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Role of ^{18}F-FDG PET/CT in assessment of HCC patients after therapeutic interventions compared to DW MRI

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Abstract

Background: Hepatocellular carcinoma (HCC) is one of the most common causes of cancer-related deaths worldwide in both men and women. Early-stage HCCs are treated either by curative surgical resection and/or by locoregional interventions, such as radiofrequency ablation or trans-arterial chemoembolization. Functional imaging as diffusion-weighted magnetic resonance imaging (DW MRI) and metabolic imaging with ^{18}F-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has been used for assessment of treatment response. This retrospective study was conducted on 29 patients known to have HCC with locoregional therapeutic interventions and referred for radiological follow-up searching for residual/recurrence neoplasia or metastatic deposits. The study aimed to assess the benefits of using the metabolic parameters of ^{18}F-FDG PET/CT in the follow-up of HCC patients after therapeutic interventions in comparison with DW MRI.

Results: Regarding qualitative assessment of residual active viable HCC by PET/CT and DW MRI, the sensitivity, specificity, PPV, NPP and accuracy were 77.3%, 91.7%, 94.4%, 68.8%, 82.4% and 95.5%, 75%, 87.5%, 90%, 88.2%, respectively. The optimal cutoff point of the SUVmax to differentiate viable from non-viable HCC was 3.4 (AUC = 0.898), with sensitivity, specificity, PPV and NPV of 77.27%, 100.0%, 100.0% and 66.7%, respectively. The optimal ADC cutoff value for discrimination between viable and non-viable HCC was 1247 mm^2/s (AUC = 0.976) with sensitivity, specificity, PPV and NPV of 90.48%, 100.0%, 100.0% and 83.3%, respectively. New hepatic lesions were found in 38.2% of patients by DW MRI, while detected only in 26.5% of patients by PET/CT. The PET/CT revealed extrahepatic metastasis in 44.1% of patients, while detected only in 8.8% of patients by DW MRI.

Conclusions: DWI was more sensitive than PET/CT for detecting tumor residual and hepatic recurrence compared to PET/CT which was much better in detecting distant metastases.

Keywords: Diffusion-weighted imaging, Hepatocellular carcinoma, Therapeutic interventions, Positron emission tomography, Locoregional intervention

Background

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor and the third most common cause of cancer-related deaths in males and females worldwide [1, 2]. High incidence and mortality for HCCs in many regions around the world are largely attributed to dissemination of hepatitis C virus infection [3]. Advances in therapeutic options make curative treatment possible for almost a third of patients if the cancer was detected in its early stage [1]. Early diagnosis, appropriate evaluation of tumor characteristics, accurate staging and proper assessment of treatment response are essential for treating patients with HCC [4]. Early-stage HCC can be treated by surgical resection and/or locoregional interventions, such as radiofrequency ablation (RFA) or

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trans-arterial chemoembolization (TACE). Liver transplantation is an alternative option in unresectable HCC that has not metastasized [4]. Locoregional therapies (LRT) can be used to downstage patients prior to liver transplantation. Thus, the evaluation of tumor response after LRT is essential in directing management in HCC [2]. In a high proportion of cases the disease recurs after attempts at curative therapy [3]. Conventional anatomic imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), often provide equivocal results when used for assessment of treatment response with difficulty in identifying whether residual masses consist of viable tumor tissue or represent post-treatment changes using these methods [5]. A diffusion-weighted image (DWI) is a type of MRI that reflects tissue cellularity. An apparent diffusion coefficient (ADC) is a quantitative value that is calculated from a DWI that correlated with the pathological grades of tumors (high-grade tumors tended to be associated with low ADCs) [4]. Metabolic imaging with ^{18}F-FDG PET/CT has been a very successful modality for detection, staging and restaging various cancers with excellent sensitivity and specificity in certain cancers [6–8]. PET/CT is a unique combination of the cross-sectional anatomic information provided by CT and the metabolic information provided by PET, which is acquired during a single examination [9–11]. ^{18}F-FDG PET detects an increase in metabolic rate and therefore can be a sensitive tool for the diagnosis and follow-up of metastatic liver tumors [5]. ^{18}F-FDG PET/CT provides a detailed comparison of morphologic post-treatment changes and metabolic activity, which are useful for treatment monitoring and for detection, with high accuracy, of viable tumor following RFA and TACE for HCC [5]. It could guide the optimal treatment (combined strategy) in those patients with HCCs with a high standardized uptake value (SUV) ratio by providing a more aggressive locoregional therapy or a concomitant treatment using another modality, in order to improve survival rates [3]. Detection of extrahepatic FDG-avid metastases originating from HCC has also been reported; especially in cases of less-differentiated HCC, metastases appear to be more FDG avid [12]. So, this study aimed to assess the benefits of using the metabolic parameters of ^{18}F-FDG PET/CT in the follow-up of HCC patients after therapeutic interventions, in comparison with diffusion MRI.

Methods

Patients

This is a retrospective study, conducted from January 2017 to September 2021 on 32 patients known to have HCC on top of liver cirrhosis presented for radiological follow-up after therapeutic interventions to search for residual/recurrent neoplasia or metastasis. The study received the approval of the institutional ethical committee, and written or informed consents from all patients were taken after explaining the aim of the study.

Inclusion criteria

Patients under regular follow-up post-therapy and patients with elevated tumor marker (AFP) post-therapy, other imaging modalities findings are not conclusive, patients with portal vein thrombosis (for assessment of the type of thrombosis, benign or malignant), and patients planned to perform hepatic transplantation to exclude extrahepatic metastatic disease.

Exclusion criteria

Patients known to have contraindications for MRI (e.g., metal implants as cochlear implants, implanted magnetic device, cardiac defibrillators and pacemakers or claustrophobia), patients with bad general condition needing life support and patients with severe hepato-renal disease, high serum creatinine > 2 mg/dl, patients known to have severe allergy to contrast material. Also, patients with blood glucose level > 200 mg/dl at time of the study and first trimester pregnancy.

Patient preparation

All patients were asked to fast at least 6 h prior to scan with good hydration. All metallic items were removed including pants with zipper, bra, belts, bracelets, etc., and the patients were given gown to wear. Serum glucose was routinely measured prior to ^{18}F-FDG injection, and it should be below 200 mg/dl (including diabetic patients who were advised to properly control their blood glucose level before examination). An intravenous (I.V) cannula was inserted in the patient's arm for administration of ^{18}F-FDG. The patients were instructed to avoid any kind of strenuous activity prior to the examination (for a minimum of 24 h) and following injection of the radiotracer to avoid physiologic muscle uptake of FDG. To reduce brown fat uptake, a controlled temperature (warm) environment was provided for patients before ^{18}F-FDG injection and low carbohydrate, high fat, protein-permitted diet before the examination. Before MRI scanning, detailed explanation of imaging procedure, including practicing of breath holds, was done.

Technique of ^{18}F-FDG PET/CT scan

The radioactive tracer (^{18}F-FDG) was injected intravenously in a dose of 0.1 mCi/kg body weight. All patients were kept in a warm temperature quiet room and asked to rest without vigorous activity keeping their movements, including talking, at an absolute minimum and void just before imaging. Scanning by a hybrid PET/CT

scanner (GE Discovery and Philips Gemini TF (Time-of-Flight) PET/CT machines) was performed 60 min after injection. The patient was positioned supine on the table with a comfortable head fixation position and their arms raised above their heads. We performed low-dose non-enhanced CT scan first and then whole-body PET scan. Triphasic contrast-enhanced CT scan was then performed. The whole study took approximately 20–30 min. Typical whole-body PET/CT scanning began from the skull base and extended caudally to the level of the mid-thighs, the arterial phase CT covering the region of the abdomen from the base of the lungs down to the iliac bones, the venous phase covering from the skull bases down to the mid-thighs and the delayed phase covering the same region as the arterial phase. The total length of CT coverage was an integral number of bed positions scanned during acquisition of PET data. (Approximately 6–7 bed positions are planned in 3D acquisition mode for scanning the entire patient with 3–5-min acquisition at each bed position.) The study was performed with the patient breathing quietly. The scanning parameters for low-dose attenuation correction CT were 120 kV, 100MA, collimator width of (64×0.625 mm), pitch of 0.8, gantry rotation time of 0.5 s, and field of view of 50 cm. The scanning parameters for high-dose diagnostic CT were 120 kV, 300MA, collimator width of (64×0.625 mm), pitch of 0.8, gantry rotation time of 0.5 s, and field of view of 50 cm. The helical data were retrospectively reconstructed at 1-mm interval. The patient was injected about 100 ml of non-ionic iodinated contrast material using dual syringe Medrad (Stellant) automated injector with injection rate about 2.5 ml/sec; then, liver was scanned in arterial (15–30 s scanning delay), portal (60–90 s scanning delay) and equilibrium/delayed (2–5 min scanning delay) phases. Hundreds of transaxial PET and CT images were transferred to a dedicated workstation to be reconstructed and then reformatted into coronal and sagittal images to facilitate image interpretation. For each of these sets of PET and CT images, corresponding "fusion" images, combining the two types of data, also were generated.

Technique of DW MRI

The MRI studies were done using 1.5 T MR machines (MR Systems Achieva release 3.2.3.4 2016-6-27 SRN: 35073 and GE HEALTH CARE 1.5-T MRI scanner, USA). The patient is positioned supine on the MRI table. All patients were subjected to MRI study with the basic sequences including T1, T2, and diffusion study with ADC map. The study took about 10–20 min: Axial T1 WIs (with TR 550 ms and TE 24 ms) and axial and coronal T2 WIs (with TR 7300 ms and TE 115 ms). All these sequences are single-shot spin echo with flip angle 90°. Slice thickness = 5 mm; spacing = 1 mm; acquisition matrix = 256×224; number of averages = 1; acquisition type = 2D. Axial diffusion-weighted images were acquired with EP technique; images obtained with $b = 0$, $b = 200$ and $b = 800$ were included in the evaluation and in the comparison with the other sequences. TR = 2300 ms, TE = 63 ms, EPI factor = 80, slice thickness = 5 mm, gap = 1 mm, flip angle = 90, acceleration factor = 2, FOV 32–44 cm, number of signal averages (NSA) = 2, acquisition time 39 s, half scan factor = 2, bandwidth = 250 kHz, acquisition matrix 192×160, reconstruction matrix = 256×256.

Image interpretation

The FDG PET/CT images were evaluated by two radiologists of 12 and 8 years of experience in nuclear imaging, while the MRI images were evaluated blindly and independently by 2 radiologists of 15 and 10 years of experience in abdominal imaging.

The findings were correlated with the findings derived from triphasic contrast-enhanced CT images according to the American Association for the Study of Liver Diseases (AASLD) and LI-RADS v2018 lexicon [13, 14]: LR-TR non-viable for a non-enhancing lesion. LR-TR viable for residual or recurrent tissue within or along the treated HCC or de novo lesions associated with one or more of the following features: 1—arterial phase hyper-enhancement (APHE), 2—washout appearance, 3—enhancement similar to pretreated HCC. Also, the findings were correlated with alpha-fetoprotein (AFP) serum level and histopathologic results (specially in cases with negative CT and elevated AFP).

The main followed lesion was assessed qualitatively in the PET/CT images according to the ^{18}F-FDG accumulation within the main followed lesion or operative bed in surgically treated lesions and any de novo lesions in comparison with the surrounding normal liver tissue, whether visually increased or not. Adequate intervention is considered when the intervention bed appears completely photopenic with no detectable FDG uptake seen within. Recurrent and residual disease defined when the intervention bed margin shows one or more nodular/focal areas of increased FDG uptake, not to be mistaken with reactive hyperemia that appears as uniform low-grade metabolic activity. Satellite/new lesions were defined as the presence of single or multiple hepatic nodules demonstrating focal FDG uptake higher than the surrounding liver parenchyma. Also, metastasis sites were defined by correlating the tracer abnormally high uptake sites and the underlying pathology within the diagnostic body contrast CT images.

Quantitative assessment in the PET/CT images of the suspicious lesions is done by identifying areas of

pathologically increased FDG uptake avoiding physiologic uptake. Standardized uptake value (SUV) was independently measured by using region of interest (ROI) drawn on the area of maximal metabolic activity on every axial slice of tumor-related increased FDG uptake; SUVmax was defined as the highest pixel value related to the neoplasm burden in each study.

Qualitative evaluation of the suspected lesions whether the main followed hepatic lesion, new hepatic lesions or suspected metastasis was done by DW-MRI as follows: Malignant lesions were defined as lesions with visually restricted diffusion, measured as increased signal intensity in the DWI, and corresponding decreased signal intensity in the ADC map in comparison with the surrounding normal liver tissue. Benign lesions were defined as lesions with visually facilitated diffusion, has no increased signal intensity in the DWI in comparison with the surrounding normal liver tissue, either similar to the normal liver intensity or decreased and also no decreased signal intensity in the ADC map in comparison with the surrounding normal liver tissue.

While qualitative DWI (signal intensity) was used to predict the nature of the lesion (benign or malignant), quantification of water diffusion was done by obtaining DWIs with multiple b values, which is referred to the ADC value. It is measured in the ADC map by drawing a spherical volume of interest (VOI) on the suspected area to be measured. The area with the more diffusion restriction will show bright signal on DWI and a lower ADC value than that of the area with the less diffusion restriction. The apparent diffusion coefficient (ADC) value was applied for the main followed lesion only, and the mean ADC value was documented as mm^2/s.

Two cases were treated surgically with clear operative bed and no evidence of local recurrence/residual neoplasia within the surrounding normal hepatic tissue. In these two cases, no quantitative assessment was done by either the PET/CT SUV, or the DW MRI ADC value.

Statistical analysis

Results were tabulated and statistically analyzed. All tests were two-sided and were performed at the 5% level of significance by using SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL). Descriptive statistics included median (IQR), mean (x) and standard deviation (SD) and analytic statistics included chi-square test ($\chi 2$), Student's t test, Mann–Whitney test (U), Spearman correlation and ROC curve analysis (cutoff values, sensitivity and specificity). P value < 0.05 was considered statistically significant.

Results

A total of 32 patients were enrolled in this study (22 males and 10 females), with ages ranging from 20 to 77 years (the mean age was 59.47 ± 10.84 years), and a total of 34 treated lesions were studied. Most of the studied lesions were treated by RFA 13 (38.2%) and TACE 13 (38.2%), while 3 (8.8%) lesions were treated by ethanol injection, 3 (8.8%) lesions were treated surgically and only 2 (5.9%) lesions were treated by both RFA and ethanol injection. Findings of triphasic PET/CT based upon LI-RADS v2018 revealed LR-TR viable HCC in 22 (64.7%) lesions and LR-TR non-viable/well-treated HCC in 12 (35.3%) lesions (Table 1).

The qualitative assessment of the PET/CT revealed residual active viable HCC in 18 lesions (52.9%) and non-viable HCC in 16 lesions (47.1%) with sensitivity, specificity, PPV, NPP and accuracy of 77.3%, 91.7%, 94.4, 68.8 and 82.4%, respectively. The DWI qualitative assessment revealed 24 lesions (70.6%) with restricted diffusion and 10 lesions (29.4%) showing no diffusion restriction, with sensitivity, specificity, PPV, NPP and accuracy of 95.5%, 75%, 87.5%, 90% and 88.2%, respectively (Figs. 1, 2, 3).

Regarding the quantitative assessment, the mean value of the SUVmax for the residual viable HCC was significantly higher than the non-viable treated HCC ($P < 0.001$), while the mean ADC value of the viable HCC was significantly lower than the non-viable HCC ($P < 0.001$).

The optimal cutoff point of the SUVmax to differentiate viable from non-viable HCC was 3.4 (AUC = 0.898),

Table 1 Demographic data, therapeutic intervention modalities and triphasic CT wash-in/out criteria of the studied patients

	Triphasic CT		Test value	*P* value	Sig.
	Negative	Positive			
	No. 12	No. 22			
Age					
Mean ± SD	61.00 ± 6.81	58.64 ± 12.58	0.602*	0.551	NS
Range	52–74	20–77			
Sex					
Female	3 (25.0%)	8 (36.4%)	0.458*	0.498	NS
Male	9 (75.0%)	14 (63.6%)			
Therapeutic intervention					
TACE	3 (25.0%)	10 (45.5%)	4.640*	0.326	NS
RFA	6 (50.0%)	7 (31.8%)			
Ethanol	0 (0.0%)	3 (13.6%)			
Surgery	2 (16.7%)	1 (4.5%)			
RFA and ethanol	1 (8.3%)	1 (4.5%)			

*Chi-square test; *Independent t-test

TACE Trans-arterial chemoembolization, *RFA* radiofrequency ablation, *CT* computed tomography

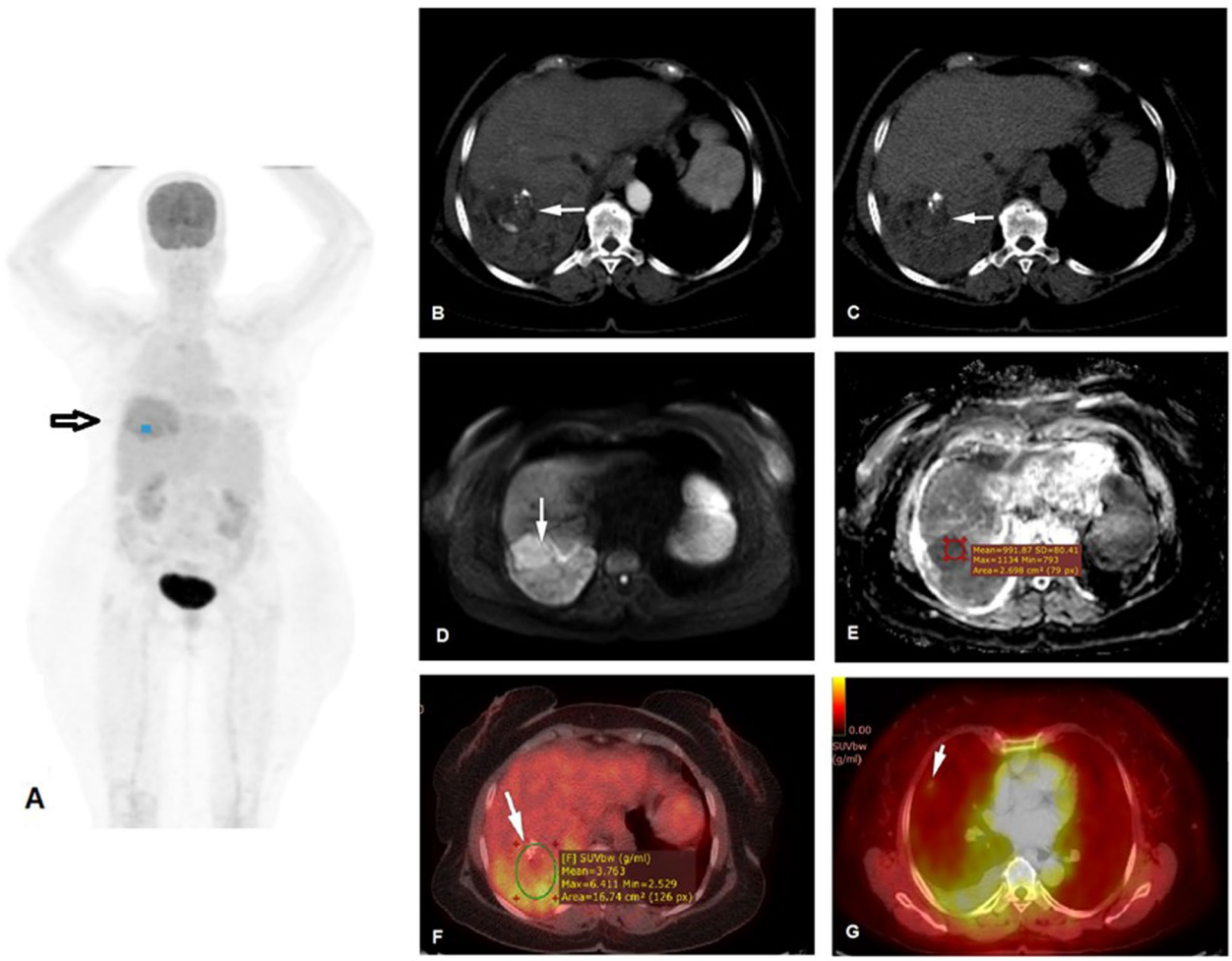

Fig. 1 A 66-year-old female patient with a history of segment VII HCC, underwent TACE. TR-LR viable lesion with increased FDG uptake and diffusion restriction, as well as mildly active metastatic pulmonary nodule, with no de novo lesions. MIP image (**A**) showing focal hepatic right lobar upper segmental increased tracer uptake. Arterial (**B**) and delayed (**C**) triphasic CT showing partial lipiodol retention, and residual/recurrent viable tumoral tissue (white arrow) shows APHE and washout. DWI (**D**) and ADC map (**E**) shows restricted diffusion in the embolized HCC (white arrow) with mean ADC value measuring 991 mm^2/s. Fused PET/CT study shows peripheral increased FDG uptake in the embolized HCC (white arrow) achieving SUVmax of 6.4 (**F**) and mild FDG uptake in a pulmonary nodule (white arrow) (**G**)

which revealed sensitivity, specificity, PPV and NPV of 77.27%, 100.0%, 100.0% and 66.7%, respectively. On the other hand, the optimal ADC cutoff value for discrimination between viable and non-viable HCC was 1247 mm^2/s (AUC = 0.976) with sensitivity, specificity, PPV and NPV of 90.48%, 100.0%, 100.0% and 83.3%, respectively (Fig. 4, Table 2).

New hepatic lesions were found on 13 patients (38.2%), all of them were detected by DW MRI, while detected only in 9 patients (26.5%) by PET/CT (Figs. 2, 5).

The PET/CT revealed extrahepatic metastatic lesions in 15 (44.1%) patients (Figs. 1, 2, 5), while DW MRI revealed extrahepatic metastatic lesions only in 3 (8.8%) of them.

Discussion

Hepatocellular carcinoma is one of the most common malignant tumors worldwide. Early detection and treatment of recurrent HCC after surgical and locoregional interventional managements are important for patient survival [1]. Assessment of tumor response after various therapeutic interventions is important to determine whether the tumor is completely eradicated or needs additional treatment [15]. Diffusion-weighted imaging represents a promising noninvasive diagnostic tool for the evaluation of HCC treatment responses to locoregional therapies. ADC value changes have been shown to occur early after treatment and correlate well with tumor necrosis [5]. PET/CT is a unique combination of the

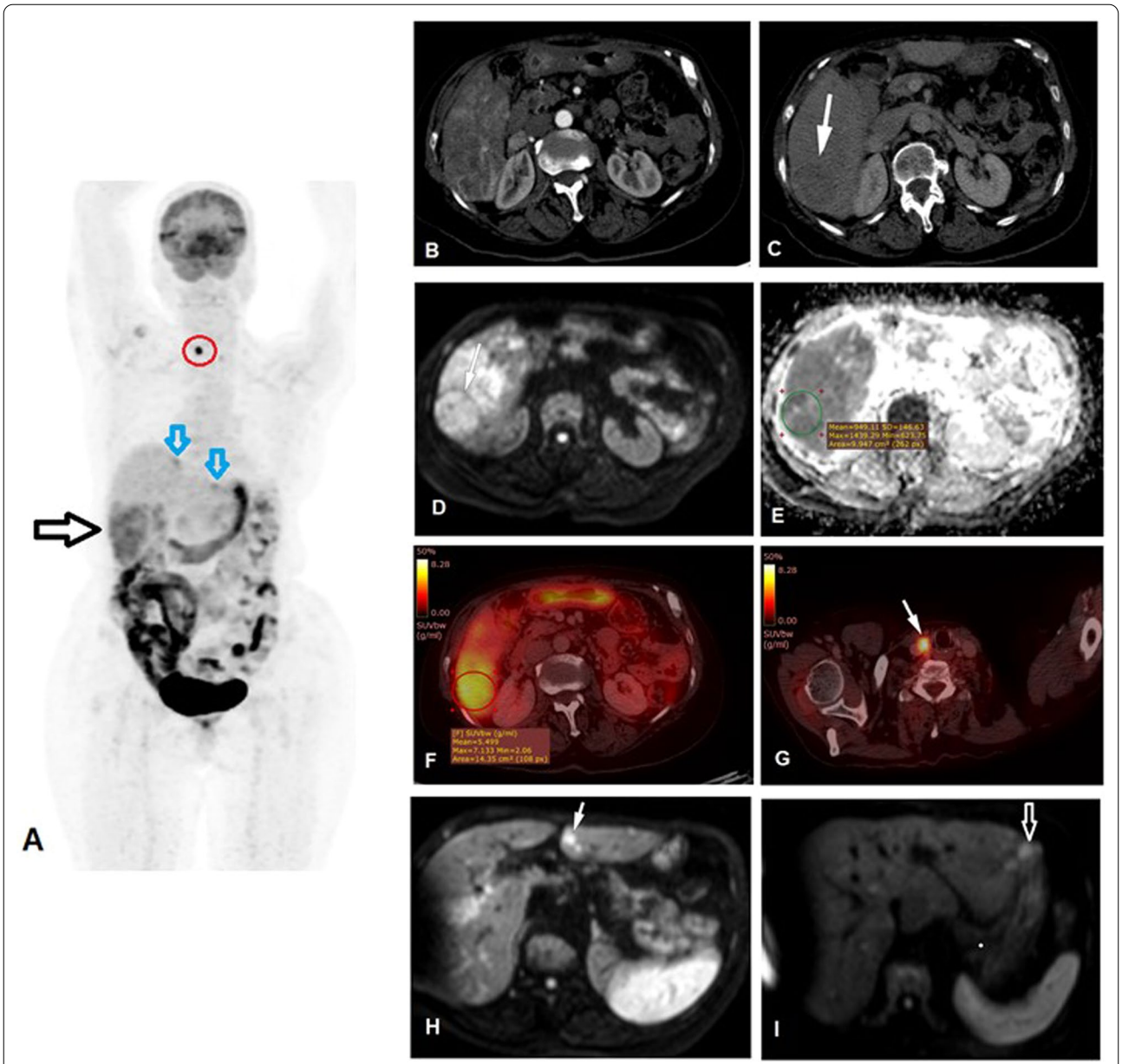

Fig. 2 A 69-year-old female patient with a history of segment VI HCC, had both RFA and ethanol injection. TR-LR viable lesion with increased FDG uptake and diffusion restriction, also had active metastatic cervical lymph node, with two de novo hepatic lesions. MIP image (**A**) showing focal hepatic right lobar lower segmental increased tracer uptake (horizontal black arrow), two left lobar upper segmental small nodular tracer uptake (vertical blue arrows), and lower neck focal increased nodular uptake. Arterial (**B**) and portovenous (**C**) triphasic CT show residual/recurrent viable tumoral tissue (white arrow) shows APHE and washout. DWI (**D**) and ADC map (**E**) shows restricted diffusion in the ablated HCC (white arrow) with mean ADC value measuring 949 mm^2/s. Fused PET/CT images show increased FDG uptake in the ablated HCC (red circle) achieving SUVmax of 7.1 (**F**) and focal increased FDG uptake in a right lower deep cervical lymph node (white arrow) (**G**). De novo two small hepatic left lobar lesions with restricted diffusion are noted at the DW MR axial images (**H** and **I**)

cross-sectional anatomic data provided by CT and the metabolic data provided by PET. It has the advantage of local therapy assessment as well as detection of extrahepatic spread of HCC which is crucial for planning of liver transplantation [16].

Our study showed that qualitative method using PET/CT and DW MRI in assessment of HCC patients after therapeutic interventions had a sensitivity of 74.60% and 81.30%, specificity of 57.54% and 69.20%, PPV of 87.5% and 94.1%, NPV of 90.0% and 68.58% as well as accuracy

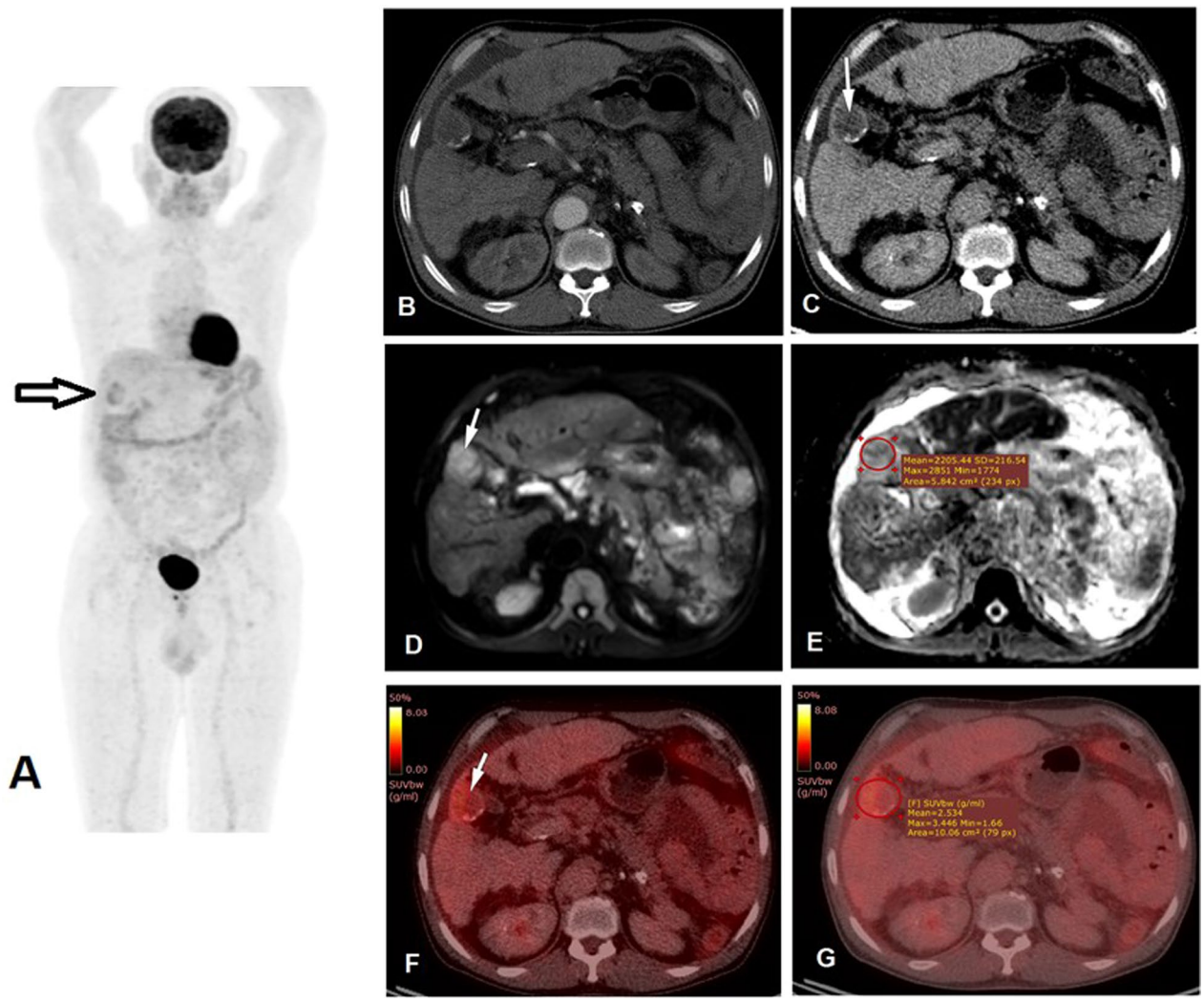

Fig. 3 A 56-year-old male patient with a history of HCC at segment V, underwent TACE. It was TR-LR non-viable, yet, with increased peripheral FDG uptake in PET/CT and diffusion restriction in DWI. No definite de novo lesions and also no detected metastatic lesions. MIP image (**A**) showing focal hepatic right lobar lower segmental increased tracer uptake (black arrow). Arterial (**B**) and portovenous (**C**) triphasic CT of the lesion showing traces of lipiodol retention, with no evidence of enhancing residual/recurrent viable tumoral tissue (white arrow). DWI (**D**) and ADC map (**E**) of the lesion shows restricted diffusion bright signal within the embolized HCC (white arrow); however, the mean ADC value was elevated measuring 2205 mm^2/s. Fused PET/CT images show peripheral increased FDG uptake in the embolized HCC (white arrow), achieving SUVmax of 3.4 (**F** and **G**) identical to our cutoff value

of 88.2% and 82.4%, respectively. For the PET/CT, similar results were also noted by Kim et al. and Song et al.; they revealed a sensitivity of 87.5% and 89.3%, specificity of 71.4% and 65.7% and accuracy of 80% and 80.2%, respectively [17, 18]. For the DW MRI, Ebeed et al. revealed 82.3% sensitivity and 73.9% specificity and Saleh et al. revealed a lower sensitivity of 52.6% and higher specificity of 90.5% [19, 20].

In this study, the range of SUVmax of the lesions with residual/recurrent activity was 2.20–17.20 with median (IQR) 5.55 (3.6–7.9), while the range of ADC value of the same lesions was 690–1310 with mean 1055.71 ± 164.83. In the same line, the study by Hetta W and Atyia H found that the median value of tumor SUVmax in positive cases was 6.6 (ranged from 1.4 to 24), most of them were poorly differentiated HCCs, yet a single case measured about 1.4 SUVmax (well-differentiated HCC type) [21]. In the study done by Ahn et al., the median value of tumor SUVmax was 4.3 (ranged from 2.0 to 11.6) [22]. Also, a study done by Song et al., over 83 patients with HCC to investigate the correlation of ^{18}F-FDG PET/CT with clinical features and the prediction of treatment response,

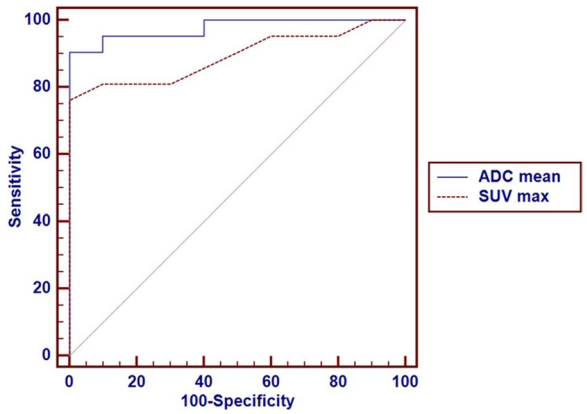

Fig. 4 ROC curve of ADC mean and SUVmax as a predictor of residual HCC viable tumor and local hepatic recurrence

found that SUVmax ranged from 1.5 to 20.8, with a cutoff value of 4.0 [23]. The study by Abduljaleel et al. revealed that the mean ADC value of ablated zones was significantly decreased in patients with residual lesion than in patients without residual lesion [5]. The study by Yu et al. reported that the mean ADC value for necrotic lesions was 1.16 and 1.24×10^{-3} mm^2/sec as detected by reader 1 and 2, respectively [24].

Our study showed that SUVmax value of PET/CT and ADC mean value of MRI in assessment of HCC patients after therapeutic interventions had a sensitivity of 77.27%, and 90.48%, specificity of 100.0% and 100.0%, PPV of 100.0% and 100.0%, NPV of 66.7% and 83.3% with a cutoff value > 3.4 and > 1247, at AUC of 0.898 and 0.976, respectively. In the same line, the study by Ahmed et al. found that the sensitivity, specificity, PPV, NPV and accuracy of SUVmax were 85.24%, 75%, 87.24%, 75% and 82%, respectively [25]. These results are comparable to many studies as Song et al., who reported that SUVmax sensitivity, specificity and accuracy for detection of viable HCC after TACE were 89.29%, 65.71% and 80.22%, respectively in detection of local viable tumoral tissue following TACE [23]. Also, a higher ADC mean cutoff value was reported by Ebeed et al. who revealed a sensitivity of 76.5% and specificity of 65.2% at a cutoff value of 1380 mm^2/s [19].

The specificity and accuracy of quantitative ADC value were higher than the DWI qualitative assessment alone

Table 2 Correlation between qualitative and quantitative assessment by DWI MRI and PET/CT with triphasic CT findings

	Triphasic CT		Test value	*P* value	Sig.
	Negative	Positive			
	No. 12	No. 22			
DW MRI					
Facilitated diffusion	9 (75.0%)	1 (4.5%)	18.565*	0.000	HS
Restricted diffusion	3 (25.0%)	21 (95.5%)			
ADC mean					
Mean ± SD	1594.20 ± 303.17	1055.71 ± 164.83	6.447˙	0.000	HS
Range	1280–2205	690–1310			
PET/CT					
No visually significant tracer uptake	11 (91.7%)	5 (22.7%)	14.812*	0.000	HS
Visually significant tracer uptake	1 (8.3%)	17 (77.3%)			
SUVmax					
Median (IQR)	2.55 (2.3–2.8)	5.55 (3.6–7.9)	− 3.563‡	0.000	HS
Range	1.80–3.40	2.20–17.20			

*Chi-square test; ˙Independent t-test; ‡Mann Whitney test

DWI MRI diffusion-weighted magnetic resonance imaging, *PET/CT* positron emission tomography/computed tomography, *ADC* apparent diffusion coefficient, *SUV* standardized uptake value

(See figure on next page.)

Fig. 5 A 57-year-old male patient with a history HCC underwent right lobectomy, had TR-LR viable recurrent lesion at segment IV, with two active focal lesions having diffusion restriction at segments IV and III, as well as active metastatic pulmonary nodules. Arterial (**A**), venous (**B**) and delayed (**C**) triphasic CT show recurrent HCC at segment IV (white arrow) shows APHE and washout. DWI (**D**) and ADC map (**E**) shows two focal lesions of restricted diffusion in segment IV (white vertical arrow) with mean ADC value measuring 798 mm^2/s, and also at segment III (red horizontal arrow). Fused PET/CT (**F**) and PET (**G**) images show increased FDG uptake in both lesions, achieving up to 7.7 SUVmax. Fused PET/CT (**H**) image revealed active right lung metastatic nodules (white arrows)

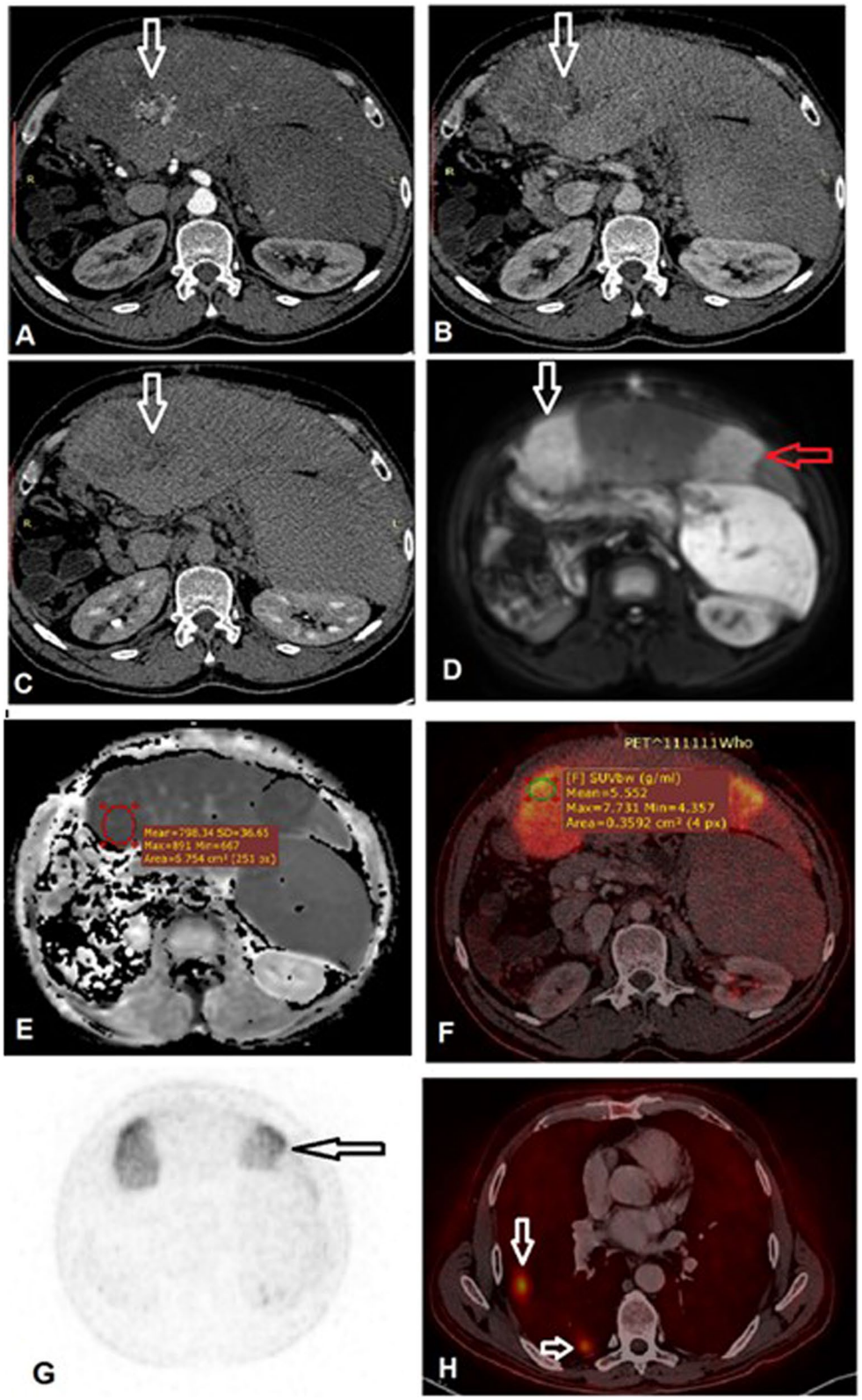

Fig. 5 (See legend on previous page.)

for the detection of residual/recurrent HCC. The present study also showed a significant negative correlation between SUVmax with ADC value. Our results agree with the study by Tyng et al., who found the existence of a significant inverse correlation between SUVmax and ADC values in HCC (high values of SUVmax are associated with low values of ADC) [26]. Also, the study of Regier et al. [27] verified the significant inverse correlation between these two quantitative variables (SUVmax and ADC) in 41 patients. Another study by Nunez et al. [28] observed an inverse significant correlation between the mean SUV and the mean ADC. These results demonstrate that there is a direct relationship between the mobility of water molecules in the tissue evaluated by DW-MRI and glycolytic metabolism evaluated by PET/CT, possibly related to tumor aggressiveness.

On the other hand, the studies by Freihat et al., Min et al. and Surov et al. found that SUVmax was not significantly correlated with the ADC value [29–31]. The explanation for the lack of correlation is the fact that both imaging parameters explain different tissue microstructures characteristics. DWI assesses the water molecule motion in the tissue and is affected by the cellularity, proliferation rate and cell count which, in clinical use, is affected by ROI size placement and inter-observer variability, while metabolic activity was independent of tumor size and shape because tumor is segmented by adaptive thresholding [32, 33].

DW MRI was better than FDG PET/CT in detecting new non-treated hepatic lesions. In our study, de novo HCC lesions were found in 13 patients (38.2%) based on triphasic CT LI-RADS criteria, all of them were also diagnosed by MRI, while diagnosed by FDG PET/CT in only 9 patients (26.5%).

FDG PET/CT had a great advantage in detecting extrahepatic metastases; in our study, extrahepatic metastases were detected by FDG PET/CT in 15 patients, three of them only were also seen in the DWI, as some of the metastases were detected within the abdominal LNs and the other metastatic lesions were seen sporadically distributed within the body.

In the present study, 13 lesions (38.2%) were treated by RFA, 13 lesions (38.2%) by TACE (38.2%), 3 lesions (8.8%) had ethanol injection, 3 lesions (8.8%) had surgical management and only 2 lesions (5.9%) were managed by both ethanol injection and RFA. A study by Kim et al. revealed that, during follow-up, disease progression was observed in RFA as well as TACE patients and combination therapy of TACE with RFA is a safe and effective treatment for patients with medium-to-large HCC, with the long-term beneficial effect of retarding tumor progression [34]. According to our results, we found no significant difference in detecting residual or recurrent viable HCC on using different methods of therapeutic interventions (P value > 0.05).

So, we proposed that if a local residual or recurrent tumoral tissue is suspected following therapeutic intervention, the imaging modality of choice should be MRI with basic anatomical and dynamic sequences, and also functional images such as DWIs and ADC; however, if distant metastasis is suspected, high serum levels of alpha-fetoprotein or liver transplantation is intended, then PET/CT is the imaging modality of choice.

Conclusions

^{18}F-FDG PET/CT and DW MRI are effective functional imaging modalities for assessment of HCC patients after therapeutic intervention. DWI was more sensitive than PET/CT for detecting hepatic tumor residual and recurrence, and adding the quantitative assessment using the ADC value increases its accuracy, compared to PET/CT which was much better in detecting distant metastases. Also adding triphasic protocol to the diagnostic contrast whole-body CT of the standard PET/CT protocol will be of great diagnostic benefit with no additional risks nor costs upon the patient.

Abbreviations

HCC: Hepatocellular carcinoma; ^{18}F-FDG: ^{18}F-Fluorodeoxyglucose; PET/CT: Positron emission tomography/computed tomography; MRI: Magnetic resonance imaging; DWI: Diffusion-weighted images; RFA: Radiofrequency ablation; TACE: Trans-arterial chemoembolization; LRT: Locoregional therapies; ADC: Apparent diffusion coefficient; SUV: Standard uptake value; mg/dL: Milligram per deciliter; mCi: Millicurie; Kg: Kilogram; mL: Milliliter; mA: Milliampere; kV: Kilovolt; s: Second; mm: Millimeter; AFP: Alpha-fetoprotein; NPV: Negative predictive value; PPV: Positive predictive value.

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Author contributions

IT carried out the PET/CT studies and collected the data. SA, MH and HA participated in the design of the study. IT performed the statistical analysis, and SA drafted the manuscript. All authors read and approved the final manuscript.

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Availability of data and material

All data generated or analyzed during this study are included in this article.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Research Ethics Committee (REC) of Ain Shams University, Faculty of Medicine (FMASU M D 212/2018), and written informed consent was obtained from all patients to participate in the study.

Consent for publication

Written informed consent was obtained from all patients for publication of the study.

Competing interests
The authors declare that they have no competing interests.

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