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Added Value of PET/CT in Assessment of Hepatocellular Malignancy Post Radiofrequency Ablation

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ABSTRACT

Background: Following loco-regional interventional treatment, patient survival depends on the early identification and management of residual or recurrent hepatocellular carcinoma (HCC).

Objective: The goal of this study is to determine whether PET/CT (positron emission tomography/computed tomography) can help detect tumoral activity that is still present following radiofrequency ablation (RFA) for HCC in its early stages.

Patients and Methods: Seventy participants participated in this prospective cohort research with HCC of both sexes aged 18 and above, who underwent RFA. A Philips hybrid system with a 16 MDCT scanner was used to perform PET/CT one month after RFA.

Results: Alpha-fetoprotein level was notably reduced after ablation than before ablation (P<0.001). The average value (± SD) of the liver standardized uptake value max was 2.3 (±0.48) cm. The PET/CT can predict unresolved lesions with 95.7% accuracy, 100% negative predictive value, 62.5% positive predictive value, 95.4% specificity, and 100% sensitivity. The PET/CT and triphasic CT scans revealed a high degree of agreement (Kappa =0.747).

Conclusions: Due to its ability to quantify metabolic activity, PET/CT proved to be quite sensitive in detecting tumour remains after RFA with excellent diagnostic judgement for a final diagnosis.

Keywords: PET/CT, Hepatocellular Malignancy, Radiofrequency Ablation, Alpha-fetoprotein.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and one of the leading causes of cancer-related death worldwide [1]. It ranks as the third most common cause of cancer-related death globally, ranking fourth in Egypt and sixth overall, respectively [2].

For patients with HCC, surgical excision—either by orthotropic liver transplantation or hepatic resection—is the best treatment option [3]. Many patients are regrettably not candidates for surgical resection, and attempts have been undertaken to treat the unresectable HCC with a variety of other therapies [4]. Radiofrequency ablation (RFA) is a well-established, minimally invasive technique for treating HCC, particularly in patients unsuitable for surgical resection or liver transplantation. It induces coagulative necrosis by converting radiofrequency energy into thermal energy, effectively destroying tumor cells. Due to its favorable safety profile and high local control rates, RFA has become a widely accepted local ablative therapy. Recent recommendations from the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend RFA as the initial line of treatment for patients with early-stage HCC (Barcelona Clinic Liver Cancer stage 0 or A) who do not meet the surgical criteria [5,6].

Following RFA therapy, patients should be concerned about the possibility of a local site recurrence (LSR), which can range from 3.6% to 27% of cases, largely depending on the size of the treated lesion. Early discovery of a local site recurrence, especially when it is small, is critical since recurring therapy can lead to complete tumour eradication [7].

After a liver-specific contrast agent has been administered, imaging modalities such as contrast-enhanced ultrasonography, magnetic resonance imaging (MRI), and computed tomography (CT) have been employed to evaluate the efficacy of the treatment [8]. However, in the early days following RFA, post-procedural tissue changes—such as edema, hyperemia, or necrosis—can complicate the interpretation of MRI and CT imaging, making it challenging to accurately assess residual or recurrent tumor tissue. In triphasic CT, for example, reactive tissue may appear as a hypodense region surrounding the ablated lesion. The difference between this and both living tumour tissue and necrotic regions is often blurry [9].

18F-fluoro-2-deoxy-D-glucose (18F-FDG) is a method of functional imaging used in positron emission tomography (PET) to offer metabolic details about the lesion [10]. Its excellent sensitivity and specificity make it useful for diagnosis, therapeutic monitoring, and the identification of recurrent tumors of different types of cancer [11,12]. However, due to uneven absorption, it is less effective in detecting primary HCC. While the effectiveness of 18F-FDG PET in identifying early HCC is still up for discussion, it seems to be a good choice for tracking liver tumours [13].

Using 18F-FDG PET and triphasic CT together is a great way to see how well the treatment is working [14]. Lesions that showed increased FDG uptake at PET become completely photogenic immediately following RFA, indicating that ablation is complete. The presence of specific regions of higher FDG uptake within the

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ablated zone indicates the presence of persistent disease. Functional and morphologic data sets can be precisely merged in a single session using combined PET/CT systems [15].

This research aims to assess the efficacy of PET/CT compared to triphasic CT in identifying individuals with HCC who still have tumour activity after RFA.

PATIENTS AND METHODS

Seventy patients with HCC of both sexes aged 18 and above, participated in this prospective observational study at the HCC Unit of Tropical Medicine Department and Pet CT Unit of Radiology Department, Tanta University Hospitals for a period from March 2025 to June 2025.

Ethical approval:

Following institutional ethical committee approval of Tanta University (approval code: 36264PR1162) and registration at clinicaltrials.gov (NCT06960031). The patient gave their informed written consent. Every patient received a unique code number and gave their written, informed permission. The study was conducted in accordance with the Helsinki Declaration.

Blood glucose levels exceeding 150 mg/dl at the beginning of the study and a history of contrast allergy, increased levels of serum creatinine greater than 2 mg/dl, were excluded from the study. Also, lesions <10 mm were excluded due to their low FDG uptake and limited detectability on PET/CT, which may compromise accurate assessment of treatment response. In accordance with the most recent EASL guidelines (2024), lesions that were eligible for RFA were those that met the following criteria: they were classified as either Child A or B, had a single HCC or nodule less than 3 cm in size, did not have any vascular invasion or extrahepatic dissemination, and were situated away from main veins or bile ducts to guarantee a safe and successful ablation [5,6].

Along with a thorough medical history and all previous imaging studies, including a CT, the patient underwent preoperative laboratory testing that included serum creatinine, serum alpha-fetoprotein (AFP), and fasting blood glucose (a six-hour fast was observed before to sampling).

Technique of FDG PET/CT technique examination:

Hybrid PET/CT scans were conducted one month following the RFA using a Philips system equipped with a 16 MDCT scanner. Various bed configurations were employed to generate PET images of the entire body, beginning at the brain and ending at the knee. Each bed had an axial file of around 15 cm and a specific resolution of 4 mm. Each bed's emission scan took around two minutes to get, for a total time of twelve to seventeen minutes.

The patient was instructed to maintain a below 150 mg/dl of blood glucose and to fast for 6–8 hours before the examination before receiving the tracer injection. This scan was performed 45-60 minutes after injecting 0.1 mCi 18F-FDG/kg. Following the injection of 100 mL of non-ionic iodinated contrast medium (Omnipaque 300) at a rate of 2-3 mL/s, a diagnostic triphasic transmission scan with contrast enhancement was performed.

The CT was performed with the following parameters: 0.5 tube rotation time, 120 kV, 350 mA, and slice thickness of 5 mm. On the GE workstation. Using many planes to reformat the images, we looked at the PET/CT, PET, and CT combined types of images. While the venous phase encompasses the same visual area as PET scans, the arterial phase extends over the abdominal region, from the base of the lungs to the iliac bones, and the delayed phase spans the area between the bases of the skull and the inferior pubic rami. For the PET scans, the maximum intensity projection images in three dimensions were recreated.

The following criteria were used to assess the accuracy of the results, according to the AASLD [5]:

Benign findings: (resolved lesions)

An AFP reduction at 20 ng/L has a sensitivity of 60:80% and a specificity of 70:90%. Consideration is given to the decrease in laboratory serial AFP prior to and following the RFA without tracer uptake, as well as the elimination of contrast enhancement.

Residual lesions: (unresolved)

The triphasic contrast-enhanced computed tomography (CECT) images obtained prior to and following the RFA with nodular tracer uptake were compared, whether the area of ablation showed a peripheral contrast enhancement and whether the laboratory serial AFP was consistently greater following the RFA were taken into consideration.

Hepatocellular carcinoma (HCC) remnants were found in lesions that exhibited arterial phase nodular hyperenhancement and delayed phase washout during the triphasic CECT component.

The disease activity in 18F-FDG PET/CT was assessed using semi-quantitative or qualitative methods: The quantitative evaluation is predicated on the discovery of elevated 18F-FDG uptake in a specific area relative to the normal liver background. The semi-quantitative evaluation included maximum SUV (standardised uptake value) and TSUvmax/LSUV mean (tumour SUV max/normal liver SUV mean), two measures of uptake efficiency. A region of interest (ROI) was defined for normal liver uptake in addition to the ROI surrounding the tumour. The same approach was utilised to assess the lymph nodes, lungs, bones, and other organs in order to detect distant metastases.

The primary outcome was the sensitivity of FDG PET/CT to predict HCC post-RFA. The secondary outcomes were the accuracy, positive predicted value (PPV), negative predictive value (NPV), and specificity

of FDG PET/CT in post-RFA follow-up, the average ablated area diameter, the average liver SUV max, the AFP level prior to and following ablation, and the CT scan.

Sample Size:

The World Health Organisation (WHO) and the Centres for Disease Control and Prevention (CDC) created the statistical tool EpI-Info 2002 to assess the sample size. The sample size (60) was established by considering the following parameters: A prior study [9] found that the sensitivity of FDG PET/CT to predict HCC after RFA was 66.7% with a 95% confidence level. In order to combat dropout, ten cases were introduced. Therefore, we recruited 70 cases.

Statistical analysis

We used SPSS version 26.0 to do the statistical analysis. We used histograms and the Shapiro-Wilks test to check if the data were distributed normally. Mean ± SD were used as quantitative parametric data, and the independent T-test was used to compare them. Using the Mann-Whitney test, we compared quantitative non-parametric data that were reported as the median and interquartile range ("IQR"). There was a comparison of the frequency and percentage values of the qualitative variables using the X^2-test or Fisher's exact test. For statistical purposes, a P value below 0.05 was deemed significant.

RESULTS

Tables (1) summarize the baseline demographic and liver disease characteristics of the studied patients. The overall mean age (± SD) was 57.4 (±9.51) years, of them 47 (67.14%) were males and the mean BMI in our patients was 26.3 (±4.52) Kg/m^2.

Table (1): Demographic data of the studied patients

Parameters		(n=70)
Age (years)		57.4 ± 9.51
Sex	**Male**	47 (67.14%)
	Female	23 (32.86%)
Weight (Kg)		75.6 ± 10.62
Height (cm)		170.3 ± 7.7
Body mass index (Kg/m^2)		26.3 ± 4.52

Data are presented as mean ± standard deviation or as frequency (Percentage).

HCV and HBV were present in 58 (82.86%) and 12 (17.14%) patients respectively. Liver disease severity according to Child Pugh score was mainly Child A in 55 (78.57%) patients. The average size of the HCC lesion was 4.1 (±2.08) cm. Segment VIII was the most frequently involved liver segment, with 19 patients (27.14%), followed by segment VII in 17 patients (24.29%). AFP level was significantly decreased after RFA (Table 2).

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

Parameters		(n=70)
HCV		58 (82.86%)
HBV		12 (17.14%)
Liver disease severity	**Child Pugh A**	55 (78.57%)
	Child Pugh B	15 (21.43%)
Segment affected	**II**	4 (5.71%)
	III	4 (5.71%)
	IV	7 (10%)
	V	7 (10%)
	VI	12 (17.14%)
	VII	17 (24.29%)
	VIII	19 (27.14%)
Size of lesion (cm)		4.1 ± 2.08
Serum creatinine (mg/dL)		1.2 ± 0.31
Fasting blood glucose (mg/dL)		149.3 ± 13.62
AFP level (ng\L)	**Before ablation**	78 (66 – 100.25)
	After ablation	23.5 (14 - 45.5)
	P value	**<0.001***

HCV: Hepatitis C virus, HBV: Hepatitis B virus. AFP: Alpha-fetoprotein. Data are presented as frequency (Percentage), as mean ± standard deviation, or as median (Interquartile range).

As shown in table (3), CT scan one month following RFA showed a non-enhanced focal lesion in 65 (92.86%) of the patients which means no residue. 18F-DG PET/CT in post-RFA one month follow-up showed resolved lesions in 62 (88.57%) patients versus 8 (11.43%) patients with residual tumoral activity.

Table (3): Diameter of ablated area, liver SUV max, CT scan before and after ablation, and 18F-DG PET/CT in the post-RFA follow-up of the studied patients

Parameters		(n=70)
Diameter of ablated area (cm)		3.1 ± 0.79
Liver SUV max (cm)		2.3 ± 0.48
CT scan before ablation	**Positive HCC arterial enhanced focal lesion**	70 (100%)
CT scan after ablation	**Non-enhanced focal lesion**	65 (92.86%)
	Peripheral enhancement	5 (7.14%)
18FDG PET/CT in radiofrequency ablation	**Resolved lesions**	62 (88.57%)
	Residual tumoral activity	8 (11.43%)

SUV max: Standardized uptake value maximum, CT: Computed tomography, HCC: Hepatocellular carcinoma, 18F-DG PET/CT: Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography. Data are presented as mean ± standard deviation or as frequency (Percentage).

Table (4) demonstrates a comparative analysis between patients with residual tumoral activity and those with resolved lesions based on PET/CT findings and revealed no statistically significant differences in demographic parameters (age, sex, BMI), liver disease etiology (HCV/HBV), or laboratory markers such as serum creatinine and fasting blood glucose. However, size of lesion and AFP levels before and after ablation were substantially greater in the residual activity group, suggesting AFP as a potential marker of incomplete ablation. Moreover, segmental distribution showed a significant difference between groups, with a higher proportion of residual activity seen in segment II. Diameter of ablated area was markedly reduced in the residual activity group.

CT findings after ablation differed significantly, with 5 patients (62.5%) of residual activity cases showing peripheral enhancement, while cases with resolved lesions demonstrated complete lack of enhancement.

Table (4): Comparison between patients with and without residual tumoral activity after RFA according to PET/CT findings

Parameters		Resolved lesions (n=62)	Residual tumoral activity (n=8)	P value
Age (years)		58.03 ± 9.5	52.88 ± 8.82	0.150
Sex	**Male**	44 (70.97%)	3 (37.5%)	0.104
	Female	18 (29.03%)	5 (62.5%)	
Weight (kg)		75.9 ± 10.9	73.38 ± 8.4	0.530
Height (cm)		170.65 ± 7.66	167.25 ± 7.85	0.244
BMI (Kg/m^2)		26.25 ± 4.59	26.46 ± 4.19	0.903
HCV		52 (83.87%)	6 (75%)	0.618
HBV		10 (16.13%)	2 (25%)	
Liver disease severity	**Child Pugh A**	51 (82.26%)	4 (50%)	0.059
	Child Pugh B	11 (17.74%)	4 (50%)	
Segment affected	**II**	1 (1.61%)	3 (37.5%)	**0.005***
	III	4 (6.45%)	0 (0%)	
	IV	7 (11.29%)	0 (0%)	
	V	7 (11.29%)	0 (0%)	
	VI	11 (17.74%)	1 (12.5%)	
	VII	15 (24.19%)	2 (25%)	
	VIII	17 (27.42%)	2 (25%)	
Size of lesion (cm)		3.9 ± 2.05	5.88 ± 1.39	**0.011***
Serum creatinine (mg/dL)		1.26 ± 0.3	1.13 ± 0.38	0.248
Fasting blood glucose (mg/dL)		148.87 ± 13.29	153 ± 16.54	0.424
AFP level (ng\L)	**Before ablation**	75.5 (63.5-93.25)	178.5 (155.5-187.5)	**<0.001***
	After ablation	21.5 (12.25-30)	118.5 (110-129.75)	**<0.001***
Diameter of ablated area (cm)		3.17 ± 0.76	2.46 ± 0.82	**0.017***
Liver SUV max (cm)		2.28 ± 0.49	2.25 ± 0.4	0.860
CT scan before ablation	**Positive HCC arterial enhanced focal lesion**	62 (100%)	8 (100%)	1.000
CT scan after ablation	**Non-enhanced focal lesion**	62 (100%)	3 (37.5%)	**<0.001***
	Peripheral enhancement	0 (0%)	5 (62.5%)	

BMI: Body mass index. HCV: Hepatitis C virus, HBV: Hepatitis B virus, AFP: Alpha-fetoprotein.SUV max: Standardized uptake value maximum, CT: Computed tomography, HCC: Hepatocellular carcinoma, 18F-DG PET/CT: Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography. Data are presented as frequency (Percentage), as mean ± standard deviation, or as median (Interquartile range)

The triphasic CT scan and PET/CT did not substantially differe from one another. The PET/CT and CT scans showed a high degree of agreement. (Kappa =0.747). The PET/CT could predict unresolved lesions with 100% sensitivity, 95.4% specificity and 95.7% accuracy (Table 5).

Table (5): Role of PET/CT in the prediction of residual tumoral activity compared to triphasic CT scan

		Triphasic CT scan			P value
		Yes	No		
PET/CT	Yes	5	3		0.250 McNemar test
	No	0	62		
Sensitivity	Specificity	PPV	NPV	Accuracy	Kappa
100%	95.4%	62.5%	100%	95.7%	0.747

PET/CT: positron emission tomography/computed tomography, PPV: Positive predictive value, NPV: Negative predictive value.

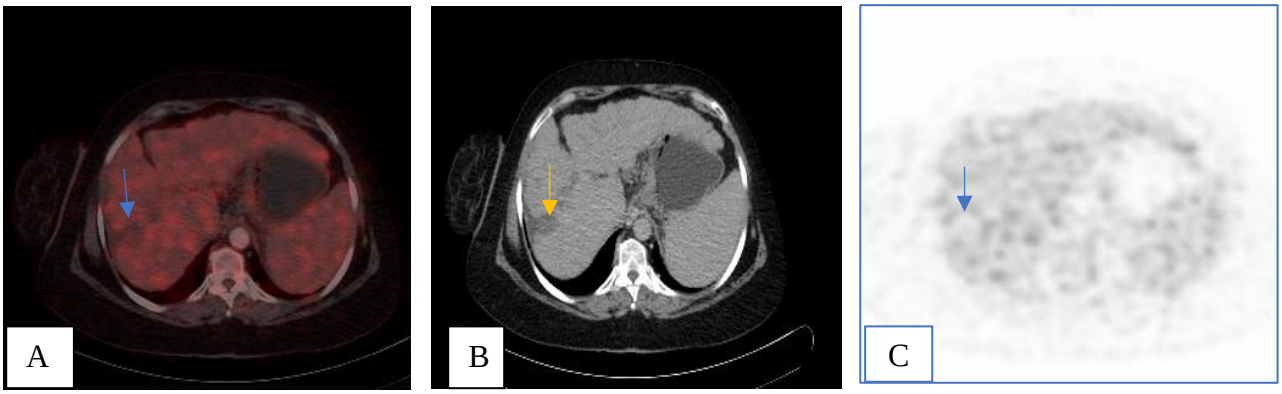

Fig. (1): (A) Female patient aged 56 years, with liver HCC had radiofrequency, preparing for liver transplant and referred to PET/CT 1 month after RFA. (A, B & C) Axial PET/CT, CT & PET images shows photopenic area (blue arrow) related to the site of previously ablated sub-capsular focal lesion at segment VII with no contrast enhancement (yellow arrow) with retraction of overlying capsule denoting good ablation with no residual tumoral activity confirmed by decreased level of alfa fetoprotein (25 ng/ml).

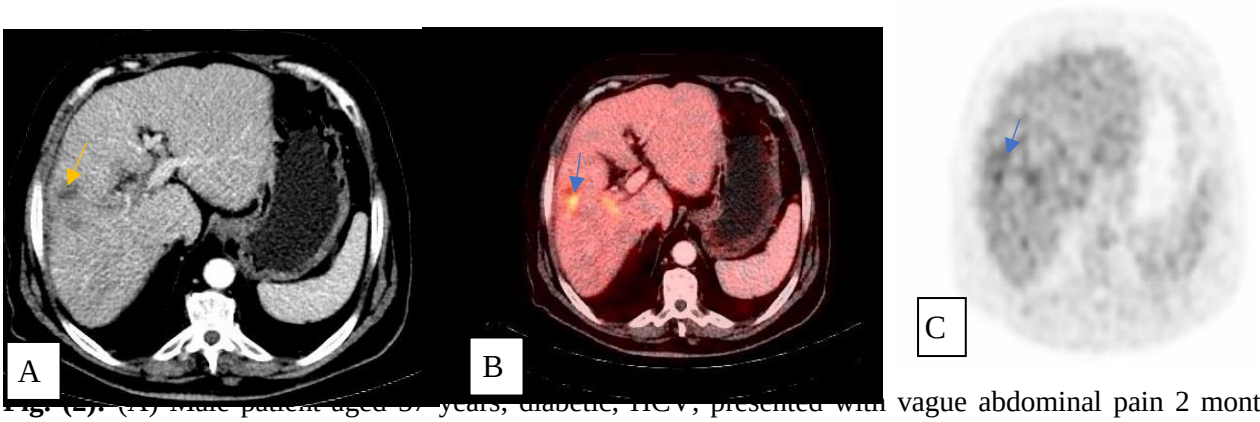

Fig. (2): (A) Male patient aged 57 years, diabetic, HCV, presented with vague abdominal pain 2 months ago CT abdomen and pelvis with contrast revealed → cirrhotic liver with right hepatic lobe enhancing focal lesion with criteria of HCC biopsy was taken reveled moderately differentiated HCC, radifrequency ablation was done and follow up after 6 weeks. (A , B & C) Axial CT, PET/CT & PET images show peripherally metabolically active (blue arrow) right hepatic lobe hypo dense lesion (Yellow arrow) seen at segment V SUV max 6 denoting residual tumoral activity confirmed by Still elevated alfa fetoprotein (98 ng/ml).

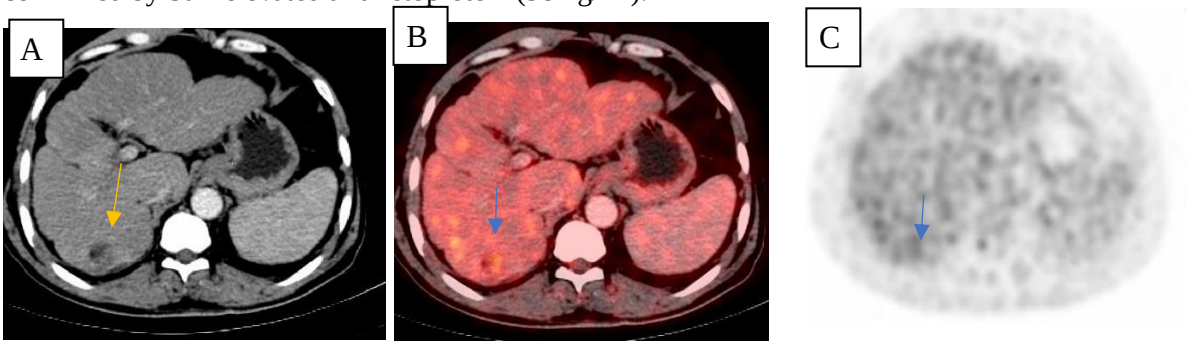

Fig. (3): (A) Male patient aged 53 years, diagnosed hepatocellular carcinoma, complaining of abdominal pain 3 months ago underwent radiofrequency ablation 5 weeks ago. (A, B & C) Axial CT, PET/CT & PET images show right hepatic lobe segment VII hypodense focal lesion shows heterogenously peripheral enhancement at contrast enhanced CT (yellow arrow) with peripheral increased metabolic activity of the same lesion (blue arrow) showing low peripheral FGD uptake with SUV max 3.4 at PET/CT images denoting residual tumoral activity.

DISCUSSION

One of the most prevalent malignant tumors in the world is HCC. There are now possibilities for HCC treatment, including RFA [16]. Following locoregional interventional treatment, patient survival depends on the early identification and management of residual or recurrent HCC. To determine if the tumor has been eliminated or whether additional therapy is needed, It is essential to use MRI, CT, and PET CT to evaluate the tumor response following RFA [17].

PET/CT is a special blend of metabolic information from PET and cross-sectional anatomic data from CT. It determines the extent to which HCC has migrated outside the liver in order to prepare for a liver transplant. In contrast to morphological imaging, FDG-PET assesses tumour vitality by looking at glucose metabolism, not at its form [18]. The purpose of this research was to compare the efficacy of PET/CT with triphasic CT in identifying patients with HCC who had persistent tumoral activity after RFA.

According to our research, the median AFP decreased dramatically from 78 prior to ablation to 23.5 following ablation (P<0.001), which is consistent with the findings of **Zytoon *et al.* [19],** who reported a decline in AFP among patients with residual disease from 174 to 117 ng/mL although their post-RFA AFP levels remained elevated due to persistent tumor activity. This supports the value of AFP as a supportive, though non-definitive, biomarker for treatment monitoring.

Morover, the study by **Luo *et al.*[20]** that examined 368 patients with HCC who underwent RFA found that a post-RFA AFP ratio (post-/pre-RFA) lower than 37.9 was linked to improved survival and recurrence rates. Additionally, a meta-analysis by **He *et al.*** [21] demonstrated that post-treatment AFP response could predict survival in HCC patients, further supporting the prognostic value of AFP reduction after locoregional therapies like RFA .

In this study, the SUV max was utilized to assess FDG avidity within the ablated liver lesions. A lesion was considered positive when FDG uptake exceeded the physiological background activity of normal hepatic tissue. Although the mean liver SUV max did not significantly differ between the residual activity and resolved lesions groups (2.25 ± 0.4 vs. 2.28 ± 0.49, P = 0.860), PET/CT could still detect metabolically active tumor remnants in patients with normal-appearing CT. This shows that metabolic evaluation based on SUVs can identify illness that is not visible to the naked eye, lending credence to the utility of PET/CT for early evaluation after ablation. A similar SUV-based approach was employed by **Abuodeh *et al.*** [22].

In our study, PET/CT identified eight patients with residual tumor activity, five of whom had matching findings on triphasic CT, while three were negative on CT. Conversely, 62 patients showed concordant negative results on both modalities.

Concurring with our results, **Farahat *et al.*** [9] assessed the diagnostic accuracy, sensitivity, and specificity of PET/CT following RFA in patients with HCC, finding a value of 93.3%, 66.7%, and 96.3%, respectively, when utilising an SUVmax/liver SUVmean cutoff of 1.81. In our study, PET/CT achieved even higher diagnostic performance, predicting unresolved lesions with 100% sensitivity, 95.4% specificity, 62.5% PPV, 100% NPV, and an overall accuracy of 95.7%. This highlights the strong utility of PET/CT in detecting residual tumor viability post-RFA, with a high agreement with CT imaging (Kappa = 0.747).

Moreover, **Yao *et al.*** [23] has been completed. While not ideal for initial HCC diagnosis due to variable FDG uptake, PET/CT was emphasized as a useful tool in post-treatment assessment, especially when conventional imaging is inconclusive.

Similarly, **Ragheb *et al.*** [24] discovered that PET/CT had a sensitivity of 92.8% and an accuracy of 90% in patients whose AFP levels rose following interventional HCC treatment. **Ali *et al.*** [25] discovered that PET/CT had a sensitivity of 95%, specificity of 72.7%, and PPV of 92.5% after interventional therapy for the detection of active HCC. Also, **Kim *et al.*** [16] demonstrated reliable early assessment performance of PET/CT, reporting sensitivity of 87.5% and accuracy of 80% following HCC locoregional therapy.

Our trial has limitations, including a relatively limited sample size, and was conducted at a single center, **and** short follow-up following RFA that was unable to identify metastases or more residual instances. More future research involving other used techniques as biobsy and a sizable patient population is recommended.

CONCLUSIONS

Through the measurement of metabolic activity, PET/CT demonstrated a high level of sensitivity in identifying residual tumoral activity following RFA with good judgment on a definitive diagnosis.

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