ROLE OF PET/CT IN EVALUATION OF HEPATOCELLULAR CARCINOMA AFTER RADIOFREQUENCY ABLATION

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ABSTRACT:

Background: *Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and is a leading cause of cancer-related death worldwide. It is the third most common cause of death of cancer worldwide. RFA is one of the most important modalities in treatment of HCC because it is minimally invasive, low risk of morbidity and excellent tumour control. PET/CT provides a functional and morphologic data in a single session for detecting residual of HCC after RFA. Presence of focal areas with increased FDG uptake within the ablated area is suggestive of residual disease while completely photopenic lesion after ablation is suggestive of well ablation.*

Aim of the Work: *to emphasize the role of PET/CT in follow up of HCC after radiofrequency ablation.*

Patients and Methods*: This prospective observational study was conducted on thirty patients, 25 men and 5 women. The Patients were referred to radio-diagnosis department, Ain Shams University hospitals, radio-diagnosis department, PET/CT unit in a period of 8 months of data collection for patients who underwent radiofrequency ablation for HCC at the interventional radiology unit.*

Results*: The optimal cut of value of standardized uptake value ratio (SUVmax/liver SUVmean ratio) for detection of residual viable HCC after PET/CT was 1.81 with sensitivity, specificity and accuracy of 66.7%, 96.3%, 93.3% respectively.*

Conclusion: *18F-FDG PET/CT showed high diagnostic accuracy in evaluation of the intervention bed following RFA which helps in detecting residual disease. Another super added advantage is the high capability to detect wide extrahepatic metastasis in the same examination.*

Key words: *18F-FDG PET/CT, HCC, MRI, RFA, AFP.*

INTRODUCTION:

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and is a leading cause of cancer-related death worldwide. It is the third most common cause of death of cancer worldwide, also the sixth and fourth common cancer in worldwide and Egypt, respectively[(1)]**.** From the selective treatment options of liver tumors' interventional procedures such as RFA.RFA is recommended as a non-surgical technique for the treatment of early stage (Child A or B, solitary HCC or up to 3 nodules <3 cm in size). It is approved to be one of the most valuable ablative methods for respectable HCC because it is minimally invasive with low risk of morbidity, has relatively long-term survival and can be repeated[(2)]**.** Magnetic resonance imaging (MRI) (particularly with the use of liver-specific

contrast agents), contrast-enhanced ultra-sonography and contrast-enhanced computed tomography (CT) have been widely used for the assessment of treatment response after RFA. However, changes at the tissue level in response to the ablative procedure can hamper the ability to use CT and MRI imaging to unequivocally detect or rule out residual disease in the initial period after ablation[(3)].

The combination of fluorine 18-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) and triphasic CT is an effective tool for assessing the response of the therapy [(4)] .Lesions that show increased FDG uptake at PET become completely photopenic immediately after RFA, a finding that is suggestive of the completeness of ablation [(5)].Focal areas of increased FDG uptake within the ablated zone are suggestive of residual disease. Combined PET/CT systems provide accurately fused functional and morphologic data sets in a single session. The potential advantage of PET/CT compared with PET alone is based on lesion detection and localization [(6)].

AIM OF THE STUDY:

The aim of this study is to emphasize the role of PET/CT in early follow up of HCC after RFA for early detection of residual disease.

PATIENTS AND METHODS:

This is a Prospective observational Study where the data was collected from Ain Shams University hospitals, radio-diagnosis department in 8 months from (4/2021 to 12/2021) after approval of our ethical committee which waived the requirement for written consent. Our study included 30patients, 25men and 5 women. Patients age Range was 45-80 [Mean±SD =59 ± 9].The Patients were referred to the radiology unit with hepatocellular carcinoma and had underwent RFA.18F-FDG PET/CT and triphasic CT examinations were conducted in Diagnostic Radiology Department, PET/CT unit, Ain Shams hospitals. All patients were imaged using combined PET/CT machine (GE medical system; discovery IQ16 PET/CT scanner; USA).

Inclusion criteria:

- Patients who underwent RFA for HCC.
- Both sexes were included.

Exclusion criteria:

- Patients with past history of contrast allergy.
- Patients with blood glucose level >200 mg/dl at the time of the study.
- High serum creatinine> 2 mg / dl.

Patients preparation:

All the patients were subjected to :full history taking,full previous radiological investigations as computed tomography and laboratory investigations was as follows: serum creatinine,serum AFP,fasting blood glucose (fasting was 6 hours before sampling).

Technique of FDG PET/CT technique examination: Hybrid PET and CT images were performed using PET/CT system (GE medical system; discovery IQ16 PET/CT scanner; USA), PET/CT was carried out for all the patients 1month after the procedure at PET/CT unit, radiology department, Ain Shams University. The study was approved by the institutional ethical committee, the whole-body PET images from the skull vault down to the knee were performed using several bed positions acquisition, each bed was approximately 15cm axial filed with 4mm special resolution. The time of acquisition of the emission scan was about 2 min. for each bed, with a total time range between 12 and 17 min. The patients were informed

to fast 6–8 h before the examination and the blood glucose level was kept below 200 mg/ dl before injecting the tracer. The scan was performed 45–60 min after injection of 0.1 mCi 18 F-FDG/kg. A diagnostic triphasic contrast-enhanced transmission scan was done immediately after PET images, after injection of 100 millilitres of non-ionic iodinated contrast media (omnipaque 300) at a rate of2–3 ml/s. CT has been performed with the following parameters: 350 mA, 120 kV, 0.5 tube rotation time and 5 mm slice thickness. The arterial phase covering the region of the abdomen from the base of the lungs down to the iliac bones, the venous phase covering the same field of view as the PET images and the delayed phase covering from the skull bases down to the inferior pubic rami, GE workstation was used to review the PET, CT and the fused PET/CT images, multi-planner reformatted images; 3D maximum intensity projection images were reconstructed for the PET images, two radiologists with experience in hepatic imaging reviewed all PET/CT scan images. To determine the accuracy of the results (according to AASLD (American association for the study of liver disease) it was as follows:

Benign findings:(resolved lesions) was considered if contrast enhancement disappeared when comparing triphasic CECT images before and after the RFA with no tracer uptake as well as reduction of laboratory serial AFP (Alfa feto protein) before and after RFA, AFP cut of values 20ng\L have sensitivity and specificity ranges from 60:80%, 70:90% respectively and AFP >400ng\L is considered diagnostic for HCC (100 % sensitivity).

Residual lesions: (unresolved) was considered if the ablated area had a peripheral contrast enhancement when comparing the images of triphasic CECT before and after the RFA with nodular tracer uptake as well as persistently elevated laboratory serial AFP (Alfa feto protein) after RFA.

- Intra-hepatic HCC residue was noted as part of the lesions showing nodular hyper-enhancement in the arterial phase and washout in the delayed phase of the triphasic CECT component.

- In 18F-FDG PET/CT, disease activity was assessed either qualitatively or semi-quantitatively:

Qualitative evaluation: was based on detection of focal 18F-FDG uptake that was higher than the surrounding normal liver background.

Semi-quantitative evaluation: was including the SUVmax (standardized uptake value) and the ratio of tumour SUVmax to normal liver SUV mean (TSUVmax/LSUVmean) was evaluated by drawing region of interest (ROI) encircling the tumour and drawing ROI for normal liver uptake.

Lymph node, lung, bone and other organs were checked in the same way to assess whether there were distant metastases or not.

Statistical analysis:

Data management and statistical analysis were done using statistical package of social service (SPSS) version 25. (IBM, Armonk, New York, United States). Quantitative data were assessed for normality using the Shapiro-Wilk test and direct data visualization methods. According to normality testing, numerical data were summarized as means and standard deviations or medians and ranges. Categorical data were summarized as numbers and percentages were compared before and after ablation using Wilcoxon's signed ranks test. CT scan findings were compared before and after ablation using the sign test. All statistical tests were two-sided. P values less than 0.05 were considered significant.

RESULTS

Table (1): General characteristics of the studied patients

General characteristics		
Age (years)	Mean ±SD	59 ±9
Gender	Males 'n (%)	25 (83.3)
	Females' n (%)	5 (16.7)
Weight (kg)	Mean ±SD	82 ±11
Height (cm)	Mean ±SD	171 ±7
BMI	Mean ±SD	28.3 ±5.2

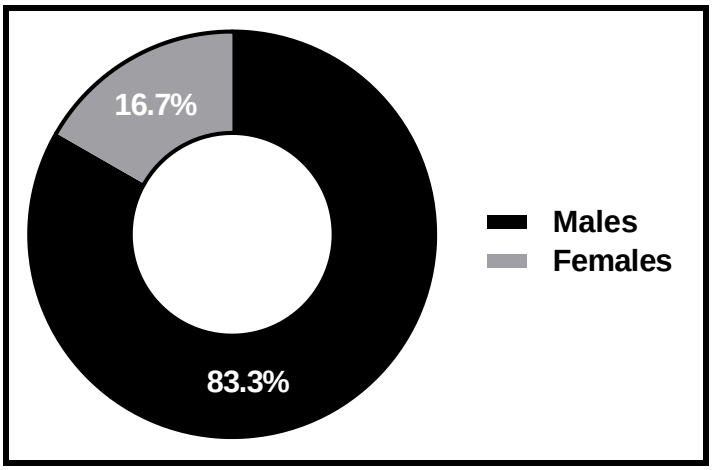

Diagram (1): Gender distribution of the studied patients

The mean age of the studied patients was 59 ±9 years. There was a male predominance; most patients (83.3%) were males. The mean weight and height were 82 kg and 171 cm, respectively. The mean BMI was 28.3.

Table (2): Liver disease characteristics in the studied patients

		n (%)
HCV	Positive	25 (83.3)
HBV	Positive	5 (16.7)
Liver disease severity	CHILD PUGHA	24 (80.0)
	CHILD PUGHB	6 (20.0)
Segment affected	II	2 (6.7)
	III	2 (6.7)
	IV	3 (10.0)
	V	3 (10.0)
	VI	5 (16.7)
	VII	7 (23.3)
	VIII	8 (26.7)

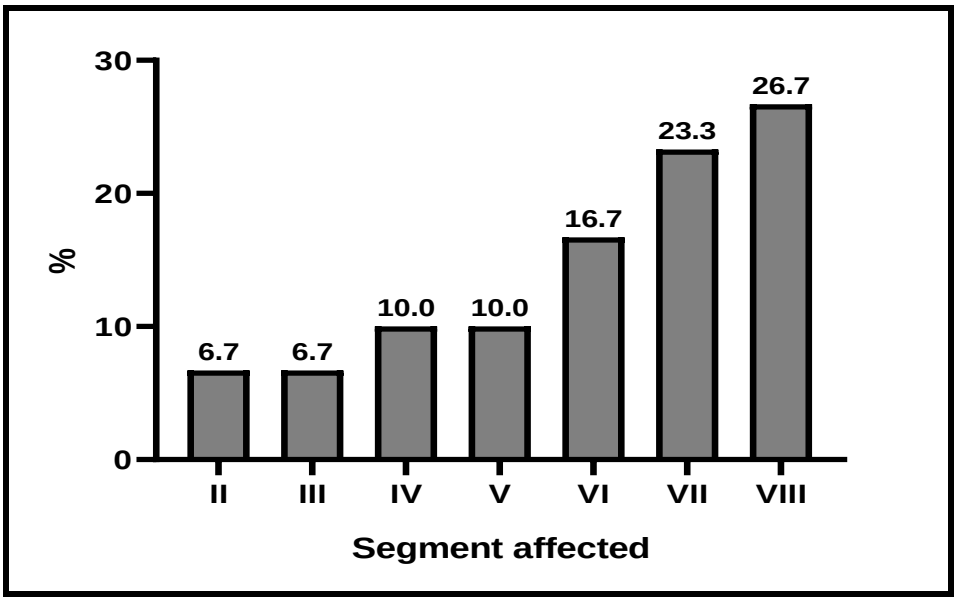

Diagram (2): Segment affected in the studied patients

Most patients had HCV (83.3%), and only 16.7% had HBV. Most patients showed CHILD PUGH A (80.0%). The most frequent segment affected was VII (23.3%), while the least frequent affected segments were II and III (6.7% for each).

Table (3): AFP level before and after ablation

AFP	Median (range)	P-value
Before ablation	77 (45 - 214)	< 0.001
After ablation	23 (7 - 144)	

Wilcoxon's signed ranks test was used.

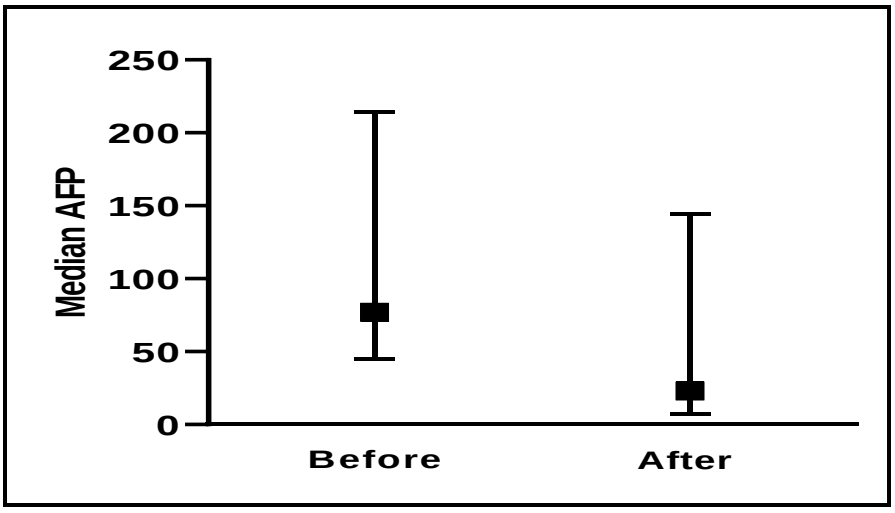

Diagram (3): AFP level before and after ablation

The median AFP significantly declined from 77 before ablation to 23 after ablation (P <0.001).

Table (4): the mean diameter of ablated area and the mean of Liver SUV max:

	Mean ±SD
Radiofrequency ablation diameter (cm)	3.1 ±0.7
Liver SUV max	2.24 ±0.41

The mean radiofrequency ablation diameter was 3.1 ±0.7cm. The mean liver SUV max was2.24 ±0.4.

Table (5): CT scan before and after ablation.

CT scan		n (%)	P-value
Before ablation	Positive HCC arterial enhanced focal lesion	30 (100.0)	< 0.001
After ablation	Non-enhanced focal lesion	27 (90)	
	Peripheral enhancement	3 (10)	

The sign test was used, before ablation, all patients showed positive HCC arterial enhanced focal lesion, while after ablation, the situation significantly changed (P < 0.001); only three patients showed peripheral enhancement, and most of the patients (90%) showed non-enhanced focal lesions.

- **PET/CT scan after ablation**
- PET/CT was positive with peripheral FDG uptake in 3 patients while 27 patients were negative with no FDG uptake. Two of these 3 patients were positive in triphasic CT.

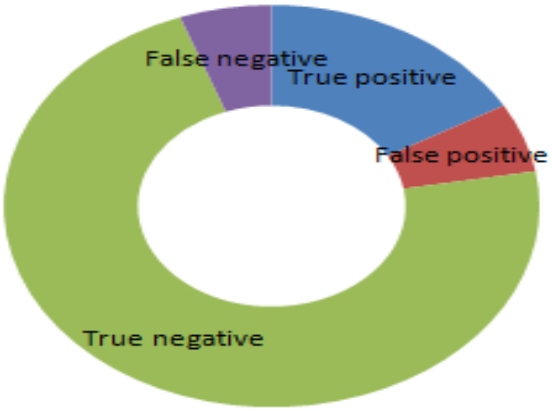

Diagram (4): The results after PET/CT

- True negative patients, true positive, false negative and false positive representing 87%, 7%, 3%, 3% respectively.
- The mean Tumor SUVmax of the 3 positive cases was 4.4.
- The mean Tumor SUVmax/mean liver SUV of the 3 positive cases was 1.81.
- PET/CT showed sensitivity and specificity of 66.7%, 96.3% respectively with positive predictive value (PPV) of 66.7%, negative predictive value (NPV) of 96.3% and accuracy of 93.3%.

Table (6): the value of FDG PET/CT in post RFA follow up

Modality	Sensitivity	Specificity	PPV	NPV	Accuracy
PET	66.7%	96.3%	66.7%	96.3%	93.3%

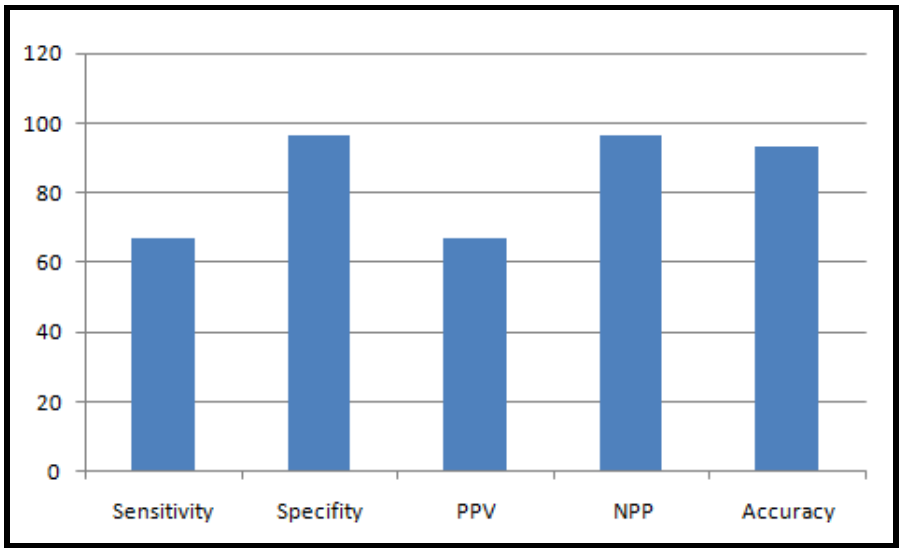

Diagram (5): the value of FDG PET/CT in post RFA follow up

Illustrative cases:

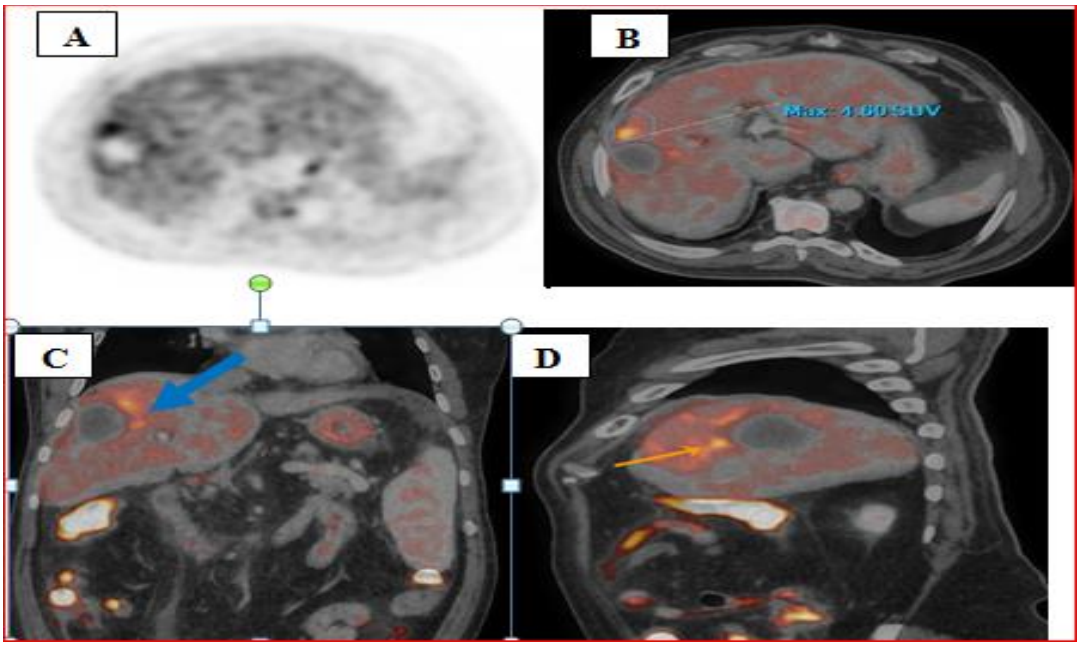

Fig. 1; 45 years old male patient with history of HCC diagnosed with typical enhancement criteria of HCC by triphasic CT and elevated alpha feto-protein (144 ng/ml) underwent radiofrequency ablation and referred for PETCT I month later after RFA.

A, B axial,C coronal,D sagital fused PET/CT images showing positive case marginal focal slightly increasing metabolic activity along anterior aspect of ablated lesion achieving about 4.6 SUV max denoting residual disease which was confirmed by increased level of alpha fetoprotein (98 ng/ml).

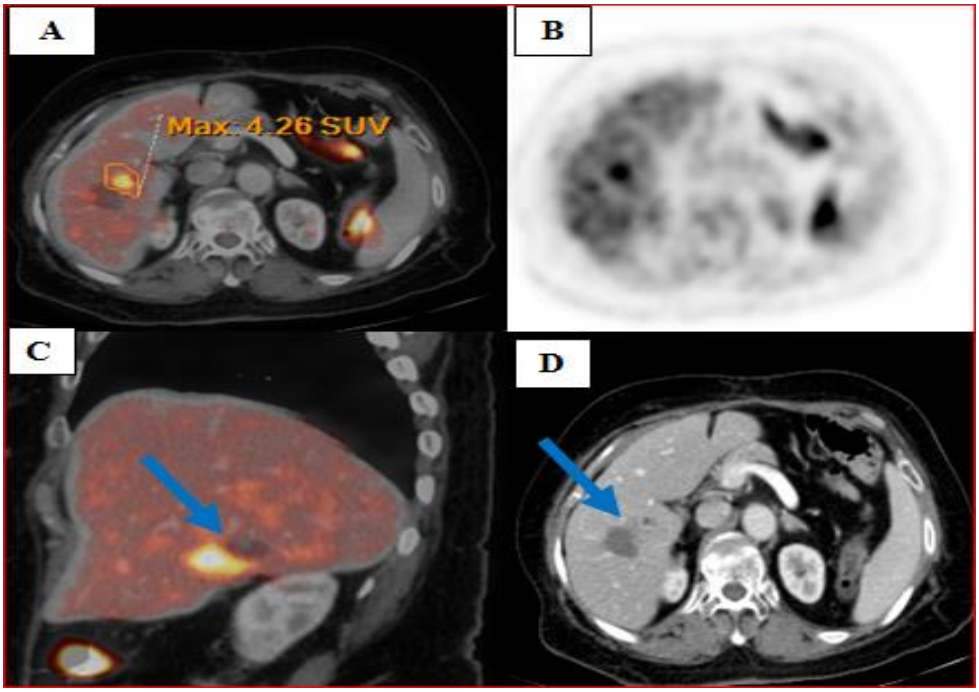

Fig. 2; 70years old male patient with history of HCC diagnosed with typical enhancement criteria of HCC by triphasic CT and elevated alpha feto-protein (155ng/ml) underwent radiofrequency ablation, referred for PETCT I month later after RFA.

A, B, axial, C sagittal fused PET/CT images showing positive case with hyper metabolic area with peripherally anteriorly FDG uptake. D,axial triphasic CECT showing faint enhancing focal area surrounding the ablated area.

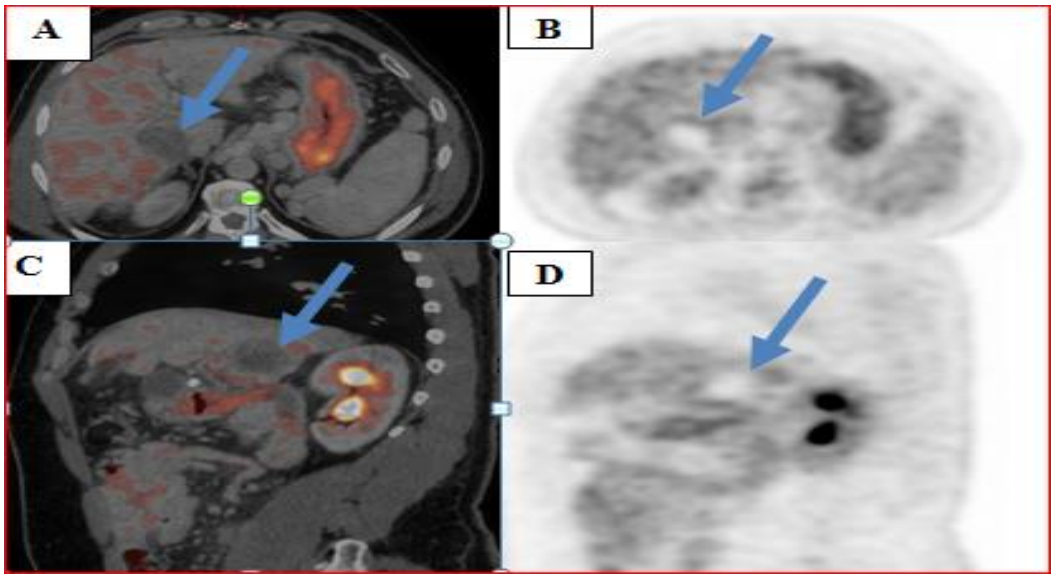

Fig. 3; 49 years old male patient with history of HCC diagnosed with typical enhancement criteria of HCC by triphasic CT and elevated alpha feto protein (98ng/ml) underwent radiofrequency ablation, referred for PETCT 1 month after RFA.

A, B axial and C,D sagittal fused PET/CT images showing negative case with no contrast enhancement and photopenic area at the site of the RF ablated lesion denoting good ablation which was confirmed with decreased level of alpha fetoprotein (29ng/ml).

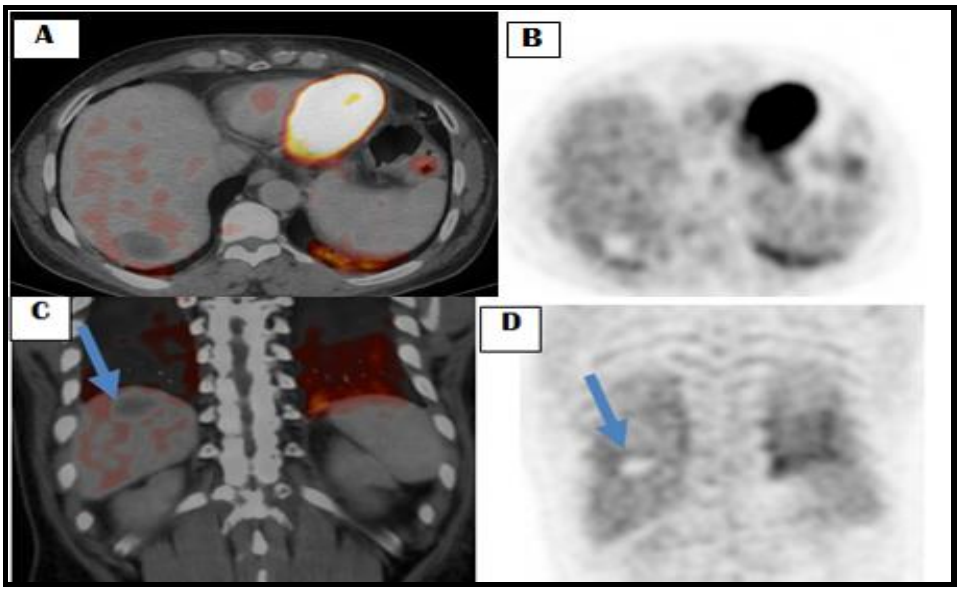

Fig. 4; 51 years old male patient with history of HCC diagnosed with typical enhancement criteria of HCC by triphasic CT and elevated alpha feto protein (98 ng/ ml) underwent radiofrequency ablation, referred for PETCT I month later after RFA.

A, B axial and C,D coronal fused PET/CT images showing negative case with no contrast enhancement and photopenic area at the site of the RF ablated lesion denoting well ablation which was confirmed with dramatic decrease level of alpha fetoprotein (32 ng/ ml).

DISCUSSION:

Hepatocellular carcinoma is one of the most common worldwide malignant tumors. Treatment modalities such as RFA are now available to manage HCC. Early detection and treatment of residual or recurrent HCC after loco- regional interventional treatment are important for patient survival. Assessment of tumor response after RFA by MRI, CT and PET CT is important to determine whether the tumor is completely eradicated or needs additional treatment.

MRI and CT are the most widely used tools to assess patients who underwent loco-regional intervention procedures such as RFA which is based on reduction of the size or changes of the internal structure as well as enhancement pattern. The evaluation of treatment response depended on the presence or absence of contrast enhancement for determination of therapeutic response (Kim et;al).[7]

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 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 the viability which is based on glucose metabolism and it is not influenced by tumor morphology **(**Tsurusaki et al)[8].

Using serial AFP measurements to monitor treatment of HCC is well established and several expert groups recommend serial follow-up to monitor treatment efficacy (Kim et al)[7].

In our study PET/CT was positive in 3 patients two of them were positive in triphasic CT with Subtle reduction of AFP levels indicating residue, the other one with peri ablation rim of FDG uptake was negative in CT with no peripheral enhancement and dramatic decreasing titer level of AFP indicating false positive regional hyperaemia. While triphasic CT

was positive with peripheral enhancement and subtle reduction of AFP levels in 3 patients indicating residue two of them were positive by PET/CT and one was negative which was considered false negative. The remaining 27 patients were negative by triphasic CT with dramatic deceasing titer levels of AFP indicated well ablated HCC.

PET/CT showed sensitivity and specificity of 66.7%, 96.3% respectively with positive predictive value (PPV) of 66, 7%, negative predictive value (NPV) of 96.3% and accuracy of 93.3%.

The ratio of male /female in positive PET CT patients was 2:1 while in negative patients 23:4. In the study of *(Ida et; al)*[9] the ratio was 5:6 in positive PET CT patients while in negative patients 68:42.

The median AFP between all patients in our study before ablation was 77 with the range of 45 - 214 which correlates with the study of *(Ida et; al)*[9] Which had median of AFP 18.0 with the range 1.8–1594.5.

The mean of AFP before RFA among patients with residue was 184 while post RFA was 115 which correlates with study of *(Zytoon et al*[10]*)* which mentioned that mean of AFP before RFA among patients with residue was 174 while post RFA was 117.

The median AFP significantly declined from 77 before ablation to 23 after ablation (P <0.001).

The avidity of FDG uptake was defined in our study as maximum standardized uptake value (SUV max). Positive FDG uptake was considered when the lesion uptake was higher than the physiological background activity of normal liver tissue which was also adopted by the study done by (*Abuodeh et al)*[11].

In our study the median value of Tumor-SUVmax in the positive cases was 4.6 matching with the study done by (*Ahn et al)*[12] which had 4.3 for the median value of Tumor-SUVmax.

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.

Although PET-CT has been found to show suboptimal sensitivity in detection of well differentiated HCC where the lesion shows FDG uptake similar to the surrounding normal liver activity, in spite of that it is useful in the detection of extra hepatic spread of HCC with superior accuracy in comparison with CT and MRI. According to *(Elmenshawy et al)*[13] 18F-FDG PET had been used in many institutes to assess extra hepatic metastasis before liver transplantation for HCC.

(Wong et al)[14] stated that PET achieved higher accuracy than standard computed tomography alone (95% versus 50%) in classifying the Milan-criteria status. The Milan criteria are the benchmark for selection of patients with underlying cirrhosis for liver transplantation. These criteria use the size and number of the HCC as parameters in the absence of extra hepatic involvement.

In our study PET/CT showed sensitivity, specificity and positive predictive value of 66.7%, 96.3%, and 66.7% respectively. These results were comparable to many studies as (Ali et al)[15] who reported that PET /CT sensitivity, specificity and positive predictive value for detection of viable HCC after interventional therapy were 95%, 72.7%, 92.5%, respectively.

(Ragheb et al)[16] stated that PET/CT in patients with unexplained rising alpha fetoprotein post HCC interventional management achieved sensitivity 92.8%, specificity 88.4%, accuracy 90%, positive

predictive value 81.25%, and negative predictive value 95.8%.

Also, (*Kim et al)*[7] 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 (*Soliman et; al)*[17] 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. The limitation of our study was the limited sample size and one month follow up after RFA which could not help in detecting metastasis or more residual cases.

Conclusion:

The FDG PET/CT demonstrated a high sensitivity in detection of residue of tumour after RFA with good judgement on definite diagnosis by measuring metabolic activity. 18F-FDG PET/CT is a valuable imaging tool to investigate the patients who have rising serum AFP level after HCC treatment .Further prospective studies with a large number of patients and established protocol are needed to substantiate our results.

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دور التصوير الطبقى بالبوزيترون المنبعث المدمج مع الاشعة المقطعية فى تقييم سرطان الخلايا الكبديه بعد العلاج بالتردد الحرارى

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الملخص العربي

الخلفية: سرطان الخلايا الكبدية هو أكثر أنواع الأورام الخبيثة الأولية شيوعًا في الكبد وهو سبب رئيسي للوفاة المرتبطة بالسرطان في جميع أنحاء العالم. وهو ثالث أكثر أسباب الوفاة شيوعًا بسبب السرطان في جميع أنحاء العالم . يعتبر العلاج بالتردد الحرارى أحد الأساليب المهمة في علاج سرطان الكبد لانه يعتبر تدخل غير جراحى و ذو نسبة مضاعفات ضئيله وجيد فى القضاء على الاورام. يوفر الفحص الطبقى البوزيترونى المدمج مع الاشعه المقطعيه بيانات وظيفية وتشريحيه للكشف عن بقايا سرطان الكبد بعد العلاج بالتردد الحرارى.وجود بؤره بالمنطقة المعالجه بالتردد الحرارى بها زياده فى استهلاك المادة المشعة (١٨فلوروديوكسى جلوكوز) دلاله على وجود اورام متبقية وعدم وجود اى امتصاص لهذه الماده المشعه يدل على القضاء الجيد على الورم.

هدف العمل: التأكيد على دور الفحص الطبقى البوزيترونى المدمج مع الاشعه المقطعيه في متابعة سرطان الكبد بعد العلاج بالتردد الحرارى.

المرضى والطرق: أجريت هذه الدراسة الاستطلاعية على ثلاثين مريضاً ، ٢٥ رجلاً و ٥ نساء. تمت إحالة المرضى إلى قسم التشخيص الإشعاعي ، مستشفيات جامعة عين شمس ، قسم التشخيص الإشعاعي ، وحدة الفحص الطبقى البوزيترونى المدمج مع الاشعه المقطعيه خلال فترة ٨ أشهر من جمع البيانات للمرضى الذين خضعوا لعملية استئصال سرطان الخلايا الكبديه في وحدة الأشعة التداخلية.

النتائج: اظهر الكشف عن بقايا الخلايا السرطانيه بالكبد بعد الفحص الطبقى البوزيترونى المدمج مع الاشعه المقطعيه حساسية ونوعية ودقة ٦٦.٧٪ ، ٩٦.٣٪ ، ٩٣.٣٪ على التوالي.

الخلاصة: يعتبر الفحص الطبقى البوزيترونى المدمج مع الاشعه المقطعيه ذو دقة تشخيصية عالية في تقييم التدخل بعد العلاج بالتردد الحرارى مما يساعد في اكتشاف الخلايا السرطانيه المتبقية.

الكلمات الأساسية: ١٨فلوروديوكسى جلوكوز, التصوير الطبقى البوزيترونى المدمج مع الاشعه المقطعيه,الخلايا الكبديه السرطانية,الرنين المغناطيسى, العلاج بالتردد الحرارى, ألفا فيتو بروتين.