

# PET/CT in patients with liver lesions of different nature

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**Abstract** Although FDG PET/CT evaluation of liver nodules still has limited application in routine clinical practice compared with the conventional imaging modalities (US, CT and MRI), it nevertheless seems to have certain potentially useful roles in this setting. Two major determinants of the diagnostic sensitivity of PET/CT in hepatocellular carcinoma (HCC) are (1) the degree of differentiation (related to varying levels of glucose transporters and glucose-6-phosphatase activity, with well-differentiated tumors being suggested to show low expression of GLUT and high dephosphorylating enzyme activity and undifferentiated tumors to show high expression of glucose transporters and low dephosphorylating enzyme activity), and (2) the size of the lesion. The diagnostic efficacy of FDG PET/CT could be enhanced on delayed imaging. An inverse correlation has been described between FDG PET/CT and choline/acetate PET. The literature underlines the role of choline and acetate in detecting and staging well- or moderately differentiated HCC, in which these PET tracers demonstrate better efficacy compared with FDG. The dual-tracer approach using tracers like FDG and acetate is suggested to provide the best diagnostic accuracy. Disease

prognostication and staging of extrahepatic metastasis both benefit from whole-body staging with FDG PET/CT. In cholangiocarcinoma, the major factors determining the sensitivity of FDG PET/CT are (1) hilar versus peripheral subtype and (2) nodular versus infiltrating morphology. FDG PET/CT can serve an adjunct to conventional imaging in differentiating benign from malignant lesions, with hemangioma, FNH, and hepatic adenoma usually showing tracer accumulation similar to, or lower than, the background physiological liver activity although a small number of false positives are observed. The non-FDG tracers have been investigated in this setting in a limited number of patients and have been found not to be of incremental value.

**Keywords** FDG PET/CT · Liver lesions · Hepatocellular carcinoma · Cholangiocarcinoma

## Introduction: pathophysiological overview of hepatic lesions and their common imaging characteristics on conventional imaging modalities

The liver is an important organ from the oncological perspective. Primary hepatic neoplasms are particularly common in the presence of diffuse liver diseases such as cirrhosis, hemochromatosis, and steatohepatitis. Also, the liver is the most common site of metastatic seeding from a number of gastrointestinal malignancies. The factors favoring the seeding and rapid growth of metastatic deposits in the liver include (1) its high blood flow (about 25 % of cardiac output), (2) its favorable microscopic anatomy (liver sinusoids and gaps in the subendothelial basement membrane), and (3) its rich biochemical environment [1].

With the widespread use of cross-sectional imaging modalities (i.e. CT and MRI of the abdomen), there has

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been a substantial increase in incidentally identified hepatic masses (a finding referred to as hepatic incidentaloma and highlighted by Little et al. in 1990 [2]). Hepatic incidentaloma is a frequent clinical finding in surveillance imaging studies in patients with chronic diffuse liver diseases.

### Benign hepatic lesions

Up to 20 % of the population has a benign hepatic lesion, the most common being cavernous hemangioma and focal nodular hyperplasia (FNH) [3]. Benign masses can be subdivided into two groups according to the future course of management:

1. Lesions requiring serial monitoring or intervention and lesions such as hepatic adenomas that require interval monitoring or intervention (ablation or resection) due to their potential for malignant transformation and hemorrhage.
2. Lesions not requiring any further evaluation or follow-up: these include hepatic cysts, cavernous hemangiomas, FNH (average incidence: 8 %), focal fat in a normal liver, and focal normal tissue in a fatty liver.

### Malignant hepatic lesions

The most commonly encountered primary malignant hepatic masses include intrahepatic cholangiocarcinoma (CCA) and hepatocellular carcinoma (HCC). Patients with cirrhosis are predisposed to developing HCC and CCA and the incidence of both these malignancies has increased over the past three decades. Characterization of hepatic lesions in cirrhosis is a challenge and frequently requires multiple imaging modalities. HCCs are diagnosed on the basis of the following characteristics: (1) early arterial enhancement on contrast CT or MRI examinations, (2) early washout, and (3) the presence of a pseudo-capsule. Venous washout, defined as a hypervascular mass that becomes hypointense relative to adjacent parenchyma on delayed post-contrast images, has been reported as an imaging finding that increases the specificity for HCCs. Cholangiocarcinomas are well-defined homogenous masses which enhance somewhat later than do HCCs. These characteristics are typical, but size, calcification, necrosis, and hemorrhage may alter the appearance of both HCCs and CCAs. Therefore, the diagnosis of HCC and CCA may not be clear in spite of the use of a combination of imaging techniques.

The role of functional imaging techniques in the aforementioned situations needs to be evaluated. These techniques might be considered more helpful if they could characterize the lesions appropriately and thereby guide management [3]. Isotope imaging using gamma photon-emitting tracers has been available since the 1960s, while clinical PET was developed in the 1970s. The use of positron emitters to label a

wide range of cell ligands is an attractive approach for quantifying cellular processes, with targeted biomarkers including  $^{18}\text{F}$ -fluorodeoxyglucose (FDG). Of the various PET tracers, FDG, a biomarker of glucose metabolism, is the most widely used radiotracer in current PET clinical practice [4].

### Metabolic mechanism of FDG in cancer cells versus normal hepatocytes

Tumor imaging using FDG is based on the principle of increased glucose metabolism of cancer cells. Both FDG and glucose are taken up into cells via glucose transporters (GLUTs). GLUTs are glycoproteins of which, to date 12 isoforms have been identified in different organs. Normal hepatocytes express GLUT-2, GLUT-9, and GLUT-10. The expression of GLUTs, predominantly GLUT-1 and GLUT-3, is significantly higher in many cancer cells than in normal cells. Once in the cell, glucose or FDG is phosphorylated by hexokinase to glucose-6-phosphate or FDG-6-phosphate (FDG-6-P), respectively. The expression of hexokinase and the rate of phosphorylation of glucose or FDG are often higher in cancer cells than in normal cells; hexokinase II is predominantly expressed in cancer cells. Glucose-6-phosphate travels further down the glycolytic or oxidative pathways to be metabolized, unlike FDG-6-P, which cannot be metabolized. In normal cells, glucose-6-phosphate or FDG-6-P can undergo dephosphorylation and can exit the cells. In many cancer cells, however, the expression of glucose-6-phosphatase is often significantly low; therefore, glucose-6-phosphate or FDG-6-P is only minimally dephosphorylated and remains within the cell. Because FDG-6-P cannot be metabolized, it is trapped in cells as a polar metabolite and can be visualized by PET (Fig. 1) [5].

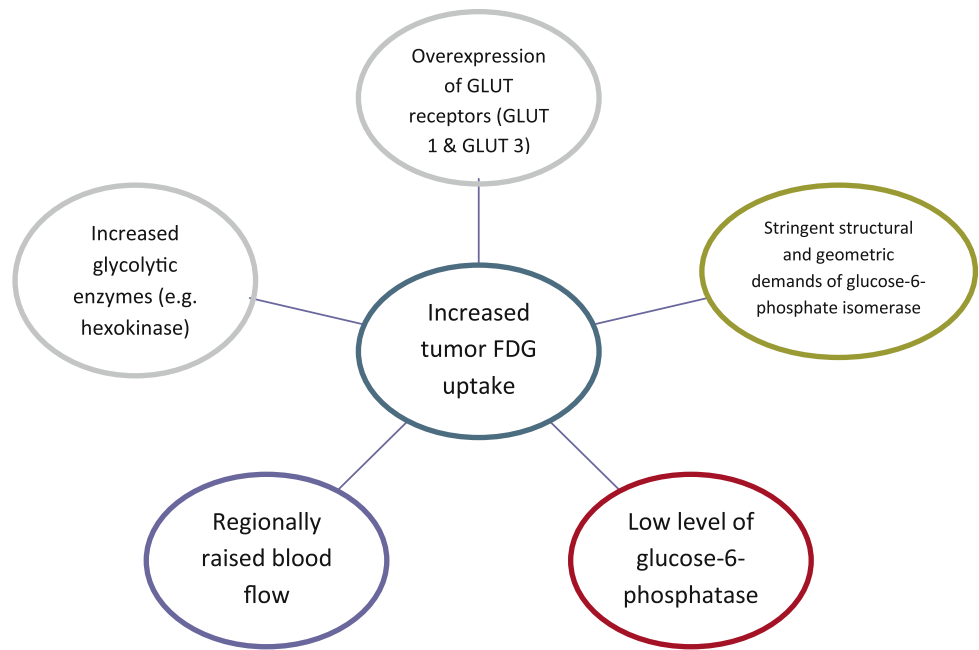
The liver is the major producer of non-dietary glucose, at a rate of 2.0 mg/kg/min, which helps to maintain glucose homeostasis [6, 7]. In normal liver parenchyma, the concentration of glucose-6-phosphatase is high, which causes rapid clearance of FDG from the liver. This may account for the mild intensity of the normal liver on whole-body PET, especially on delayed imaging [8]. In fact, in many publications and in clinical routine, the signal intensity of the liver on PET has often been used as a reference for background uptake [4, 9]. This review assesses the clinical role of PET in the imaging of unknown liver lesions and summarizes the usefulness of PET/CT in aiding the characterization of atypical liver lesions.

### Hepatocellular carcinoma

#### Diagnosis and staging

Early HCC without portal vein invasion can be resected surgically. This is the only curative treatment. However,

**Fig. 1** Factors contributing to increased tumor FDG uptake. Reproduced with permission from [5] (color figure online)



**Table 1** Salient findings of studies documenting FDG PET/CT to be beneficial in detecting extrahepatic disease in patients with primary HCC

Study	Number of patients	Salient findings
Ho et al. [26]	19	Poorly differentiated HCCs, which are more likely to metastasize, also tend to be FDG avid. The detection rates are size dependent, being 83 % for metastases larger than 1 cm and 13 % for lesions with a diameter of 1 cm or less
Yoon et al. [27]	87	Extrahepatic metastases were identified in 24 out of 87 patients. FDG PET identified four lymph node metastases and six bone metastases that had not been found using MRI or CT. FDG PET results changed the management in five (28 %) patients
Nagaoka et al. [28]	21	PET alone detected 52 out of 58 (89.6 %) extrahepatic metastases
Kawaoka et al. [29]	34	FDG PET/CT was found to show a higher sensitivity for the detection of bone metastases from primary HCC, compared with multi-detector helical CT (MDCT) and bone scintigraphy. The mean sensitivity and specificity values for diagnosis of bone metastasis were 41.6 and 94.5 % for MDCT, 83.3 and 86.1 % for FDG PET/CT, and 52.7 and 83.3 % for bone scintigraphy, respectively

patients with HCC often present late and mostly have a poor prognosis. Therefore, diagnostic confirmation and accurate assessment of the extent of disease are paramount for the selection of appropriate management. Currently, triple-phase contrast-enhanced CT (CECT) and MRI are the gold standard imaging modalities used for the differentiation of HCC from other liver pathologies and for delineating the extent of the tumor accurately [4]. The role of FDG PET/CT in the diagnosis of HCC is controversial and not yet well established, particularly in view of the limited sensitivity of the technique in well-differentiated HCCs. Wudel et al. [10], in a study of one of the largest series submitted to FDG PET for evaluation of HCC (*n* = 91 patients), found the sensitivity of FDG PET for the

detection of HCC to be 64 %. In a comparative study by Khan et al. [11] the sensitivity of FDG PET in the diagnosis of HCC was found to be 55 %, compared with 90 % for CECT. The overall sensitivity of FDG PET/CT in detecting HCC has been shown to be relatively limited, with a reported range of 50–65 % [8, 10–13, 20].

FDG PET as a non-invasive prognostic indicator

Although the sensitivity of FDG PET for the diagnosis of HCC has been found to be limited, its dichotomous behavior in well differentiated and poorly differentiated HCCs can be utilized in disease prognosis. Studies have shown that there are different levels of GLUTs and

glucose-6-phosphatase activity in HCC (well-differentiated tumors: low expression of GLUTs and high dephosphorylating enzyme activity; undifferentiated tumors: high expression of GLUTs and low dephosphorylating enzyme activity), leading to differential FDG uptake according to tumor grade and differentiation [11, 14–16]. Torizuka et al. [14] showed that FDG uptake by HCC lesions correlates with the degree of differentiation of the HCC; high-grade HCCs have increased FDG uptake [mean ( $\pm$ SD) standardized uptake value (SUV),  $6.89 \pm 3.39$ ] compared with low-grade HCCs (mean SUV,  $3.21 \pm 0.58$ ) ( $p < 0.005$ ). Shiomi et al. [16] showed that in HCC, the tumor-to-non-tumor SUV ratio correlates with tumor-volume doubling time ( $r = -0.582$ ;  $p = 0.006$ ) and also that cumulative survival rate can be predicted on the basis of the SUV ratio. The patients were divided into two groups of similar size: group A ( $n = 24$ ) had SUV ratios of 1.5 or less, and group B ( $n = 24$ ) had SUV ratios  $>1.5$ . The authors showed that the cumulative survival rate was significantly lower in group B than in group A ( $p = 0.026$ ). Similarly, Kong et al. [17] showed that patients with HCC who had mean SUVs of 7 or higher had a significantly ( $p = 0.0003$ ) lower median survival time (4 vs. 15 months).

Thus, in conclusion, FDG uptake acts as an in vivo imaging marker of differentiation and SUVs can provide insight into the histopathological nature of the tumor.

#### Diagnostic sensitivity of FDG PET/CT in HCC: the determinants

1. Histological character: because of the above-mentioned variability, it is likely that FDG PET is better able to detect higher grade HCCs and, conversely, less able to detect low-grade HCCs. For this reason, FDG PET has been determined [8] to be insufficiently sensitive for diagnosing primary HCC. The differences in FDG uptake in HCCs have been primarily attributed to different levels of glucose-6-phosphatase in hepatocytes (in addition to differences in GLUT expression). This enzyme converts FDG-6-P back to FDG, which can then be cleared from the cells. In malignant cells, however, low levels of glucose-6-phosphatase lead to increased FDG-6-P accumulation. However, the activity of glucose-6-phosphatase within HCCs is variable and depends on the degree of differentiation. Well-differentiated HCCs have high levels of glucose-6-phosphatase leading to dephosphorylation of FDG-6-P and thus, low FDG accumulation, whereas poorly differentiated HCCs have low levels of glucose-6-phosphatase and tend to be FDG avid [11].
2. Size of the lesion: in one study, the sensitivities for detecting HCC were found to be 27, 48, and 93 % for

tumors measuring 1–2, 2–5 cm, and more than 5 cm, respectively [18]. Limited detection of small lesions is a known technical limitation of PET, which is related to the spatial resolution of the camera, partial volume effects, and respiratory motion. This size limitation means that PET is not reliable in the morphological distinction between small HCCs, regenerative nodules, and premalignant dysplastic nodules [4].

Combining these two factors, the sensitivity of the technique is higher in larger and poorly differentiated tumors.

3. Effect of delayed imaging: the sensitivity of FDG PET/CT has been reported to be a function of the timing of imaging, being found to be higher when imaging is delayed by 2 and by 3 h. This is due to a decrease in SUV of normal tissue, which leads to an increase in the T/N uptake ratio [19, 20].

PET as a useful modality for selecting patients for liver transplantation: advantage over conventional Milan criteria

Hepatocellular carcinoma is a major indication for liver transplantation and selection of patients can be challenging. In HCC patients treated with surgical resection with curative intent, a high T/N ratio, i.e. of more than 2, was found to be an independent predictor of recurrence and poor survival [21]. A T/N-ratio cut-off of 1.15 was found to be an independent predictor of 1-year progression-free survival on multivariate analysis: 94 vs. 54 % [22]. Recently, in a retrospective single-center study of 43 patients, a positive pre-transplantation PET was found to be predictive of microvascular invasion and tumor recurrence after liver transplantation: the HCC recurrence rate was 50 % in PET-positive patients vs 3.8 % in PET-negative patients [23]. Furthermore, patients with tumors “beyond the Milan criteria” (based mainly upon size and number of lesions) and a negative preoperative PET had a poorer 3-year recurrence-free survival (80 %) compared with those with tumors meeting the Milan criteria (94 %), and a significantly better one than those with tumors beyond the Milan criteria and a positive PET (35 %) [23]. These findings suggest that a subset of patients with advanced HCC, who may benefit from liver transplantation due to low biological aggression of their tumor, may be identified by PET.

#### Detection of extrahepatic metastases

One of the main advantages of PET over other imaging modalities is that it provides whole-body imaging allowing the detection of multifocal and extrahepatic disease.



Although extrahepatic disease is relatively rare in HCC, especially in well-differentiated tumors, its detection can significantly change patient management. Several studies assessing FDG PET for diagnosis and staging of HCC have reported unsuspected extrahepatic metastases [11, 24, 25] (Table 1).

#### Multidimensional role of FDG PET/CT in HCC: beyond diagnosis

Wudel et al. [10] found that, although only 64 % of HCCs accumulated FDG, FDG PET had a clinically significant impact in 26 out of 91 patients (28 %) with HCC. This impact was achieved through guiding the biopsy of a large necrotic tumor, identifying distant metastases, monitoring response to treatment with regional therapy, detecting recurrence. The authors concluded that FDG PET should be considered part of the staging and management of selected patients with HCC. Fusions of FDG PET and CT images have been shown to provide improvement of lesion detection, localization, and differentiation between physiological versus pathological uptake on both CT and FDG PET images alone [6]. The addition of CT to PET can also be very useful for detecting HCC in cases in which the lesion is not FDG avid, given that 70 % of HCCs are visible on unenhanced CT as hypodense lesions, and an additional 20 % are visible as hyperdense lesions [6].

#### HCC hyperperfusion detected by early dynamic (ED) FDG PET study

A recent pilot study by Jan-Henning et al. [30] has provided initial proof of principle that a simplified ED FDG PET/CT protocol (using standard tracer activities and involving visual examination of ED FDG PET images of the liver and comparison of tumor versus liver ED SUV time-activity curves) effectively detects hypervascularization of HCC liver nodules measuring 1.5 cm or more. These results suggest that this protocol can be easily added to conventional static whole-body FDG PET/CT in everyday practice. ED FDG PET/CT using an even more streamlined methodology might replace or supplement established contrast-enhanced morphological imaging of HCC, especially in patients with contraindications to CT, ultrasonography (US), or MRI contrast medium or to those procedures themselves.

#### Novel non-FDG PET tracers

In view of the limited sensitivity of FDG for routine diagnosis of HCC, the role of other, novel biomarkers has been explored in the context both of HCC and of other tumor types.

#### Fluorine-18-labeled fluorothymidine (FLT) PET

FLT, which is a marker of tumor proliferation, was used in the detection of HCC in 16 patients and was reported to show a sensitivity of 69 %. The authors also suggested that the level of FLT uptake had prognostic value, with reduced overall survival being found in lesions with high uptake. However, the small sample size rendered this finding statistically insignificant [31].

#### <sup>11</sup>C-acetate-PET: the promise of the dual-tracer approach

Since FDG PET, because of the variability in FDG uptake, has been shown to have limited sensitivity for the detection of some HCC tumors, <sup>11</sup>C-acetate PET has been used to complement FDG PET in a dual-tracer PET scanning approach. Ho et al. [26] found that well-differentiated HCCs preferentially accumulate <sup>11</sup>C-acetate, whereas poorly differentiated tumors tend to preferentially accumulate FDG. Delbeke et al. [32] suggested that differential uptake of tracers by lesions can narrow down a differential diagnosis. When a lesion accumulates both tracers or accumulates only <sup>11</sup>C-acetate, HCC should be favored in the differential diagnosis [32], whereas when it accumulates only FDG, a non-HCC malignancy should be favored; if the lesion is negative for both tracers, a benign pathology is more likely [32]. However, it must be remembered that when the mass does not concentrate <sup>11</sup>C acetate but does accumulate FDG, poorly differentiated HCC should be considered in the differential diagnosis. Considering the observed differences in tracer uptake in HCC lesions, dual-tracer PET could lead to increased sensitivity in detecting all HCCs. Ho et al. [26] found that none of the 23 HCC lesions in their study population were negative for both tracers (100 % sensitivity using both tracers). HCC tumors with no evident FDG uptake were detected by <sup>11</sup>C-acetate uptake, and vice versa.

In an assessment of dual-tracer (<sup>11</sup>C-acetate and FDG) PET/CT, Park et al. [18] prospectively evaluated the value of PET/CT using these two tracers for the detection of primary and metastatic HCC. The overall sensitivities of FDG, <sup>11</sup>C-acetate, and dual-tracer PET/CT in the detection of 110 lesions in 90 patients with primary HCC were 60.9, 75.4, and 82.7 %, respectively. The sensitivities according to tumor size (1–2, 2–5, and ≥5 cm) were 27.2, 47.8, and 92.8 %, respectively, for FDG and 31.8, 78.2, and 95.2 %, respectively, for <sup>11</sup>C-acetate [18]. In the same study, FDG was found to be more sensitive than <sup>11</sup>C-acetate in the detection of extrahepatic metastases (85.7 vs. 77 %). The addition of <sup>11</sup>C-acetate to FDG PET/CT increases the overall sensitivity for the detection of primary HCC, but not for the detection of extrahepatic metastases. This may be the result of increased FDG PET sensitivity in the

detection of poorly differentiated HCC tumors, which are often more likely to be more aggressive, and thus associated with metastases [26]. Overall, for identification and staging of HCC metastasis, Ho et al. [26] found dual-tracer PET/CT to have a sensitivity of 98 %, a specificity of 86 %, a positive predictive value (PPV) of 97 %, a negative predictive value (NPV) of 90 %, and an accuracy of 96 %. These values, as expected, all represent significant improvements over either imaging modality alone.

In summary, because of the variable glucose metabolism of HCCs, FDG PET has been found to be of mixed utility in the detection of HCCs, showing sensitivities of 55–64 % and better visualization of larger than of smaller tumors. FDG PET appears to provide insight into the metabolic activity of the tumor, with higher FDG uptake correlating with higher grade cancers and predicting prognosis. FDG PET has also been shown to be helpful in the detection of regional and extrahepatic metastases, with a disproportionate number of metastatic HCCs being found to be FDG avid; FDG PET/CT is the most sensitive examination for detecting HCC extrahepatic metastases. Finally, <sup>11</sup>C-acetate in conjunction with FDG was shown in one study [18] to vastly increase the detection rate of HCC on PET imaging.

#### PET/CT in disease restaging following therapeutic intervention in HCC

Sun et al. [33] evaluated the usefulness of FDG PET/CT in post-therapy assessment. A population of 25 patients with HCC (21 males; 4 females) was examined for suspected relapse after previous surgical procedures, mainly partial resection (9 patients), trans-arterial-chemo-embolization (TACE) (6 patients), TACE + partial resection (8 patients), and TACE + radiofrequency ablation + percutaneous ethanol injection. The PET/CT results were compared with those of biopsy or clinical follow-up and demonstrated an overall sensitivity of 89.5 %, a specificity of 83.3 %, and an accuracy of 88 % in detecting HCC recurrence. Moreover, FDG PET explained rising alpha-fetoprotein levels in 14 patients, monitored response to therapy in 12 patients, identified extrahepatic metastases in 10 patients, identified tumor growth or thrombosis in the portal vein in six patients, and guided surgical resection of extrahepatic metastases in two patients [33].

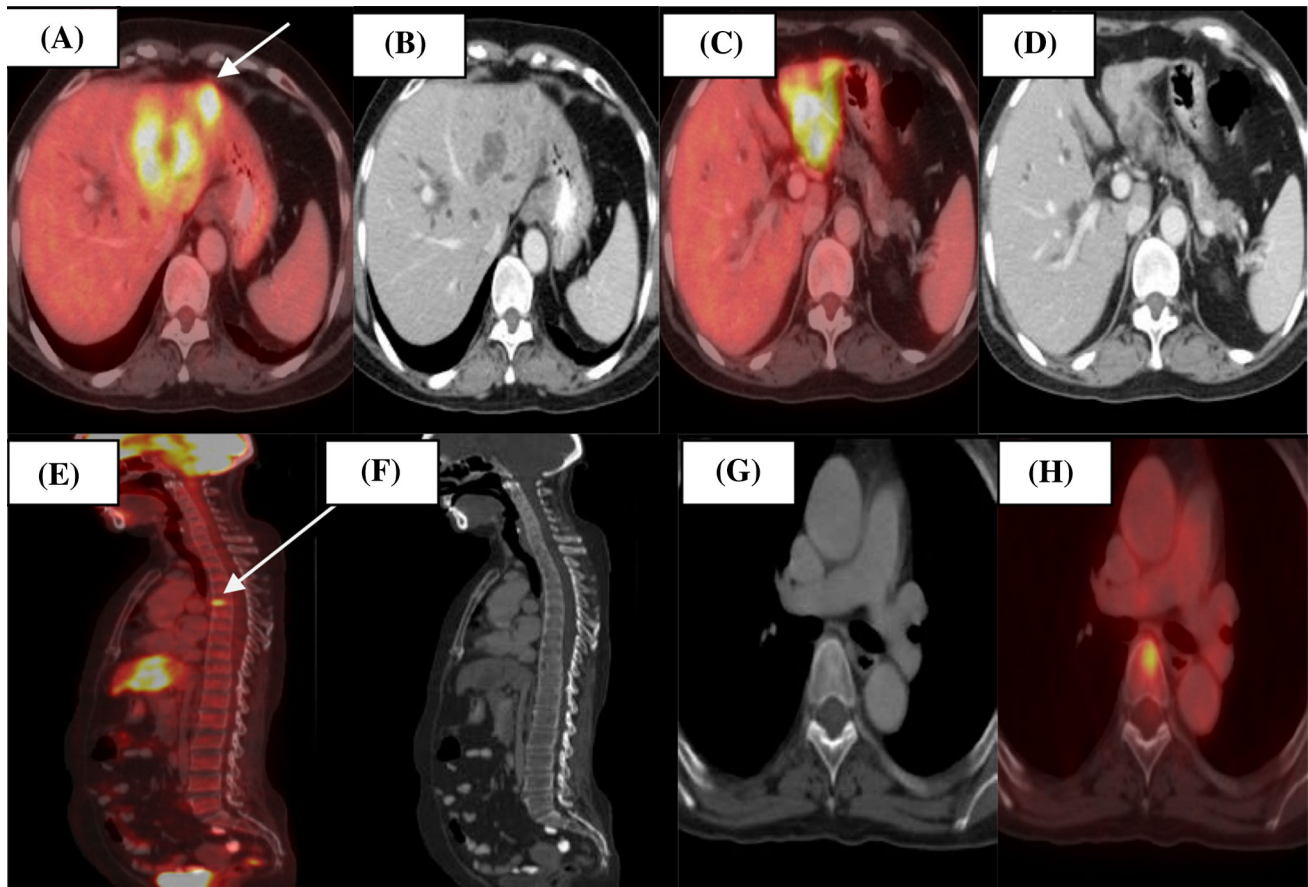
#### Cholangiocarcinoma (Figs. 2, 3)

Cholangiocarcinoma is a rare primary tumor arising from the bile duct epithelium and accounting for <2 % of all tumors; however, it is the second most common primary hepatobiliary cancer after HCC. The diagnosis of CCA often presents a challenge due to its varied radiological features,

which can mimic benign biliary pathologies, and the broad spectrum of its growth pattern. CCAs are classified anatomically as intrahepatic, perihilar, or extrahepatic. Perihilar lesions arise at the level of the bifurcation of the hepatic ducts, whereas intrahepatic CCA arises from beyond second-order bile ducts. The growth pattern of CCA is also classified according to the Japanese Liver Cancer Group as follows: exophytic when it is mass-like, infiltrating when it grows along the ducts (Klatskin tumors), intraductal (polypoid), or mixed pattern (mass-like and infiltrating). The infiltrating type is the most common in the perihilar region [4]. Overall, the prognosis of this tumor is dismal, recording a five-year survival rate as low as 17 %; however, improved survival (22–32 %) at 5 years has been reported with portal or arterial embolization followed by trisegmentectomy. Therefore, preoperative assessment for hepatic and extrahepatic metastases is likely to be of prognostic value [9].

It has been shown that surgery is often the only curative option able to prolong survival. Biliary obstruction with jaundice is the most common clinical feature in hilar CCA, whereas it is uncommon in peripheral CCA. The diagnosis of CCA has been based on the clinical picture, laboratory data, radiological imaging, and histology, although the latter is often inconclusive in differentiating CCA from metastatic adenocarcinoma. Currently, workup generally consists of MRI, including magnetic resonance cholangiopancreatography, CT, endoscopic retrograde cholangiopancreatography, and percutaneous transhepatic cholangiography. Studies show that, although FDG PET/CT has no statistically significant advantage over CECT, MRI or MR cholangiography in the diagnosis of primary biliary tumors, it is very valuable in detecting regional and distant metastases not seen on conventional imaging [6].

GLUT-1 is not expressed in normal bile ducts but has been described to be strongly expressed in CCA [13, 34]. Overall, CCA appears to be highly FDG avid, prominently in nodular or mass-forming CCAs. In assessing the ability of FDG PET to detect and diagnose CCA, Kluge et al. [35] retrospectively examined the cases of 20 patients with CCA and found that FDG PET showed sensitivity, specificity, and diagnostic accuracy values of 92.3, 92.9, and 92.6 %, respectively. Delbeke et al. [25] evaluated eight patients with CCA, and all lesions demonstrated intense FDG uptake. One study of 22 patients with primary sclerosing cholangitis [36] showed that FDG PET/CT of the liver performed after a delay (about 120 min after injection) was able to differentiate benign strictures from extrahepatic and hilar CCA in all 22 lesions, using an SUVmax greater than 3.6 as a threshold. In assessing the ability of FDG PET to detect and diagnose CCA, Kim et al. [37], in a prospective study, found the following overall values for sensitivity, specificity, PPV, NPV, and accuracy of FDG PET/CT in primary tumor detection: 84.0, 79.3, 92.9, 60.5, and 82.9 %, respectively.



**Fig. 2** Patient presenting with liver mass. Hematoxylin- and eosin-stained step sections suggested poorly differentiated adenocarcinoma with large areas of necrosis. **a, b, c,** and **d** Fused PET/CT and CECT axial images show metabolically active necrotic lesion involving segments IV, II, and III. **a, b** CECT and PET/CT fused axial images

show metabolically active enhancing nodular metastatic lesion involving left lobe of liver (*white arrow*). **e, f** Fused PET/CT and CT sagittal images and **g, h** axial images show metabolically active lesion with sclerotic margin involving D6 vertebral body (*white arrow*) (color figure online)

respectively. Otherwise, a recent study by Jadvar et al. [38] investigating the use of FDG PET/CT in the evaluation of patients with known or suspected recurrent and metastatic cholangiocarcinoma found sensitivity and specificity to be 94 and 100 %, respectively. These results indicate that false-positive cases in this setting are minimal.

Sensitivity of FDG-PET/CT in detecting cholangiocarcinoma: the determinants

#### *Hilar CCA versus peripheral CCA*

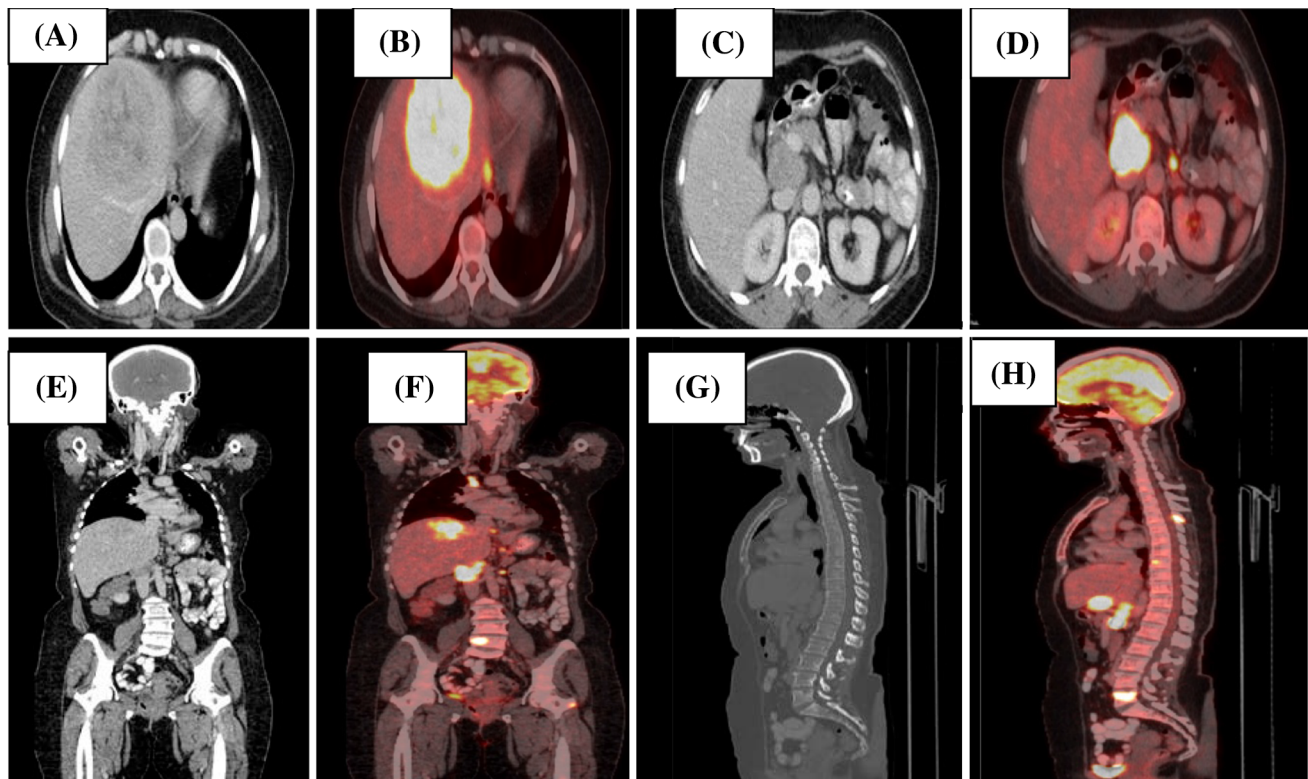
Hilar and extrahepatic CCA, however, have been reported to show lower uptake on FDG PET than peripheral CCA, a finding that may be associated with the smaller size and/or higher mucin content of hilar tumors compared with peripheral ones [34, 39, 40]. Peripheral CCA accounts for about 10 % of all CCAs and often has a characteristic central photopenia on FDG PET, which corresponds to the central core of fibrotic tissue and a desmoplastic reaction

provoked by the neoplastic cells; on CECT or MRI, central photopenia is shown by early moderate peripheral enhancement followed by progressive and concentric filling [41, 42]. The sensitivity of FDG PET/CT in detecting primary hilar or extrahepatic CCA tumors has been found to be 18–58.8 % [38, 43–45], significantly lower than that found for peripheral nodular tumors. Kato et al. [39] reported 100 % specificity for regional nodal involvement on FDG PET. PET should be considered in the workup of patients for extrahepatic metastases, especially in cases of peripheral CCA; peripheral CCA usually reaches a large size before it becomes clinically apparent because it does not obstruct the central biliary system.

#### *Nodular versus infiltrating morphology*

In 36 patients who underwent imaging for CCA, Anderson et al. [43] found the sensitivity of FDG PET for detection of these lesions to be 85 % ( $n = 22$ ) for those with a nodular morphology, but only 18 % ( $n = 14$ ) for those





**Fig. 3** Patient presenting with liver mass. Immunohistochemistry suggests metastatic adenocarcinoma consistent with primary origin in the pancreaticobiliary tract, including intrahepatic cholangiocarcinoma. **a, b** CECT axial image and fused PET/CT images show metabolically active large irregularly shaped heterogeneously enhancing lesion involving segments IV and VIII of right lobe of liver with

few areas of necrosis. **c, d** CECT and fused PET/CT axial images show metabolically active retroperitoneal nodal mass. **e, f** CECT and fused PET/CT coronal and **g, h** sagittal images show metabolically active mediastinal, retroperitoneal nodes, and few skeletal lesions (color figure online)

with an infiltrating morphology. Periductal infiltrating CCAs rarely form a focal mass [43] and FDG uptake is, therefore, streaky. These data suggest that FDG PET is accurate in predicting the presence of nodular CCA (mass >1 cm), but less effective for the infiltrating type [38, 43].

#### FDG PET/CT in the staging of metastatic CCA

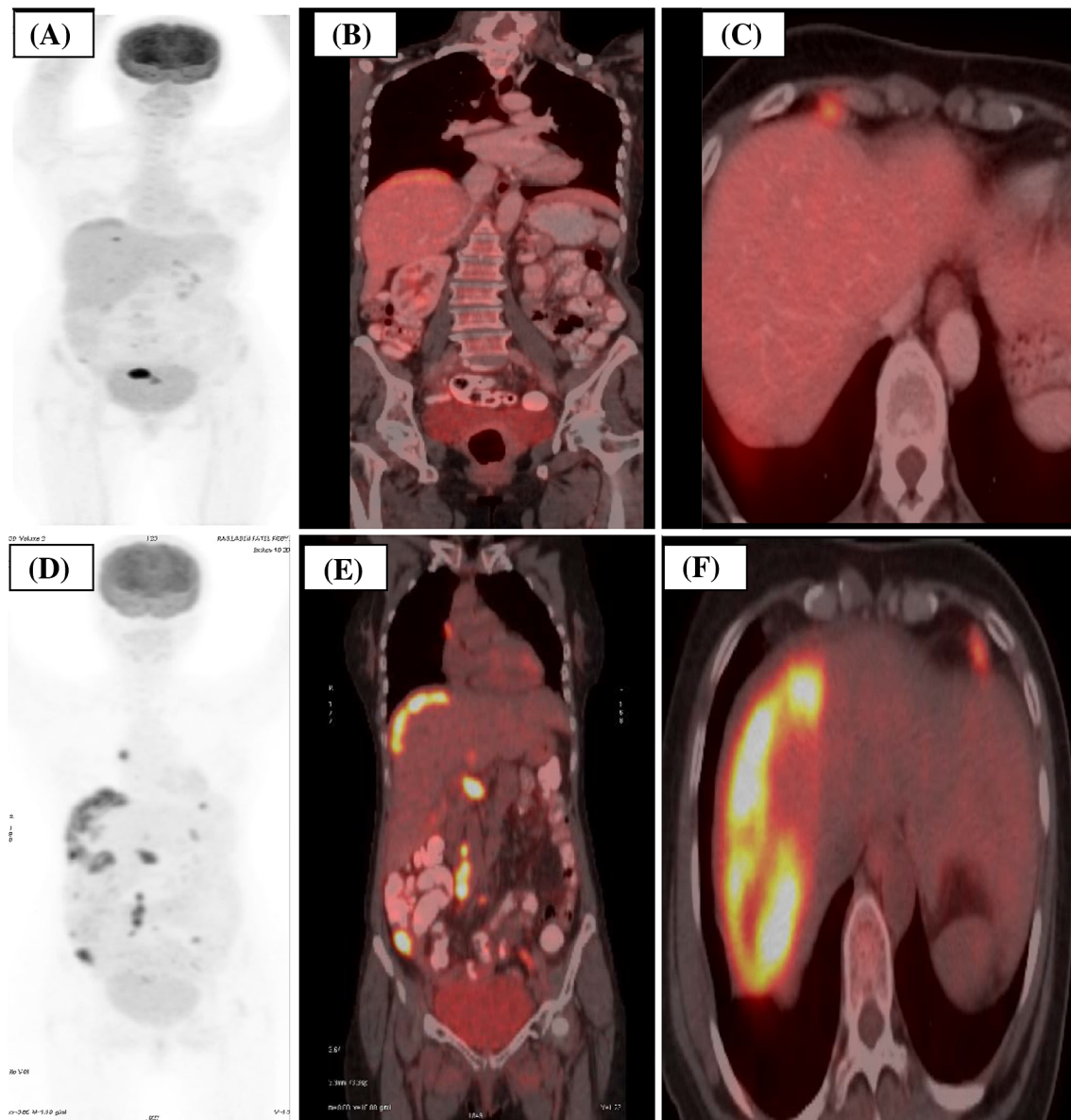
Although FDG PET and FDG PET/CT have not been shown to be highly beneficial in diagnosing primary CCA, they are beneficial in the detection and staging of metastatic CCA. Kim et al. [37], in a study of 123 patients with suspected CCA, found FDG PET to show greater accuracy in the diagnosis of regional lymph nodes metastases (75.9 vs 60.9 %;  $p = 0.004$ ) and distant metastases (88.3 vs. 78.7 %;  $p = 0.004$ ) compared with CT. Seo et al. [46] also found FDG PET to be a more accurate and specific detector of lymph node metastases in 35 patients when compared with either CT or MRI. The diagnostic accuracy rates of FDG PET, CT, and MRI in the detection of lymph node metastases were 86, 68, and 57 %, respectively; their sensitivities were 43, 43, and 43 %, and their specificities 100, 76, and 64 %, respectively.

Several other studies [37, 47, 48] have shown that FDG PET stands out for its ability to detect occult metastases that were not diagnosed by standard imaging. Thus, FDG PET/CT staging has an important impact on the selection of therapy [49]; indeed, FDG PET has been shown to change surgical management in 17–30 % [43, 49, 50] of patients evaluated for CCA, primarily as a result of the detection of unsuspected or unknown metastases and, thus, of upstaging [50].

In summary, the sensitivity of FDG PET and FDG PET/CT in diagnosing CCA appears to be dependent on both the morphological characteristics and the location of the lesion, with nodular forms and peripherally located lesions being easier to detect than infiltrating and hilar lesions. FDG PET and FDG PET/CT have been shown to be very beneficial in detecting regional and distal metastases from CCA, and this can impact on patient management.

#### Liver metastasis (Fig. 4)

Metastatic disease accounts for the majority of malignant lesions in the liver. Often, the presence of liver metastases is the main determinant of survival in cancer patients and



**Fig. 4** Patient with recurrent ovarian mass. Hematoxylin- and eosin-stained step sections suggested endometrioid carcinoma with poor differentiation. **a** PET and **b** Fused PET/CT coronal, and **c** PET/CT axial images show diffuse FDG uptake along the segment VII and VIII subcapsular area of the liver without any CT evident lesion.

Follow-up PET/CT scan was done after chemotherapy, radiotherapy, and brachytherapy 8 months after the previous scan. **d** PET and **e** Fused PET/CT coronal and **f** PET/CT axial images show progression with diffuse involvement of right lobe of the liver almost throughout segments V, VI, VII, and VIII (color figure online)

guides the therapeutic strategy, particularly in those affected by colorectal cancer [51, 52]. Zimmerman et al. [34] studied the expression of GLUT-1 in hepatic metastases originating from different primaries and reported that GLUT-1 was overexpressed in hepatic metastases from 3 of 5 lung primaries, 7 of 11 pancreatic primaries, 7 of 9 colon primaries, 2 of 7 breast primaries, 2 of 2 squamous cell primaries, 1 of 3 biliary tract primaries, and none of the neuroendocrine primaries that were examined. To our knowledge, expression of other GLUTs, such as GLUT-3, in hepatic metastases has not previously been reported.

FDG PET has been shown to be highly sensitive in detecting hepatic metastases from different primaries. Delbeke et al. [25] studied the diagnostic value of FDG PET in hepatic metastases measuring 1 cm or more and detected all 66 metastatic lesions originating from various primaries, such as the colon, pancreas, esophagus, sarcoma, and parotid. Similar results, which showed the overall greater sensitivity of PET compared with that of spiral CT, have been reported by others, particularly in the case of CT findings that were indeterminate [53]. D'Souza et al. [54] showed the superiority of PET/CT over CECT in the



detection of untreated hepatic metastases in a prospective study evaluating 45 patients with suspected liver metastases from various primary cancers. The sensitivity and specificity in the detection of hepatic metastases were 87.9 and 16.7 %, respectively, for CECT, and 97 and 75 %, respectively, for PET/CT.

In cases of known solitary hepatic metastasis diagnosed using CT, several groups have reported the discovery, using FDG PET, of additional hepatic metastases [55–57]. Such findings in the preoperative evaluation of solitary hepatic metastasis are very important as detection of additional lesions often changes the management. Retrospective data by Fernandez et al. showed that the use of FDG PET in the presurgical assessment of patients with colon cancer liver metastases (candidates for partial hepatectomy) was associated with long-term survival: the survival of patients assessed using FDG PET was superior to that of patients with the same condition in whom only standard anatomical imaging methods were used in the selection for surgery. Presumably, PET made it possible to select those patients who did not have extrahepatic metastases and were, therefore, most likely to benefit from partial hepatectomy [58]. Additionally, in cases of suspected recurrent colorectal cancer, FDG PET is more sensitive than CT for discovering hepatic metastases and has the potential to detect metastatic disease earlier than CT, when it is more amenable to curative resection [57, 59]. The use of FDG PET should be considered, in particular, in patients with increased carcinoembryonic antigen levels.

Yang et al. reviewed PET and MRI studies of 30 patients with histopathologically proven ( $n = 27$ ) or clinically suspected ( $n = 3$ ) hepatic metastases from non-hepatic primaries. The sensitivity, specificity, PPV, and NPV on MRI were 85.7, 100, 100, and 89 %, respectively, compared with 71, 93.7, 90.9, and 79 %, respectively, on PET. The differences in the results between the two methods were not statistically significant [60]. Böhm et al. [61] reported similar results.

A meta-analysis of the literature on detection of hepatic metastases from colorectal, gastric, and esophageal cancers using ultrasonography, CT, MRI, and PET found that in studies reporting specificities higher than 85 %, the mean weighted sensitivity was 55 % (95 % CI 41, 68) for US, 72 % (95 % CI 63, 80) for CT, 76 % (95 % CI 57, 91) for MRI, and 90 % (95 % CI 80, 97) for PET. The conclusion was that at equivalent specificity, PET is the most sensitive non-invasive imaging modality for diagnosing hepatic metastases from colorectal, gastric, and esophageal cancers [62]. CT can achieve higher sensitivity, but at the expense of specificity. This was shown by Marom et al. [63] in metastatic lung cancer: in a prospective study of 100 patients, nearly twice as many lesions in the liver were identified using CT than using PET; however, all of the incremental

lesions identified on CT were false positives. False-negative PET results for hepatic metastases, due to the lower image resolution of PET compared with that of spiral CT and MRI, have been reported by various authors [53, 61, 64].

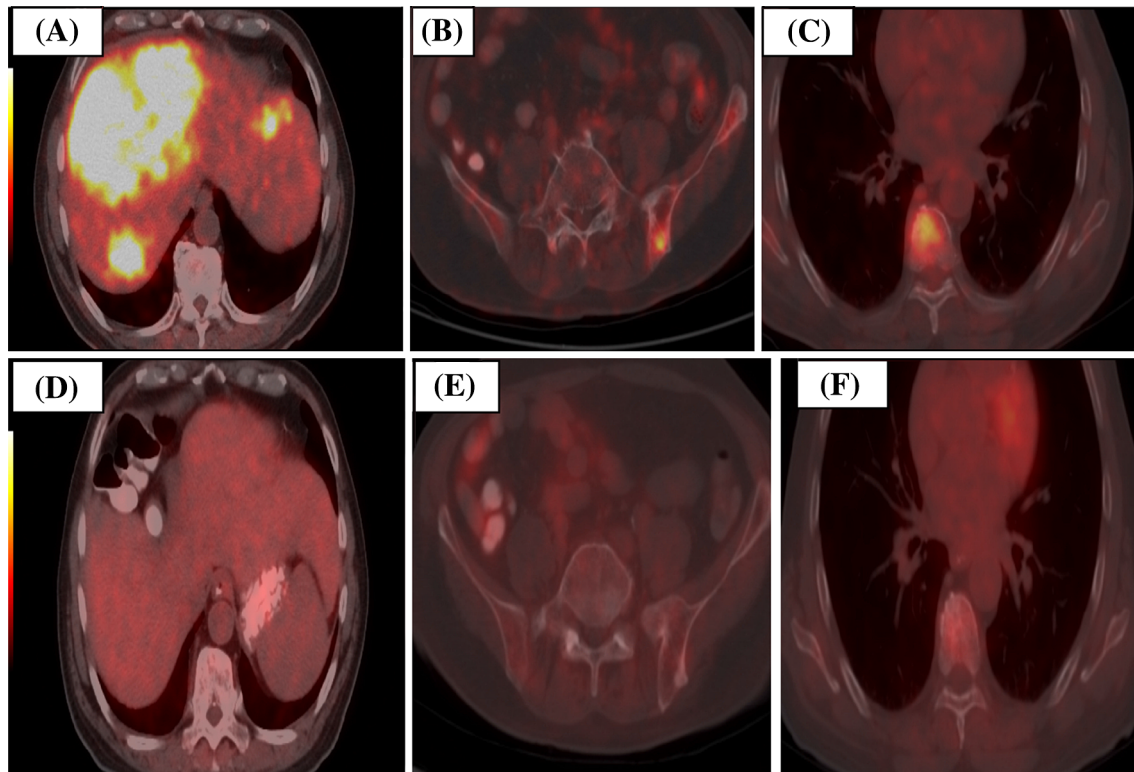
In summary, liver metastases are generally FDG avid and, therefore, easily detected by FDG PET. This sensitivity has been found to be equal or superior to that of both CT and MRI. Furthermore, FDG PET has been found to be able to detect extrahepatic metastases that were missed by conventional imaging. This leads to upstaging of patients and a significant change in their management. For this reason, the use of FDG PET and PET/CT in presurgical imaging has been shown to decrease the number of futile operations and improve patient selection for surgical removal of solitary hepatic metastasis.

### Neuroendocrine tumors

The current standard for functional imaging of neuroendocrine tumors is somatostatin receptor scintigraphy (SRS) [65]. Several studies have evaluated PET versus SRS and reported overall sensitivities of 58 % for PET and 89 % for SRS. The sensitivities for detection of primary tumors varied according to the location, a sensitivity of 91 % being reported for ileal tumors with SRS versus only 36 % with FDG PET, while for pancreaticoduodenal tumors the values were 90 and 79 %, respectively. The sensitivity for detection of hepatic metastases with unknown neuroendocrine primary was 100 % with SRS versus 86 % with PET. In direct comparison with PET, SRS showed significantly higher detection rates for hepatic and osseous metastases from neuroendocrine tumors but not for lymph node metastases. Only in neuroendocrine tumors with a proliferation index of more than 15 % has PET been found to outperform SRS, recording a sensitivity of 92 vs 69 % (Fig. 5) [65]. On multivariate analysis, FDG PET was found to be a predictor of progression-free survival [66]. The predictive value of PET for progression-free survival was confirmed in another study including 96 patients with neuroendocrine tumors of whom 66 % had hepatic metastases; an SUV<sub>max</sub> of more than three was found to be an independent predictor of progression-free survival on multivariate analysis [67]. Thus, PET has only a complementary role in the detection of neuroendocrine pancreaticoduodenal and poorly differentiated tumors, in which SRS can occasionally fail to identify the primary tumor, and a role as a predictor of progression-free survival.

### Lymphoma (Fig. 6)

Primary hepatic lymphoma (PHL) is extremely rare, although it has been described in patients with HCV-



**Fig. 5** Patient presenting with liver mass. Immunohistochemistry suggested neuroendocrine carcinoma. **a** Fused PET/CT axial image shows metabolically active lesions involving both lobes of the liver. **b, c** PET and fused PET/CT axial images show metabolically active

sclerotic metastatic lesions involving left iliac bone and D10 vertebra. **d, e, f** Fused PET/CT axial images show right hepatectomy status with complete metabolic response involving liver and skeletal lesions (color figure online)

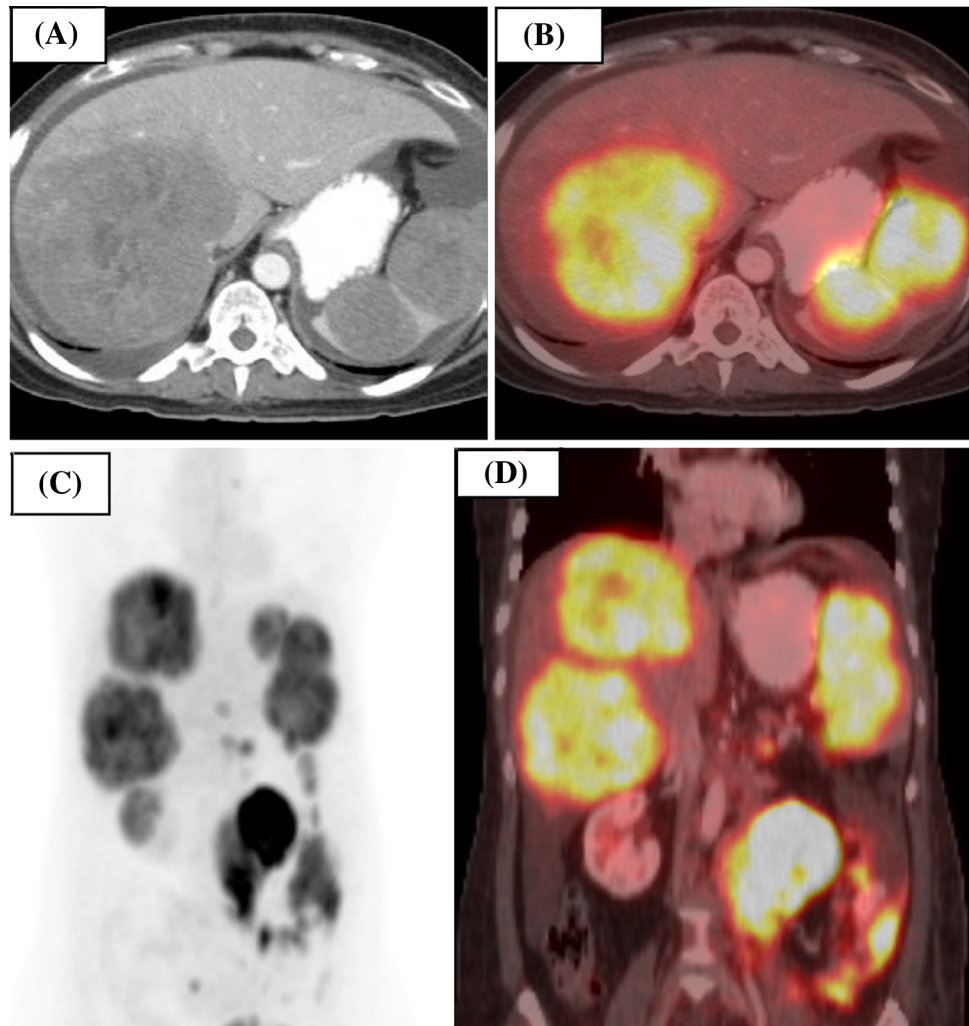
positive liver disease. Most commonly, it presents as a solitary hepatic mass, but multiple masses as well as diffuse patterns have been described. On US, PHL is usually homogeneously hypoechoic; on CT, it typically presents as a hypoattenuating lesion. A central area of low intensity indicating necrosis may be present. Enhancement patterns on dynamic imaging are quite variable; 50 % of PHL lesions show no enhancement at all, 33 % show patchy enhancement, and 16 % show ring enhancement. On MRI, PHL presents as hypointense or isointense on T1-, and hyperintense on T2-weighted images. However, most of these radiological findings are non-specific and such lesions are often misdiagnosed as HCC or as metastases. PHL accumulates FDG and the feasibility of PET for evaluating it has been well described. However, due to its rarity, there are no large studies evaluating the accuracy, sensitivity, or specificity of PET for this disease entity. Secondary extranodal hepatic lymphoma is more common and PET is used for assessment of treatment response in patients with lymphoma undergoing chemotherapy. Lesions measuring >1.5 cm and FDG accumulation exceeding hepatic and splenic FDG are considered positive for lymphoma [68].

Increased focal concentration of FDG against a background of relatively lower normal hepatocyte uptake is usually regarded as the hallmark of metastatic involvement of the liver from a known primary. A very unusual hepatic uptake pattern was reported in a case of Hodgkin disease, in which the FDG PET showed intensely diffuse hepatic tracer uptake and was the earliest indicator of extensive hepatic involvement by the disease process. The term “hepatic superscan”, used to describe this hitherto undescribed entity and referring to the presence of intense diffuse hepatic tracer uptake coupled with surprisingly low brain and cardiac FDG uptake, originates from its apparent similarity with the superscan seen in conventional skeletal scintigraphy [69].

#### Identification of primary tumor in case of hepatic metastases from unknown primary (CUP syndrome) (Fig. 7)

The incidence of carcinoma of unknown primary (CUP) in cancer patients is 0.5–7 % at the time of the initial diagnosis and primarily connotes metastatic cervical lymphadenopathy [70–72], in which the site of the primary

**Fig. 6** Patient presenting with liver mass. Immunohistochemistry suggested NHL of DLBCL type **a** CECT axial image showed two heterogeneously enhancing lesions with internal necrosis involving the right lobe of the liver. **b** Fused PET/CT axial image shows metabolically active liver lesions. **c**, **d** PET and fused PET/CT coronal images show metabolically active lesions involving liver, spleen, left kidney, and a left paraaortic nodal mass (color figure online)



tumor is detected in around 10–35 % of cases using conventional imaging modalities [70, 71]. FDG PET/CT is a potentially useful method that allows non-invasive, single whole-body imaging and has been shown to identify the primary tumor in patients with CUP better than the conventional methods and, in addition, to offer accurate staging and disease prognostication [71, 72]. Efforts have been made to clarify the potential role of FDG PET/CT in patients with gastrointestinal manifestations such as malignant ascites. In one study, it was inferred that FDG PET/CT can be a powerful imaging tool for identifying tissue origin in liver cirrhosis patients with suspected cancers or with cancers of unknown primary sites [73]. Elevated FDG absorption was found in 23 of 28 cases in the following sites: gastrointestinal tract ( $n = 10$ , 43.5 %), prostate ( $n = 5$ , 21.7 %), peritoneum ( $n = 4$ , 13.3 %), and ovary ( $n = 4$ , 13.3 %). Cancer was confirmed by pathology in 20 cases after open or laparoscopic surgeries. Five patients were found to have benign ascites; three of these were found to be false positive due to tuberculosis. SUV

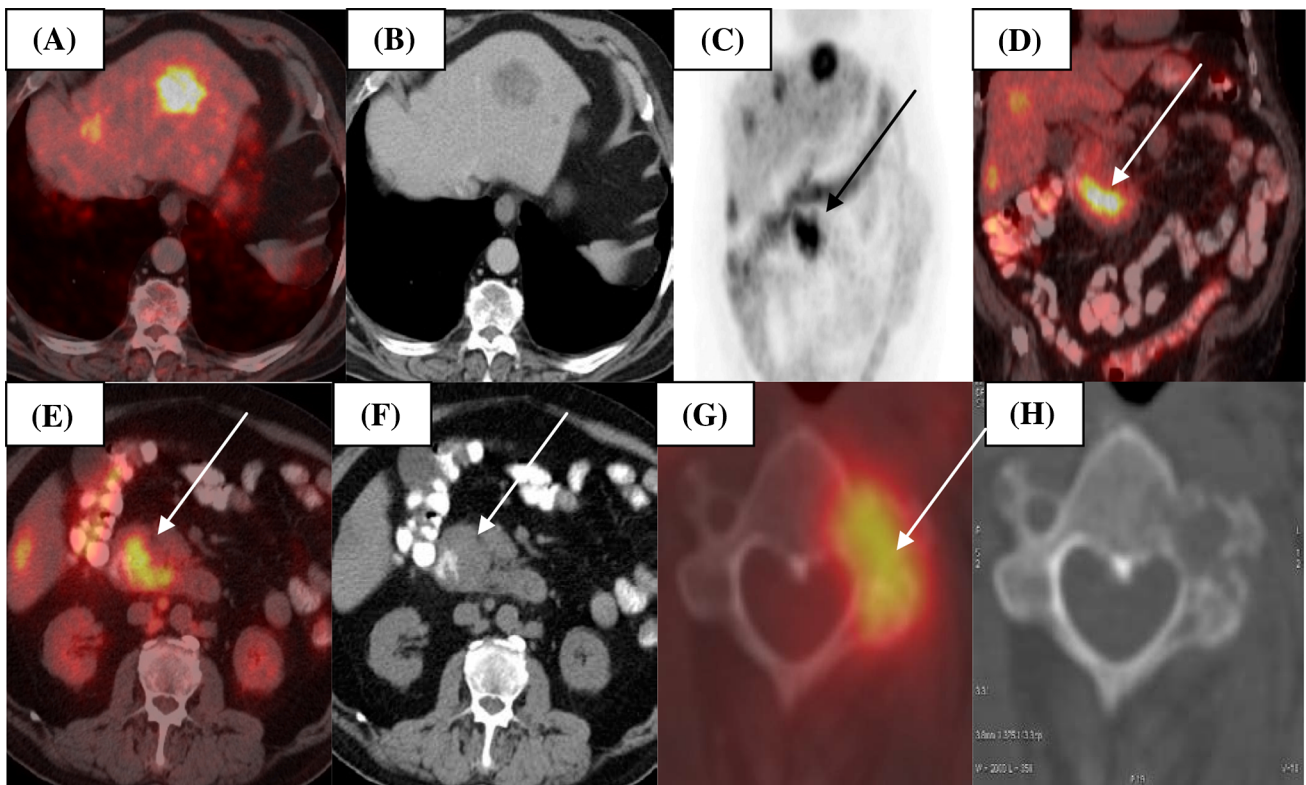
values were significantly higher for tumors than for benign lesions (mean values, 6.95 vs. 2.94;  $p = 0.005$ ) [73].

#### Characterization of liver lesions: PET/CT with FDG and novel tracers versus morphological imaging

Differentiating benign from malignant liver lesions (Fig. 8)

Benign liver lesions have a high prevalence; therefore, in addition to lesion detection, accurate lesion characterization is very important. Anatomical techniques with US, CT, and increasingly advanced imaging with contrast MRI and diffusion-weighted imaging are used for liver lesion assessment; however, in a proportion of patients, findings remain indeterminate due to morphologically atypical lesions [4]. In concordance with the American College of Radiology Appropriateness Criteria guidelines for the initial characterization of liver lesions, functional imaging is an additive modality in this setting, aiding





**Fig. 7** Patient presenting with liver lesions on ultrasonography. Hematoxylin- and eosin-stained step sections suggested metastatic adenocarcinoma. Immunohistochemistry suggested CK7 and CK20 positive and CEA and AE1 strong positive. **a** Fused PET/CT **b** CECT axial images show metabolically active lesions involving both lobes of liver with largest FDG avid lesion in segment IV. **c**, **d** PET and fused PET/CT coronal images and **e**, **f** fused PET/CT and CT axial

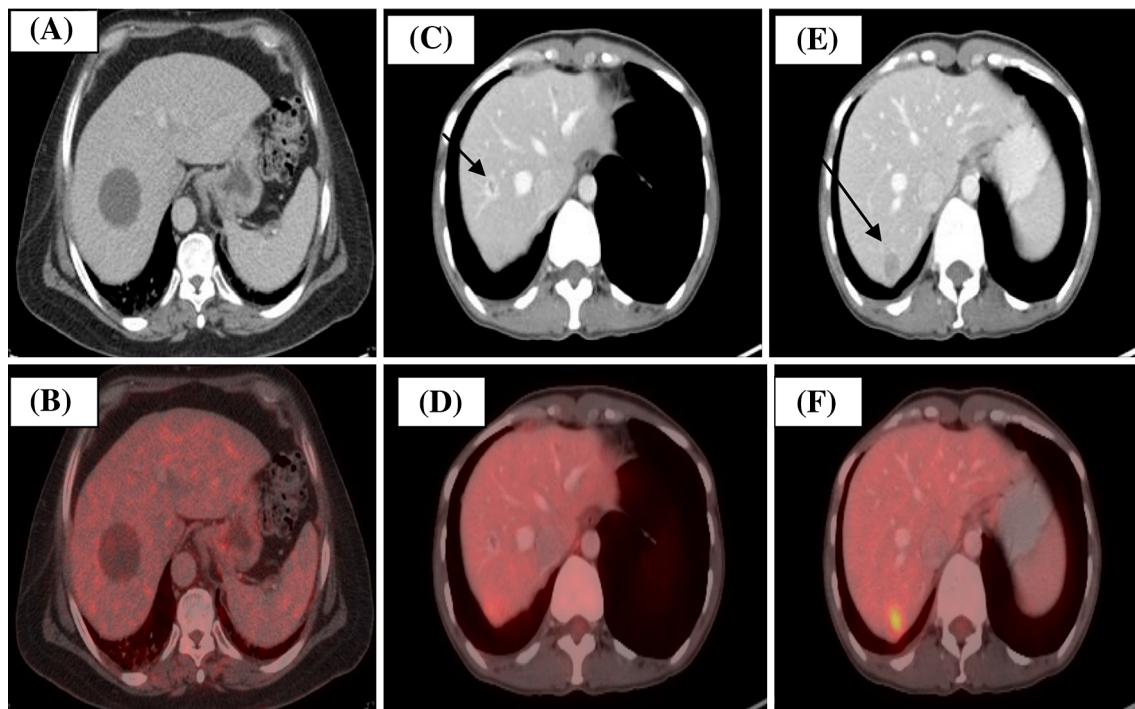
images show metabolically active lesion involving 2nd part of the duodenum extending up to the duodenojejunal junction (*black and white arrows*) suggesting the probable primary site with few metabolically active retroperitoneal lymph nodes. **g** and **h** Fused PET/CT axial images show metabolically active lytic lesion involving body, pedicle, and transverse process of C3 vertebra on left side (*white arrow*) (color figure online)

differentiation of atypical benign vascular and other liver lesions from malignancy, and, in most cases, obviating the need for biopsy and histopathological assessment. FDG PET is not routinely indicated in patients with no history of malignancy; however, it is useful as part of the imaging workup in patients with a history of malignancy [74].

As early as 1998, it was shown that functional imaging with PET is additive to anatomical imaging for the differentiation of benign from malignant liver lesions. Delbeke et al. [25], further delineating the role of PET in evaluating liver masses, showed that FDG PET was able to differentiate between benign and malignant hepatic lesions in 110 patients who were referred for examination of hepatic lesions >1 cm at the largest diameter. The authors found that all benign hepatic lesions ( $n = 23$ ), including adenoma and FNH, had poor uptake and an SUV<sub>max</sub> <3.5, except for one of three abscesses that showed definite uptake (inflammatory lesions, granulomatous ones in particular, demonstrate FDG uptake due to activated macrophages) [75]. All 66 liver metastases and 16 of 23 HCCs had avid FDG uptake.

Benign hepatic cysts (2–7 % of the population) are characterized using anatomical imaging techniques. These lesions are indeterminate in a proportion of CT studies, particularly when only a few millimeters in size. Liver US or MRI invariably help to characterize these cysts. MRI is, in general, a more accurate and useful modality than PET for small cystic lesions. Small lesions (especially sub 5–10 mm) can be beyond the resolution of PET; cystic metastases and mucinous histology disease are also often false negative or show low intensity of uptake (i.e. low SUV measurements) on FDG imaging, due to the low tumor cell density within cystic and mucinous lesions. It is, therefore, clinically important to understand the precise histological subtype of the tumor when evaluating patients using PET, for example, the vast majority of colorectal cancer histologies are FDG avid; colorectal mucinous histology disease is an exception [76].

Hemangioma is the most common benign liver tumor (7 % of autopsy cases). In a small proportion of cases, morphological imaging is indeterminate. Functional FDG imaging can differentiate benign atypical hemangioma (including giant heterogeneous hemangioma and rapidly



**Fig. 8** **a** CECT axial and **b** fused PET/CT axial images show large well-defined ametabolic lesion involving segments VII and VIII of the right lobe of the liver suggesting a benign cyst. **c** CECT axial and **d** fused PET/CT axial images show ametabolic hypodense lesion with peripheral nodular enhancement suggesting hemangioma (*black*

*arrow*) in patient with breast carcinoma. In the same patient **e** CECT and **f** fused PET/CT axial images show metabolically active hypodense lesion involving the right lobe of the liver suggesting a metastatic lesion (*black arrow*) (color figure online)

filling hemangioma) from metastatic disease, as the former is FDG negative [25, 77], thus avoiding the need for histopathological correlation and, therefore, the risk of hemorrhage due to biopsy of a benign vascular liver lesion.

PET is also useful in indeterminate cases of FNH (the second most common benign liver neoplasm after hemangioma) and hepatic adenoma (hemorrhage is detected in a proportion of cases and it can be atypical on anatomical imaging). Kurtaran et al. [78] showed that malignant liver lesions accumulate more FDG than FNH lesions do (mean,  $10.07 \pm 3.79$  and  $2.12 \pm 0.38$ , respectively). Furthermore, FNH lesions showed normal or even decreased accumulation of FDG compared with background liver tissue. Ho et al. [8] found that FNH lesions can show mildly increased levels of  $^{11}\text{C}$ -acetate uptake ( $^{11}\text{C}$ -acetate SUVmax, 3.59, with a T/N ratio of 1.25).

Magini et al., in 2009, reported a prospective study in which they examined 31 patients with 43 lesions. On FDG PET, they obtained six true positives out of seven lesions due to consequential diseases, with a sensitivity of 85.7 %, and 33 true negatives out of 36 FNH lesions, with a specificity of 91.7 %. Using acetate PET, they found two true-positive lesions out of seven caused by neoplasms, with a sensitivity of 28.6 %, and 34 true negatives out of 36 FNH lesions, with a specificity of 94.4 %. The authors

concluded acetate PET offered no additional diagnostic advantage over what is achieved with FDG PET for differentiating FNH from liver neoplasms [79].

In terms of other benign liver lesions, hepatic hamartoma can be difficult to distinguish from metastasis on anatomical imaging, particularly when a single, large, enhancing hamartoma is observed. Hamartomas do not show FDG accumulation; therefore, PET is useful for confirming a benign lesion [80]. In addition to the previously mentioned liver abscesses, hepatic sarcoid is a benign lesion that is positive on FDG radiotracer imaging [81]. Seromas associated with liver surgical resection margins are usually negative; they can also show inflammatory uptake on FDG imaging [81], although they have a typical CT and MRI morphological appearance.

Epithelioid hemangioendothelioma of the liver is a very rare vascular tumor in children with intermediate malignant potential. The typical imaging findings of coalescent peripheral hepatic masses with capsular retraction contribute to the diagnosis. In one report, FDG PET/CT was performed for disease staging in the presence of a strong suspicion of celiac nodal involvement, which was confirmed after laparotomy and histological analysis. The use of PET/CT allows better staging at initial diagnosis and thus better management with improved follow-up in these patients [82].



## Differentiating FNH and hepatic adenoma

FNH usually shows FDG accumulation similar to, or even less than, the background physiological liver activity levels, a small number of false positives being observed [83]. Likewise, most hepatic adenomas do not show uptake on FDG PET imaging, again with a small number of false positives; this also applies to hepatic adenomatosis [84, 85]. Preliminary work suggests that novel PET radiotracers could be useful in differentiating FNH and hepatic adenoma, although further data are needed. In a prospective series of 23 patients (11 adenomas, 12 FNH),  $^{18}\text{F}$ -fluorocholine differentiated the two pathologies: all adenomas showed an SUV ratio of 1.12 or less, whereas all FNH lesions assessed showed an SUV ratio of 1.22 or more; further work with larger patient series is required in order to draw definitive conclusions [86].

**Conflict of interest** Swati Rachh and Sandip Basu declare no conflict of interest.

**Human and Animal Studies** This article does not contain any studies with human or animal subjects performed by any of the authors.

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