Original Paper, Oncology

Added Value of 18 F-FDG PET/CT as a Molecular Imaging to Diagnose Biological Behavior of Hepatocellular Carcinoma

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ABETRACT

Aim of work: To evaluate the role of FDG-PET/CT as additive imaging tool to evaluating the aggressiveness and extent of the hepatocellular Carcinoma (HCC) and assessment of extra-hepatic metastatic spread. ***Patients and Methods:*** A retrospective analysis of 77 patients with suspicious liver lesion of HCC on ultra-sonographic examination. All patients were subjected to Tri-phasic CT and 18 FDG PET/CT qualitatively and quantitatively with SUV max calculation. All patients had histo-pathological examination with assessment of different grades of HCC. None of them received chemotherapy or radiotherapy. ***Results:*** The studied patients were 65 males (84.4%) and 12 females (15.6%) with mean age of 55.26±9.69 years. Seventy-two patients proved to have HCC (54 patients had poorly differentiated tumors, 8 patients with moderate differentiation and 11 patients were well differentiated tumors) and 5 patients had only liver cirrhosis. Serum Alfa fetoprotein (AFP) level was recorded in 38 patients, it was (< 100 ng/ml) in 8 patients, (100-400 ng/ml) in 7 patients and > 400 ng/ml in 23 patients. Tri-phasic CT showed criteria of malignancy in 71 patients with false negative result in (92.2%) one patient with poorly differentiated tumor. PET/CT showed metabolic activity in 54/ out of 72 patients (70.1%), all positive PET/CT patients had poorly differentiated tumor. Mean SUV max of liver lesions was 5.51 ±4.1. And Mean SUV max of liver parenchyma was 2.35 ±0.6. Both Tri-phasic CT and PET/CT showed positive metastatic lymph nodes in 20 patients (27.8%). PET/CT was able to detect additional mediastinal lymph nodes metastases in two patients. Total extra hepatic metastases (lung, bone and adrenal) detected by PET/CT were 14 patients (19.4%) compared to only one patient with adrenal metastases detected by abdominal Tri-phasic CT. Sensitivity,

Specificity and Accuracy of PET/CT were 75%, 100% and 76-6% compared to 98.6%, 100% and 98.7% for Tri-phasic CT, respectively. ***Conclusion:*** 18F-FDG PET has an additional role in the evaluation of biological behavior of HCC with more metabolically active lesions seen in poorly differentiated HCC and in detecting extra-hepatic metastases.

Keywords: FDG PET/CT, MIBG, Neuroblastoma osseous infiltrates

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INTRODUCTION:

Radiology plays a major role in HCC diagnosis as HCC is characterized by neo-arterial vascularization with a typical imaging pattern. Current international guidelines have restricted the use of the liver biopsy to the characterization of hepatocellular nodules which remain diagnostically equivocal after imaging. Thus pathologists are facing very challenging and often well differentiated lesions, leading to difficulties in distinguishing high grade dysplasia and well differentiated HCC [(1)]**.**

Accurate diagnosis and staging are essential for the optimal management of cancer patients. 18 F-FDG PET/CT has emerged as a powerful imaging tool for the detection of various cancers. It is a valuable tool for staging and restaging of some tumors and has an important role in the detection of recurrence in asymptomatic patients with rising tumor marker levels and patients with negative or equivocal findings on conventional imaging techniques. It also allows for monitoring response to therapy and permitting timely modification of therapeutic regimens. In about 27% of the patients, the course of management is changed [(2).]

45%-50% of cases with hepatocellular carcinoma demonstrate FDG uptake higher than the liver parenchyma, whereas 50%-55% of cases show FDG uptake similar to that of liver parenchymaas well and moderately differentiated HCC has a rate of gluconeogenesis comparable with normal liver tissue, resulting in similar uptake of 18F-FDG [(3).]

Major advantage of 18F-FDG PET/CT is the capability to perform full-body examinations, the potential to detect intrahepatic recurrence and extra hepatic metastases in one single examination and the possibility of distinguishing new active disease from scar or necrotic tissue [(4).]

The whole-body nature of the 18F-FDG PET/CT study also contributes to the increased sensitivity through detection of distant metastatic lesions. Tumors with intense 18F-FDG uptake are more metabolically active and biologically aggressive[5,6].

HCC carries a high risk of invasion of the portal vein. The detection and etiologic characterization of these thrombi are essential for treatment planning, particularly in patients with hepatic tumors, because malignant thrombosis is a negative prognostic factor. The management of HCC with portal vein thrombosis is complicated and controversial [7].

This aim of this work is to evaluate the role of FDG-PET/CT as additive imaging tool to evaluating the aggressiveness and extent of the hepatocellular Carcinoma, vascular invasion and assessment of extra-hepatic metastatic spread.

MATERIAL AND METHODS:

A retrospective analysis of all cases of Hepatocellular carcinoma referred to Alpha scans Center during the period November 2011 to December 2014. All patients did not receive any chemotherapy and/or radiotherapy.Almost all patients were subjected Tri-phasic CT and 18 FDG PET/CT in 97 patients included in this study only 77 patients had proved histo-pathological diagnosis with 5 of them had no evidence of malignancy.

Eligibility criteria: All patients were evaluated with suspicious liver lesion, Alpha Feto Protein measurement if available, Histopathology confirmation and the ethical committee of NEMROCK center has given approval for the study.

Excluding criteria: Patients with uncontrolled diabetes, Patients with previous chemotherapy or radiation, Presence of clinical suspicious of 2nd cancer and patient with no available histo-pathological prove.

A-PET/CT imaging:

Patients were fasting for at least 6 hours before the PET/CT study. Diabetic patients can be fast for 4.5 h after taking their oral medication together with a meal with blood sugar should be controlled and less than 160 mg/ml. PET images were acquired during normal breathing in the three-dimensional mode for 4 minutes per bed position 60 minutes after intravenous administration of 18F-FDG (5 MBq/kg of body mass) in an infusion line connected

to saline. PET/CT imaging will be performed using a 64 detector row LYSO PET/CT (Gemini TF, Philips Medical Systems). Approximately 60 minutes after FDG was injected, a scout image will be initially obtained for subject localization. Whole body, from base of the skull to med thighs, volumetric axial CT will be obtained using a low-dose protocol after the administration of oral manitol 5%. Subsequently, 3D PET data will be acquired using about 11 frames lasting 1.30 minutes each using sequential 50% overlapping scans, PET images are reconstructed by using standard reconstruction algorithm Ordered Subsets – Expectations Maximization (OSEM). Attenuation correction of PET images is performed by using attenuation data from the low dose CT component of the examination; emission data are corrected for scatter, random events and dead-time losses by using the manufacturer's software.

Criteria for Tri-phasic CT and PET/CT Interpretation:

(A)PET/CT interpretation

Interpretation of PET/CT scans were done independently by 2 experienced physicians blinded to the clinical situation and any disagreement was resolved by consensus.

Qualitative evaluation: A visually abnormal focus of FDG uptake was defined as a focal uptake relatively higher than that of surrounding tissue with no similar activity seen in the contra lateral side of the body.

Quantitative evaluation: The intensity of FDG uptake within specific lesion is calculated by using a volume of interest over the lesion.

(B) Tri-phasic CT imaging:

The CT component of the study comprises a multi-detector CT examination from the base of the skull to the upper thighs (120 mA, 140 kVp, table speed = 13.5 mm per rotation). The CT images were also used for attenuation correction of the PET images, On the basis of complementary Tri-phasic CT scan in all patients have hyper enhancement, iso/mixed enhancement and iso/mixed enhancing pattern in arterial, porto venous and equilibrium phases were suggested to be malignant lesions respectively. Also metastasis appears hyper vascular enhancing on arterial phase with mixed pattern on port venous and equilibrium phase. However, hypo-vascular metastasis appears hypo-enhancing on arterial phase and shows maximum enhancement on porto-venous phase.

(C) Pathological assessment: Final assessment was done according to pathological diagnosis for different grade of HCC.

Statistical analysis: The data was coded and entered using the statistical package SPSS version 15. The data was summarized using descriptive statisticsfor qualitative and quantitative variables which are not normally distributed. Number and percentage were used for qualitative values. Statistical differences between groups were tested using Chi and ANOVA, square test for qualitative variables. Sensitivity, specificity, positive predictive value; negative predictive value and total accuracy were used to test validity of studied parameters. Kappa agreement measure was used to test agreement between studied parameters. P-Values less than or equal 0.05 were considered statistically significant. Comparison of results of PET/CT with CT and histopathology were done on patients based analysis.

RESULTS:

The current retrospective study included 77 with suspicious hepatic lesions referred to Alfa Scan Radiology Centre proved to have malignant lesions in 72 patients and 5 patients had only liver cirrhosis. The study included 65 males(84.4%) and 12 females patients (15.6%) with mean age of 55.26±9.69.

Alpha fetoprotein measurements: Serum Alfa fetoprotein (AFP) level was documented in only 38 patients. 8 patients had elevated AFP level (< 100 ng/ml), 7 patients had AFP level (100-400) ng/ml Twenty three had AFP > 400 ng/ml.

Diagnostic CT scans: All of the 77 patients had abdominal Tri-phasicCT. CT showedhepatic focal lesion with criteria of HCC in 71 patientsand CT was negative in 6 patients. 35 patients of them (49.2%) had multiple lesions and 36 patients had single hepatic lesions (51.9%).

PET/CT scans:54 patients (70%) were positive for metabolically active hepatic HCC. While 23 patients had false negative study (30%) Out of these patients 5 of them had only liver cirrhosis with no malignancy. PET/CT showed single lesion in 38 patients and 16 patients had multiple lesions ***(Table 1 & Figure 1).***

Table 1: Comparison of Tri-phasic CT and PET/CT in evaluation of 77 Patients of HepaticFocal lesions.

	Positive patients		False Negative patients		True Negative patients	
	NO	%	NO	%	NO	%
Tri-phasic CT	71	92.2	1	1.3	5	6.5
PET/CT	54	75	18	22.5	5	6.5

SUV calculations:

Semi-quantitative analysis; SUV was obtained for liver parenchyma as well as HCC hepatic lesions, extra-hepatic LN involvement and distant metastases. mean SUV for liver lesions and normal liver parenchyma in the 54 patients was ranging from 2.1 -26 with mean SUV max of 5.51 ±4.1, while the SUV liver parenchyma of 54 patients was ranging from 1.5-3.5 with mean SUV max of 2.35 ±0.6 . The mean SUV max ratio was 2.98±3.86 ***(Table 2).***

Table 2.18F-FDG SUV uptake in liver lesions and liver parenchyma in 54 patients with poorly differentiated HCC.

	Range of SUV	Mean of SUV max±SD	Mean SUV max ratio
SUV^{lesion}	2.1 -26	5.51±4.1	2.98±3.86
$SUV^{liver\ parenchyma}$	1.5-3.5	2.35±0.6	

Liver Histopathology: 77 patients performed liver biopsy, all patients showed signs of cirrhosis. However, 72 of them had HCC and the other 5 patients showed no evidence of malignancy. Histopathology of the Hepatocellular Carcinoma (HCC) showed well or moderately differentiated HCC in 18 patients (23.4%), while 54 patients had poorly differentiated HCC (70.1%). The remaining five patients were put under clinical and follow-up investigations showed no evidence of HCC.

Correlation of PET/CT, Tri-phasic CT with Histopathology:

PET/CT detected 54 patients with poorly differentiated HCC and was negative in 18 patients with well and moderately differentiated HCC, while Tri-phasic CT detected 71 patients with HCC and showed negative results in only one patient. 53 patients had poorly differentiated hepatocellular carcinoma, 10 patients had well differentiated hepatocellular carcinoma and 8 patients had moderately differentiated hepatocellular carcinoma ***(Table 3 and Figure 2).***

Table 3: Correlation of PET/CT, Tri-phasic CT and grade of histopathology.

	Tri-phasic CT		PET/CT	
	NO	%	NO	%
Well Differentiated HCC	10	13.9	----------	----------
Moderated Differentiated HCC	8	11.1	----------	----------
Poorly Differentiated HCC	53	73.6	54	75

5 patients proved to have only liver cirrhosis; one patient with poorly differentiated HCC was not detected by Tri-phasic.

Correlation of Alpha Feto Protein Level and Pathological Grade: Among the 72 patients, Alpha Feto Protein value was available in only 38 patients, it was positive in 30 out of 38 patients with poorly differentiated carcinoma with 21 patients of them had AFP level > 400 ng/ml . In well and moderately differentiated carcinoma, AFP was positive in 8 patients with 6 patients had AFP level < 400ng/ml ***(Table 4).***

Table 4: correlation between level of AFP and grade of HCC.

	Well/ moderately Differentiated		Poorly differentiated	
AFP(ng/ml)	**No**	**%**	**No**	**%**
<100	3	37.5%	5	16.7%
100-400	3	37.5%	4	13.3%
>400	2	24%	21	70%
Total	8	100%	30	100%

All PET/CT patients had poorly diffrentiated tumors with 30 out of 38 patients of them had raised AFP. (9 patients of them had AFP < 400 ng/ml, while 21 patients had AFP level > 400 ng/ml) ***(Table 4).***

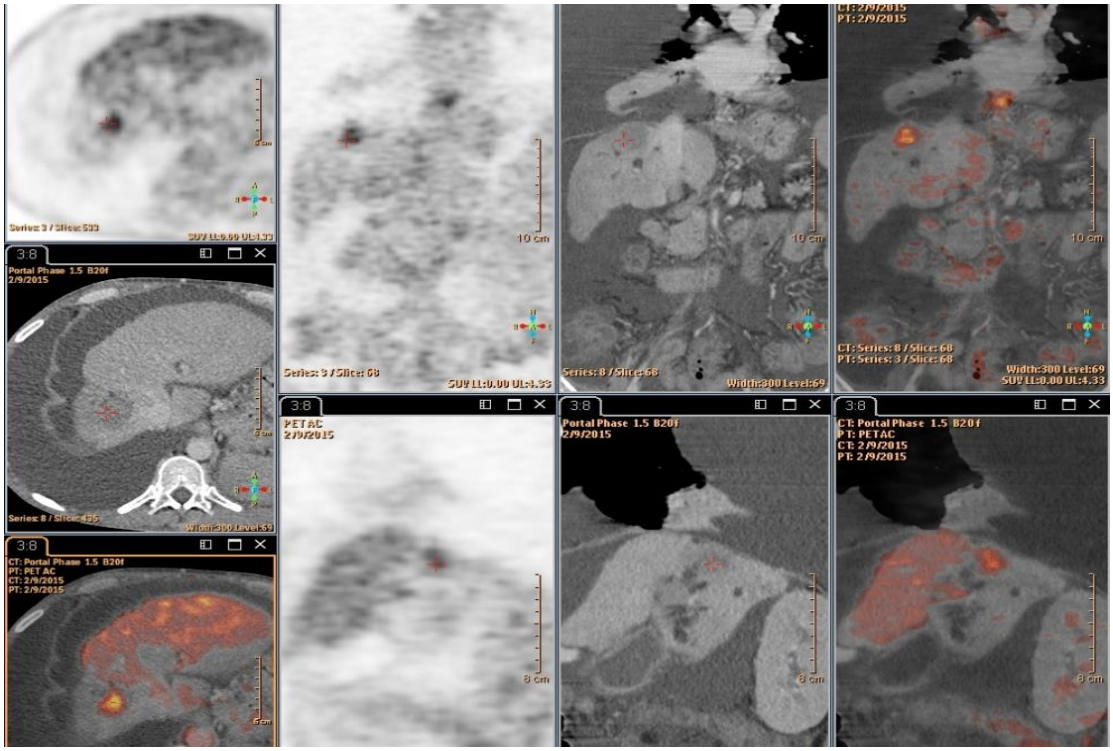

Figure (1): 49-year-old male patient with liver cirrhosis with multible focal lesions in segments V / VII / VIII with SUVmax 3.8 – 4.4 with hypoenhancement in triophasic CT.

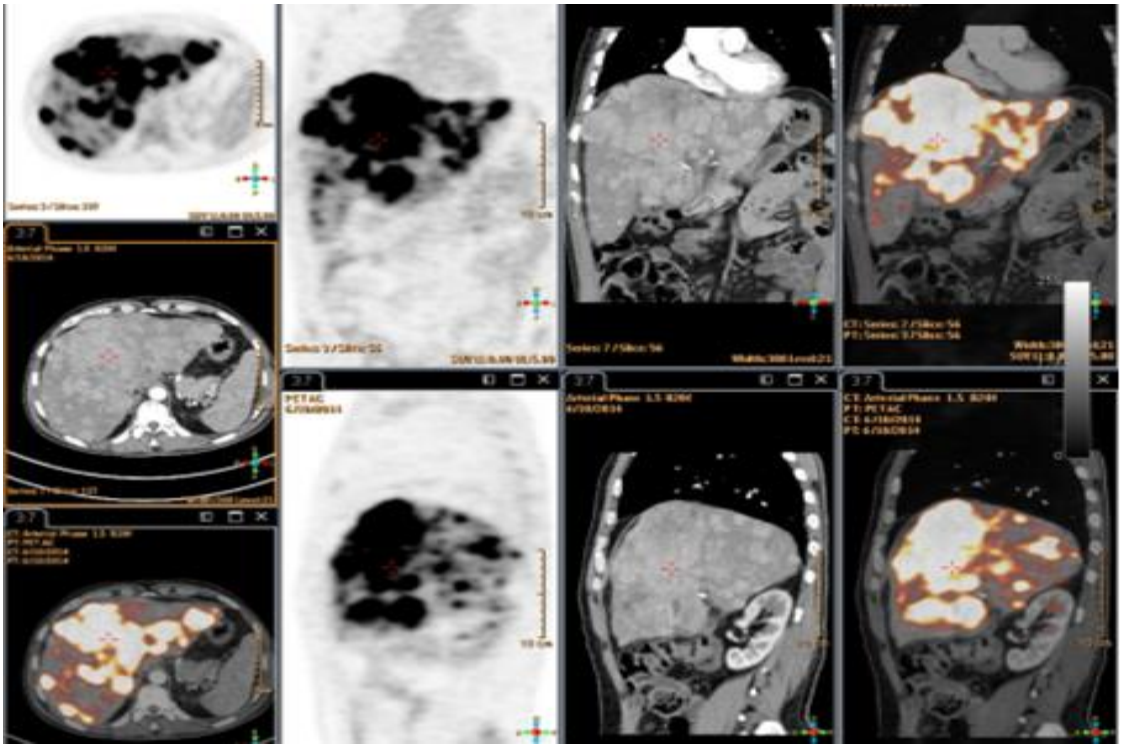

Figure (2): 62 ys old male with liver cirrhoses with multiple hepatic focal lesions of large size and hetrogenous enhancement in triphasic CT, Biopsy revealed multi-centric poorly differentiated adenocarcinoma

Correlation between AFP and mean SUV: Correlation between AFP and mean SUV max revealed high level of mean SUV max in patients with AFP >400 ng/ml of 6.7 ±3 as compared for 6.4±5.2 in patients with AFP ranging from 100-400 ng/ml and lowest mean SUV max is seen in those with AFP<100 ng/ml **.**

Extra hepatic involvement using PET/CT and diagnostic CT:

(A) **Lymph node involvement:**Tri-phasic CT showed criteria of positive metastatic lymph nodes involvement in 20 patients (27.8%). Groups of lymph node involved were the gastric, mesenteric, porto-caval, porta-hepatislymph nodes.

PET/CT positive for the metastatic lymph node involvement in the same groups detected by the Tri-phasic CT, also, it was able to detect additional lymph nodes in two patients in mediastinal.

(B) **Extra-hepatic metastasis:** Tri-phasic abdominal CT detected one patient with adrenal metastasis. PET/CT was able to identify 14 patient's extra hepatic metastases being done for the whole body with 7 patients had lungmetastases, 6 patients had bone metastases in addition to one patient with adrenal metastases. Total extra hepatic metastases detected by PET/CT were 14 patients (19.4%).

Sensitivity and Specificity of PET/CT as compared to Tri-phasic CT in Detection of HCC:

PET/CT detected 54 patients with poorly differentiated HCC it was true negative in 5 patients with liver cirrhosis .18 patients had false negative results, proved to be positive for hepatocellular carcinoma with Tri-phasic CT with histopathology of moderately and well differentiated. Sensitivity, Specificity and Accuracy of PET/CT were 75%. 100% and 76-6% as compared to 98-6%, 100% and 98.7% for Tri-phasic CT respectively ***(Table 5).***

Table 5. Sensitivity, Specificity and Accuracy of PET/CT vsTri-phasic CT in detection of HCC.

	Sensitivity	**Specificity**	**Accuracy**
Tri-phasic CT	98.6%	100%	98.7%
PET/CT	75%	100%	76.6%

DISCUSSION:

The detection of HCC early in its development, is critical to improve the survival of affected patients. All current guidelines recommend ultrasonography (US) as the primary imaging test for surveillance, and two guidelines advocate the ancillary use of serum biomarkers[8]. Currently, all guidelines endorse multiphasic CT and MR imaging with serum biomarkers as first-line modalities for this purpose [9].

Wolfort.et al, (2010)[10], in retrospective study of 20 patients showed correlation between FDG-PET positivity, tumor size, a-fetal protein level (AFP), and histologic grade. All patients on liver transplant service with biopsy proven HCC that underwent FDG-PET of the 20 patients, who underwent 18F-FDG PET, increased FDG uptake was noted in 14 patients (70%). FDG-PET detected only 2 of 8 tumors < 5 cm, While 12 with tumors > 5 cm and/or multiple lesions were detected by FDG-PET. AFP levels < 100 ng/ml, PET /CT was positive in 5 of 9 patients. In patients with AFP level > 100 ng/ml, 6 of 7 patients had positive scans.

Histologically, 6 well-differentiated, 6 moderately differentiated, and 2 poorly differentiated HCC were detected FDG-PET detected 4 of 6 patients for both well- and moderately differentiated HCC and 2 Patients with poorly differentiated HCCs. The sensitivity of FDG-PET in detecting HCC < 5 cm in size is low than, for larger tumors. There was a strong correlation of sensitivity and FDG uptake intensity with tumor size and elevated AFP levels.

In current study, there is good correlation with AFP with degree of liver differentiation as 6 out of the 8 patients had ALP < 400 ng/ml, while 21 out of the 32 patients had AFP > 400 ng/ml (P value <0.01). So there is strong correlation of sensitivity of FDG PET/CT uptake and AFP level (P < 0.001).

Lee et al. (2011) and Song et al., (2013)[11,12], found that the tumor SUV max and mean SUV ratio were a good prognostic factors. Also, ***Song et al***. confirmed that the TSUV max/L SUV mean (SUV ratio) is the better prognostic factor.

In the present study, FDG PET/CT was positive for detection of primary HCC in 54 of 72 patients (75%) with poorly differentiated HCC. mean SUV was ranging from 2.1 -26 with mean SUV max of 5.51±4.11 while the SUV $^{\text{liver parenchyma}}$ of 54 patients was ranging from 1.5-3.5 with mean SUV max of 2.35 ±0.57. There was a strong increase in T/N ratio

allowing for better lesion detection by visual inspection on the PET/CT scan in poorly differentiated HCC. mean SUVmax ratio of Parenchyma was 2.98±3.86.

The pathology of the focal hepatic lesion in the present study were poorly differentiated and well/mod differentiated hepatocellular carcinoma the number of each group was 54 patients with pathology proved poorly differentiated HCC and 10 patients with well differentiated HCC, 8 with moderately differentiated. The correlation between PET/CT and Tri-phasic CT with histopathology grade of HCC revealed that PET/CT is more accurate in detection of poorly differentiated HCC with poor detection of well and moderate differentiated HCC. While, Tri-phasic CT detected 18 patients with well and moderate HCC and 53 with poorly differentiated HCC, while Tri-phasic CT was false negative in only one patient with lesion in candela lobe which is supplied by portal Vein. Such lesions were positive in PET/CT.

Several studies have shown that fusion of PET data with CT improves not only the sensitivity of PET but also its specificity[13,14;] . The advantage of PET/CT over PET alone can be attributed to the low anatomic resolution of PET and the difficulty in lesion localization on PET. Morphologic data from CT assist in improving the diagnostic accuracy of nonspecific lesions with increased 18F-FDG uptake. [15, 16].

FDG PET sensitivity in the detection of poorly differentiated HCC tumors is reflecting more aggressive, and thus associated with metastases. Overall, for identification and staging of HCC metastases. [17], found dual-tracer PET CT to have a sensitivity of 98%, a specificity of 86%. Positive predictive value (PPV) of 97% a negative predictive value (NPV) of 90%, and accuracy of 96%.

In the present study, Limited sensitivity of PET/CT of 75% is related of reflection of fumor biology with higher detection of poorly differentiated HCC while high specificity 100 % of 18F-FDG-PET in detecting HCC may be explained in a part that most of the included lesions were suspicious for HCC. PET/CT with dedicated contrast enhanced CT raised the sensitivity to 98%. Several studies have shown that fusion of PET data with CT improves not only the sensitivity of PET but also its specificity.

Although FDG PET can help to differentiate tumors, it may also be useful in the staging of HCC as a complementary modality to CT by detecting unsuspected regional and distant metastases [18]. In a study by [19], pretreatment FDG PET examinations were performed on 87patients with HCC who underwent MRI or CT studies, to assess whether there

were any extra hepatic metastases which was identified in 24 of 87 patients. All of the extra hepatic metastases were detected by FDG PET. In addition, FDG PET identified fumor lymph node metastases not seen in CT.

In the present study, 18F-FDG PET/CT detected extra hepatic HCC metastases in 19.4 %, with definite metastatic lesions in lungs, LNs, bone and adrenals as adrenal, whereas abdominal Tri-phasic CT detected only single patient of extra hepatic metastasis in adrenals. Also, 4 patients with negative PET/CT for hepatic primary HCC had extra hepatic metastases in lung in 2 patients and 2patientsin mediastinal LN.

In the setting of extra hepatic disease, FDG-PET seems to be an effective accurate method for HCC staging[20].

CONCLUSIONS:

18F-FDG PET has an important role in the evaluation of biological behavior of HCC with more metabolically active lesions seen in poorly differentiated HCC. Also, FDG PET/CT imaging is superior in detecting extra-hepatic metastases

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