Received:
22 March 2016

Revised:
5 May 2016

Accepted:
19 May 2016

<http://dx.doi.org/10.1259/bjr.20160265>

Cite this article as:

Ozaki K, Harada K, Terayama N, Matsui O, Saitoh S, Tomimaru Y, et al. Hepatocyte nuclear factor 1 α -inactivated hepatocellular adenomas exhibit high 18F-fludeoxyglucose uptake associated with glucose-6-phosphate transporter inactivation. *Br J Radiol* 2016; **89**: 20160265.

FULL PAPER

Hepatocyte nuclear factor 1 α -inactivated hepatocellular adenomas exhibit high ¹⁸F-fludeoxyglucose uptake associated with glucose-6-phosphate transporter inactivation

^{1,3}KUMI OZAKI, MD, PhD, ²KENICHI HARADA, MD, PhD, ¹NOBORU TERAYAMA, MD, PhD, ³OSAMU MATSUI, MD, PhD, ⁴SATOSHI SAITOH, MD, PhD, ⁵YOSHITO TOMIMARU, MD, PhD, ⁶TAKESHI FUJII, MD, PhD and ³TOSHIFUMI GABATA, MD, PhD

¹Department of Radiology, Takaoka City Hospital, Takaoka, Japan

²Department of Human Pathology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

³Department of Radiology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan

⁴Department of Hepatology, Toranomon Hospital, Tokyo, Japan

⁵Department of Surgery, Toyonaka Municipal Hospital, Toyonaka, Japan

⁶Department of Pathology, Toranomon Hospital, Tokyo, Japan

Corresponding author: Dr Kumi Ozaki

E-mail: ozakik-rad@umin.org

Objective: This immunohistochemical study aimed to elucidate the molecular mechanism underlying the increased fluorine-18 fludeoxyglucose (FDG) uptake in hepatocyte nuclear factor 1 α (HNF1 α)-inactivated hepatocellular adenomas (H-HCAs).

Methods: Three resected H-HCAs were studied using FDG positron emission tomography. Each maximum standardized uptake value (SUV_{max}) was determined. Resected samples were subjected to immunohistochemical staining for the following glucose metabolism-related proteins: glucose transporter 1 (GLUT1) and glucose transporter 2 (GLUT2), indicative of uptake and transport of glucose into cellular cytoplasm; hexokinase 2 (HK2) and hexokinase 4 (HK4), glucose phosphorylation; glucose-6-phosphate transporter 1 (G6PT1), uptake and transport

of glucose-6-phosphate into endoplasmic reticulum; and glucose-6-phosphatase (G6Pase), dephosphorylation.

Results: All three H-HCAs exhibited increased FDG intake, with an average SUV_{max} of 6.6 (range: 5.2–8.2). No sample expressed GLUT1 and HK2; all the samples exhibited equivalent GLUT2 and HK4 expression, equivalent or slightly increased G6Pase expression and significantly decreased G6PT1 expression relative to the non-neoplastic hepatocytes of background liver.

Conclusion: The increased FDG uptake observed in H-HCAs is associated with GLUT2 and HK4 expression and G6PT1 inactivation.

Advances in knowledge: H-HCA exhibits a high FDG uptake owing to the inactivation of G6PT1, which is transcriptionally regulated by HNF1 α .

INTRODUCTION

Hepatocellular adenomas (HCAs) are benign hepatocellular neoplasms that can be subclassified into the following four groups according to genotype and phenotype:^{1,2} hepatocyte nuclear factor 1 α (HNF1 α) inactivated, β -catenin activated, inflammatory and unclassified.

HNF1 α -inactivated HCA (H-HCA) was reported to have the least risk of malignant transformation among the HCA subtypes and can be observed even if the maximum dimension is <5 cm.^{3,4} Radiologically, H-HCA generally exhibits a homogeneous arterial enhancement during the hepatic arterial phase, although this arterial enhancement does not persist during the portal phase. In addition, HNF1 α inactivation causes increased fatty acid synthesis

and impaired fatty acid transport, resulting in excessive intratumoral lipid accumulation and thus, diffuse steatosis within the tumour is a major characteristic imaging finding.⁴ Therefore, it is important to distinguish H-HCAs from fat-containing hypervascular lesions requiring surgical resection, particularly hepatocellular carcinoma (HCC) with fat deposition. However, it is sometimes difficult to distinguish these lesions using only CT and MRI findings.

Fluorine-18 fludeoxyglucose (FDG) positron emission tomography (PET) is a clinical molecular imaging modality that elucidates cellular glucose metabolism. Many studies have described the usefulness of FDG-PET for the detection of several types of primary tumours and metastases.⁵ However, the sensitivity of FDG-PET for the detection

of HCC, especially well-differentiated or moderately differentiated HCC, is limited because glucose-6-phosphatase (G6Pase) expression in HCC cells leads to the rapid disappearance of FDG from these cells in a manner similar to that observed in the surrounding hepatocytes.⁶ Benign hepatocellular nodules, such as focal nodular hyperplasia and HCA, also commonly exhibit a similar FDG uptake and retention pattern as the normal liver tissue owing to the same mechanism.⁷ Therefore, FDG-PET has been considered as less useful for not only detecting hepatocellular lesions but also differentiating well to moderately differentiated HCCs from benign hepatocellular lesions.

However, several reports have described HCAs with high FDG uptake.^{8–16} Interestingly, all such HCAs subjected to an immunohistochemical subtype analysis were subclassified as H-HCAs.^{8–12} In addition, we recently experienced three cases of H-HCA with a high FDG-PET uptake. However, the mechanism underlying this increased FDG uptake has not been clarified. The purpose of the present study was to elucidate the molecular mechanisms underlying the increased FDG uptake of H-HCA using immunohistochemistry and to discuss the molecular background and possible clinical significance of this finding.

METHODS AND MATERIALS

This retrospective study was approved by the institutional review boards of our institution. All patients consented to the use of their medical records for research purposes.

Patients and lesions

Three H-HCAs from three patients who underwent PET/CT scans at our institution and co-operating hospitals from 2009 to 2013 were evaluated in this study. For all three nodules (average size: 19.0 mm, range: 15–25 mm), HCA diagnoses were confirmed by surgical resection. All patients were female, with an average age of 47.7 years (range: 38–61 years). None of the patients had a remarkable past or family history or notable physical examination findings. No risk factors of HCA, such as oral contraceptive use, alcohol abuse, diabetes mellitus and obesity, were detected. The patients had an average body mass index of 21.5 kg m^{-2} (range: $20.3\text{--}23.2 \text{ kg m}^{-2}$). None of the patients had chronic liver disease or hepatitis B or C virus infection, and all blood chemistry parameters and tumour marker levels were within normal limits. The clinical features of the patients and lesions are listed in Table 1.

Imaging techniques and analyses

All PET/CT studies were performed using a PET/CT system (Discovery-ST-Elite16; GE Medical Systems, Waukesha, WI/

Aquiduo; Toshiba Medical Systems, Tochigi, Japan). All patients were instructed to fast for at least 5 h before undergoing PET. Image acquisition was initiated approximately 1 h after the i.v. injection of FDG (4.0 MBq kg^{-1}). The mean plasma glucose level at the time of FDG injection was 83.7 mg dl^{-1} (range, $68\text{--}105 \text{ mg dl}^{-1}$).

Brain-to-pelvis CT was performed immediately prior to PET using a multidetector spiral CT scanner [section thickness: $3\text{--}3.75 \text{ mm}$, pitch: $1.375\text{--}1.5$, 120 kV , automatic tube current ($30\text{--}200 \text{ mA}$, depending on the patient's total body mass)]. Whole-body PET was subsequently performed over an area identical to that covered by CT. The acquisition time was $2.5\text{--}3.0\text{-min}$ per bed position, with eight bed positions. Emission data were reconstructed using a three-dimensional ordered-subset expectation maximization algorithm (20 subsets, 2 iterations) of a 128×128 matrix, using the CT data for attenuation correction. In addition, each maximum standardized uptake value (SUV_{max}) in the tumour was determined.

In addition, we also analyzed CT and MRI findings to determine whether our cases were typical or not. Contrast-enhanced CT images were obtained with a CT system (Aquilion 64 or Asteion, Toshiba Medical Systems, Tokyo, Japan) with the following parameters: voltage, 120 kV ; amperage, $200\text{--}350 \text{ mA}$; rotation period, 0.5 s ; detector collimation, 0.5 mm ; pitch, 1.0 ; and section thickness, 5 mm . Following unenhanced CT, a dynamic contrast-enhanced study was performed $30\text{--}35 \text{ s}$ (arterial phase), $50\text{--}60 \text{ s}$ (portal phase) and $110\text{--}120 \text{ s}$ (equilibrium phase) after the completion of an i.v. injection of a non-ionic contrast material with 600 mg of iodine per kilogram with an injection duration of 30 s .

MR images were obtained with a 1.5-T unit system (MAGNETOM Symphony; Siemens Medical Solutions, Erlangen, Germany/Vantage Atlas MRT-2003; Toshiba Medical Systems, Tokyo, Japan). In each patient, a single-shot fast spin-echo sequence (repetition time/echo time, $4.6\text{--}5.5/1.89\text{--}2.5 \text{ ms}$; flip angle, $10\text{--}20^\circ$) with varying echo times (short and long echo times of 80 and 120 ms , respectively), a fat-suppressed T_2 weighted fast spin-echo sequence ($4000\text{--}8000/80\text{--}90 \text{ ms}$; flip angle, $80\text{--}90^\circ$) and T_1 weighted in- and opposed-phase gradient-echo sequences (echo times, $4.6\text{--}5.5$ and $2.3\text{--}2.75 \text{ ms}$, respectively; flip angle, $70\text{--}90^\circ$) were used. For the contrast enhancement study, images were obtained during the hepatobiliary phase, 20 min after the i.v. injection of a dose of 0.1 ml kg^{-1} of gadoxetic acid (Primovist, $0.25 \text{ mmol ml}^{-1}$ of solution; Bayer Schering Pharma, Berlin, Germany). A section thickness of $4\text{--}8 \text{ mm}$ was used in all sequences.

Table 1. Clinical features of patients and lesions

Case	Age	Male/female	Size (mm)	Location (segment of the liver)	Oral contraceptive	Diabetes mellitus	Alcohol abuse	Body mass index (kg m^{-2})	Chronic liver disease
Case 1	61	Female	15	S5	No	No	No	23.2	No
Case 2	38	Female	25	S3	No	No	No	20.9	No
Case 3	44	Female	17	S3	No	No	No	20.3	No

Histopathologic diagnosis

HCAs were diagnosed by consensus between two liver pathologists (KH and TF, each with >20 years' experience). Peculiarly, we focus attention on inflammatory cell infiltration and increased cell density by evaluating the presence of inflammatory cells and the cellular density of H-HCAs relative to that of the hepatocytes of the background liver, which might be a possible relation to the observed high FDG.

Immunohistochemistry testing analysis

The specimens were subjected to immunohistochemical staining to analyze the expression of glucose metabolism-related proteins expressed in human hepatocytes, namely glucose transporter 1 (GLUT1) and glucose transporter 2 (GLUT2), hexokinase 2 (HK2) and hexokinase 4 (HK4), glucose-6-phosphate transporter 1 (G6PT1) and G6Pase, in addition to liver fatty acid-binding protein, β -catenin, glutamine synthetase and serum amyloid A. We evaluated one specimen, which included the tumour and background liver tissue, per nodule. Details about the antibodies used for this analysis are shown in Table 2.

Immunohistochemistry was performed as follows: deparaffinized sections were heat treated in buffer, as shown in Table 2. After blocking the endogenous peroxidases, the sections were incubated in a protein block solution (DakoCytomation, Glostrup, Denmark) for 30 min and subsequently incubated overnight at 4 °C with a primary antibody. Next, the sections were incubated for 1 h at room temperature with antimouse/antirabbit immunoglobulins conjugated to a peroxidase-labelled polymer (Envision; DakoCytomation). The cells were finally treated with the chromogen 3,3'-diaminobenzidine tetrahydrochloride, followed by light counterstaining with haematoxylin.

Two pathologists (KH and TI) blindly and individually evaluated the expression intensity of each protein in the tumour relative to that in non-neoplastic hepatocytes, using the following scale: no expression, decreased expression, equivalent expression or increased expression. Protein expression was evaluated in the largest area of each nodule.

RESULTS

During PET scans, all three H-HCAs exhibited a high FDG uptake, with an average SUV_{max} of 6.6 (range, 5.2–8.2) (Table 3; Figure 1). All three nodules exhibited similar imaging and

histopathological findings. Unenhanced CT revealed homogeneous hypodense nodules. These lesions exhibited a slightly inhomogeneous enhancement on hepatic arterial phase images, with washout on portal venous and delayed phase images. T₂ weighted MR images revealed slight hyperintensity in the lesions, with visible diffuse steatosis on in-phase and opposed-phase images. Hepatobiliary phase images obtained 20 min after i.v. contrast administration exhibited homogeneous hypointensity. No haemorrhaging was observed in any lesion (Figure 2). The CT and MRI findings were typical with respect to those described in previous reports.^{3,4,17}

Macroscopically, each specimen was a relatively demarcated, yellowish-brown mass without a definite capsule. Microscopically, each lesion comprised mildly enlarged, proliferating hepatocytes without nuclear atypia that were arranged in a thin trabecular pattern. Diffuse steatosis was observed within the lesion, whereas few areas of haemorrhage or abnormal vessels were observed. A fibrous capsule, septum and portal tracts were not observed, and a ductular reaction was not evident. Immunohistochemical evaluation of the lesions revealed reduced expression levels of liver fatty acid-binding protein and no nuclear expression of β -catenin, glutamine synthetase or serum amyloid A. These features were compatible with H-HCA.^{1,2} In all three H-HCAs, little inflammatory cell infiltration was observed, and the cellular density was similar to that of the background liver. A histological analysis of the surrounding normal liver tissues revealed an almost normal appearance (Figure 3).

All three H-HCAs exhibited very similar glucose metabolism-related protein expression patterns. GLUT1 expression was absent from both the tumour cells of HCA and the non-neoplastic hepatocytes of background liver, although erythrocytes as internal controls were constantly positive. GLUT2 was expressed at similar levels in both types of tissue. Similarly, HK2 expression was not observed in the tumour or background liver, whereas HK4 was expressed at similar levels in both tissues. G6Pase expression was similar to or slightly elevated relative to the background liver, whereas G6PT1 expression was significantly decreased relative to the hepatocytes of background liver (Table 3; Figure 4).

DISCUSSION

All H-HCAs analyzed in the present study exhibited increased FDG uptake, in contrast to other benign hepatocellular nodules

Table 2. Antibodies used for immunohistochemistry

Glucose metabolism-related proteins	Antibodies	Antigen retrieval buffer	Dilution	Clone	Company	Colour
Glucose transporter 1	MM	EDTA	1 : 400	SPM498	Abcam	DAB
Glucose transporter 2	MM	Tris-EDTA	1 : 300	199017	R&D	DAB
Hexokinase 2	RP	EDTA	1 : 100	-	Atlas	DAB
Hexokinase 4	RP	EDTA	1 : 100	-	Atlas	DAB
Glucose-6-phosphatase	RP	Citrate	1 : 100	-	Atlas	DAB
Glucose-6-phosphate transporter 1	RP	Tris-EDTA	1 : 1000	-	MBL	DAB

DAB, 3,3'-diaminobenzidine tetrahydrochloride; EDTA, ethylenediaminetetraacetic acid; MM, mouse monoclonal; RP, rabbit polyclonal.

Table 3. Maximum standard uptake values (SUV_{max}) and immunohistochemistry test results

Case	SUV _{max}	Glucose transporter 1	Glucose transporter 2	Hexokinase 2	Hexokinase 4	Glucose-6-phosphatase	Glucose-6-phosphate transporter 1
Case 1	5.2	No	Equivalent	No	Equivalent	Increased	Decreased
Case 2	8.2	No	Equivalent	No	Equivalent	Equivalent	Decreased
Case 3	6.5	No	Equivalent	No	Equivalent	Equivalent	Decreased

Decreased, decreased expression compared with background liver; equivalent, equivalent degree of expression compared with background liver; increased, increased expression compared with background liver; no, no expression.

(e.g. focal nodular hyperplasia), other HCA subtypes and well to moderately differentiated HCC. This finding is important not only for the differential diagnosis but also for avoiding the misdiagnosis of H-HCA as a malignant neoplasm. In cases involving a high FDG uptake, possible reasons other than enhanced glucose metabolism should be considered; these include the degree of malignancy, degree of differentiation, inflammatory cell infiltration, increased cellular density and a response to fat accumulation. The present cases exhibited a benign, well-differentiated hepatocellular tumour, very little inflammatory cell infiltration and similar cellular densities in the lesion compared with normal liver tissues. In addition, previous reports described the SUV_{max} associated with fat accumulation as high as approximately 3.5 inches.^{18,19} However, as the increased FDG uptake associated with H-HCA led to higher SUV_{max}, we suspect that the above-mentioned alternative factors had no significant effect on the increased FDG uptake in the present cases.

On the other hand, several experimental studies have reported metabolic abnormalities in H-HCA, including activation of

glycolysis, citrate shuttle and fatty acid synthesis pathways. The predicted consequences of these abnormalities include increased lipogenesis and suppressed gluconeogenesis.²⁰ Therefore, we focused on glucose metabolism and investigated the expression of proteins related to glucose metabolism, which might correlate with increased FDG uptake.^{8,21}

Glucose and glucose analogues such as FDG enter the cell through transmembrane transporters or GLUTs. In the cytosol, glucose is phosphorylated by hexokinase (HK) to glucose-6-phosphate and is subsequently metabolized to carbon dioxide and water (glycolysis). FDG is also converted to FDG-6-phosphate once it enters the cell. However, a subtle stereochemical difference prevents the glycolytic metabolism of FDG-6-phosphate, which thus accumulates in the cells. However, the effect of HK can be reversed by G6Pase, a gluconeogenesis pathway enzyme that is strongly expressed in the liver and can dephosphorylate glucose or FDG in the endoplasmic reticulum in co-operation with G6PT, thus enabling these molecules to leave the cell.²²

In a normal liver tissue, G6PT is located within the endoplasmic reticulum membrane, where it forms the G6Pase complex with G6PT1, glucose-6-phosphate transporter 2 and glucose-6-phosphate transporter 3, respectively, which allow glucose-6-phosphate, phosphate and glucose to cross the endoplasmic reticulum membrane²² (Figure 5). However, tumour cells often express low levels of G6Pase, thereby metabolically trapping FDG-6-phosphate inside the cell and causing increased FDG accumulation in the tumour. In addition, several isoforms/isozymes of glucose transporter and HK have been identified. We investigated the isoforms/isozymes that are thought to be associated with glucose metabolism in benign hepatocellular tumours. Specifically, elevated GLUT1 levels have been observed in several cancers, such as lung, gastric and breast cancer.²³ GLUT2 is expressed in several normal tissue cells, including hepatocytes, and its overexpression has been observed in some HCCs,²⁴ whereas HK2 expression is increased in many cancer cells,^{20,25,26} HK4 or glucokinase and is mainly expressed in the liver and other normal tissues.²¹ Furthermore, G6PT1 is thought to correlate with HNF1 α activation,²⁰ and at this moment, the immunohistochemical reagent for other G6PTs was non-existent.

Through an immunohistochemical analysis, we observed an equivalent expression of GLUT2 and HK4, equivalent or increased expression of G6Pase and decreased expression of

Figure 1. Fluorine-18 fludeoxyglucose (FDG) positron emission tomography/CT indicating increased FDG uptake in the lesion, with a maximum standard uptake value of 8.2 (Case 2) (arrowhead indicates the tumour).

Figure 2. Representative radiological findings (Case 2): unenhanced CT showing a homogeneous hypodense nodule. The lesion is exhibiting a slight inhomogeneous enhancement on the hepatic arterial phase image and washout on the portal venous phase image. T_2 weighted MRI is revealing a slightly hyperintense lesion; diffuse steatosis was confirmed by the definite loss of signal on the opposed-phase images (arrowheads are indicating the tumour). T2WI, T_2 weighted image.

G6PT1 in H-HCA lesions from our cases, relative to the background liver. These immunohistochemical findings indicate that FDG is transported into the cytoplasm by GLUT2 and is phosphorylated by HK4. The inactivation of G6PT1 prevented

the uptake of phosphorylated FDG into the endoplasmic reticulum; as a result, phosphorylated FDG was not dephosphorylated and was instead retained in HCA cells, although G6Pase expression was not decreased. Accordingly, a high FDG

Figure 3. Representative histological findings (Case 2): the lesion comprised mildly enlarged, proliferating hepatocytes without nuclear atypia that were arranged in a thin trabecular pattern. Diffuse steatosis was observed. The surrounding liver tissue exhibited normal haematoxylin and eosin (HE) staining. Immunohistochemical evaluation revealed reduced liver fatty acid-binding protein (LFABP) expression (original magnification, 200 $\times$).

Figure 4. Representative images of glucose metabolism-related protein expression (Case 2): glucose transporter 1 (GLUT1) and hexokinase 2 (HK2) were not expressed in the tumour or background liver. Membranous glucose transporter 2 (GLUT2) expression was equivalent to that of the background liver. Hexokinase 4 (HK4) and glucose-6-phosphatase (G6Pase) were expressed equivalently in the tumour and background liver. Glucose-6-phosphate transporter 1 (G6PT1) expression was decreased in the tumour relative to the background liver. In all images, the background liver is shown on the left and the tumour is shown on the right (original magnification, 200 $\times$).

uptake was observed in H-HCA lesions. We surmised that this increased uptake (or retention) of FDG in H-HCAs depends on the inactivation of G6PT1. Interestingly, a previous report described the expression patterns of GLUT1 and GLUT2 in H-HCA. According to that study, GLUT2 was expressed, which was consistent with our results; however, the earlier study did not mention a comparison with the background normal liver.⁸

As mentioned above, the importance of glucose transporter, HK and G6Pase has been assessed in previous attempts to elucidate the molecular mechanism by which FDG-PET is taken up into liver tumours and tumorous lesions. In contrast, previous studies have paid little attention to G6PT1 with respect to FDG uptake. As G6PT and G6Pase work in concert to maintain glucose homeostasis,²³ the inactivation of G6PT1 in H-HCA might cause a dysfunction in G6Pase activity, despite the equivalent or increased G6Pase expression in lesions relative to the surrounding liver tissue. Regarding the decreased expression of G6PT1, experimental transactivation studies have shown that HNF1 α is required for G6PT1 gene transcription and that HNF1 α inactivation causes G6PT1 deficiency.²⁷ In addition, Rebouissou et al conducted a microarray analysis of the gene expression profiles of H-HCAs and found that the expression of G6PT1, which encodes G6PT1, was significantly decreased in H-HCAs, indicating repression of the gluconeogenesis pathway.²⁰ These authors also discovered an increase in G6Pase expression in H-HCAs, indicating a G6Pase complex dysfunction. Those

earlier findings strongly corroborate the results obtained in the present study. Therefore, we speculate that the consistently increased FDG uptake and retention observed in H-HCA lesions are likely due to the inactivation of G6PT1 in tumour cells.

To the best of our knowledge, no previous report has described FDG uptake in other HCA subtypes. Regarding the imaging findings associated with HCA, several reports have described diffuse intratumoral fat deposition as a relatively specific MRI feature of H-HCA,⁴ although a case of diffuse fat deposition in another HCA subtype was also reported.²⁸ Therefore, a definite differential diagnosis of each HCA subtype is not considered possible using only conventional imaging modalities. Although FDG-PET might have clinical value in the discrimination of H-HCA from other HCA subtypes, care should be taken to avoid the misdiagnosis of H-HCA as a malignant tumour because of the high FDG uptake during PET studies.

Other hypervascular fat-containing lesions, such as HCC with fat deposition and angiomyolipoma, should also be considered in the differential diagnosis. Most HCCs with fat deposition are well differentiated,²⁹ and because of G6Pase expression, the FDG uptake in well-differentiated HCCs was reported to equal that in the background liver.⁶ Therefore, HCCs with fat deposition may not exhibit increased FDG uptake. Angiomyolipoma sometimes exhibits increased FDG uptake in association with the infiltration of inflammatory cells, although this is an atypical

Figure 5. Glucose-6-phosphatase (G6Pase) complex: the G6Pase complex comprises G6Pase and glucose-6-phosphate transporter 1 (G6PT1), glucose-6-phosphate transporter 2 (G6PT2) and glucose-6-phosphate transporter 3 (G6PT3), respectively, which allow G6Pase, phosphate and glucose to cross the endoplasmic reticulum membrane. Experimental transactivation studies revealed that hepatocyte nuclear factor 1 α (HNF1 α) inactivation causes G6PT1 deficiency.²²

finding.³⁰ However, a strong early enhancement and characteristic early drainage into the hepatic vein on dynamic CT or MRI³¹ may be helpful for the distinction of angiomyolipoma from H-HCA.

Our study had several limitations. First, very few cases were analyzed. Second, glucose metabolism-related protein expression patterns were analyzed by immunohistochemistry alone. Ideally, the expression patterns will be confirmed through a polymerase chain reaction analysis of gene expression, but such an analysis is difficult to perform using formalin-fixed specimens. We believe that our data are sufficient to conclude

that H-HCA exhibits particular imaging features, including a high FDG uptake. In addition, FDG-PET is an expensive modality and is not routinely available for hepatic nodule diagnosis.

CONCLUSION

H-HCA exhibits a high FDG uptake owing to the inactivation of G6PT1, which is transcriptionally regulated by HNF1 α . This knowledge may alter the management of such patients perhaps with consideration of further non-invasive characterisation with MRI $\pm$ percutaneous biopsy rather than labelling the patient as having metastatic disease purely based on the PET/CT findings.

REFERENCES

1. Zucman-Rossi J, Jeannot E, Nhieu JT, Scoazec JY, Guettier C, Rebouissou S, et al. Genotype-phenotype correlation in hepatocellular adenoma: new classification and relationship with HCC. *Hepatology* 2006; **43**: 515–24. doi: <http://dx.doi.org/10.1002/hep.21068>
2. Bioulac-Sage P, Laumonier H, Couchy G, Le Bail B, Sa Cunha A, Rullier A, et al. Hepatocellular adenoma management and phenotypic classification: the Bordeaux experience. *Hepatology* 2009; **50**: 481–9. doi: <http://dx.doi.org/10.1002/hep.22995>
3. Katabathina VS, Menias CO, Shanbhogue AK, Jagirdar J, Paspulati RM, Prasad SR. Genetics and imaging of hepatocellular adenomas: 2011 update. *Radiographics* 2011; **31**: 1529–43. doi: <http://dx.doi.org/10.1148/rg.316115527>
4. van Aalten SM, Thomeer MG, Terkivatan T, Dwarkasing RS, Verheij J, de Man RA, et al. Hepatocellular adenomas: correlation of MR imaging findings with pathologic subtype classification. *Radiology* 2011; **261**: 172–81. doi: <http://dx.doi.org/10.1148/radiol.11110023>
5. Fass L. Imaging and cancer: a review. *Mol Oncol* 2008; **2**: 115–52. doi: <http://dx.doi.org/10.1016/j.molonc.2008.04.001>
6. Izuishi K, Yamamoto Y, Mori H, Kameyama R, Fujihara S, Masaki T, et al. Molecular mechanisms of [18F]fluorodeoxyglucose accumulation in liver cancer. *Oncol Rep* 2014; **31**: 701–6. doi: <http://dx.doi.org/10.3892/or.2013.2886>
7. Delbeke D, Martin WH, Sandler MP, Chapman WC, Wright JK Jr, Pinson CW. Evaluation of benign vs malignant hepatic lesions with positron emission tomography. *Arch Surg* 1998; **133**: 510–5; discussion 515–6. doi: <http://dx.doi.org/10.1001/archsurg.133.5.510>
8. Nakashima T, Takayama Y, Nishie A, Asayama Y, Baba S, Yamashita Y, et al. Hepatocellular adenoma showing high uptake of (18)F-fluorodeoxyglucose (FDG) via an increased expression of glucose

- transporter 2 (GLUT-2). *Clin Imaging* 2014; **38**: 888–91. doi: <http://dx.doi.org/10.1016/j.clinimag.2014.06.005>
9. Lee SY, Kingham TP, LaGratta MD, Jessurun J, Cherqui D, Jarnagin WR, et al. PET-avid hepatocellular adenomas: incidental findings associated with HNF1- α mutated lesions. *HPB (Oxford)* 2016; **18**: 41–8. doi: <http://dx.doi.org/10.1016/j.hpb.2015.07.001>
 10. Lim D, Lee SY, Lim KH, Chan CY. Hepatic adenoma mimicking a metastatic lesion on computed tomography-positron emission tomography scan. *World J Gastroenterol* 2013; **19**: 4432–6. doi: <http://dx.doi.org/10.3748/wjg.v19.i27.4432>
 11. Sumiyoshi T, Moriguchi M, Kanemoto H, Asakura K, Sasaki K, Sugiura T, et al. Liver-specific contrast agent-enhanced magnetic resonance and ^{18}F -fluorodeoxyglucose positron emission tomography findings of hepatocellular adenoma: report of a case. *Surg Today* 2012; **42**: 200–4. doi: <http://dx.doi.org/10.1007/s00595-011-0067-7>
 12. Fosse P, Girault S, Hoareau J, Testard A, Couturier O, Morel O. Unusual uptake of ^{18}F FDG by a hepatic adenoma. *Clin Nucl Med* 2013; **38**: 135–6. doi: <http://dx.doi.org/10.1097/RLU.0b013e318279b95a>
 13. Sanli Y, Bakir B, Kuyumcu S, Ozkan ZG, Gulluoglu M, Bilge O, et al. Hepatic adenomatosis may mimic metastatic lesions of liver with ^{18}F -FDG PET/CT. *Clin Nucl Med* 2012; **37**: 697–8. doi: <http://dx.doi.org/10.1097/RLU.0b013e3182443ced>
 14. Stephenson JA, Kapasi T, Al-Taani O, Dennison AR. Uptake of ^{18}F FDG by a hepatic adenoma on positron emission tomography. *Case Rep Hepatol* 2011; **2011**: 276402. doi: <http://dx.doi.org/10.1155/2011/276402>
 15. Buc E, Dupre A, Golfier C, Chabrot P, Flamein R, Dubois A, et al. Positive PET-CT scan in hepatocellular adenoma with concomitant benign liver tumors. *Gastroenterol Clin Biol* 2010; **34**: 338–41. doi: <http://dx.doi.org/10.1016/j.gcb.2010.01.018>
 16. Patel PM, Alibazoglu H, Ali A, Fordham E, LaMonica G. “False-positive” uptake of FDG in a hepatic adenoma. *Clin Nucl Med* 1997; **22**: 490–1. doi: <http://dx.doi.org/10.1097/00003072-199707000-00012>
 17. Ichikawa T, Federle MP, Grazioli L, Nalesnik M. Hepatocellular adenoma: multiphasic CT and histopathologic findings in 25 patients. *Radiology* 2000; **214**: 861–8. doi: <http://dx.doi.org/10.1148/radiology.214.3.r00mr28861>
 18. Keramida G, Potts J, Bush J, Verma S, Dizdarevic S, Peters AM. Accumulation of (18)F-FDG in the liver in hepatic steatosis. *AJR Am J Roentgenol* 2014; **203**: 643–8. doi: <http://dx.doi.org/10.2214/AJR.13.12147>
 19. Kamimura K, Nagamachi S, Wakamatsu H, Higashi R, Ogita M, Ueno S, et al. Associations between liver (18)F fluoro-2-deoxy-D-glucose accumulation and various clinical parameters in a Japanese population: influence of the metabolic syndrome. *Ann Nucl Med* 2010; **24**: 157–61. doi: <http://dx.doi.org/10.1007/s12149-009-0338-1>
 20. Rebouissou S, Imbeaud S, Balabaud C, Boulanger V, Bertrand-Michel J, Tercé F, et al. HNF1 α inactivation promotes lipogenesis in human hepatocellular adenoma independently of SREBP-1 and carbohydrate-response element-binding protein (ChREBP) activation. *J Biol Chem* 2007; **282**: 14437–46. doi: <http://dx.doi.org/10.1074/jbc.M610725200>
 21. Kawai S, Mukai T, Mori S, Mikami B, Murata K. Hypothesis: structures, evolution, and ancestor of glucose kinases in the hexokinase family. *J Biosci Bioeng* 2005; **99**: 320–30. doi: <http://dx.doi.org/10.1263/jbb.99.320>
 22. Burchell A. Molecular pathology of glucose-6-phosphatase. *FASEB J* 1990; **4**: 2978–88.
 23. Carvalho KC, Cunha IW, Rocha RM, Ayala FR, Cajaiba MM, Begnami MD, et al. GLUT1 expression in malignant tumors and its use as an immunodiagnostic marker. *Clinics (Sao Paulo)* 2011; **66**: 965–72. doi: <http://dx.doi.org/10.1590/S1807-59322011000600008>
 24. Paudyal B, Paudyal P, Oriuchi N, Tsushima Y, Nakajima T, Endo K. Clinical implication of glucose transport and metabolism evaluated by ^{18}F -FDG PET in hepatocellular carcinoma. *Int J Oncol* 2008; **33**: 1047–54.
 25. Shinohara Y, Ichihara J, Terada H. Remarkably enhanced expression of the type II hexokinase in rat hepatoma cell line AH130. *FEBS Lett* 1991; **291**: 55–7. doi: [http://dx.doi.org/10.1016/0014-5793\(91\)81102-E](http://dx.doi.org/10.1016/0014-5793(91)81102-E)
 26. Mathupala SP, Rempel A, Pedersen PL. Glucose catabolism in cancer cells. Isolation, sequence, and activity of the promoter for type II hexokinase. *J Biol Chem* 1995; **270**: 16918–25. doi: <http://dx.doi.org/10.1074/jbc.270.28.16918>
 27. Hiraiwa H, Pan CJ, Lin B, Akiyama TE, Gonzalez FJ, Chou JY. A molecular link between the common phenotypes of type 1 glycogen storage disease and HNF1 α -null mice. *J Biol Chem* 2001; **276**: 7963–7. doi: <http://dx.doi.org/10.1074/jbc.M010523200>
 28. Ishii M, Kazaoka J, Fukushima J, Gunji M, Aoyama T, Fukusato T, et al. A case of β -catenin-positive hepatocellular adenoma with MR imaging sign of diffuse intratumoral fat deposition. *Abdom Imaging* 2015; **40**: 1487–91. doi: <http://dx.doi.org/10.1007/s00261-014-0342-3>
 29. Prasad SR, Wang H, Rosas H, Menias CO, Narra VR, Middleton WD, et al. Fat-containing lesions of the liver: radiologic-pathologic correlation. *Radiographics* 2005; **25**: 321–31. doi: <http://dx.doi.org/10.1148/rg.252045083>
 30. Kumasaka S, Arisaka Y, Tokue A, Higuchi T, Nakajima T, Tsushima Y. A case of multiple hepatic angiomyolipomas with high (18)F-fluorodeoxyglucose uptake. *BMC Med Imaging* 2014; **14**: 17. doi: <http://dx.doi.org/10.1186/1471-2342-14-17>
 31. Jeon TY, Kim SH, Lim HK, Lee WJ. Assessment of triple-phase CT findings for the differentiation of fat-deficient hepatic angiomyolipoma from hepatocellular carcinoma in non-cirrhotic liver. *Eur J Radiol* 2010; **73**: 601–6. doi: <http://dx.doi.org/10.1016/j.ejrad.2009.01.010>