FDG and other radiopharmaceuticals in the evaluation of liver lesions

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Received: 26 June 2013 / Accepted: 20 February 2014 / Published online: 13 March 2014
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Abstract Liver nodules are common findings in medical practice, both in patients with and in those without chronic liver disease. These lesions have to be interpreted according to clinical history and biochemical findings. Conventional imaging (US, CT and MRI) is still the gold standard for evaluating liver nodules, while diagnostic flowcharts do not currently include PET/CT. Since the 1990s many studies have been conducted to assess a possible role for FDG PET or PET/CT in several liver pathologies. According to the literature, FDG PET (and later PET/CT) could be useful in detecting, staging and grading hepatocellular carcinoma, often leading to a change in therapy, and may even detect intrahepatic cholangiocarcinoma with adequate sensitivity. Moreover, FDG can allow more accurate staging of hepatic involvement deriving from other tumors (often underestimated by conventional imaging) and, therefore, more appropriate therapy in affected patients. Finally, FDG PET can also be used to evaluate ^{90}Y microsphere therapy response. Other conditions (e.g., primary hepatic lymphoma when conventional imaging is inconclusive) may benefit from the use of FDG PET/CT, while benign lesions (e.g., focal nodular hyperplasia) show low FDG avidity. As regards non-FDG tracers, choline and acetate (ACE) have been evaluated in comparison with FDG and found to show good efficacy in detecting and staging well- or moderately differentiated HCC. However, their sensitivity in poorly differentiated HCC is very low, suggesting that dual-tracer investigation (FDG and choline/FDG and ACE) could

be useful when non-invasive grading is required. Despite promising results, PET evaluation of liver nodules still seems to be far from routine application, mostly because of cost-related issues.

Keywords Liver · FDG · Choline · Acetate

Introduction

The diffusion and improvement of imaging techniques over the past decade have led to a higher detection rate of incidental liver lesions, which have become very common findings in medical practice. These are very often identified in asymptomatic patients, in which case we talk of “hepatic incidentaloma”, a term coined by Little et al. [1].

Choosing the correct approach is mandatory. Important aspects to be taken into consideration are the patient’s history (the presence of congenital diseases such as primary sclerosing cholangitis or liver fluke infection, but also other factors such as alcohol abuse or professional exposure), physical examination (abdominal tenderness, signs of chronic liver disease, weight loss), and specific biochemical parameters, especially α -fetoprotein (AFP) and transaminases.

Patients should also be tested for hepatitis C (HCV) and hepatitis B (HBV) virus infection before any further steps are taken.

Epidemiology of common hepatic lesions

Liver lesions are usually classified as neoplastic (either benign or malignant) or non-neoplastic, although many authors also distinguish between lesions occurring in cirrhotic and in non-cirrhotic livers. Table 1 provides a list of

Color figures online at <http://link.springer.com/article/10.1007/s40336-014-0059-X>

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Table 1 The most frequent hepatic lesions are summarized and they are classified into neoplastic (benign and malignant ones) and non malignant

Benign lesions	Low-grade dysplasia
	Focal fatty liver
	FNH
	Hemangioma
	HA
	Nodular regenerative hyperplasia
	Partial nodular transformation
	Focal fatty infiltration
	Bile duct adenoma
Malignant lesions	High-grade dysplastic nodule
	HCC (including fibrolamellar)
	Metastasis
	Cholangiocarcinoma
	Lymphoma
	Hemangioendothelioma
	Melanoma
	Neuroendocrine tumor
Non-neoplastic lesions	Sarcoma (angiosarcoma, leiomyosarcoma)
	Hydatid
	Liver abscess

possible hepatic lesions, although only the most common [hepatocellular carcinoma, intrahepatic cholangiocarcinoma (ICC), metastases from other malignancies, focal nodular hyperplasia and hepatocellular adenoma] are discussed in the present article.

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide and the first most common cause of death in patients with cirrhosis [2, 3], a condition affecting up to 80–90 % of patients with HCC [4]. It has been demonstrated that regenerative nodules are very common in the cirrhotic liver and can develop into HCC, via low-grade dysplastic nodules (DNs) through high-grade DN to well-differentiated HCC. Rare histotypes (such as fibrolamellar HCC) may occur in non-cirrhotic livers; fibrolamellar HCC is typically lobulated, large (usually >12 cm) with a calcified central scar.

A fifth of all ICCs are intrahepatic (adenocarcinoma or papillary or mucinous carcinoma): risk factors include cirrhosis, primary sclerosing cholangitis, bile duct adenoma, bile duct cysts, biliary papillomatosis, Caroli's disease, and liver fluke.

The liver is the most common site of metastatic diffusion of gastrointestinal, pancreas, breast, neuroendocrine and lung malignancies; single or multiple metastatic lesions may occur and they can involve both hepatic lobes at the same time.

Other causes of liver lesions (e.g., hepatic lymphoma) are rare. Such lesions tend to be solitary when they are

primary lesions, whereas multiple lesions are more likely to be secondary.

Evidence exists that that up to 20 % of the world's population is diagnosed with benign hepatic lesions [5], cavernous haemangioma and focal nodular hyperplasia (FNH) being the most common types.

FNH has an incidence of 8 %; FNH lesions are made up of hepatocytes, bile duct elements, Kupffer cells and collagenous tissue. Some authors hypothesize that FNH could be a response to a vascular anomaly, often asymptomatic, isolated and found incidentally in young to middle-aged women. It is often initially linked to oral contraceptive use.

Hepatocellular adenoma (HCA) is a rare tumor that, too, can occur in women on oral contraceptives (85–98 %), and also in men on anabolic steroids. It is often reported as multifocal and steatotic, and is associated with a high risk of hemorrhage if larger than 4–5 cm and occurring during pregnancy; HCAs are considered premalignant and only 10 % of those smaller than 10 cm develop into HCC.

Focal fatty infiltration of the liver occurs in patients with fatty liver (10 %), both when fat accumulates focally and when focal sparing is present, and is usually observed in the anteromedial segment of the left lobe [6].

The therapeutic management of benign masses may include monitoring or surgical removal.

Conventional imaging in the diagnosis of hepatic liver lesions

Both benign and malignant liver lesions are detectable on ultrasonography (US), Doppler US or contrast-enhanced US. Computed tomography (CT), especially when performed as a 'dual-phase' technique (i.e., in the hepatic arterial-dominant phase and in the portal venous-dominant phase) or 'triple-phase' (tri-phasic) technique (with the addition of an early arterial phase), is widely used as a second-level diagnostic procedure.

Magnetic resonance imaging (MRI), especially contrast-enhanced MRI, is considered the most sensitive and specific technique for the evaluation of liver lesions. All the main hepatic lesions are detectable on MRI: MRI sensitivity ranges from 53 to 78 % in detecting HCC (and 68–90 % in detecting metastasis); some studies showed the lesion-based sensitivity of MRI to be 72 % (compared with 65 % for CT and 46 % for US) [7], but for small tumors (1–2 cm), the sensitivity of MRI is low (44–47 %) and equivalent to that of CT (40–44 %) [8].

In 2012 the European Association for the Study of the Liver (EASL) published a diagnostic algorithm for the evaluation of nodules found incidentally on US [9]: if a nodule is smaller than 1 cm, a further US after an interval of 4 months is recommended. Nodules larger than 1 cm

have to be evaluated by 4-phase CT or by dynamic contrast-enhanced MRI: if HCC features are evident using one or both of these techniques, biopsy is not needed, otherwise it becomes mandatory.

Positron emission tomography (PET) and the liver

^{18}F -fluorodeoxyglucose (FDG)

FDG is one of the most widely used radiopharmaceuticals in PET centers, mainly because of its uptake mechanism which makes it ideal for clinical use.

After intracellular transportation and phosphorylation, ^{18}F -FDG-6- PO_4 is locked within the cell, and can therefore no longer be metabolized; cellular uptake of FDG depends on both the expression of membrane glucose transporters within the cell membrane and on the dephosphorylating enzyme activity, which is down-regulated in tumor cells.

FDG is often produced according to Hamacher's method [10], which is based on the nuclear reaction between ^{18}O (p, n) and ^{18}F .

Physiological uptake of FDG occurs in several organs: brain, heart, intestine, liver, kidney, bladder, muscles, larynx and stomach, and its half-life (110 min) and decay characteristics (beta emission) make it ideal for clinical use.

FDG in HCC

Over time, numerous publications have evaluated and demonstrated the usefulness of FDG PET/CT in the diagnostic management of HCC, showing its capacity to help identify the tumor and, above all, to provide clinical data on its aggressiveness (grading) and spread (staging). FDG PET/CT has also proved effective in the evaluation of the response to therapy, providing reliable information for comparison over time.

In vivo tumor grading and correlation with sensitivity of FDG

The literature clearly states that the sensitivity of PET/CT is influenced by the biological behavior and grade of HCC, since glucose transporter activity in these tumors is not as strong as in other types of malignant tumor, while dephosphorylating enzyme activity is proportionally related to the differentiation of the tumor (higher grade of differentiation = higher enzyme activity). Accordingly, FDG uptake is thought to be weak in well-differentiated tumors, which show low expression of cell membrane glucose transporters and high dephosphorylating enzyme activity, but strong in undifferentiated tumors, which are characterized by high expression of glucose transporters

and low dephosphorylating enzyme activity. This is a useful distinction for tumor prognosis.

A study of the possible correlations between glucose metabolism in HCC (evaluated through FDG PET scanning), in vivo measurement of enzyme activity and tumor grading was published in 1995 [11]. In this study, 17 patients underwent a dynamic PET scan during their pre-surgical staging. Each patient was sequentially scanned within 48–60 min of the injection, and the results were compared with the actual activity of hexokinase and glucose-6-phosphatase and with the histological surgical report.

The results were interesting: semi-quantitative uptake values (SUVs) of high-grade HCCs were found to be significantly higher than those of low-grade HCCs ($p < 0.005$), and these parameters also correlated significantly with hexokinase activity.

Trojan et al. [12] found that the sensitivity of FDG PET/CT in identifying liver tumors was linked to the grade of the lesions. His study included 14 patients with hepatic cirrhosis and suspicion of HCC, who were studied with PET, US, contrast-enhanced CT, and helical CT. Data on histological grading, p53 protein expression and serum AFP levels were also gathered for each patient. Six patients were diagnosed with well-differentiated HCC while eight were diagnosed with moderately differentiated or anaplastic HCC. Only seven patients were positive on PET (overall sensitivity of 50 %), while 14/14 were positive on US and 11/14 were positive on CT. Furthermore, 7/8 patients with moderately or poorly differentiated HCC, but none of the patients with well-differentiated HCC, showed increased FDG uptake. Two patients with strong p53 expression demonstrated increased tumor ^{18}F -FDG uptake and extrahepatic metastases. The possible connection between SUV (or SUV_{max}) and HCC tumor grade was studied by Hatano et al. [13] in 2006, in a cohort of 31 patients referred for partial hepatic resection. The results of this study were clear: of the 7/31 patients (23 %) with a tumor to non-tumor SUV ratio above 2, 57 % (4/7) had anaplastic or poorly differentiated HCC, as opposed to only 32 % of those with $\text{SUV} < 2$. A higher overall survival ratio was also found in the patients with $\text{SUV} < 2$.

A more recent study, published in 2010 [14], highlighted the correlation between tumor size, AFP levels and histological type of the primary tumor. This study retrospectively analyzed data of all HCC patients who underwent FDG PET/CT in Shreveport, Louisiana, between 2000 and 2004, enrolling 20 patients (14 positive on PET/CT, overall sensitivity: 70 %) to evaluate the sensitivity of PET/CT in diagnosing (group 1) and staging (group 2) HCC lesions. While the sensitivity was rather low in group 1 (28.6 %), the authors observed accurate staging in group 2, with a

sensitivity of 84.6 %. Dividing the same cohort on the basis of other parameters yielded further interesting data.

With regard to tumor size, the sensitivity of PET/CT rises with bigger lesions, ranging from 25 % in rather small nodules (diameters up to 5 cm) to 100 % in tumor lesions bigger than 5 cm diameter.

Analyzing AFP levels, values lower than 100 ng/ml result in a sensitivity of 55.6 %; this rises to 85.7 % in patients with higher AFP levels. Finally, considering tumor histology, PET/CT was found to be positive in all moderately or well-differentiated tumors.

Staging and re-staging HCC with FDG

In the staging phase of the diagnostic algorithm, especially in the field of oncology, a whole-body investigation can offer important data able to contribute to optimal therapeutic choices. FDG PET (or PET/CT) is therefore a potentially excellent diagnostic technique in this phase.

Sugiyama et al. [15] investigated the usefulness of FDG PET in detecting HCC distant metastases. They evaluated 19 patients with suspected extrahepatic metastasis from HCC (14 patients with lesions documented on conventional imaging, 5 with raised markers). The detection rate of FDG PET was 83 % (24 out of 29 metastases in the ganglia, bone and abdominal district) for lesions greater than 1 cm in diameter, and 13 % for smaller lesions. In five patients the lesions were surgically removed on the basis of the PET scan results, and there were no false positives (specificity = 100 %). FDG PET (or PET/CT) can also be useful when patients need re-evaluation.

Wudel et al. [16] published an interesting retrospective study, using the clinical data of 91 patients with HCC who had undergone FDG PET scans between 1993 and 2001. The patients were divided into two groups. In “group 1” 67 patients with proven and untreated hepatic lesions were included: in 43 cases FDG abnormal accumulation was present and in 20 cases FDG PET led to changes in therapy assessment, guiding biopsy or identifying distant metastases. 24 patients were included in “group 2” and they were investigated for HCC recurrence, but had no prior FDG PET. In six patients distant metastases were detected.

Positivity on PET/CT was then related to tumor grade and levels of intratumoral fibrosis, but not to tumor necrosis or liver cirrhosis. The global sensitivity of FDG PET/CT for HCC was 64 %, and it had a significant impact in 28 % of the patients.

Later studies (e.g., by Sun et al. [17]) were performed to evaluate the usefulness of FDG in post-therapy assessment. These authors examined a database of 25 patients with HCC (21 males; 4 females) with suspected relapse after previous surgical procedures, mainly partial resection (9

Fig. 1 FDG PET/CT axial (a) and coronal (b) fused scan performed in a 64-year-old male patient with CT-known hepatic liver nodule in HCV-related cirrhosis; in order to evaluate the aggressiveness of the lesion, the patient was evaluated by PET/CT before being placed on transplantation list. PET/CT scan, as shown in this figure, demonstrated a large focal uptake at the VI hepatic segment; this finding not only overlapped with the CT one, but also suggested that the nodule was probably undifferentiated (color figure online)

patients), trans-arterial chemo-embolization (TACE, 6 patients), TACE + partial resection (8 patients), and TACE + radiofrequency ablation (RFA) + percutaneous ethanol injection (PEI). 19/25 patients had positive FDG PET scans (17 true positives and two false positives due to post-surgery inflammation). Validation of the results came from biopsy or clinical follow-up and demonstrated a sensitivity of 89.5 %, a specificity of 83.3 % and an accuracy of 88 % in detecting HCC recurrence. Moreover,

FDG PET explained increases in AFP 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.

Figure 1 shows the FDG PET/CT scan of a patient with an HCC nodule.

FDG in intrahepatic cholangiocarcinoma

Studies regarding the usefulness of FDG PET in evaluating ICC are here analyzed in chronological order.

First, a retrospective study published in 2003 looked at the possible use of FDG PET in primary ICC lesions [18]. The study included 21 patients (10 females, 11 males), with either hilar (10 patients) or peripheral (11 patients) lesion localizations. Diagnosis was based on CT, MRI, chest X-ray and bone scintigraphy, followed by PET/CT scanning. The results were extremely satisfying for peripheral tumors (specificity = 100 %), for which a correspondence was found between the extension of the lesion, identified through contrast-enhanced CT or contrast-enhanced MRI, and the area of increased uptake on FDG PET. With regard to the patients with hilar tumors, 9/10 were true positives, 1/10 was a false negative. One lesion, not reported by MRI, was true positive on FDG PET. With regard to staging, five new lymph-node lesions, missed by both CT and MRI, were identified through FDG PET/CT. Moreover, unsuspected distant metastatic lesions were detected in 4/21 patients, all of whom presented with peripheral ICC. The authors concluded that PET/CT is equally useful for detection of central and peripheral lesions, and also a useful means of identifying distant metastases in peripheral disease and completing the diagnostic algorithm in patients with hilar tumors not identified by conventional imaging.

A larger retrospective study on the same topic, published in 2004 [19], included 50 patients with suspected lesions of the biliary tract (36 patients with suspected ICC and 14 patients with suspected gallbladder carcinoma). The ICC patients were divided into two groups on the basis of tumor size (maximum diameter of 1 cm vs. infiltrating mass). In 31/36 patients, the diagnosis of ICC was ultimately confirmed, and the overall sensitivity was 85 % for smaller, nodular lesions and only 18 % for infiltrating masses.

In the evaluation of distant metastases, the overall sensitivity was 65 %, with three false negatives for carcinomatosis and one false positive in a patient with primary sclerosing cholangitis. Moreover, 7 out of 12 patients with biliary stent showed uptake. The result of the PET/CT scan impacted on the surgical workup in 30 % of patients.

PET/CT was compared with CT in a 2006 prospective study of 61 patients with biliary tract tumor, regional lymph nodal involvement and distant metastases, recruited between 2001 and 2005. All the conditions were validated through biopsy or by cytological means [20]. The sensitivity PET/CT was found to be 100 % for gallbladder tumors, while the sensitivity and specificity values for ICC were 93 and 80 %, respectively (better than those obtained with contrast-enhanced CT). The accuracy of PET/CT was similar in both intrahepatic and extrahepatic tumors, but a much higher sensitivity was obtained in the detection of distant metastases (100 vs. 25 % on contrast-enhanced CT) than of regional lymph nodes (12 vs. 24 % with contrast-enhanced CT). FDG PET impacted on patient management in just 17 % of cases.

Another retrospective study, published in 2007 by Jadvar et al. [21], investigated the possible use of FDG PET/CT in suspected ICC relapse. Their study included 24 patients (13 M; 11 F), 8 of whom were studied solely through PET while 16 also underwent a low-dose CT which was later fused with PET images. Twelve patients then received surgery, 6 received surgery and chemotherapy, and 6 surgery and combined chemoradiation therapy. The follow-up ranged from 2 to 8 months. Fusion of PET images and CT allowed correct localization of several lesions, showing an overall sensitivity and specificity of 94 and 100 %, respectively, which were therefore higher than the values recorded with CT alone (82 and 43 %, respectively).

FDG in liver metastases from other malignancies

Metastatic diseases account for the majority of malignant lesions in the liver and up to 25 % of patients with known solid malignant tumors have hepatic metastases at the time of diagnosis [22]. Liver metastases can originate from numerous primary cancers (colorectal, mammary, lung, pancreatic, gastric, esophageal, melanoma and sarcoma among others). The use of FDG PET/CT in liver metastases has proved effective for staging purposes, as well as for planning a more correct therapeutic approach to the disease (sometimes even guiding surgery). The response to therapy with ^{90}Y microspheres can also be evaluated with FDG.

Many factors may possibly influence the uptake of FDG in metastatic lesions, as highlighted by Delbeke et al. [23]. In their study, 110 patients with hepatic lesions measuring 1 cm or more on CT images were submitted to a PET scan. This process allowed the authors to obtain a better anatomical localization and to then compare these data with biopsy and/or surgery results.

In evaluating metastases from adenocarcinoma or sarcoma, FDG PET showed a sensitivity of 100 %;

conversely, the sensitivity of the technique was 57 % (16/23) in patients with HCC. All the benign lesions ($n = 23$), hepatic adenoma (HA) and focal nodular hyperplasia (FNH) were FDG negative.

An important role for PET and PET/CT in colorectal cancer has been hypothesized in the last decade, after it became clear that CT staging could underestimate the extent of the disease. This affirmation was the basis for two studies published in 2004, the first one by Selzner et al. and the second one by Fernandez et al.

The prospective study conducted by Selzner [24] hypothesized that pre-surgical staging of patients based solely on CT could underestimate liver metastases in colorectal cancer, and therefore a further evaluation with hybrid PET/CT would be useful. Seventy-five patients underwent both a regular CT and a PET/CT before surgery. Sensitivity was slightly higher with CT (95 %) versus PET/CT (91 %). However, PET/CT showed a specificity of 100 %, twice that of CT (50 %), and was also superior to CT in identifying local (colorectal) relapse (93 vs. 53 %) and in localizing distant metastases (89 vs. 64 %).

Fernandez et al. [25] conducted a retrospective study in 2004 to evaluate the impact of FDG PET on 101 patients (56 males; 44 females) who had undergone hepatic resection (single or multiple) for metastatic colorectal cancer between 1995 and 2002. All had a pre-surgery PET and a 5-year follow-up. The hypothesis was that a PET/CT study in postsurgical follow-up could help to improve survival rates compared with a follow-up based on conventional imaging. Their results were very promising, showing that PET/CT could increase survival rates from 30 % (the rate recorded with follow-up conducted using CI alone) to 58 %. The most relevant prognostic factor was tumor grade (higher grades being related to lower survival rates).

There is also evidence that FDG PET/CT impacts on the therapeutic management of patients, although the findings are statistically less relevant. A 2010 Italian multicenter study on this topic [26] involved 43 patients (17 males; 26 females; mean age 53 years) with known liver metastases from colorectal (18 patients), breast (6 patients), ovarian cancer (4 patients) or non-small cell lung cancer (15 patients). PET/CT data were then compared with surgical and cytological evidence or long-term follow-up. The results of the PET/CT study led to a change in the therapeutic approach in 28 % of the patients.

Tumor localization for better surgery assessment was investigated in a single study that evaluated the combined role of PET/CT and US in preoperative tumor localization [27]; the study evaluated 31 patients, 15 of whom had already received preoperative chemotherapy. The sensitivity of PET/CT was found to be 63 % and, if it is associated with intraoperative US, this can rise to 93 %, while the positive-predictive values were 81 and 89 %,

respectively. In the patients who had undergone preoperative chemotherapy, the sensitivity of PET/CT alone was 77 %; combined with preoperative US, it rises to 100 %. It must be underlined that it is not clear what kind of chemotherapy planning had been performed.

Finally, PET/CT has been used to evaluate response to ^{90}Y microsphere treatment of colorectal liver metastasis, as reported by Zerizer et al. [28]. These authors evaluated 121 liver lesions in 25 patients with liver-dominant metastatic colorectal cancer and submitted them to both FDG PET and CT after ^{90}Y microsphere radio-embolization. Changes in SUV_{max} , tumor density (measured in Hounsfield units) and size were considered and related to one another and to tumor markers and progression-free survival (PFS) at 2 years using Kaplan–Meier plots.

Fifteen patients were found to be partial responders according to FDG PET results and only two according to CT data, while ten patients were found to have stable disease according to FDG versus 23 according to CT results. The responses on FDG PET/CT were highly correlated with tumor markers and significantly predicted PFS, while the CT response did not.

Previous administration of chemotherapy could be the most important limitation in the use of FDG PET/CT for studying metastatic liver lesions, as it could reduce metabolic activity, and thus uptake, even in the persistence of lesions.

A publication from 2007 [29] confirms this hypothesis, demonstrating that both PET and CT showed higher sensitivity in patients treated surgically (27 patients, 33 lesions, sensitivity of 93.3 and 87.5 %, respectively) compared with patients who received neo-adjuvant chemotherapy with bevacizumab (48 patients, 122 lesions, sensitivity of 49 and 65.3 %, respectively). On the basis of these results, the authors concluded that CT is more useful than PET in patients who receive neo-adjuvant therapy.

FDG in hepatic lymphoma

Secondary hepatic involvement by lymphoma is common, especially in patients with non-Hodgkin's lymphoma (NHL). Evidence exists that liver is the second most frequent site of extranodal distant diffusion from lymphoma [30].

Primary hepatic lymphoma (PHL) is extremely rare, accounting for approximately 0.016 % of all NHL; T cell lymphoma accounts for approximately only 5–10 % of these rare cases, 90 % being of the B-cell type [31]. According to their diffusion, PHLs can be classified into two distinct patterns, nodular (more frequent) and diffuse liver infiltration (less frequent) [32].

To our knowledge, no extensive work has to date been published regarding the usefulness of FDG PET in PHL,

only a few interesting case reports. In one of these [33], the authors suggested that PHL can be suspected on the basis of a patient's history, in particular when HCV-related chronic liver inflammation is known to be present and some biochemical parameters are out of range (increased alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and lactate dehydrogenase levels).

FDG PET is certainly useful when conventional imaging is inconclusive. Kaneko et al. [34] reported the case of a man with HCV infection who had undergone CT and MRI. CT showed diffusely infiltrated hypovascular lesions throughout the liver, with no intrahepatic portal venous thrombosis, while MRI showed a very low apparent diffusion coefficient value. PET showed very high FDG uptake and this finding, together with the ones provided by conventional imaging, suggested liver involvement by NHL and this hypothesis was confirmed by biopsy. Also Kang et al. [35] reported a case of NHL in which liver involvement was the predominant clinical manifestation and led to abdominal pain, hepatosplenomegaly, thrombocytopenia, elevated alanine aminotransferase, aspartate aminotransferase, bilirubin, lactate dehydrogenase and alkaline phosphatase. The abdominal CT scan was inconclusive, showing only diffuse hepatosplenomegaly. PET/CT showed increased FDG uptake of the liver, spleen and long bones and US-guided biopsy of liver confirmed a diagnosis of NHL (diffuse large B-cell type).

FDG in benign hepatic liver lesions (FNH and hepatic adenoma, HA)

Benign lesions usually show poor uptake, as Delbeke et al. [23] pointed out in 1998 in their study of 110 patients with liver nodules larger than 1 cm, in which the 23 patients with benign lesions (HA, FNH, abscess) showed SUV values lower than 3.5 with a lesion-to-background ratio lower than 2.

Some papers reported abnormal FDG uptake in patients with histologically proven adenoma: Fosse et al. [36] recently described the case of a young patient with breast cancer whose liver showed multiple hepatic hyperechoic nodular lesions on US examination; MRI was inconclusive while PET/CT showed abnormal FDG uptake, even though the nodules were adenomas.

FDG uptake in FNH has been studied in several publications.

Kurtaran et al. [37], studied eight asymptomatic patients incidentally diagnosed with FNH lesions between 2 and 8.5 cm in diameter; the results were validated through biopsy. Those patients were compared with a control group comprising eight patients: two with melanoma and six with colorectal cancer. The results demonstrated that FDG

uptake in FNH was normal or even reduced compared to the background (SUVs between 1.5 and 2.5), while the opposite was observed in the control group (SUVs between 6.20 and 16). The authors also considered a BMI-corrected SUV_{max} (SUV_{LBM}), which gave findings similar to the SUV data, ranging between 0.9 and 2.22 in patients with FNH and 5.9–16.3 in the control group.

A larger prospective study [38] was published in 2009, regarding 31 patients with 43 lesions. The main objective was to investigate the usefulness of FDG in detecting FNH and HA and whether FDG uptake in these benign conditions was significantly different from that observed in malignant lesions. The patients also underwent US, contrast-enhanced US, CT and/or MRI, FDG PET, ACE PET and, if imaging was still inconclusive, biopsy. The lesions detected on FDG scans (36 FNH, 5 HA, 1 HCC and 1 metastatic) included seven non-FNH lesions; in six of these seven findings, FDG was positive (sensitivity 85.7 %) while 33/36 FNHs were not FDG avid (specificity 91.7 %). The usefulness of ACE will be discussed further below.

Choline-based radiotracers

Choline is a precursor of cell membrane phospholipids; it is metabolized into phosphorylcholine through the choline kinase metabolic pathway, then (through choline dehydrogenase and betaine aldehyde dehydrogenase) into betaine and finally, through the enzyme choline acetyltransferase, into acetylcholine.

For nuclear medicine purposes, it can be radiolabeled with ^{11}C in the form of ^{11}C -choline (CHOL), as Hara et al. [39] described in 1998, through the $^{14}N(p, \alpha)$ nuclear reaction. Normal uptake has been described in all glands (pituitary, salivary glands, pancreas) and in liver, kidney, bowel and stomach; CHOL has a half-life of about 20 min and decays by β -emission.

It has been widely demonstrated that CHOL can be used as an imaging tracer in cancer, especially in prostate and liver cancer. The only limitation is the short half-life of ^{11}C , which limits the use of CHOL to PET centers which have access to a cyclotron on-site. Alternative tracers might be used if a cyclotron is unavailable: ^{18}F -fluoroethylcholine (fluoroethyl-dimethyl-2-hydroxy-ethylammonium; FEC) and ^{18}F -fluorocholine (F-Ch) have been studied, particularly in prostate cancer [40, 41].

Some different choline-based radiotracers have been studied in animal models in order to assess the differences in their possible clinical use. In particular, Kolthammer et al. [42], in 2011, compared the use of CHOL and FEC in studying a woodchuck model of HCC by dynamically acquiring sequential images for 50 min after injection. The results showed a substantial equivalence of the two

radiopharmaceuticals (the tumor-to-background ratio was 1.3 for FEC and 1.5 for CHOL).

Choline radiotracers (and comparison with FDG) in HCC and other liver malignancies

Talbot et al. [43] published a “proof-of-concept” prospective study comparing F-Ch with FDG in the evaluation of HCC. They gathered 12 patients with either a new diagnosis or recurrence of HCC, evaluated through the American Association for the Study of Liver Disease (AASLD) criteria and biopsy. All patients underwent F-Ch PET/CT and nine also had an FDG PET/CT scan. Patient-based analysis of the F-Ch scans showed a detection rate of 100 % in both the new diagnosis and the relapse groups, with a tendency towards high SUV_{max} values (15.6 ± 7.9) in well-differentiated tumors. All of the nine patients who underwent both procedures were positive on both.

A later study by Yamamoto et al. [44] evaluated 16 lesions in 12 patients using CHOL and FDG PET scans. According to the authors, CHOL has a higher detection rate than FDG in detecting HCC (63 vs. 50 %, respectively), but they also stated that the two tracers should be used in a complementary way in detecting HCC, because in moderately differentiated lesions CHOL had a better detection rate than FDG (75 vs. 42 %), while the opposite was true for poorly differentiated forms (CHOL sensitivity = 25 %; FDG sensitivity = 75 %).

Talbot et al. [45] recently proposed more evidence on the topic of FDG and F-Ch in the evaluation of primary liver cancer. Their 2010 prospective study evaluated the use of F-Ch and compared it with FDG in detecting HCC and other malignancies in patients with known cirrhosis or chronic liver disease. Eighty-one patients were included in the study, 59 of whom were validated through biopsy and more than 6 months’ follow-up. In the 34 patients found to have HCC, F-Ch showed a sensitivity of 88 %, a value higher than that of FDG, which only reached 68 %. In particular, of the 11 patients with well-differentiated tumors, 6 were positive for F-Ch while none were positive for FDG uptake. With regard to patients with positive lesions from other primary tumors or with benign findings, the sensitivity of FDG was higher than that of F-Ch (78 vs. 89 % and 62 vs. 91 %, respectively).

It seems reasonable to affirm that the two examinations should be considered complementary to each another.

Wu et al. [46] seem to confirm this statement in a 2011 prospective study which enrolled 76 patients with HCC who underwent a preliminary FDG PET/CT scan and then, if this was negative, a CHOL PET/CT study.

Their results showed that the uptake value in FDG PET/CT-positive patients (48/76, 61.1 %) was statistically

Fig. 2 CHOL PET/CT coronal (a) and axial (b) scan performed in a 62-year-old male patient. He was suffering from exotoxic cirrhosis, with neurological signs (drowsiness and disorientation) due probably to the accumulation of ammonium. Since FDG PET/CT was negative but CT showed a suspect finding, the patient underwent a CHOL PET scan; as we can notice, it showed abnormal uptake in the II liver segment and the presence of a huge abdominal effusion. The patient died 2 months later because of a leg infection, which caused fever, severe wasting and cachexia (color figure online)

related to the grade of differentiation, while this was not the case for CHOL uptake, where sensitivity was 85.7 % for poorly differentiated tumors and 72 % for well-differentiated lesions. The authors estimated a sensitivity of 89.5 % for dual-tracer investigation as opposed to 63.1 % for an FDG investigation alone.

Figure 2 shows the CHOL scan of a patient with an HCC nodule.

Choline radiotracers in benign lesions

At present and to our knowledge, no review has been published regarding usefulness of choline radiotracers in the extensive evaluation of benign liver lesions. However, a recent study by van den Esschert et al. [47] showed that CHOL can differentiate hepatocellular adenoma from FNH. This prospective study enrolled 21 patients with liver lesions bigger than 2 cm in diameter and with benign characteristics (suspicious for either hepatocellular adenoma or FNH). Ten

were than diagnosed with FNH and 11 with hepatocellular adenoma. All of them underwent F-Ch PET/CT and were validated through surgery or biopsy. The mean lesion-to-background (SUV ratio) value in the two groups was found to be 1.68 ± 0.29 for FNH and 0.88 ± 0.18 for HA. On the basis of these findings, the authors established a cut-off value for SUV ratio of between 1.12 and 1.22 which correctly distinguished between the two conditions with 100 % sensitivity and specificity.

^{11}C -acetate (ACE)

Acetate, or acetic acid, is quickly converted into acetyl-CoA by acetyl-CoA synthetase, and then involved in two different and opposite metabolic pathways: an anabolic one, which leads to the synthesis of cholesterol and fatty acids, and a catabolic one, whereby, in mitochondria, it is oxidized via the tricarboxylic acid cycle. It has been widely demonstrated that the enzyme fatty acid synthetase is overexpressed by tumor cells and that in these same cells most of the acetate is used to synthesize fatty acids, which are then incorporated into intracellular phosphatidylcholine membrane microdomains, contributing to tumor growth and metastasis [48].

For nuclear medicine purposes, acetate is radiolabeled with ^{11}C , giving rise to ^{11}C -acetate (ACE) by proton bombardment of natural nitrogen through the $^{14}\text{N}(\text{p}, \alpha)^{11}\text{C}$ nuclear reaction.

ACE synthesis is more often based on the method of Roeda et al. [49], which leads to the creation of a compound with a short half-life (20.38 min). Patient management is easy as no fasting or particular preparation is required; the physiological uptake organs are the pancreas, bowel, kidneys and spleen.

ACE (and comparison with FDG) in HCC

Several comparative studies between ACE and FDG have been conducted over the past decade, trying to assess the possible added value of using different metabolic tracers to better target surgery and especially therapy. These publications are here discussed in chronological order.

Ho et al. [50] published a prospective study which ultimately included 57 patients (39 nine with HCC, 3 with ICC, 10 with hepatic metastases from other malignancies and five with benign pathologies, which included FNH, HA and hemangioma); data were validated through biopsy in all but five of the patients (two with hemangioma and three whose metastases were considered clinically evident). The aim of the study was to identify differences between FDG and ACE metabolic activity in HCC and in other causes of

hepatic lesions. The patients were divided according to the number of lesions. In group 1 (32 patients, 55 lesions), which included patients with fewer than three lesions, the ACE scan showed a sensitivity of 87.3 % and the FDG scan a sensitivity of 47.5 %, with 34 % concordance between tracers. In the second group, which consisted of seven patients who had at least three multifocal lesions, tracer behavior differed according to histological type. Well-differentiated lesions showed higher ACE uptake while the opposite was true for less-differentiated ones. None of the 16 non-HCC malignant lesions (ICC and other primaries) showed any uptake of AC, while, of the benign lesions, only FNH showed mild uptake (SUV_{max} of 3.59 with a lesion-to-background ratio of 1.25).

An interesting study was published in 2012 by a Swedish group [51]; these authors underlined that most of the papers on HCC and molecular imaging were written by Asian groups and concerned Asian patients, but HCC epidemiology is different in Europe, where cirrhosis is strictly connected with alcohol abuse, compared with Asia, where it is mainly linked to HCV or HBV infection (80 %). Their retrospective study included 44 patients with primary HCC: 13/44 HCCs were FDG avid, 34 were ACE avid and 8 tumors were positive for both radiopharmaceuticals. The authors concluded that the two tracers must be considered complementary, since dual-tracer PET significantly increased the detectability of HCC. In four of the eight patients positive for both tracers, different activity distribution within the same tumor lesion was detected: areas that were “hot” using one tracer were relatively “colder” using the other tracer and vice versa. Furthermore, uptake of ACE in the normal liver parenchyma is higher than uptake of FDG, therefore lowering the lesion-to-background ratio.

Very recently Cheung et al. [52] published a retrospective study on the use of dual-tracer (ACE and FDG) imaging in 43 patients with HCC and qualifying for liver transplantation (LT) according to the Milan criteria, which includes patients with single liver lesions smaller than 5 cm or a maximum of three lesions smaller than 3 cm, no macroscopic vascular invasion and no extrahepatic metastasis. These patients underwent both preoperative dual-tracer PET/CT and contrast-enhanced CT within a 1-month period and the imaging results were compared with post-surgery data (tumor size, vascular involvement and distant lesions). 22/43 patients ended up having an LT while the other 21 underwent only partial hepatectomy (PH). The groups were then analyzed for accuracy of the patient-based and lesion-based selection criteria.

FDG gave similar results in the LT and PH groups considering both sets of selection criteria (40.9 vs. 38.1 % and 32.4 vs. 33.3 %).

Much higher sensitivity values resulted from the analysis of the ACE scans; in both groups (LT and PH),

Fig. 3 ACE PET/CT scan of a patient with already known HCC. The patient had already undergone to both TACE and RFA treatment; as regards the liver relapse in this patient, the last CT scan was negative, but it showed a distant adrenal lesion. It can be observed that in the axial upper abdominal scan (**a**) a small uptake area is present in the VII liver segment and also the right adrenal gland showed abnormal uptake (lower abdominal scan, **b**) (color figure online)

patient-based and lesion-based criteria performed similarly (90.9 vs. 91.2 % and 95.2 vs. 95.8 %, respectively). Dual-tracer investigation was useful only for LT patients, whereas it showed no advantages in PH patients. It is important to acknowledge that the sensitivity of CT was significantly lower than that of the dual-tracer study (77.3 % with patient-based criteria, 67.6 with lesion-based criteria in the LT group; 42.9 % with patient-based criteria and 37.5 % with lesion-based criteria in the PH group).

Figure 3 shows an ACE PET/CT scan.

ACE in benign lesions

The usefulness of ACE PET has also been investigated in benign lesions, especially FNH.

As already discussed, Magini et al. [38] used the technique in 31 patients with 43 lesions, 36 of which were

attributed to FNH; this corresponded to 94.4 % specificity, since 34/36 FNH lesions were true negatives. Dual-isotope PET offered no additional diagnostic advantage compared with FDG alone in detecting FNH.

In the same year, Huo et al. [53] suggested that dual-time ACE PET imaging might be useful for evaluating FNH. Their study only included two patients, one diagnosed with FNH and one with HCC. Both patients underwent two ACE scans (8–10 min and 23–25 min after radiotracer administration) and both had positive ACE PET scans, although the two conditions displayed opposite trends, with the HCC patient showing higher ACE uptake on the late scan and the FNH patient lower uptake on the second scan.

Pioneering research

A new tracer, a non-barbiturate imidazole (^{11}C -metomidate or MTO), has been recently proposed for evaluation of liver lesions, in particular HCC and FNH. Roivainen et al. [54] conducted a study in which they prospectively enrolled 33 patients (120 lesions) and submitted them to MRI, ACE PET, MTO PET and biopsy. According to the histological reports, 14 patients had HCC (group 1), 9 had FNH (group 2) and 10 had other types of hepatic tumor (group 3). The overall tumor detection rate was 39 % for MTO and 33 % for ACE; in a patient-based evaluation, MTO sensitivity was 46 % (vs. 50 % for ACE) in group 1 and 78 % (vs. 44 % for ACE) in group 2. The patient-based MTO specificity was 63 % in group 1 and 75 % in group 2 (vs. 79 and 71 % for ACE, respectively).

Several other radiotracers have recently been proposed for the non-invasive analysis of hepatic regional functionality. Sørensen et al. [55] tested the possible use of 2-[(^{18}F) fluoro-2-deoxy-D-galactose PET/CT (FDGal) in quantifying regional hepatic function non-invasively: nine patients with cirrhosis were submitted to dynamic FDGal PET/CT with blood sampling from a radial artery and a liver vein, while hepatic blood flow was measured by indocyanine green infusion. Calculation, from both blood measurements and PET data, of hepatic systemic clearance and hepatic intrinsic clearance of FDGal showed that a 20-min dynamic FDGal PET/CT with arterial sampling provides an accurate measure of regional hepatic metabolic function in patients with cirrhosis, thus paving the way for the development of non-invasive investigation of liver health status.

Conclusions

On the basis of this analysis of data published between 1995 and 2013, it can be stated that the efficacy of FDG PET in the diagnostic management of HCC, i.e., in

identifying the tumor, correctly assessing its biological behavior (grading), establishing its diffusion to the body (staging) and evaluating how therapy affects its natural history, has been extensively demonstrated. The sensitivity of this radiotracer has been successfully correlated with tumor size, AFP levels and histological grade and it is possible to affirm that larger lesions, with elevated levels of AFP and a poorly differentiated cellular population will show higher FDG uptake, and also have a poorer prognosis.

FDG PET has also been shown to be useful in other malignancies, such as ICC, in which evidence shows that it could play a role in staging, metastatic disease assessment and diagnostic management of patients with para-hilar or central lesions not detected through conventional imaging.

In secondary lesions from other primaries, imaging with FDG has been shown to be capable of impacting on the therapeutic course of the patient, providing a more accurate staging, guiding surgery (i.e., the choice of the correct approach) and allowing evaluation of response to therapy (e.g., with ^{90}Y microspheres). Previous chemotherapy is undoubtedly one limitation of the usefulness of FDG PET, as it can cause a reduction in the metabolic activity and therefore in the uptake, even if the lesion is still present.

In benign lesions, it has been shown that no significant FDG uptake occurs. This is particularly true of FNH and thus makes it difficult to investigate this condition through PET imaging.

Comparisons of choline-based radiotracers with FDG for the diagnosis of HCC revealed that they show efficacy for well-differentiated tumors. This also applies to ACE, whereas in the diagnostic assessment of benign lesions this tracer is not considered effective.

The possible added value of a dual-tracer evaluation could have an impact on the outcome of selected patients. A thorough analysis of the nature of the lesions, their grade and biological characteristics is always mandatory.

As of today, other radiopharmaceuticals are being tested and synthesized with a view to improving the evaluation of liver lesions, but none of them yet has sufficient literature data on the basis of which to express a judgment about their potential clinical impact in the future.

Despite the existing proof of usefulness, EASL guidelines published in 2012 do not contemplate standardized use of PET/CT in the evaluation of liver nodules, probably due to the different biological behaviors of tumors which can affect the sensitivity of the scan, making it difficult to find the best tracer for the individual patient. Also, the high costs associated with the technique and the relative lack of PET centers seem to preclude larger and more precise evaluations.

Conflict of interest All the authors (Ilaria Grassi, Joshua James Morigi, Cristina Nanni and Stefano Fanti) declared to have no conflict of interest.

Ethical standard This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Little JM, Kenny J, Hollands MJ (1990) Hepatic incidentaloma: a modern problem. *World J Surg* 14:448–451
2. Bosch FX, Ribes J, Cleries R, Diaz M (2005) Epidemiology of hepatocellular carcinoma. *Clin Liver Dis* 9:191–211
3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. *CA Cancer J Clin* 61:69–90
4. El-Serag HB (2011) Hepatocellular carcinoma. *N Engl J Med* 365:1118–1127
5. Blechacz B, Gores GJ (2010) Positron emission tomography scan for a hepatic mass. *Hepatology* 52:2186–2191
6. Assy N, Nasser G, Djibre A, Beniasvili Z, Elias S, Zidan J (2009) Characteristics of common solid liver lesions and recommendations for diagnostic workup. *World J Gastroenterol* 15:3217–3227
7. Yu NC, Chaudhari V, Raman SS, Lassman C, Tong MJ, Busuttill RW, Lu DS (2011) CT and MRI improve detection of hepatocellular carcinoma, compared with ultrasound alone, in patients with cirrhosis. *Clin Gastroenterol Hepatol* 9:161–167
8. Sangiovanni A, Manini MA, Iavarone M, Romeo R, Forzenigo LV, Fraquelli M, Massironi S, Della Corte C, Ronchi G, Rumi MG, Biondetti P, Colombo M (2010) The diagnostic and economic impact of contrast imaging techniques in the diagnosis of small hepatocellular carcinoma in cirrhosis. *Gut* 59:638–644
9. European Association for Study of Liver; European Organisation for Research and Treatment of Cancer (2012) EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *Eur J Cancer* 48:599–641
10. Hamacher K, Coenen HH, Stocklin G (1986) Efficient stereospecific synthesis of no-carrier-added 2- ^{18}F -fluoro-2-deoxy D-glucose using aminopolyether supported nucleophilic substitution. *J Nucl Med* 27:235–238
11. Torizuka T, Tamaki N, Inokuma T, Magata Y, Sasayama S, Yonekura Y, Tanaka A, Yamaoka Y, Yamamoto K, Konishi J (1995) In vivo assessment of glucose metabolism in hepatocellular carcinoma with FDG-PET. *J Nucl Med* 36:1811–1817
12. Trojan J, Schroeder O, Raedle J, Baum RP, Herrmann G, Jacobi V, Zeuzem S (1999) Fluorine-18 FDG positron emission tomography for imaging of hepatocellular carcinoma. *Am J Gastroenterol* 94:3314–3319
13. Hatano E, Ikai I, Higashi T, Teramukai S, Torizuka T, Saga T, Fujii H, Shimahara Y (2006) Preoperative positron emission tomography with fluorine-18-fluorodeoxyglucose is predictive of prognosis in patients with hepatocellular carcinoma after resection. *World J Surg* 30:1736–1741
14. Wolford RM, Papillion PW, Turnage RH, Lillien DL, Ramaswamy MR, Zibari GB (2010) Role of FDG-PET in the evaluation and staging of hepatocellular carcinoma with comparison of tumor size, AFP level, and histologic grade. *Int Surg* 95:67–75
15. Sugiyama M, Sakahara H, Torizuka T, Kanno T, Nakamura F, Futatsubashi M, Nakamura S (2004) ^{18}F -FDG PET in the detection of extrahepatic metastases from hepatocellular carcinoma. *J Gastroenterol* 39:961–968
16. Wudel LJ Jr, Delbeke D, Morris D, Rice M, Washington MK, Shyr Y, Pinson CW, Chapman WC (2003) The role of ^{18}F -fluorodeoxyglucose positron emission tomography imaging in the evaluation of hepatocellular carcinoma. *Am Surg* 69:117–126
17. Sun L, Guan YS, Pan WM, Luo ZM, Wei JH, Zhao L, Wu H (2009) Metabolic restaging of hepatocellular carcinoma using whole-body F-FDG PET/CT. *World J Hepatol* 1:90–97

18. Kim YJ, Yun M, Lee WJ, Kim KS, Lee JD (2003) Usefulness of ^{18}F -FDG PET in intrahepatic cholangiocarcinoma. *Eur J Nucl Med Mol Imaging* 30:1467–1472
19. Anderson CD, Rice MH, Pinson CW, Chapman WC, Chari RS, Delbeke D (2004) Fluorodeoxyglucose PET imaging in the evaluation of gallbladder carcinoma and cholangiocarcinoma. *J Gastrointest Surg* 8:90–97
20. Petrowsky H, Wildbrett P, Husarik DB, Hany TF, Tam S, Jochum W, Clavien PA (2006) Impact of integrated positron emission tomography and computed tomography on staging and management of gallbladder cancer and cholangiocarcinoma. *J Hepatol* 45:43–50
21. Jadvar H, Henderson RW, Conti PS (2007) [^{18}F]fluorodeoxyglucose positron emission tomography and positron emission tomography: computed tomography in recurrent and metastatic cholangiocarcinoma. *J Comput Assist Tomogr* 31:223–228
22. Ariff B, Lloyd CR, Khan S, Shariff M, Thillainayagam AV, Bansi DS, Khan SA, Taylor-Robinson SD, Lim AK (2009) Imaging of liver cancer. *World J Gastroenterol* 15:1289–1300
23. Delbeke D, Martin WH, Sandler MP, Chapman WC, Wright JK Jr, Pinson CW (1998) Evaluation of benign vs malignant hepatic lesions with positron emission tomography. *Arch Surg* 133:510–515
24. Selzner M, Hany TF, Wildbrett P, McCormack L, Kadry Z, Clavien PA (2004) Does the novel PET-CT imaging modality impact on the treatment of patients with metastatic colorectal cancer of the liver. *Ann Surg* 240:1027–1036
25. Fernandez F, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM (2004) Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). *Ann Surg* 240:438–450
26. Grassetto G, Fornasiero A, Bonciarelli G, Banti E, Rampin L, Marzola MC, Massaro A, Galeotti F, Del Favero G, Pasini F, Minicozzi AM, Al-Nahhas A, Córdano C, Rubello D (2010) Additional value of FDG-PET/CT in management of “solitary” liver metastases: preliminary results of a prospective multicenter study. *Mol Imaging Biol* 12:139–144
27. Wildi SM, Gubler C, Hany T, Petrowsky H, Clavien PA, Jochum W, Gerlach T, Fried M, Mülhaupt B (2007) Intraoperative sonography in patients with colorectal cancer and resectable liver metastases and resectable liver metastases on preoperative FDG-PET-CT. *J Clin Ultrasound* 36:20–26
28. Zerizer I, Al-Nahhas A, Towey D, Tait P, Ariff B, Wasan H, Hatice G, Habib N, Barwick T (2012) The role of early ^{18}F -FDG PET/CT in prediction of progression-free survival after ^{90}Y radioembolization: comparison with RECIST and tumour density criteria. *Eur J Nucl Med Mol Imaging* 39:1391–1399
29. Lubezky N, Metser U, Geva R, Nakache R, Shmueli E, Klausner JM, Even-Sapir E, Figer A, Ben-Haim M (2007) The role and limitations of 18-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan and computerized tomography (CT) in restaging patients with hepatic colorectal metastases following neoadjuvant chemotherapy: comparison with operative and pathological findings. *J Gastrointest Surg* 11:472–478
30. Lee WK, Lau EW, Duddalwar VA, Stanley AJ, Ho YY (2008) Abdominal manifestations of extranodal lymphoma: spectrum of imaging findings. *AJR Am J Roentgenol* 191:198–206
31. Mishra S, Shukla A, Tripathi AK, Kumar A (2013) Primary T-cell lymphoma of liver. *BMJ Case Rep* 22:2013
32. Kang KM, Chung WC, Lee KM, Hur SE, Nah JM, Kim GH, Back JY, Kim SK, Yang JM, Choi HJ (2005) A case of primary hepatic lymphoma mimicking hepatitis. *Korean J Hepatol* 11:284–288
33. Seshadri N, Ananthasivan R, Kavindran R, Srikanth G, Chandra S (2010) Primary hepatic (extranodal) lymphoma: utility of [^{18}F]fluorodeoxyglucose-PET/CT. *Cancer Imaging* 10:194–197
34. Kaneko K, Nishie A, Arima F, Yoshida T, Ono K, Omagari J, Honda H (2011) A case of diffuse-type primary hepatic lymphoma mimicking diffuse hepatocellular carcinoma. *Ann Nucl Med* 25:303–307
35. Kang KM, Song do S, Park JM, Jung CK, Hong YS, Kang MW, Park CW (2006) Four cases of non-Hodgkin’s lymphoma in AIDS patients. *Korean J Intern Med* 21:266–274
36. Fosse P, Girault S, Hoareau J, Testard A, Couturier O, Morel O (2013) Unusual uptake of 18FDG by a hepatic adenoma. *Clin Nucl Med* 38:135–136
37. Kurtaran A, Becherer A, Pfeffel F, Müller C, Traub T, Schmaljohann J, Kaserer K, Raderer M, Schima W, Dudczak R, Kletter K, Virgolini I (2000) ^{18}F -fluorodeoxyglucose (FDG)-PET features of focal nodular hyperplasia (FNH) of the liver. *Liver* 20:487–490
38. Magini G, Farsad M, Frigerio M, Serra C, Colecchia A, Jovine E, Vivarelli M, Feletti V, Golfieri R, Patti C, Fanti S, Franchi R, Lodi F, Boschi S, Bernardi M, Trevisani F (2009) C-11 acetate does not enhance usefulness of F-18 FDG PET/CT in differentiating between focal nodular hyperplasia and hepatic adenoma. *Clin Nucl Med* 34:659–665
39. Hata T, Kosaka N, Kishi H (1998) PET imaging of prostate cancer using carbon-11-choline. *J Nucl Med* 39:990–995
40. Hara T, Kosaka N, Kishi H (2002) Development of ^{18}F -fluoroethylcholine for cancer imaging with PET: synthesis, biochemistry and prostate cancer imaging. *J Nucl Med* 43:187–199
41. DeGrado TR, Baldwin SW, Wang S, Orr MD, Liao RP, Friedman HS, Reiman R, Price DT, Coleman RE (2001) Synthesis and evaluation of ^{18}F -labeled choline as an oncologic tracer for positron emission tomography: initial findings in prostate cancer. *Cancer Res* 61:110–117
42. Kolthammer JA, Corn DJ, Tenley N, Wu C, Tian H, Wang Y, Lee Z (2011) PET imaging of hepatocellular carcinoma with ^{18}F -fluoroethylcholine and ^{11}C -choline. *Eur J Nucl Med Mol Imaging* 38:1248–1256
43. Talbot JN, Gutman F, Fartoux L, Grange JD, Ganne N, Kerrou K, Grahek D, Montravers F, Poupon R, Rosmorduc O (2006) PET/CT in patients with hepatocellular carcinoma using [^{18}F]fluorocholine: preliminary comparison with [^{18}F] FDG PET/CT. *Eur J Nucl Med Mol Imaging* 33:1285–1289
44. Yamamoto Y, Nishiyama Y, Kameyama R, Okano K, Kashiwagi H, Deguchi A, Kaji M, Ohkawa M (2008) Detection of hepatocellular carcinoma using ^{11}C -choline PET: comparison with ^{18}F -FDG PET. *J Nucl Med* 49:1245–1248
45. Talbot JN, Fartoux L, Balogova S, Nataf V, Kerrou K, Gutman F, Huchet V, Ancel D, Grange JD, Rosmorduc O (2010) Detection of hepatocellular carcinoma with PET/CT: a prospective comparison of ^{18}F -fluorocholine and ^{18}F -FDG in patients with cirrhosis or chronic liver disease. *J Nucl Med* 51:1699–1706
46. Wu HB, Wang QS, Li BY, Li HS, Zhou WL, Wang QY (2011) F-18 FDG in conjunction with ^{11}C -choline PET/CT in the diagnosis of hepatocellular carcinoma. *Clin Nucl Med* 36:1092–1097
47. van den Esschert JW, Bieze M, Beuers UH, van Gulik TM, Bennink RJ (2011) Differentiation of hepatocellular adenoma and focal nodular hyperplasia using ^{18}F -fluorocholine PET/CT. *Eur J Nucl Med Mol Imaging* 38:436–440
48. Swinnen JV, Heemers H, Deboel L, Foulfelle F, Heyns W, Verhoeven G (2000) Stimulation of tumor associated fatty acid synthase expression by growth factor activation of the sterol regulatory element-binding protein pathway. *Oncogene* 19:5173–5181
49. Roeda D, Dolle F, Crouzel C (2002) An improvement of ^{11}C -acetate synthesis-non-radioactive contaminants by irradiation-induced species emanating from the ^{11}C carbon dioxide production target. *Appl Radiat Isot* 57:857–860

50. Ho CL, Yu SC, Yeung DW (2003) ^{11}C -acetate PET imaging in hepatocellular carcinoma and other liver masses. *J Nucl Med* 44:213–221
51. Larsson P, Arvidsson D, Björnstedt M, Isaksson B, Jersenius U, Motarjemi H, Jacobsson H (2012) Adding ^{11}C -acetate to ^{18}F -FDG at PET examination has an incremental value in the diagnosis of hepatocellular carcinoma. *Mol Imaging Radionucl Ther* 21:6–12
52. Cheung TT, Ho CL, Lo CM, Chen S, Chan SC, Chok KS, Fung JY, Yan Chan AC, Sharr W, Yau T, Poon RT, Fan ST (2013) ^{11}C -acetate and ^{18}F -FDG PET/CT for clinical staging and selection of patients with hepatocellular carcinoma for liver transplantation on the basis of Milan criteria: surgeon's perspective. *J Nucl Med* 54:192–200
53. Huo L, Wu Z, Zhuang H, Fu Z, Dang Y (2009) Dual time point ^{11}C -acetate PET imaging can potentially distinguish focal nodular hyperplasia from primary hepatocellular carcinoma. *Clin Nucl Med* 34:874–877
54. Rovainen A, Naum A, nuutinen H, Leino R, Nurmi H, Nagren K, Parkkola R, Virtanen J, Kallajoki M, Kujari H, Ovaska J, Roberts P, Seppanen M (2013) Characterization of hepatic tumors using ^{11}C metomidate through positron emission tomography: comparison with ^{11}C acetate. *EINMMI Res* 3:13
55. Sørensen M, Mikkelsen KS, Frisch K, Villadsen GE, Keiding S (2013) Regional metabolic liver function measured in patients with cirrhosis by 2- ^{18}F fluoro-2-deoxy-d-galactose PET/CT. *J Hepatol* 58:1119–1124