% respectively. These results are comparable to many studies as (9) who reported that PET /CT sensitivity, specificity and accuracy for detection of viable HCC after TACE were 89.29%, 65.71% and 80.22% respectively. Also (2) stated that the respective values for sensitivity, specificity and accuracy of PET/ CT in the evaluation

of early treatment response after interventional therapy for hepatocellular carcinoma were 87.5 %, 71.4% and 80.0 %. Also (12) stated that the sensitivity and specificity of PET/ CT in assessment of post therapeutic hepatocellular carcinoma were 100 %, and 83.3 % respectively and he stated that the relatively high sensitivity was attributed to that most positive HCC cases in his study were of poorly differentiated type which showed FDG avidity.

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