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^{68}Ga-FAPI PET/CT imaging provides better detection of hepatocellular carcinoma recurrence compared with ^{18}F-FDG: a case report

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► *Case report*

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ABSTRACT

Background: Globally, primary liver cancer is a common tumor and patients generally have a poor prognosis. Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. In most cases, the diagnosis of HCC relies on imaging. ***Case presentation:*** This study reports on a male patient diagnosed with primary HCC who went into remission after hepatectomy, chemotherapy, and splenic embolization. In the 4th year of follow-up, elevated alpha-fetoprotein was detected (325 ng/mL). However, neither computed tomography (CT) nor magnetic resonance imaging (MRI) revealed significant abnormalities. To clarify the diagnosis, 2-deoxy-2-^{18}F-fluoro-D-glucose integrated positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) was used for initial diagnosis. However, no significant FDG uptake was seen in multiple nodules of the liver. Further examination was performed using ^{68}Ga-fibroblast activation protein inhibitor positron emission tomography/computed tomography (^{68}Ga-FAPI PET/CT), which showed intense FAPI uptake in multiple lesions in the liver, providing direct evidence for the diagnosis of potential HCC recurrence. Finally, the lesions were completely resected and the diagnosis of hepatocellular carcinoma (HCC) was confirmed. ***Conclusion:*** Previous studies have shown that ^{68}Ga-FAPI PET/CT is more sensitive than ^{18}F-FDG for the detection of HCC. This study suggests that ^{68}Ga-FAPI PET/CT is a new option for patients with recurrent HCC who are not sensitive to ^{18}F-FDG.

INTRODUCTION

Primary liver cancer is ranked as the sixth most prevalent cancer and stands as the third principal cause of cancer death globally [1]. Developing countries display a heightened incidence of liver diseases [2]. Risk factors encompass hepatitis B virus, hepatitis C virus, fatty liver, alcoholic cirrhosis, obesity, smoking, and more [3]. Typically diagnosed in advanced stages, liver cancer leads to a less favorable prognosis, with hepatocellular carcinoma (HCC) comprising the majority of cases [4].

Common screening methods include liver ultrasound and al-pha-fetoprotein (AFP). In most cases, HCCs can be diagnosed based on imaging [5, 6]. Dynamic imaging using CT/MRI, especially for HCCs >20mm, reveals a distinct diagnostic profile characterized by intense contrast uptake in the arterial phase, succeeded by contrast washout in the delayed venous phase [5]. The primary advantage of diagnostic PET/CT lies in the enhanced localization of FDG uptake, contributing to an improved detection of local tumor staging [7].

While ^{18}F-FDG remains the most frequently utilized PET tracer in the clinical settings, its efficacy in the early diagnosis of HCC is limited. On the other hand, ^{68}Ga-FAPI demonstrates high sensitivity for hepatic malignant tumors, aiding in the early detection of HCC.

CASE PRESENTATION

A male patient who was diagnosed with HCC reached remission after receiving hepatectomy, an XELOX (Oxaliplatin + Capecitabine) chemotherapy regimen for 4 cycles, and a splenic embolization. At year 4 of follow-up, when the patient was 64 years old, an elevated AFP (325 ng/mL) was found. Laboratory test results of the patient were as follows:

hemoglobin 14.2 g/L, white blood cell 4420/mm3, neutrophil count 3030/mm3, platelet count 173,000/mm3, urea 6.10 mmol/L, creatinine 88 mmol/L, uric acid 296 mmol/L, aspartate transaminase 29 U/L, alanine transaminase 24 U/L, lactate dehydrogenase 184 U/L, total protein 73.5 g/L, albumin 45 g/L.

Abdominal CT scan identified multiple round hypodense nodules within the liver. A hepatic MRI revealed multiple round T2 hyperintensity nodules in the liver (figure 1).

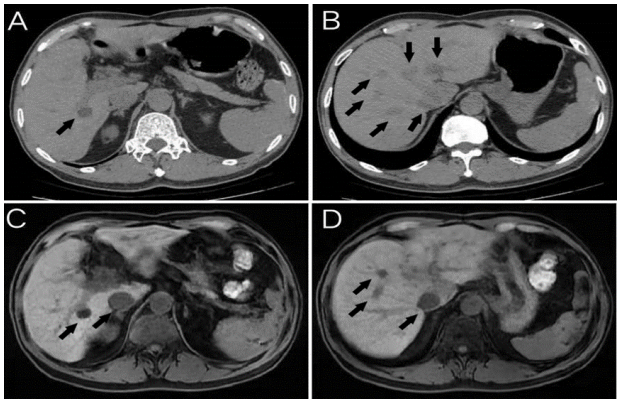

Figure 1. Abdominal CT revealed multiple round hypodense nodules in the liver (**A, B** arrowhead). Hepatic MRI revealed multiple round T2 hyperintensity nodules in the liver (**C, D** arrowhead).

The patient underwent ^{18}F-FDG PET/CT, which revealed multiple small round hypodense or isodense nodules without increased uptake (figure 2).

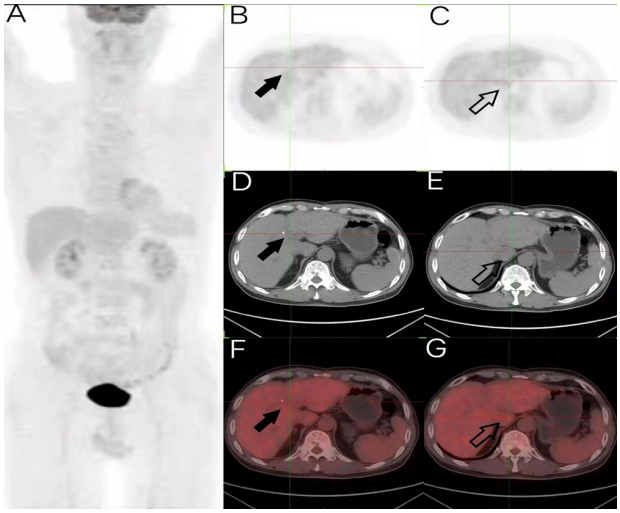

Figure 2. 18F-FDG PET/CT was performed to evaluate primary lesion. **(A)** The maximal intensity projection image and PET axial views **(B, C)** and views of CT **(D, E)** and views of fused PET/CT **(F, G)** showed some small round hypodense or isodense nodules (**B,D,F** arrowhead; **C,E,G** hollow arrow) in the liver without increased uptake.

Five days following the earlier scans, the patient underwent a ^{68}Ga-FAPI PET/CT scan. In the caudate lobe, 68Ga-FAPI PET/CT exhibited a high uptake of FAPI (SUV max: 5.3), along with a strip-shaped elevated FAPI uptake observed in the hilum of the liver (SUV max: 5.2). The liver exhibits several hypodense or isodense nodules, with the largest measuring approximately 16mm in diameter, showing no elevation in FAPI radioactivity uptake (figure 3).

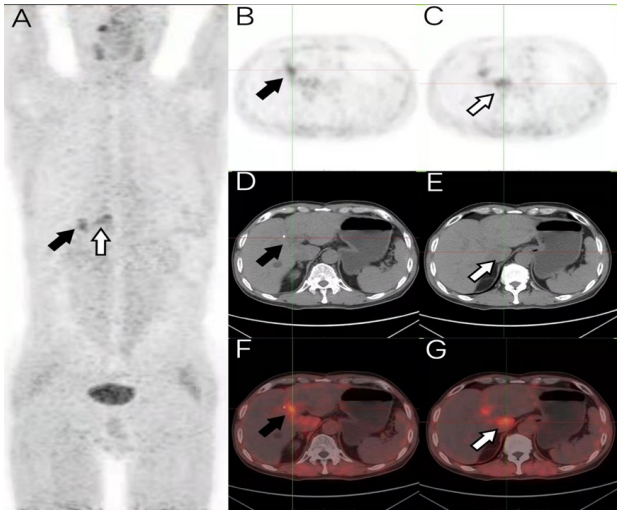

Figure 3. With the consent of the patient, a 68Ga-FAPI PET/CT scan was conducted five days following the 18F-FDG PET/CT. **(A)** The maximal intensity projection image, and axial view images of PET **(B, C)**, CT **(D, E)**, and fused PET/CT **(F, G)**, revealed higher uptake compared to 18F-FDG in caudate lobe (C, E, G hollow arrow SUVnax:5.3) and in the hilum of the liver (B, D, F arrowhead; SUVnax:5.2). In addition, some small round hypodense or isodense nodules without increased uptake in the liver were found.

Following the findings from the ^{68}Ga-FAPI PET/CT imaging, the patient underwent surgical intervention, and a biopsy was obtained for pathological analysis, confirming the recurrence of HCC.

DISCUSSION

Existing research indicates that, in individuals with cirrhosis, the sensitivity of contrast-enhanced CT or MRI in detecting HCC falls within the range of 80 to 88% [8, 9]. Dynamic contrast-enhanced CT exhibits detection sensitivity comparable to multiparametric MRI in visualizing liver tumors. Typically, HCC demonstrates uniform or uneven enhancement in the arterial phase, particularly during the late arterial phase. However, the enhancement of HCC in the portal or delayed phase was observed to be lower compared to the enhancement in liver parenchyma [10-12].

PET can reveal earlier liver lesions on account of focal metabolic changes. The primary PET tracer extensively used in oncology PET/CT imaging is ^{18}F-FDG. Studies indicate that in HCC, glucose transporters and glucose-6-phosphatase activity can vary, leading to variable ^{18}F-FDG uptake [13-16]. Typically, significantly increased ^{18}F-FDG uptake suggests malignant lesions. However, in benign, aseptic inflammatory, or infectious lesions, the markedly increased uptake of ^{18}F-FDG can also be

detected [17, 18]. A study demonstrated a correlation between uptake of FDG in HCC and the degree of HCC differentiation. High-grade HCC exhibit higher FDG uptake compared to low-grade HCC [7]. Due to the variability, FDG PET scans are likely to detect higher-grade HCCs but may not effectively detect low-grade HCCs.

^{68}Ga-FAPI PET/CT utilizes a quinoline-based FAP inhibitor (FAPI) to visualize the serine protease fibroblast activation protein (FAP), which is selectively overexpressed in cancer-associated fibroblasts (CAFs). CAFs constitute the primary component of the stroma surrounding cancer cells, particularly in desmoplastic cancers [16-19]. While active CAFs express FAP to facilitate malignancy, the stroma of healthy tissues scarcely express FAP, in addition to sites of remodeling, active tissue damage, and inflammation [16, 17, 20]. HCC is strongly related to liver fibrosis. More specifically, 80-90% of HCCs follow fibrotic or cirrhotic livers [21]. Thus, ^{68}Ga-FAPI PET/CT may efficiently identify liver tumors with a higher susceptibility than ^{18}F-FDG PET/CT.

In summary, when compared to ^{18}F-FDG PET/CT, ^{68}Ga-FAPI PET/CT demonstrates higher practicability in detecting HCC, particularly in the case of early-stage HCC. ^{68}Ga-FAPI PET/CT possesses the potential to provide more comprehensive diagnostic information across various cancers, paving the way for novel applications in tumor staging or restaging.

Abbreviations

CT: computed tomography; MRI: magnetic resonance imaging; PET/CT: Positron emission tomography/computed tomography; HCC: hepatocellular carcinoma AFP: al-pha-fetoprotein; CAFs: cancer-associated fibroblasts; ^{18}F-FDG: ^{18}Fluorine-fluoro-2-deoxyglucose; FAP: fibroblast activation protein; FAPI: fibroblast activation protein inhibitor; MIP: maximal intensity projection

Trade name and country of origin of all appliances (PET/CT), FDG, and software's used in the study：GE Discovery VCT64 PETCT (Ameracia), DC AMS PHARMA (China), Radient Viewer (China).

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***Consent for publication*:** Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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