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Role of PET CT in comparison to triphasic CT in early follow-up of hepatocellular carcinoma after transarterial chemoemoblization

Waleed M. Hetta* and Hany Rafat Atyia

Abstract

Background: The aim of the study is to compare the role of PET/CT and that of triphasic CT in hepatocellular carcinoma post chemoembolization evaluation, thus guiding clinicians for proper management strategy. Thirty patients who had transarterial chemoembolization done for HCC were subjected to both radiological modalities, ^{18}F-FDG PET/CT and triphasic CT, with the results compared.

Results: In our study, triphasic CT revealed 20 true positive results, 3 true negative results, 7 false negative results, and no false positive cases thus exhibiting calculated sensitivity, specificity, and accuracy of 74%, 100.0%, and 76.7% respectively. On the other hand, PET/CT showed 26 true positive results, 2 true negative results, 1 false negative result, and 1 false positive result to exhibit calculated sensitivity, specificity, and accuracy of 96.3%, 66.7%, and 93.3%, respectively.

Conclusion: ^{18}F-FDG PET/CT showed high diagnostic accuracy over triphasic CT in interventional bed evaluation following TACE especially for patients with non-conclusive triphasic CT results and persistent elevated levels of AFP.

Keywords: HCC, PET CT, TACE follow-up

Background

Hepatocellular carcinoma (HCC) is the most common primary hepatic tumor of adults. It is the sixth most common tumor in the world and the third most common cause of cancer-related deaths [1].

HCC is caused by malignant transformation of hepatocytes primarily due to chronic liver diseases eventually leading to cirrhosis [2].

Among the selective treatment options of liver tumors, interventional procedures, such as transarterial chemoembolization (TACE), have been widely used. The powerful cytotoxic effect of TACE combined by ischemia, followed by chemoembolization of the tumor's feeding artery, has been proved to result in therapeutic efficacy [3].

Despite good results, this interventional procedure needs close monitoring to ensure therapeutic effectiveness as the rate of residual viable malignancy in tumors larger than 3 cm can reach 48% [2]. That is why tumor response follow-up after TACE is crucial to determine whether the tumor is completely eradicated or further treatment is required.

Magnetic resonance imaging and computed tomography can serve that purpose. Both modalities can evaluate treatment response using the presence or absence of local contrast enhancement as a valuable adjunct to tumoral size change as the size criteria based on the Response Evaluation Criteria in Solid Tumors (RECIST) does not necessarily apply well to interventional therapy in such patients [4].

In comparison to morphological diagnosis, FDG PET evaluates the viability of HCC based on glucose

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metabolism, not influenced by tumor size, morphology, or lipiodol deposition [5].

Positron emission tomography (PET) uses 18-fluorodeoxy-glucose (18-FDG) as radioactive material that shows difference in metabolism among tissues, thus demonstrating the functional status of suspicious lesions [6].

The aim of this study is to emphasize the role of PET/CT in early follow-up of HCC after transarterial chemoembolization (1 month after the procedure) in comparison to triphasic CT.

Methods

This is a cross-sectional prospective study. From November 2016 to November 2018, 30 patients (24 males and 6 females) were referred to the radiology unit with hepatocellular carcinoma, for which they underwent TACE with lipiodol (two patients had a history of simultaneous combined TACE and radiofrequency ablation (RFA), one patient submitted to TACE on top of transplanted liver). Their ages ranged from 44 to 75 years with a mean age of 60.6 ± 7.35 years. ^{18}F-FDG PET/CT followed by triphasic CT examinations were done for each patient using combined PET CT machine (Philips ingenuity TF PET/CT 128 slices).

The patients were subjected to the following:

- The study was done after approval of local ethical committee, and an informed written consent was taken from each participant in the study
- Detailed careful history taking before doing the study especially for allergies and previous reactions to contrast material.
- Laboratory analysis including serum creatinine and tumor marker (alfa feto protein (AFP))
- MRI was done in seven cases (in which there were mismatches between CT and PET CT) and biopsy from the focal lesion followed by histopathologcial verification which was done in three cases (in transplanted cases)

Inclusion criteria:

- Patients of any age who underwent TACE for HCC.
- Both sexes were included

Exclusion criteria:

- Patients with a past history of contrast allergy.
- Patients with blood glucose level > 300 mg/dl at the time of the study
- High serum creatinine > 2 mg / dl
- Lesions smaller than 10 mm

All patients were subjected to PET/CT study followed by triphasic CT in supine position after a 6 h fast.

PET technique

Scans were acquired 60 min after injection of 1 mCi/10 kg of ^{18}FDG. PET was performed following the attenuation correction CT study without moving the patient. Approximately 9 to 11 bed positions were planned in three-dimensional acquisition mode for scanning the entire patient in one and a half minutes for image acquisition at each bed position.

PET/CT fusion

For each of these sets of PET and CT images, corresponding "fusion" images, combining the two types of data, were processed by special software to produce functional and anatomical images simultaneously.

CT technique

- Philips Ingenuity TF PET/CT 128 slices machine was used for PET and triphasic studies.
- For a typical whole-body PET CT study (neck, chest, abdomen, and pelvis), scanning started cranially at the level of the skull and extended caudally till the level of mid thighs. The total length of CT coverage equals an integral number of bed positions scan during acquisition of PET data.
- Scanning parameters for low-dose attenuation correction CT were 100 MA, 120 KV, pitch of 0.8, collimator width of (64 × 0.625 mm), gantry rotation time of 0.5 s, and field of view of 50 cm. The helical data was retrospectively reconstructed at 1-mm interval.
- Scanning for Triphasic CT:
  - 125–150 ml of non-ionic iodinated contrast media according to patient's weight were to be used. The volume of contrast medium delivered was 2 mL per kilogram of body weight.
  - The scanning time delay was determined by using a test bolus (15 mL at 5 mL/s) of contrast medium (contrast monitoring at the abdominal aorta just above the celiac trunk) followed by a series of single level monitoring CT scans that were acquired every 2 s from 10 up to start of decline of the level contrast.
  - Then, each patient received contrast medium (Ultravist ®-300 Bayer) at a rate of 5 mL/s through intravenous catheter by using a dual syringe power injector (Medrad®Stellant FLEX CT injection system). We use saline chaser by injection 40 cc after contrast

- After injection of intravenous contrast material, the liver was scanned at arterial, portal, and delayed phases.
- Arterial phase (after 25–30 s delay) was ideal to obtain excellent hepatic arterial opacification with minimal contrast in the portal vein.
- Portal venous phase (65–70 s delay) was excellent to show portal vein opacification.
- Delayed Phase (150–200 s delay) starting from the top of the liver to the bottom of the kidneys.

^{18}FDG PET/CT interpretation

The images obtained were to be revised by two consultant radiologists practiced with CT and PET/CT film reading for at least 3 years. The two readers were previously oriented with the patient's history of HCC and his/her previous intervention. CT scans, PET images, and fused PET-CT images then were presented simultaneously to them.

Viable HCCs could be identified by the presence of metabolically active tumor tissue with high FDG uptake and correlate this activity to its anatomical site in the corresponding CT images. The images were interpreted both visually and semi quantitatively for the regions with pathological tracer accumulation using standardized uptake values (SUV). The SUV represents a semi-quantitative assessment method of the radiotracer uptake from a static (single point in time) PET image.

Typically malignant tumors have an SUV more than normal liver background uptake. The avidity of FDG uptake was defined in our study as maximum standardized uptake value (SUV max). Positive FDG uptake is considered when the liver lesion uptake is higher than the physiological background activity in the surrounding normal liver tissue. (SUV) was measured by the region of interest (ROI) technique.

The SUVmax of the tumor and the ratio of the tumor SUVmax to the normal liver SUVmax (TSUVmax/LSUVmax) were calculated for each patient; the cutoff TSUV max/LSUV max value in the current study was 1. Viable HCCs are identified at triphasic CT by the enhancement at the arterial phase and washout at the porto-venous and delayed phases.

Statistical methods

Data were collected, revised, coded, and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations, and ranges when their distribution found parametric. Also, qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using chi-square test.

Table 1 Statistical data analysis including sex and age

		Total no. = 30
Sex	Female	6 (20.0%)
	Male	24 (80.0%)
Age	Mean ± SD	60.60 ± 7.35
	Range	44–75

Results

Thirty patients (24 males and 6 females) (Table 1) were subjected to this study. All had a history of local treatment of HCC via TACE procedure. PET/CT followed by triphasic CT were done for all patients.

The diameter of the lesions ranged between 1 and 8.5 cm with mean diameter of 4.2 cm ± 1.79 (Table 2).

Our reference standards to determine the accuracy of the results included laboratory serial AFP level monitoring for all patients, follow-up by different imaging modalities (mainly dynamic MRI study for the liver, done in seven cases with negative CT and elevated AFP) and histopathological results of the resected liver in case of transplantation (three cases).

Serial AFP monitoring results of the 30 included patients were as follows: 27 cases have had persistent elevated AFP levels while the remaining 3 patients had normal levels of AFP and were preparing for liver transplantation. Out of the 27 patients with elevated AFP levels, triphasic CT study was positive for viable tumoral tissue in 20 patients and negative in 7 patients. These 7 CT-negative patients were positive at PET/CT (3 patients with positive uptake at the interventional bed and 4 patients with extrahepatic metastatic spread). PET/CT was positive in 26 patients out of the 27 patients with elevated AFP levels, (this negative case showed typical triphasic enhancement pattern of viable HCC yet missed by PET CT being well-differentiated HCC as proved by biopsy). The other three patients with normal AFP level showed no abnormal findings on CT, yet on PET/CT there was a single false positive patient due to regional hyperemia causing increased FDG uptake (Figs. 1, 2, 3, 4).

Among the patients with positive extrahepatic metastasis detected by PET/CT, two patients were positive for osseous deposits, one for suprarenal metastasis, and one for portal vein thrombosis (Figs. 5 and 6). However, Triphasic CT studies could only detect the suprarenal metastasis and missed the osseous metastasis as well as the portal vein thrombus as it was non-enhancing so could not be reported as tumoral (Fig. 5e).

Table 2 Statistical data analysis of the size of the chemoembolized lesions

Size of lesion	Mean ± SD	4.20 ± 1.79
	Range	1–8.5

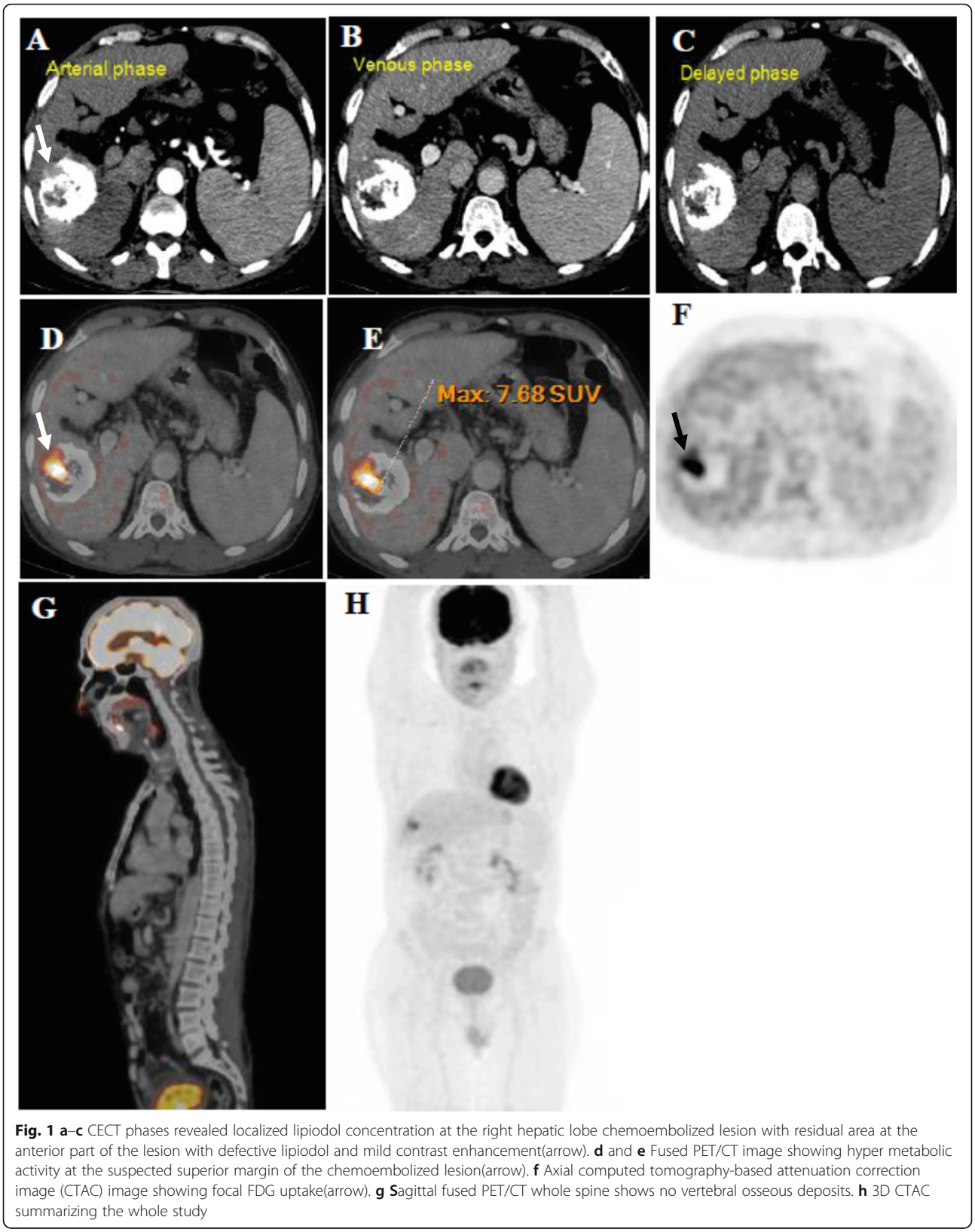

Fig. 1 **a**–**c** CECT phases revealed localized lipiodol concentration at the right hepatic lobe chemoembolized lesion with residual area at the anterior part of the lesion with defective lipiodol and mild contrast enhancement(arrow). **d** and **e** Fused PET/CT image showing hyper metabolic activity at the suspected superior margin of the chemoembolized lesion(arrow). **f** Axial computed tomography-based attenuation correction image (CTAC) image showing focal FDG uptake(arrow). **g** **S**agittal fused PET/CT whole spine shows no vertebral osseous deposits. **h** 3D CTAC summarizing the whole study

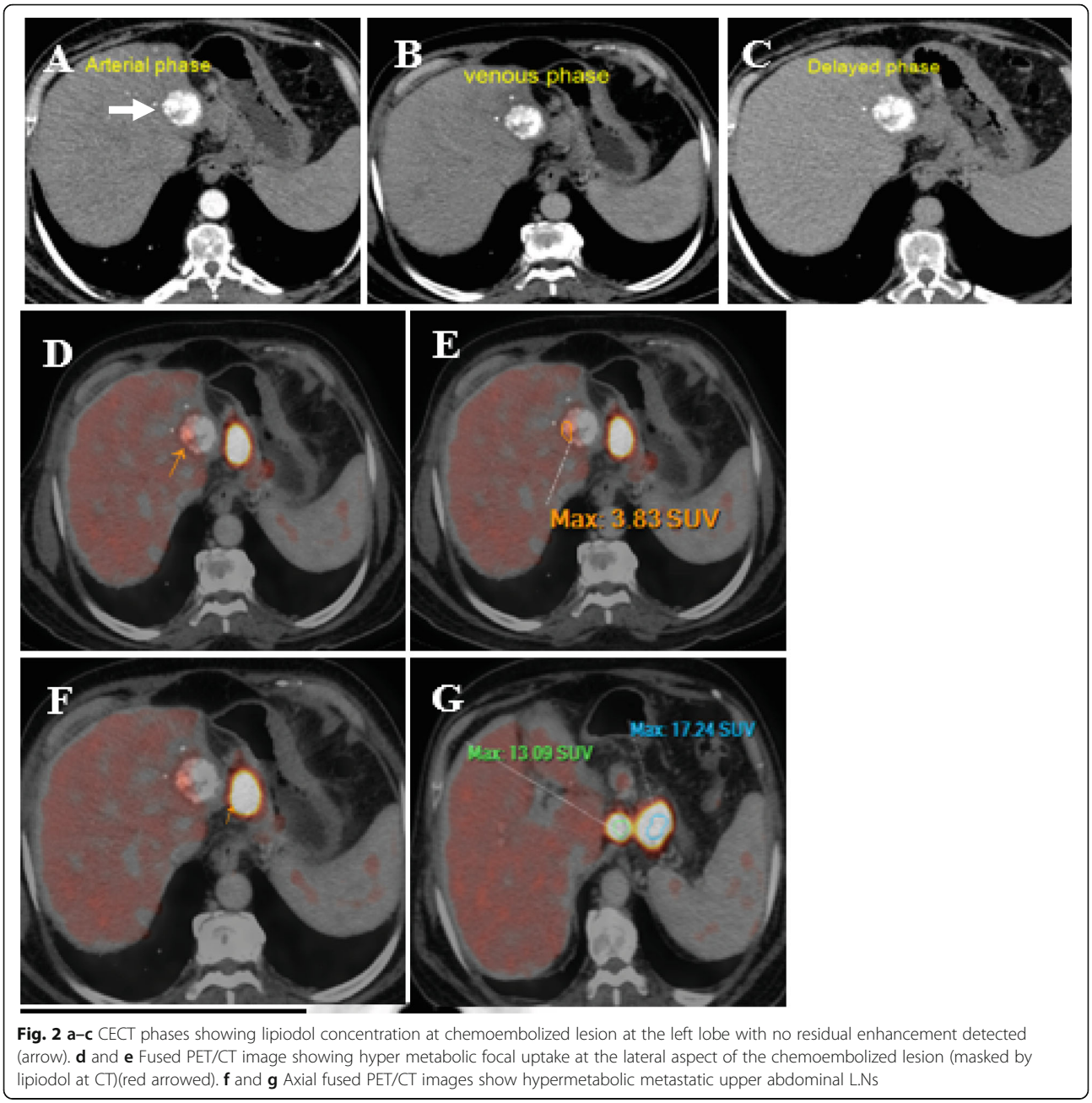

Fig. 2 a–c CECT phases showing lipiodol concentration at chemoembolized lesion at the left lobe with no residual enhancement detected (arrow). **d** and **e** Fused PET/CT image showing hyper metabolic focal uptake at the lateral aspect of the chemoembolized lesion (masked by lipiodol at CT)(red arrowed). **f** and **g** Axial fused PET/CT images show hypermetabolic metastatic upper abdominal L.Ns

The SUVmax of tumor and the ratio of the tumor SUVmax to the normal liver SUVmax (TSUVmax/LSUVmax) were calculated for each patient. The mean value of tumor SUVmax/liver SUVmax (TSUV max/LSUV max) in the positive cases was 2.9 (ranged from 1.06 to 7.2), considering that the cutoff TSUV max/LSUV max value in the current study was 1 (Table 3).

To sum the results up, triphasic CT showed 20 true positive results, 3 true negative results, 7 false negative results, and no false positive results. While PET/CT showed 26 true positive results, 2 true negative results, one false negative result, and one false positive result.

In our study, the calculated sensitivity, specificity, and accuracy of ^{18}F-FDG PET/CT were 96.3%, 66.7%, and 93.3%, respectively. Those of triphasic CT were about 74 %, 100.0%, and 76.7%, respectively. The ^{18}F-FDG PET missed a case of SUV 1.4 because it was a well-differentiated type of HCC (Table 4).

Discussion

Hepatocellular carcinoma is one of the most common malignant tumors worldwide. Early detection and treatment of recurrent HCC after loco-regional interventional treatment is crucial to patient survival [1].

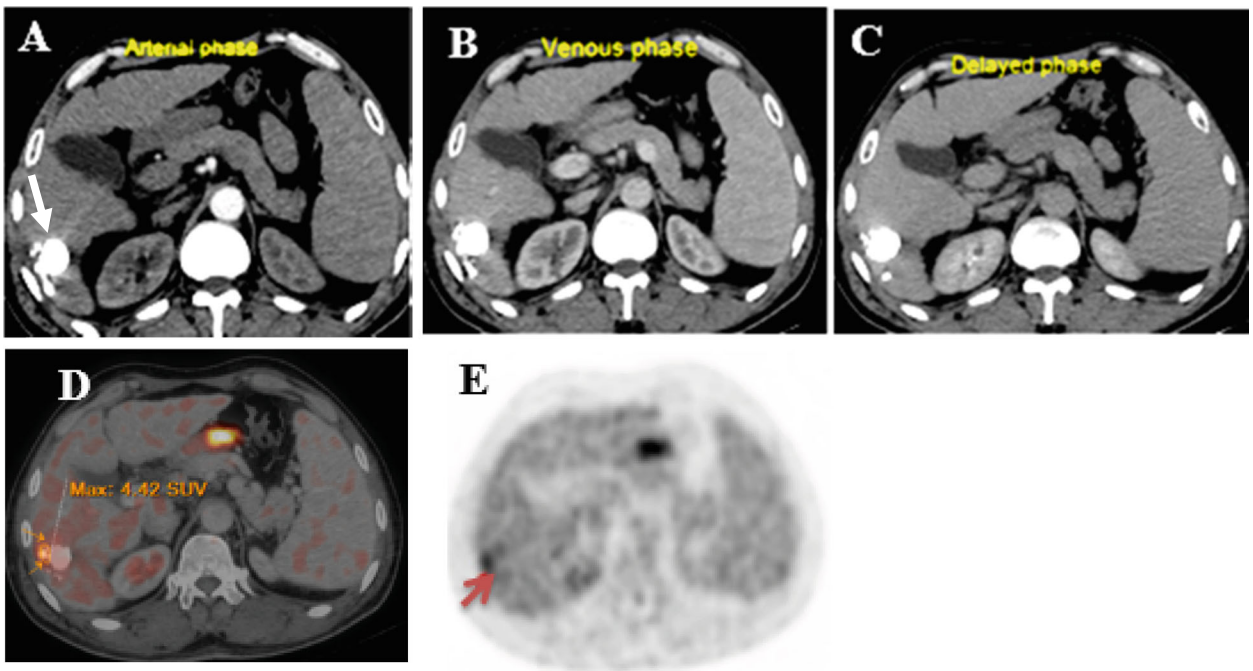

Fig. 3 **a**–**c** CECT phases showing lipiodol concentration at chemoembolized lesion at the right lobe (segment VI) with no residual enhancement detected(arrow). **d** Fused PET/CT image showing increased FDG uptake at the periphery of the embolized lesion at segment VI (masked by lipidol at CT images). **e** Axial CTAC image showing the focal FDG uptake around the embolized lesion (red arrow)

Percutaneous techniques such as TACE are now available to manage localized HCC. Tumoral response assessment after TACE is important to determine whether the tumor is completely eradicated or needs additional treatment [2].

CT and MRI are the most widely used tools to assess the patients who underwent loco-regional intervention procedures such as TACE. Both can determine not only reduction in tumoral size, but also detect the change in the internal structure and enhancement pattern that most investigators rely on as a non-separable adjunct to size change when it comes to evaluation of treatment response. As using size criteria, based on the Response Evaluation Criteria in Solid Tumors (RECIST), does not apply well to post-chemoembolization of HCC [7].

CT has been long used for post chemoembolized HCC follow-up assessment depending on the presence or absence of contrast enhancement; however, the beam-hardening artifact of the high-attenuation lipiodol on CT can surely hinder the intralesional viable tumor detection. Not to mention that after TACE, the feeding arteries of the residual tumor are significantly thinner that will affect the degree of enhancement of the tumor [4].

PET/CT is a unique combination of the cross-sectional anatomical data provided by CT and the metabolic data provided by PET. It also has the advantage of local therapy assessment as well as detection of extrahepatic spread of HCC which is crucial before patient planning for liver transplantation. In contrast to morphological image diagnosis, FDG PET evaluates viability based on glucose metabolism and is not influenced by tumor morphology or lipiodol deposition [2].

In agreement with Ali et al. [8], our study concluded that the chemoembolized lesions that become completely photopenic immediately after embolization are suggestive of successful ablation. Focal, nodular, and intense uptake of FDG within the ablated zone is suggestive of residual viable HCC while a uniform low-grade FDG uptake depicted at the periphery of the ablated lesion is suggestive of reactive tissue changes as inflammation and hyperemia.

In our study, 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). In the study done by Ahn et al. [9], the median value of tumor SUVmax was 4.3 (ranged from 2.0 to 11.6).

In a study done by Myeong Jun Song et al. [10] over 83 patients with HCC to investigate the correlation of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) with clinical features and the prediction of treatment response, he found the TSUVmax/LSUVmax in his study was 1.36 (ranged from 0.77 to

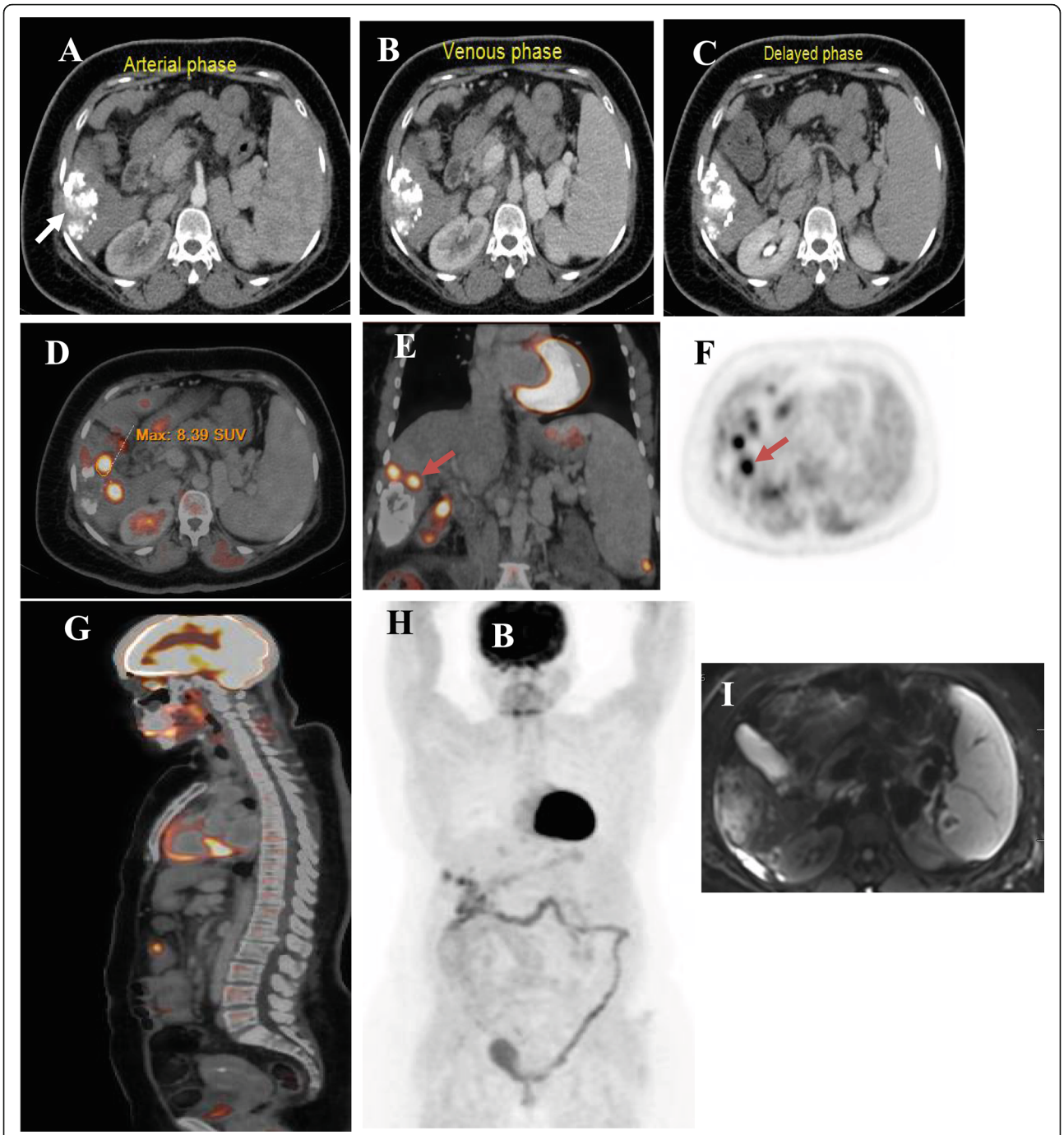

Fig. 4 a–c CECT phases show dispersed lipiodol hindering contrast enhancement detection at the chemoembolized lesion at the right lobe (arrow). **d** and **e** Fused PET/CT images show two hyper metabolic focal uptakes at the superior aspect of the chemoembolized lesion(red arrow). **f** Axial CTAC image showing the two focal FDG uptakes around photopenic center(red arrow). **g** sagittal fused PET/CT whole spine shows no vertebral osseous deposits. **h** 3D CTAC summarizing the whole study

7.64) with cut off value of 1.45 which is comparable with our study which revealed TSUVmax/LSUVmax 2.9 (ranged from 1.06 to 7.2) with cut off value of 1.

Kim et al. [11] stated that HCCs with high ^{18}F-FDG uptake are reported to be more aggressive than HCCs with low ^{18}F-FDG uptake. This is concordant with Ho et al. [12] who stated that poorly and moderately differentiated HCC have avid FDG uptake of these tumors on PET. These results are coinciding with our results where almost all positive cases of HCC were of moderately or poorly differentiated types, showing increased FDG uptake and SUV max values > 3, while the single case of

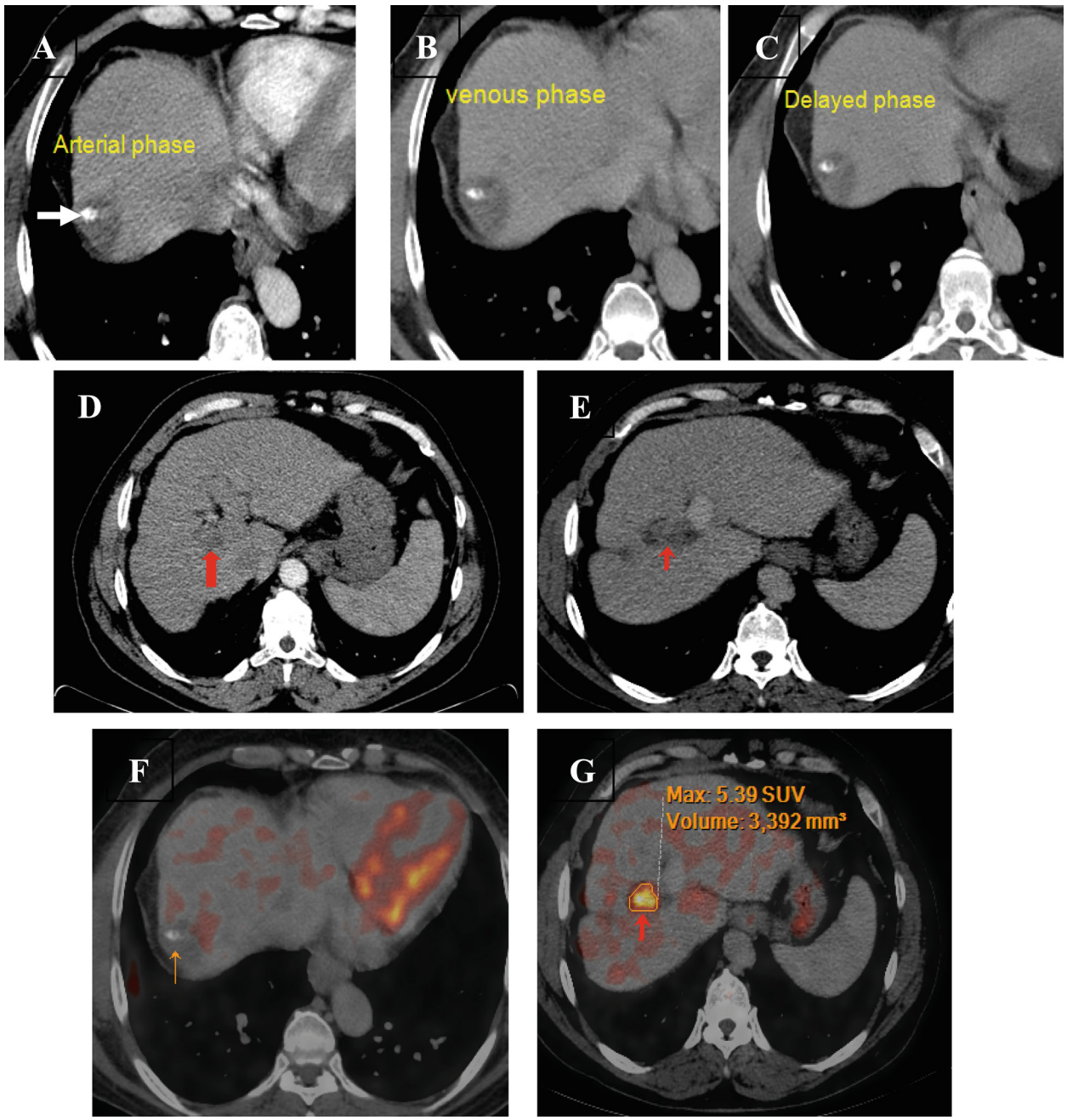

Fig. 5 **a**–**c** CECT phases show hypo dense hepatic dome focal lesion with dispersed lipiodol droplet at its centre with no contrast enchantment detected (arrow). **d** and **e** Axial CTEC shows portal vein thrombus (red arrow), not enhancing at the arterial phase. **F** Axial fused PET/CT image shows hyper metabolic portal vein thrombus denoting tumoral thrombus other than benign PV thrombus in spite of being not enhancing at the arterial phase (**g**).

well-differentiated type we encountered showed relatively low ^{18}F-FDG uptake and 1.4 SUVmax value.

The false positive interpretations of PET/CT can be attributed to physiological uptake, infection, and recent chemotherapy, whereas false negative results can be found with well-differentiated HCC and small lesion below the scanner resolution (< 10 mm) Tsurusaki et al. [2]. Therefore, we waited in our study for at least 6 weeks after TACE to get the most accurate characterization of locoregional response after chemoembolization.

Small lesions <10 mm that are below the scanner resolution might be missed unless they show avid FDG uptake on top of limited background activity so we excluded lesions less than 10 mm from our study.

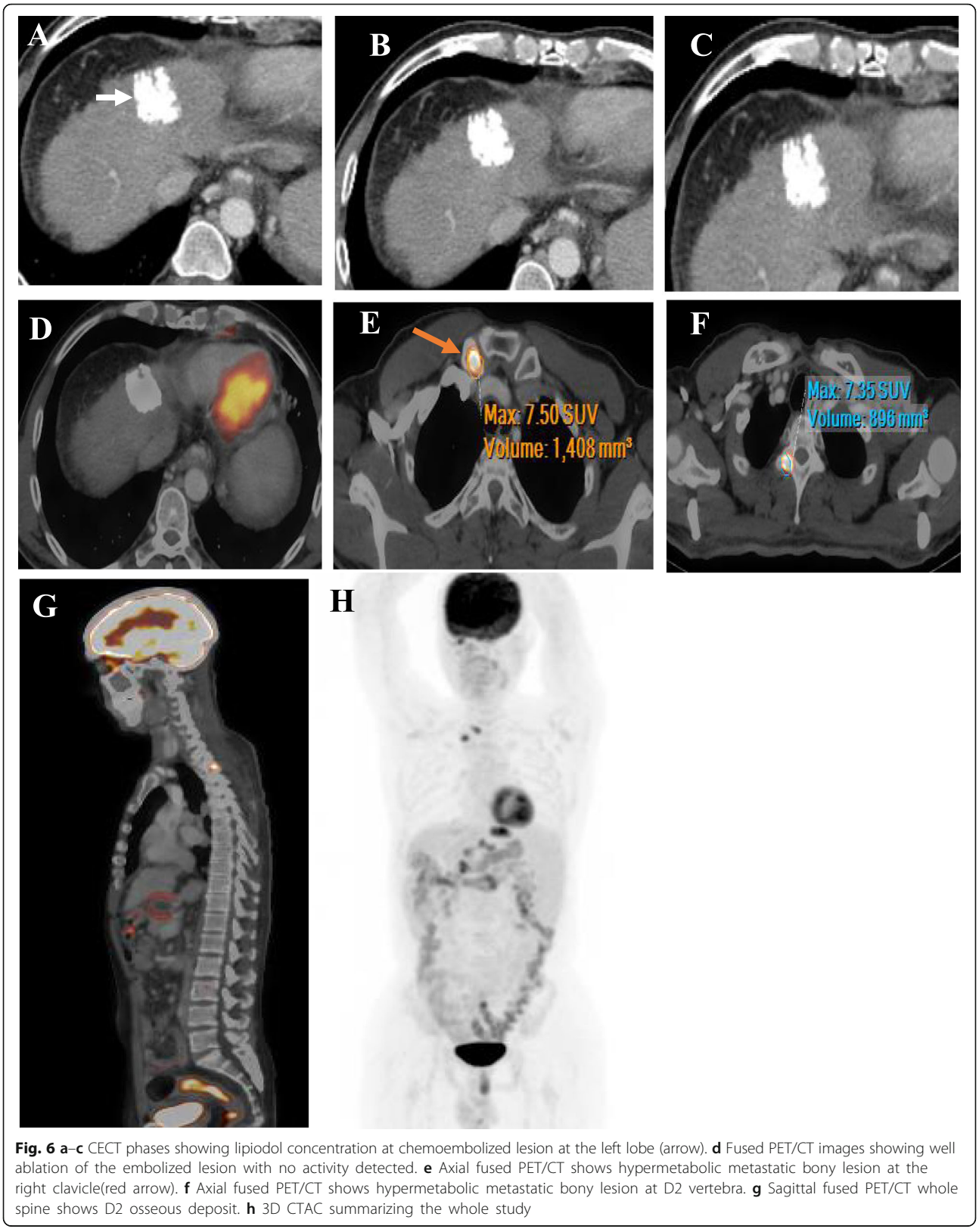

Fig. 6 **a**–**c** CECT phases showing lipiodol concentration at chemoembolized lesion at the left lobe (arrow). **d** Fused PET/CT images showing well ablation of the embolized lesion with no activity detected. **e** Axial fused PET/CT shows hypermetabolic metastatic bony lesion at the right clavicle(red arrow). **f** Axial fused PET/CT shows hypermetabolic metastatic bony lesion at D2 vertebra. **g** Sagittal fused PET/CT whole spine shows D2 osseous deposit. **h** 3D CTAC summarizing the whole study

Table 3 Statistical data analysis of SUV max and TSUV max/LSUV max

		Total no. = 30
SUV max	Mean	6.6
	Range	1.4–24
TSUV max/LSUV max	Mean	2.92
	Range	1.06–7.27

The diameter of lesions in our study ranged between 1 and 8.5 cm (with mean diameter of 4.2 cm) which is comparable to the study done by Ahn et al. [9] where the diameter of lesions ranged between 2.5 and 10.5 cm (with mean diameter of 5.5 cm).

Our study demonstrated higher sensitivity of PET/CT over triphasic CT in detection of local tumor residue/recurrence following TACE which may be masked by lipiodol artifact. Not to mention its ability to detect extrahepatic spread of HCC in a single whole-body examination that can be crucial for patient preparation for liver transplantation. PET/CT showed sensitivity, specificity, and accuracy of 96.3%, 66.7%, and 93.3%, respectively, in comparison to 74%, 100.0%, and 76 % for triphasic CT. These results are comparable to many studies as mentioned before.

Song et al. [13] reported that PET/CT sensitivity, specificity, and accuracy for detection of viable HCC after TACE were 89.29%, 65.71%, and 80.22%, respectively, in comparison to 60.71%, 77.1%, and 67.03% for contrast-enhanced computed tomography (CECT).

Kim et al. [7] found 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 %.

Our results are also correlated with the results of Jinpeng et al. [14] when he studied the recurrence of HCC after (TACE) in 29 patients; the sensitivity of the PET was 95.4% while the sensitivity of CECT was 63.8%.

Our results are nearly matched with Kim et al. [11] who studied evaluation of metabolic characteristics and viability of lipidolized hepatocellular carcinomas using ^{18}F-FDG PET/CT with sensitivity and specificity 97% and 63% for PET/CT in comparison to 87% and 100% for CECT, respectively, also Ali et al. [8] studied the role of ^{18}F-FDG PET/CT in the detection of local tumor residue/recurrence in hepatocellular carcinoma (HCC) post hepatic therapeutic intervention on 40 patients; the sensitivity of triphasic CT and PET were 76.7% and 96.7%, respectively.

Table 4 The diagnostic value of FDG PET/CT and triphasic CT in post TACE follow-up

Modality	Sensitivity	Specificity	PPV	NPV	Accuracy
CT	74 %	100.0%	100.0%	30 %	76.7 %
PET	96.3%	66.7%	96.3%	66.7%	93.3%

Conclusion

^{18}F-FDG PET/CT showed high diagnostic accuracy over triphasic CT in interventional bed evaluation following TACE especially for patients with non-conclusive triphasic CT results and persistent elevated levels of AFP. Unlike triphasic CT, it is not affected by lipiodol artifact and has the ability to detect extrahepatic spread of HCC in a single whole-body examination.

Limitations

-The financial element is the main limitation of the study as PET CT is still of high cost

-Larger number of patients and longer term studies are still needed to validate the results of this study.

Abbreviations

PET CT: Positron emitted tomography computed tomography; FDG: Fluorodeoxy-glucose; ^{18}F: Flourene 18; HCC: Hepatocllular carcinoma; TACE: Transarterial chemoembolization; RECIST: Response Evaluation Criteria in Solid Tumors; AFP: Alfa feto protein; RFA: Radiofrequency ablation; SUV: Standardized uptake value; CECT: Contrast-enhanced computed tomography; CTAC image: Computed tomography-based attenuation correction image

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Authors' contribution

WH made the design of the work and the interpretation of the data. HA did the acquisition and analysis of the data and drafted the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

The data used and/or analysed during the current study are available with the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was done after the approval of the ethical board of Ain Shams University (the reference number is not applicable), and an informed written consent was taken from each participant in the study.

Consent for publication

Written consent for publication was taken from all the participants.

Competing interests

The authors declare that they have no competing interests.

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