The Egyptian Journal of Hospital Medicine (October 2017) Vol. 69 (4), Page 2271-2277

Role of Pet/Ct in Assessment of Post Therapeutic Hepatocellular Carcinoma

Omar Hussain Omar, Mohamed Elgharib Abo Elmaaty, Ayman Mohamed Ibrahim, Sherif Sameh Soliman

Radiodiagnosis Department, Ain Shams University, Cairo, Egypt

Corresponding author: Sherif Sameh Soliman Hassan, e***mail:*** sherifsameh2000@yahoo.com.**Tel**.01005601993

ABSTRACT

Aim of the work*:* this study aimed to highlight the role of PET/CT in evaluation of post-therapeutic hepatocellular carcinoma, hence guiding the clinician to proper management strategy.

Patients and methods*:* 35 patients (32 male and 3 female) were included in this study. All patients had history of local treatment of HCC; most of the cases were treated with TACE or RFA. They had undergone ^{18}F-FDG PET/CT for evaluation of the therapeutic effect after the end of the therapy.

Results: our study demonstrated that ^{18}F-FDG PET/CT is a significant prognostic factor for tumor recurrence in post-therapeutic HCC with a cutoff TSUVmax/LSUVmax value of 1.3.

Conclusion*:* ^{18}F-FDG PET/CT imaging have a prognostic significance in evaluation of patients with post-therapeutic HCC and provide valuable information that can be used in the treatment response evaluation and clinical decision making process.

Keywords: FDG, PET, PET/CT, post-therapeutic, HCC, Hepatocellular carcinoma.

INTRODUCTION

HCC is the leading cause of death now among patients having liver cirrhosis [(1)]. Surgical treatment, including hepatic resection and liver transplantation is considered as the most effective treatment of HCC. Patients with inoperable HCC were treated via interventional treatment [(2)].

^{18}F-FDG PET /CT has been applied routinely for assessment of patients with HCC before liver transplantation, also after transplantation it can provide additional information beyond that provided by conventional modalities and contribute to the clinical management of HCC recurrence ,especially in patients with extra hepatic recurrence [(3)]. The reported increased sensitivity of ^{18}F-FDG PET/CT over CT & MRI was attributed to its ability for detection of metabolic abnormalities that precedes morphological changes by CT [(2)]. Based on gene expression profiles of HCCs, high ^{18}F-FDG uptake HCCs are reported as more aggressive than low ^{18}F-FDG uptake HCCs. Moreover, baseline PET/CT have great prognostic value in HCC patients who were treated with resection, radiotherapy, chemotherapy and TACE [(1,4)].

PATIENTS AND METHODS

From January 2015 to March 2017, thirty five patients (32 male and 3 female), their age ranged from 30 to 73 years with a median age 56 years, were referred to the radiology unit with hepatocellular carcinoma and had underwent interventional treatment for assessment by ^{18}F-FDG PET/CT. Examination was conducted in a private radiology center in Cairo. Patients had a history of local treatment, including transarterial chemoembolization (14 patients), radiofrequency ablation (13 patients), combination of these (transarterial chemoembolization and radiofrequency ablation in 2 patients) and surgical resection in 6 patients.

All patients underwent PET/CT imaging in the supine position after a 6 h fast. A combined PET/CT scanner (Philips Ingenuity TF - PET/CT, 128 MDCT) was used. Scans were acquired 60 min after intravenous injection of 5.5 MBq/kg of body weight of ^{18}F-FDG (275~528 MBq, 7.43 mCi~14.27 mCi). A low dose non contrast CT acquired within a short period of time for attenuation correction and anatomic localization followed by PET scan covering a field of view from the skull base to the mid thighs followed by injection of I.V. non-ionic contrast (with dose 1mg/kg patient body weight) and then a diagnostic 128 MDCT examination of the same regions was done. Lesions were identified by presence of metabolically active tumor tissue with high FDG accumulation and correlate this activity to its anatomical site in the combined PET/CT images.

The images were interpreted both visually and semi quantitatively for the regions with pathologic tracer accumulation using standardized uptake value (SUV). The SUV is a semi quantitative assessment of the radiotracer uptake from a static (single point in time) PET image. We rely on visual inspection and use SUV in assessing questionable lesions or in the follow-up of FDG-avid masses. Typically, malignant tumors have an

Received: / /2017
Accepted: / /2017

DOI : 10.12816/0041529

SUV of ≥3.0, whereas normal tissues such as the liver, lung, and marrow have SUVs ranging from 0.5 to 2.5. It is useful to know the tumor SUV before initiation of therapy (if available) to assess tumor grade and evaluate treatment response following radiation therapy or chemotherapy. The diagnosis of HCC was confirmed based on the European Association for the Study of the Liver (EASL) criteria in most of the cases.

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

RESULTS

Our study included 35 patients (32 male and 3 female). All patients had history of local treatment of HCC, including transarterial chemoembolization in 14 patients (40% of cases), radiofrequency ablation in 13 patients (37.1% of cases), combination of these (transarterial chemoembolization and radiofrequency ablation in 2 patients (5.7% of cases) and surgical resection in 6 patients (17.1% of cases).

Thirty cases were diagnosed with recurrence either local or distant and 5 cases showed no recurrence. Of the recurrent cases 5 were positive for vascular invasion, 8 were positive for lymph nodes recurrence (4 regional & 4 distant), 5 were positive for bone and 3 for lung metastasis. Of the recurrent cases 5 cases had only extra hepatic recurrences (**Table 1).**

Table 1: tumor characteristics according to recurrence

Vascular invasion	
Positive	**5**
Negative	**25**
Lymph nodes	
Regional	**4**
Distant	**4**
Negative	**22**
Bone metastasis	
Positive	**5**
Negative	**25**
Lung metastasis	
Positive	**3**
Negative	**27**
5 cases with only extrahepatic recurrences	

The median value of Tumor-SUVmax in the positive cases was 6.3 (ranged from 3.5 to 15), most of them were poorly differentiated HCCs, yet with a single case measuring about 2.1 SUV max (of well differentiated HCC).The diameter of the lesions ranged between 2 and 12 cm (with mean diameter of 4.5 cm).

The sensitivity of the diagnosis by ^{18}F-FDG PET/CT was 100 % in our study. While, the specificity was about 83.3%. The ^{18}F-FDG PET missed a case of SUV 2.1 because it was well differentiated type of HCC. Thus, reducing its sensitivity to 96.55% yet with the same specificity 83.3%.

The median value of Tumor SUVmax/Liver SUVmax (TSUVmax/LSUVmax) value in the positive cases was 3.18 (ranged from 1.3 to 6.8), most of them were poorly differentiated HCCs, while the single well differentiated case measured about 1.1. Thus the cutoff TSUVmax/LSUVmax value in the current study was about 1.3 or more.

Figure 1 showing a 55 years old male patient presented with post-chemoembolized HCC at sub segment IV shows concentric lipidol concentration with focal intense avidity for l8F-FDG at its lateral posterosuperior aspect and SUV max 5.6. This area corresponds to mild enhancement in the CT component of the study reflecting residual viable tumoral tissue.

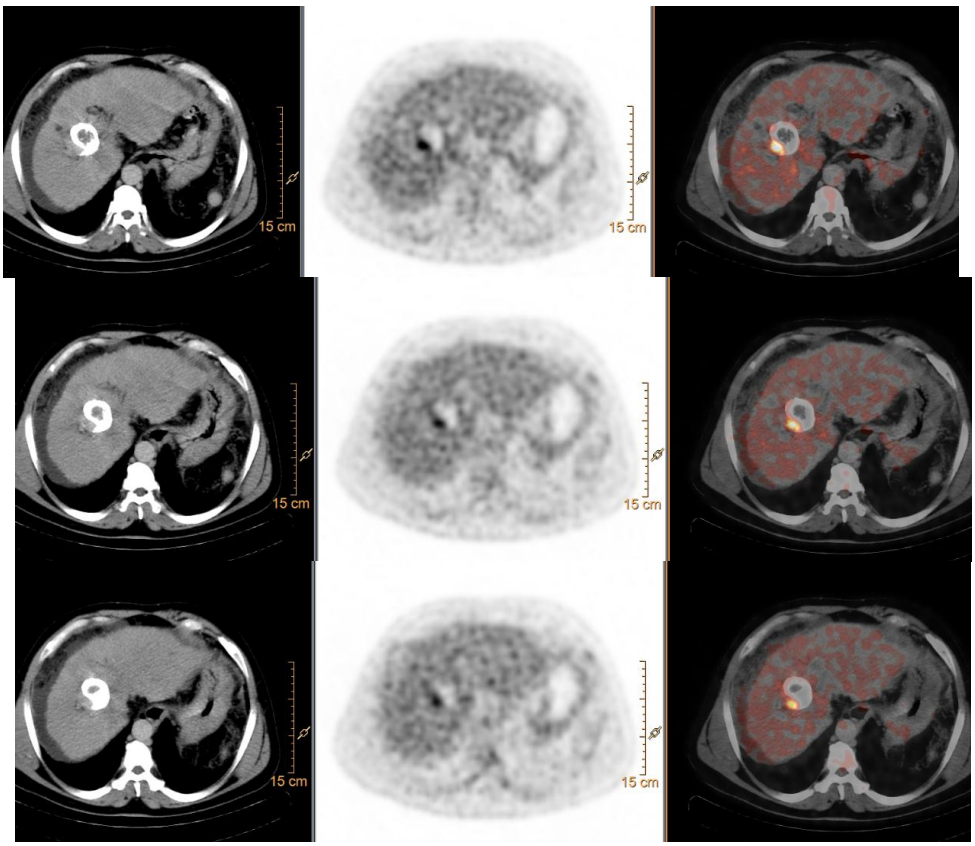
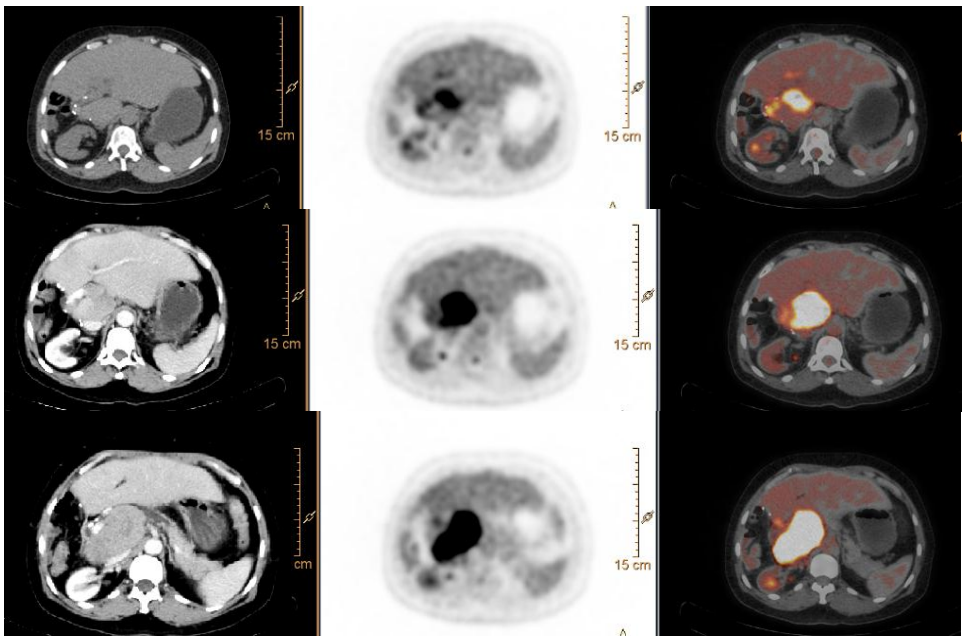


Fig. 1: case number 1; CT, PET and combined PET/CT images

Figure 2 showing a 57 years old male patient presented with surgically resected HCC with elevated alpha-fetoprotein, the images show recurrent metabolically overactive mass lesion at the caudate lobe with partial encasement of the IVC, yet no evidence of direct infiltration. The mass shows increased FDG uptake with SUVmax of 15. Few hypermetabolic peripancreatic and celiac metastatic lymphadenopathy matted together to form sizeable mass showing increased FDG uptake with SUVmax of 14.



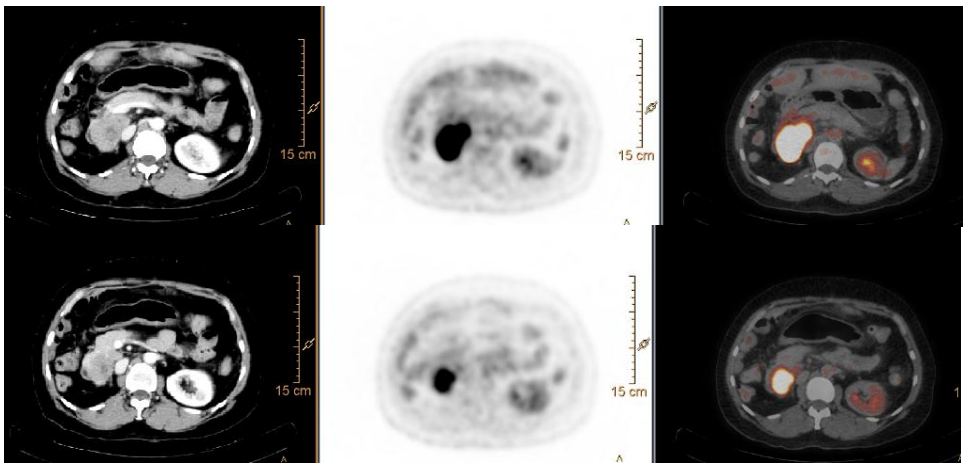


Fig. 2: case number 2; CT, PET & combined PET/CT images

Figure 3 showing a 44 years old male patient presented with radiofrequency ablated HCC showing two newly developed metabolically active hepatic focal lesions at segment II and VIII (with SUVmax of 7.2) associated with tumor thrombosis of the left portal branch (SUVmax of 10.3).

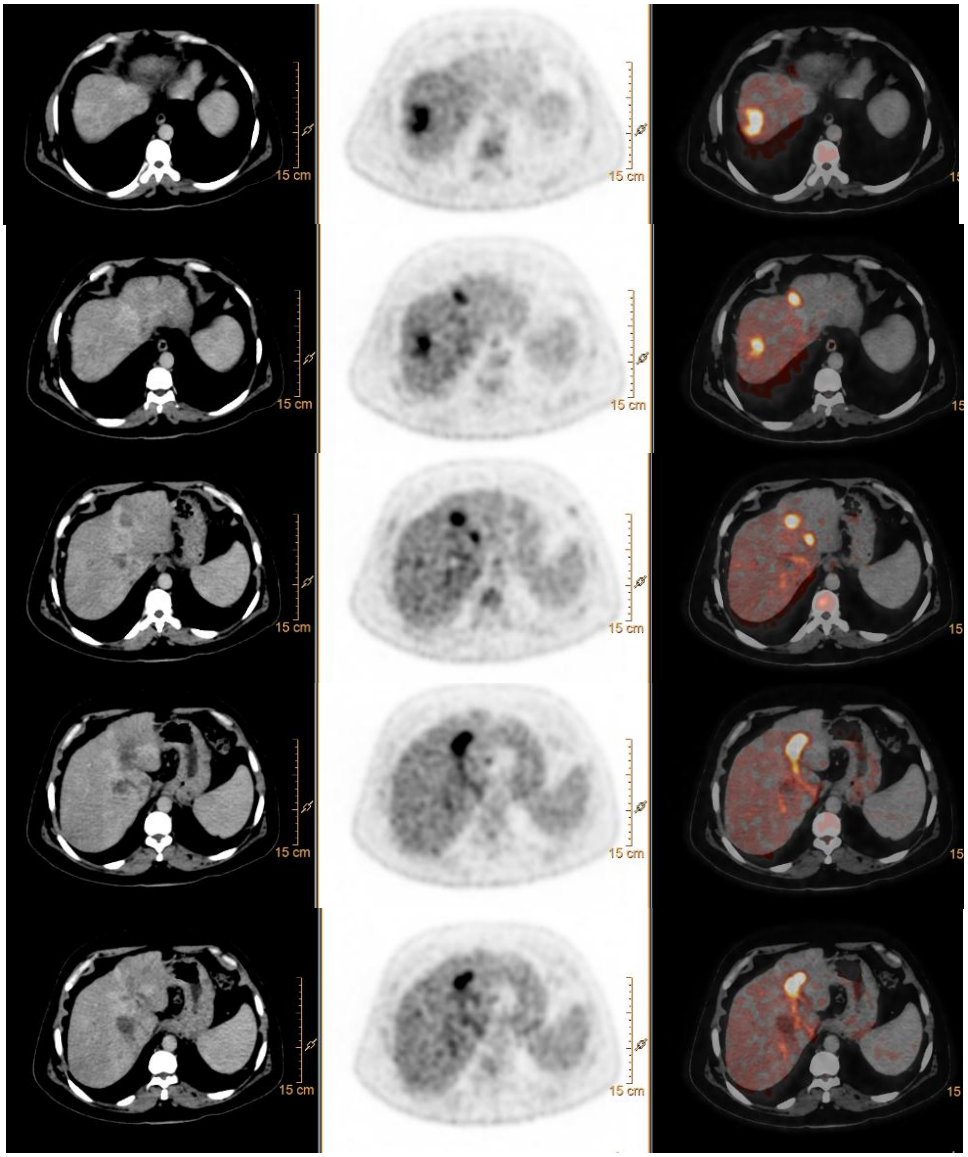


Fig. 3: case number 3; CT, PET & combined PET/CT images

Figure 4 showed a 67 years old male patient presented with multiple radiofrequency ablated HCC with elevated alpha-fetoprotein, the images show newly developed neoplastic focal hepatic lesion seen at segment IV with wide spread peritoneal, osseous and left hilar lymph node metastatic deposits.

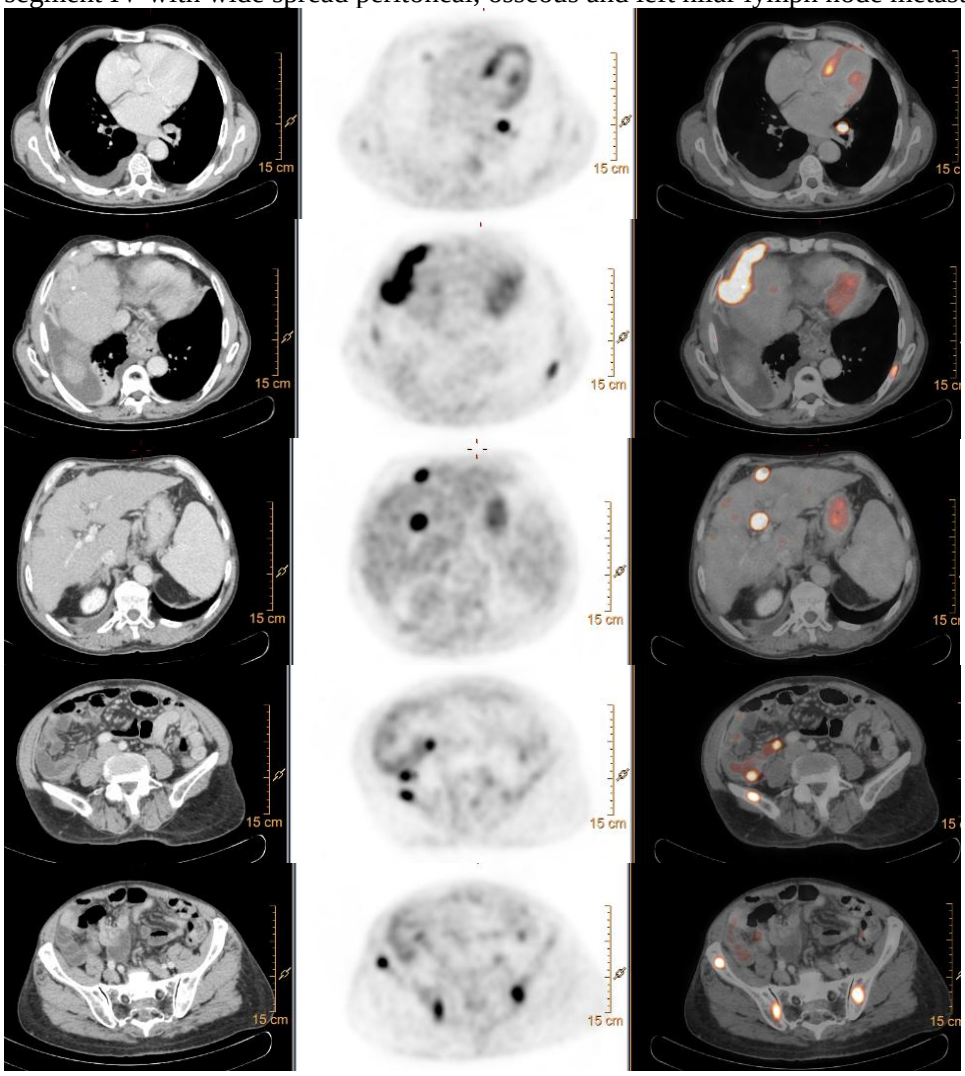


Fig. 4: case number 4; CT, PET & combined PET/CT images

DISCUSSION

The most widely used radiologic modality for screening of HCC is ultrasonography, with sensitivity around 60%. A better sensitivity is obtained with contrast-enhanced CT, around 70%, and MRI, around 80%. Yet additional 30%–50% of unknown intrahepatic sites of HCC (mostly ≤ 2 cm) are usually found at transplantation. The coupling of CT with PET brings a complementary metabolic approach to the characterization of nodules that can be useful particularly in small nodules between 0.7 and 2 cm [(5)].

We noticed that the conventional imaging modalities (such as US, CT or MRI) can't satisfy clinicians in analyzing the therapeutic effect rapid enough, because therapy evaluation by these anatomical imaging modalities requires sufficient time to confirm tumor shrinkage. Especially that the ability of contrast-enhanced CT to determine tumor viability after TACE is limited because the retained hyper-attenuating lipiodol material makes it difficult to detect contrast enhancement within a viable tumor. However the data in our study showed that FDG PET/CT as a metabolic imaging modality could evaluate therapeutic effect and prognostic value in patients with post therapeutic HCC and also can sensitively detect both primary and metastatic tumors.

Lipiodolized HCCs particularly low-grade tumors frequently showed increased ^{18}F-FDG uptake. This may be caused by increased glycolysis in residual tumors after TACE. The increased ^{18}F-FDG uptake observed in lipiodolized, compared with native tumors may be

also attributable to a more aggressive growth of residual viable tumor when TACE is not completely effective. TACE has been shown to stimulate tumor angiogenesis, thus increasing the proliferative activity of tumor cells to some degree, as after TACE tumor cells are exposed to an extremely hypoxic or even anoxic environment [(6)]. In conclusion after TACE, ^{18}F-FDG uptake was not correlated with pathologic grade, in contrast to treatment native HCCs. ^{18}F-FDG PET/CT showed high diagnostic sensitivity in detecting viable HCCs, with moderate specificity. This method may be useful in determining the viability of lipiodolized HCCs in patients with increased serum AFP concentration or normal results on multiphasic contrast-enhanced CT [(3)].

Lee *et al*. [(7)] stated that based on the gene expression profiles of HCCs, those with high ^{18}F-FDG uptake are reported to be more aggressive than HCCs with low ^{18}F-FDG uptake**.** This is in accordance with results of **Ho *et al*.** [(8)] who stated that less differentiated HCC tumors have lower levels of glucose-6-phosphatase enzyme (which is responsible for rapid clearance of FDG-6-phosphate from hepatocytes) and higher levels of hexokinase, leading to accumulation and trapping of F-FDG intracellular likely causing intense FDG uptake of these tumors on PET. And this also was noted in our study where almost all positive cases of HCC were of moderately or poorly differentiated types, showing increased FDG uptake and SUVmax value >3.5, while a single case of well differentiated type was encountered in our study showing relatively low ^{18}F-FDG uptake and 2.1 SUVmax value.

For the diagnosis of primary HCC, the sensitivity of ^{18}F-FDG PET is relatively low as FDG metabolism is nearly normal in highly differentiated HCCs but notably deteriorated in undifferentiated HCCs thus leading to the high sensitivity of ^{18}F-FDG PET in detection of undifferentiated HCCs as most of cases in the current study.

The pathology of extrahepatic metastases from primary HCC is usually moderately differentiated, poorly differentiated or undifferentiated HCC. PET can detect extrahepatic metastases with high sensitivity probably due to the relationship between histological grading and in vitro enzymatic activity of glucose metabolism. Aerobic glycolysis and glucose metabolism are increased in moderately differentiated, poorly differentiated and undifferentiated hepatoma cells [(9)].

Several studies have investigated the relationship between PET/CT and extrahepatic metastases of HCC. **Sugiyama *et al.*** [(10)] reported a detection rate of 83% for extrahepatic metastases in patients with HCC, including lesions more than 1 cm in diameter. **Nagaoka *et al.*** [(11)] also reported that PET/CT alone detected 89.6% of extrahepatic metastases.

The great advantage of the PET/CT is its capability to perform full body scanning in a single session, which help detection of the primary lesion and metastatic foci in one examination, also it has high tumor to non-tumor contrast allowing the detection of small lesions that may escape detection by conventional imaging modalities. As in case number 4 in our study where the newly developed focal hepatic lesion was small subcentimeteric and subcapsular in location and inconspicuous by CT alone yet it showed high metabolic activity on PET/CT achieving 5.4 SUV max.

Park *et al.* [(12)] has stated that ^{18}F-FDG, as a marker of dedifferentiated HCC tumor pathology, has been shown by other researchers of being a predictor of tumor recurrence and less favorable outcome after transplantation. ^{18}F-FDG has been documented by numerous data in the literature to serve as an indicator of aggressiveness for a variety of cancer types. In fact, we have also published on the role of ^{18}F-FDG in the detection of poorly differentiated HCC and microvascular invasion for patients receiving a liver transplant. Patients with HCC tumors avid for ^{18}F-FDG have significantly less favorable overall survival and an increased chance of HCC recurrence.

Extensive morphologic studies have revealed that many HCCs arise in equivocal nodular lesions, such as dysplastic nodules in the cirrhotic liver and are highly differentiated in the early stages. At the same time, it has been established that well-differentiated HCC in the early stages evolves to advanced and dedifferentiated tumor in a multistep fashion. This is particularly true for patients with chronic HBV and HCV infections [(13)].

Our study demonstrated that ^{18}F-FDG PET/CT is a significant prognostic factor for tumor recurrence in post-therapeutic HCC, with a cutoff TSUVmax/LSUVmax value of 1.3, comparable with that's of **Lee *et al.*** [(14)] in which the cutoff TSUVmax/LSUVmax value was about 1.15.

In the current study, the sensitivity of the diagnosis by ^{18}F-FDG PET/CT was 100% in our study. While the specificity was about 83.3%. This relatively high sensitivity could be attributed to that most positive HCC cases in our study were of dedifferentiated type which shows FDG avidity while the single case of well differentiated HCC was missed by PET alone yet the CT component of the PET/CT helped in its diagnosis through its arterial enhancement pattern.

Thus we realized from the current study that the diagnostic information provided by ^{18}F-FDG PET/CT examination for post therapeutic HCC is important as it can be used to improve determination of disease prognosis and treatment planning. Baseline examination by ^{18}F-FDG PET/CT for the patient before local resection, ablation or embolization of the HCC is very beneficial especially if it shows FDG avidity and increased SUV value before therapy (likely of dedifferentiated type) as the patient will gain great benefit from following up with ^{18}F-FDG PET/CT after the intervention as it help to distinguish viable metabolically active tissue from scar tissues.

The main limitations of PET/CT are motion artifact, CT artifacts, radiation exposure and cost.

Conclusion

^{18}F-FDG PET/CT imaging have a prognostic significance in the evaluation of patients with post-therapeutic HCC and provides valuable information that can be used in the treatment response evaluation and clinical decision making process.

However, a larger cohort of patients is still needed to validate the results of this study.

REFERENCES

(1) **Song MJ, Bae SH, Lee SW *et al.* (2013):** ^{18}F-fluorodeoxyglucose PET/CT predicts tumor progression after transarterial chemoembolization in hepatocellular carcinoma. Eur J Nucl Med Mol Imaging, 40:865-73

(2) **Sun L, Guan YS, Pan WM *et al.* (2009):** Metabolic restaging of hepatocellular carcinoma using whole body ^{18}F FDG PET/CT. World J. Hepatology, 1 (1): 90-97.

(3) **Kim YK, Lee KW and Cho SY (2010):** Usefulness F-FDG positron emission tomography/computed tomography for detecting recurrence of hepatocellular carcinoma in post transplant patients. Liver Transplantation, 16:767-772.

(4) **Kim JW, Seong J, Yun M *et al.* (2012):** Usefulness of positron emission tomography with fluorine-18-fluorodeoxyglucose in predicting treatment response in unresectable hepatocellular carcinoma patients treated with external beam radiotherapy. Int. J. Radiat. Oncol. Biol. Phys., 82:1172-1178.

(5) **Talbot JN, Fartoux L, Balogova S *et al.* (2010):** Detection of hepatocellular carcinoma with PET/CT:A prospective comparison of ^{18}F-fluorocholine and ^{18}F-FDG in patients with cirrhosis or chronic liver disease. J. Nucl. Med., 51: 1699-1706.

(6) **Sergio A, Cristofori C, Cardin R *et al.* (2008):** Transcatheter arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): the role of angiogenesis and invasiveness. Am. J. Gastroenterol., 103: 914-921.

(7) **Lee JD, Yun M, Lee JM *et al.* (2004):** Analysis of gene expression profiles of hepatocellular carcinomas with regard to ^{18}F-fluorodeoxyglucose uptake pattern on positron emission tomography. Eur. J. Nucl. Med. Mol. Imaging, 31: 1621-1630.

(8) **Ho CL, Chen S, Yeung DW *et al.* (2007):** Dual-tracer PET/CT imaging in evaluation of metastatic hepatocellular carcinoma. J. Nucl. Med., 48: 902–909.

(9) **Kawaoka T, Aikata H, Takaki S *et al.* (2009):** FDG positron emission tomography/computed tomography for the detection of extrahepatic metastases from hepatocellular carcinoma. Hepatology Research, 39: 134-142.

(10) **Sugiyama M, Sakahara H, Torizuka T *et al.* (2004):** ^{18}F-FDG PET in the detection of extrahepatic metastases from hepatocellular carcinoma. J. Gastroenterol., 39: 961-968.

(11) **Nagaoka S, Itano S, Ishibashi M *et al.* (2006):** Value of fusing PET plus CT images in hepatocellular carcinoma and combined hepatocellular and cholangiocarcinoma patients with extrahepatic metastases: preliminary findings. Liver Int., 26: 781-788.

(12) **Park JW, Kim JH, Kim SK *et al.* (2008):** A prospective evaluation of ^{18}F-FDG and 11 C acetate PET/CT for detection of primary and metastatic hepatocellular carcinoma. J. Nuc. Med., 49: 1912–1921.

(13) **Oikawa T, Ojima H, Yamasaki S *et al.* (2005):** Multistep and multicentric development of hepatocellular carcinoma: histological analysis of 980 resected nodules. J. Hepatol., 42: 225-229.

(14) **Lee JW, Paeng JC, Kang KW *et al.* (2009):** Prediction of Tumor Recurrence by ^{18}F-FDG PET in Liver Transplantation for Hepatocellular Carcinoma. J. Nuc. Med., 50 (5): 682-687.