Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

18F-FAPI PET/CT Reveals Intrapatient Biological Heterogeneity in FDG-Negative Hepatocellular Carcinoma: A Case Report

Junyu Tong
Tongji University Tenth People's Hospital: Shanghai Tenth People's Hospital
Wang Lin
Liaoyuan People's Hospital
Guo Ji
Tongji University Tenth People's Hospital: Shanghai Tenth People's Hospital
Hao Xi
Tongji University Tenth People's Hospital: Shanghai Tenth People's Hospital
Haidong Cai
Tongji University Tenth People's Hospital: Shanghai Tenth People's Hospital
Chao Ma
Tongji University Tenth People's Hospital: Shanghai Tenth People's Hospital
Zhongwei Lv
Lvzwjs2020@163.com

Shanghai Public Health Clinical Center https://orcid.org/0000-0003-3370-5560

Research Article

Keywords: 18F-FAPI PET/CT, hepatocellular carcinoma, tumor heterogeneity

Posted Date: November 11th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11216836/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

Background

Hepatocellular carcinoma (HCC) is characterized by substantial biological heterogeneity, which may occur between different tumor nodules within the same patient. ^{18}F-FAPI PET/CT has demonstrated potential advantages over ^{18}F-FDG PET/CT in the detection of HCC, the biological determinants responsible for heterogeneous FAPI uptake remain incompletely understood. We report a rare case of FDG-negative HCC showing discordant FAPI accumulation between two lesions within the same patient.

Case presentation

A 53-year-old man with chronic hepatitis B-related cirrhosis underwent surveillance imaging for mildly elevated serum alpha-fetoprotein (18.70 ng/mL). MRI revealed two suspicious hepatic nodules in segments VIII and VI. Both lesions were negative on ^{18}F-FDG PET/CT; however, subsequent ^{18}F-FAPI PET/CT demonstrated markedly heterogeneous uptake, with mild accumulation in the segment VIII lesion (SUVmax 4.1 vs. liver SUVmax 3.5) and intense uptake in the segment VI lesion (SUVmax 12.3). Surgical resection confirmed two HCC lesions with distinct histopathological features and Ki-67 indices (20% and 60%, respectively). Both lesions showed hepatocellular differentiation and microvascular invasion. As FAP immunohistochemistry was unavailable, the mechanism underlying the discordant FAPI uptake remains unclear.

Conclusion

This case demonstrates substantial interlesional heterogeneity of ^{18}F-FAPI uptake among multifocal FDG-negative HCCs. The discordant tracer distribution within the same patient suggests that FAPI PET/CT may provide complementary information regarding tumor biological characteristics and microenvironmental differences beyond conventional metabolic imaging.

Background

Fibroblast activation protein inhibitor (FAPI)-based PET imaging has emerged as a promising molecular imaging approach because fibroblast activation protein (FAP)-expressing cancer-associated fibroblasts (CAFs) are abundant components of the tumor microenvironment in many malignancies. Previous studies have demonstrated improved tumor-to-background contrast of FAPI PET compared with FDG PET in several liver malignancies[1–2]. Here, we report an unusual case of two FDG-negative HCC lesions in the same patient demonstrating markedly different ^{18}F-FAPI uptake patterns. Histopathological examination revealed distinct morphological and proliferative features between the two tumors. This

case highlights the potential value of FAPI PET/CT in revealing lesion-specific biological heterogeneity in multifocal HCC.

Case presentation

A 53-year-old man with chronic hepatitis B virus infection and liver cirrhosis underwent routine surveillance. Laboratory examination revealed mildly elevated serum alpha-fetoprotein level (18.70 ng/mL; reference range 0–7.00 ng/mL). Contrast-enhanced liver MRI demonstrated two hepatic nodules suspicious for HCC (Fig. 1).The segment VIII lesion (21 mm) was hypointense on T1-weighted imaging and demonstrated arterial phase hyperenhancement with delayed capsule enhancement. The segment VI lesion (23 mm) was also hypointense on T1-weighted imaging, with arterial phase hyperenhancement and delayed capsule enhancement.

Because both lesions were suspicious for malignant tumors, dual-tracer PET/CT imaging was performed for further characterization before surgical interventionC (Fig. 2). Blood glucose level at the time of ^{18}F-FDG injection was 5.6 mmol/L. Maximum-intensity-projection images demonstrated no abnormal hepatic uptake on ^{18}F-FDG PET, whereas maximum-intensity-projection ^{18}F-FAPI PET demonstrated 2 focal hotspots in the liver. On ^{18}F-FAPI PET/CT images, the segment VIII lesionshowed only mild uptake above background liver activity (SUVmax, 4.1 vs 3.5), whereas the segment VI lesion showed markedly increased uptake (SUVmax, 12.3 vs 3.5).

Histopathologic examination after surgical resection confirmed 2 hepatocellular carcinoma nodules with distinct morphologic features (Fig. 3). The segment VIII tumor was a nodular hepatocellular carcinoma (2.0×2.0×1.5 cm), with macrotrabecular and solid patterns, focal clear-cell change, necrosis, histologic grade II-III, and microvascular invasion (MVI, M1). Immunohistochemistry showed GPC-3 positivity, HBsAg positivity, focal HepPar-1 positivity, CK19 negativity, and a Ki-67 index of approximately 20%. The segment VI tumor was a nodular HCC (3.0×2.5×2.0 cm), predominantly trabecular with a macrotrabecular component, histologic grade II, and microvascular invasion (MVI, M1). Immunohistochemistry showed HepPar-1 positivity, GPC-3 positivity, HBsAg positivity, CK19 negativity, and a Ki-67 index of approximately 60%.

Discussion

^{18}F-FDG PET/CT has limited sensitivity for HC, particularly in well-differentiated lesions. In our patient, both lesions were FDG-negative despite confirmed malignancy[(3)]. In contrast, 18F-FAPI PET/CT could provid additional biological information by demonstrating marked lesion-specific differences. The higher FAPI uptake observed in the segment VI lesion may indicate differences in stromal composition, extracellular matrix remodeling, or CAF activation compared with the segment VIII lesion[(4)]. Paired lesions from the same patient reduce potential confounding factors related to systemic differences, allowing direct observation of lesion-specific molecular heterogeneity. However, because FAP immunohistochemical staining was unavailable, this hypothesis cannot be directly confirmed. This case

emphasizes the importance of considering intrapatient heterogeneity in molecular imaging interpretation. When multiple tumors occur within the same organ, individual lesions may exhibit different biological phenotypes despite similar radiological appearances[5–6]. Future studies combining FAPI PET imaging with FAP immunohistochemistry, spatial transcriptomics, and tumor microenvironment analysis may further clarify the determinants of FAPI accumulation in HCC.

Conclusion

This case highlights marked heterogeneity of ^{18}F-FAPI uptake among multifocal FDG-negative HCC lesions within a single patient. The discordant imaging patterns suggest that FAPI PET/CT may reveal differences in tumor microenvironmental characteristics that are not captured by conventional metabolic imaging. Although the underlying mechanism requires further validation, FAPI PET/CT may provide complementary biological information for individualized haracterization of HCC.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the patient in accordance with the Declaration of Helsinki. Ethics board approval was not required for this case report.

Consent for publication

The patient provided written consent for publication of clinical details and images.

Competing interests

The authors declare that they have no competing interests.

Funding:

This study was sponsored by the Natural Science Foundation of China (82603874), and the Cultivationgrant for clinical and basicintegration research of Shanghai Tenth People's Hospital (SYYYRH2025053)

Authors’ contributions:

Junyu Tong:writing-original draft; Lin Wang:editing-original image; Guo Ji and Hao Xi: performed pathological diagnosis. Haidong Cai and Chao Ma:investigation and clinical diagnosis. Zhongwei Lv supervision and writing-review & editing.

Acknowledgments

The authors thank the technical staff from Department of Nuclear Medicine for image acquisition.

Data availability

No new data were generated in this study

References

1. Kratochwil C, Flechsig P, Lindner T, et al. ^{68}Ga-FAPI PET/CT: tracer uptake in 28 different kinds of cancer. J Nucl Med. 2019;60(6):801–5. 10.2967/jnumed.119.227967.
2. Giesel FL, Kratochwil C, Lindner T, et al. ^{68}Ga-FAPI PET/CT: biodistribution and preliminary dosimetry estimate of 2 DOTA-containing FAP-targeting agents in patients with various cancers. J Nucl Med. 2019;60(3):386–92. 10.2967/jnumed.118.215913.
3. Shi X, Xing H, Yang X, et al. Comparison of PET imaging of activated fibroblasts and glucose metabolism in primary hepatic tumours. Eur J Nucl Med Mol Imaging. 2021;48(5):1593–603. 10.1007/s00259-020-05070-9.
4. Guo W, Pang Y, Yao L, et al. Imaging fibroblast activation protein in liver cancer: a single-center post hoc retrospective analysis to compare ^{68}Ga-FAPI-04 PET/CT versus ^{18}F-FDG PET/CT. Eur J Nucl Med Mol Imaging. 2021;48(5):1604–17. 10.1007/s00259-020-05095-0.
5. Calderaro J, Couchy G, Imbeaud S, et al. Histological subtypes of hepatocellular carcinoma are related to gene mutations and molecular tumour classification. J Hepatol. 2017;67(4):727–38. 10.1016/j.jhep.2017.05.014.
6. Ziol M, Poté N, Amaddeo G et al. Macrotrabecular-massive hepatocellular carcinoma: a distinctive histological subtype with clinical relevance.Hepatology. 2018;68(1):103–12. 10.1002/hep.29762

Figures

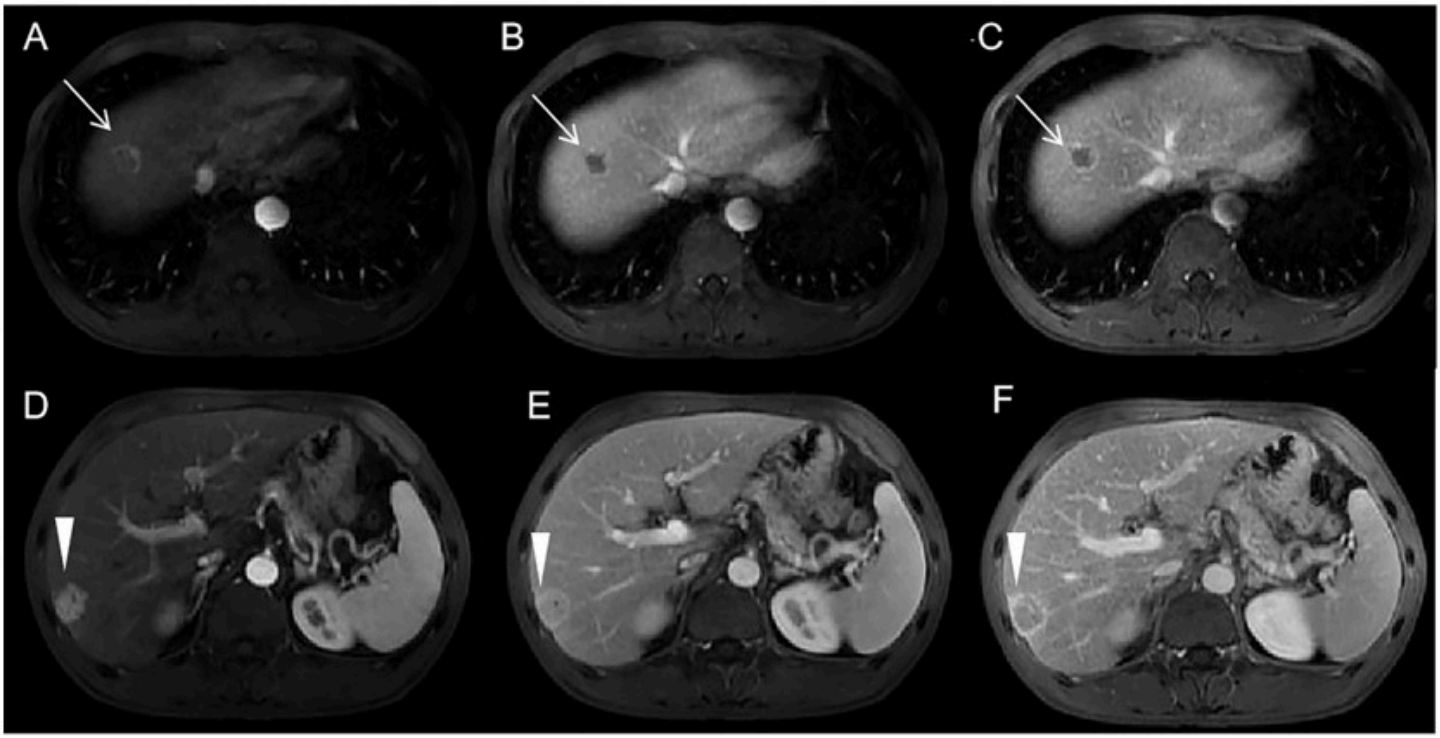


Figure 1

Liver MRI demonstrated 2 suspicious hepatic nodules. The segment VIII lesion (arrow, 21 mm) was hypointense on T1-weighted imaging (A) and demonstrated arterial phase hyperenhancement with delayed capsule enhancement (B, C). The segment VI lesion (arrowhead, 23 mm) was hypointense on T1-weighted imaging (D), with arterial phase hyperenhancement (E) and delayed capsule enhancement (F).

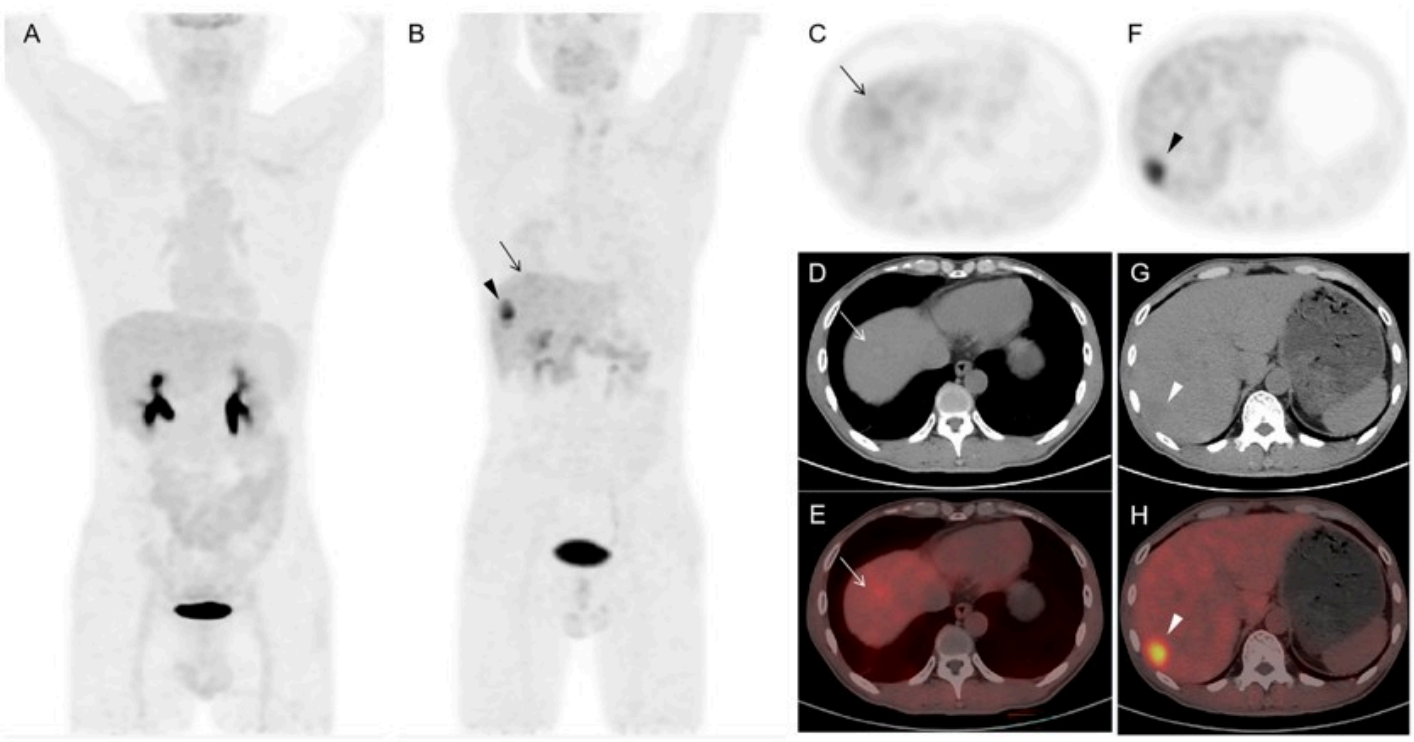


Figure 2

^{18}F-FDG PET/CT and ^{18}F-FAPI PET/CT were performed 1 day apart. ^{18}F-FDG PET Maximum-intensity-projection images demonstrated no abnormal hepatic uptake(A). ^{18}F-FAPI PET Maximum-intensity-projection demonstrated 2 focal hotspots in the liver(B). On axial ^{18}F-FAPI PET/CT images, the segment VIII lesion (arrow) showed mild uptake above background liver activity (SUVmax, 4.1 vs 3.5; S8 nodule, arrow; C, axial PET image; D, CT image; E, PET/CT fusion image), the segment VI lesion (arrowhead) showed markedly increased uptake (SUVmax, 12.3 vs 3.5;S6 nodule, arrowhead, SUV of 12.3 vs 3.5; F, axial PET image; G, CT image; H, PET/CT fusion image).

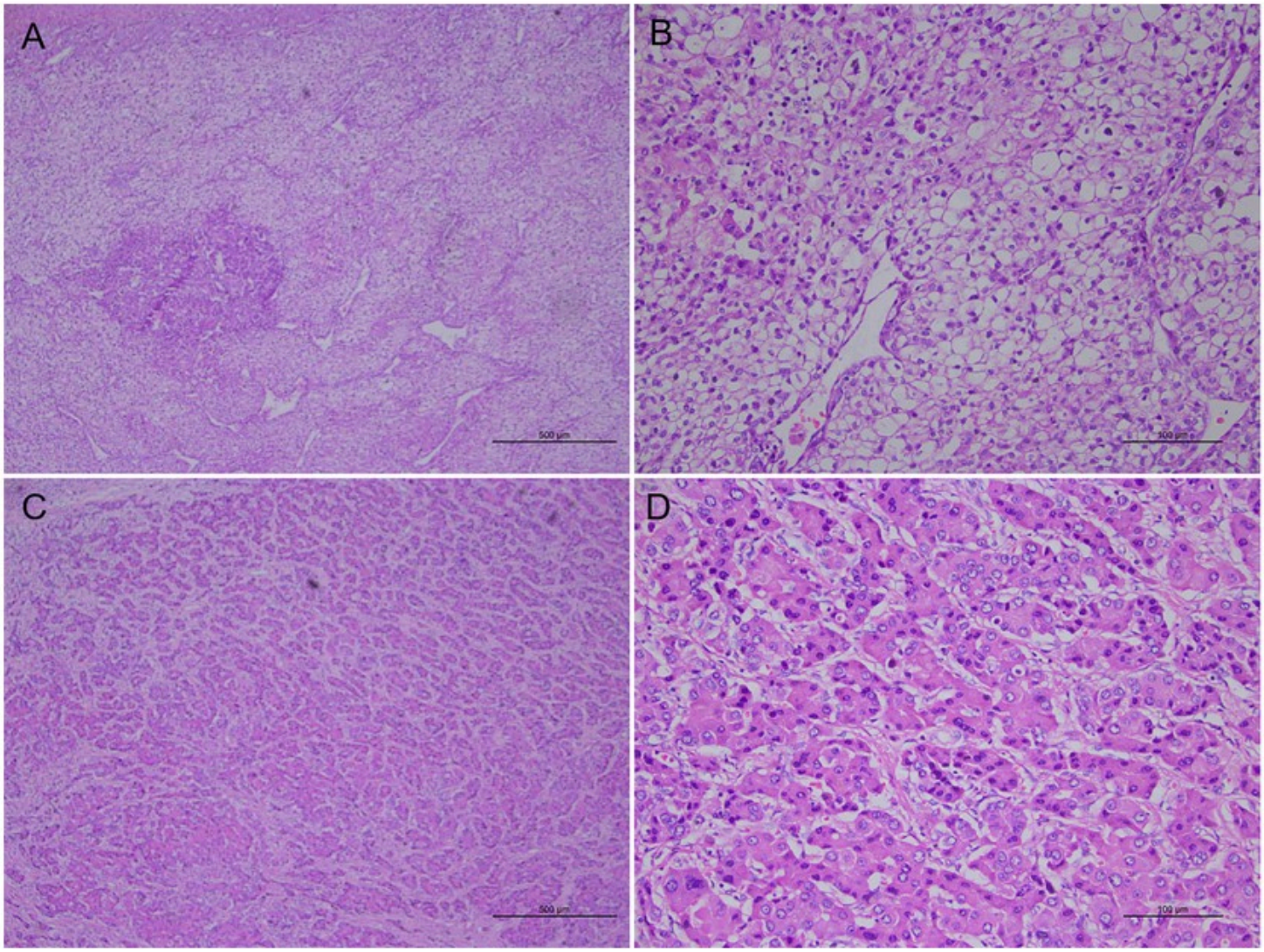


Figure 3

Histopathologic examination after surgical resection confirmed 2 hepatocellular carcinoma nodules. The segment VIII tumor was a nodular hepatocellular carcinoma (2.0×2.0×1.5 cm), with macrotrabecular and solid patterns, focal clear-cell change, necrosis, histologic grade II-III, and microvascular invasion (MVI, M1) (A, hematoxylin-eosin,×40; B, ×200). The segment VI tumor was a nodular HCC (3.0×2.5×2.0 cm), predominantly trabecular with a macrotrabecular component, histologic grade II, and microvascular invasion (MVI, M1) (C, hematoxylin-eosin, ×40; D, ×200).