Diagnostic Applications of Nuclear Medicine: Tumors of the Liver and Biliary Tract

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Abstract

In liver and biliary tumors, modern imaging techniques play an important role in therapeutic decision-making. Whether the decision involves determining if the tumor is resectable or how it is responding to treatment, nuclear imaging has the potential to facilitate the decision-making process. Here we cover various studies that investigate the comparative effectiveness of cross-sectional morphologic imaging alone and in combination with functional nuclear medicine imaging. Specifically, we discuss the role of nuclear imaging in the diagnosis, characterization, and treatment of patients with primary and secondary liver or biliary tract malignancies.

Keywords

Primary tumors • Hepatocellular carcinoma • Hepatoma • Gallbladder carcinoma • Cholangiocarcinoma • Biliary cancer • Colorectal metastases • Neuroendocrine metastases • [^{11}C]Acetate • 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) • PET/CT • MRI • CT scan • Staging • Resectability • Recurrence • Nuclear imaging • Diagnostic

Glossary

[^{18}F]FDG	2-deoxy-2-[^{18}F]fluoro-D-glucose
ACS	American Cancer Society
AFP	Alpha Fetoprotein
AI	Arterial infusion
CA	Cancer antigen
CA 19–9	Carbohydrate antigen 19–9, a tumor-associated marker
CEA	Carcinoembryonic antigen, a tumor-associated marker
CRC	Colorectal cancer
CT	X-ray computed tomography
DOTA	2-(4-Isothiocyanatobenzyl-1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid (macrocyclic coupling agent to label compounds of biological interest with metal radionuclides)
DOTANOC	DOTA-1-Nal^3-octreotide
DOTATATE	DOTA-Tyr^3-octreotate
DOTATOC	DOTA-octreotide
FOLFOX	Chemotherapy regimen based on FOL– Folinic acid F – Fluorouracil OX – Oxaliplatin

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GBC	Gallbladder cancer
HCC	Hepatocellular carcinoma
HPB	Hepatopancreaticobiliary
IgG_4	Immunoglobulin G4
MIBG	Metaiodobenzylguanidine
MRCP	Magnetic Resonance Cholangiopancreatography
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NETs	Neuroendocrine Tumors
OS	Overall survival
PET	Positron emission tomography
PET/CT	Positron emission tomography/computed tomography
PFS	Progression-free survival
PSC	Primary sclerosing cholangitis
PTCS	Percutaneous transhepatic
SRS	Somatostatin receptor scintigraphy
SUV	Standardized uptake value
SUV_{max}	Standardized uptake value at point of maximum
TACE	Transcatheter arterial chemoembolization

Contents

Introduction

The tumors arising from the liver are among some of the most frequent and lethal human tumors worldwide. The liver is also the most common site of metastases from gastrointestinal tumors via portal circulation and is thought to be a barrier to the disseminated spread of cancer to other organs. Multimodality treatment of liver tumors necessitates accurate imaging to guide management decisions. Traditionally, a high-resolution cross-sectional imaging study with a multidetector CT scan or an MRI with triple-phase contrast has been considered the gold standard. Several advances in imaging technologies specifically nuclear imaging of these tumors have significantly improved our ability to evaluate the true extent of disease. In this chapter we review the role of nuclear imaging in the complex and often challenging treatment of primary and secondary liver and biliary malignancies.

Metastatic Tumors

Colorectal Metastases

Colorectal cancer metastases are the most common malignant lesions of the liver. Approximately half of the patients diagnosed with colorectal cancer (CRC) will develop liver metastases. Historically, these patients were treated with chemotherapy that resulted in suboptimal response, and none of the patients survived beyond five years (Fig. 1). The management of CRC liver metastases has undergone a paradigm shift over the last two decades. Surgical resection of CRC metastases has resulted in overall survival that approaches 30% at five years for a selected group of patients. Improvements in the quality and safety of hepatic resections, combined with the widespread use of ablative technologies as well as with arterial infusion pump placement, have broadened the selection criteria for patients who can benefit from potentially curative therapies. [^{18}F]FDG-PET/CT scans can play an important role at every stage of the management of these complex patients.

a. Operative Planning and Resectability
   The role of PET/CT in staging of the primary lesion in colorectal cancer has been studied extensively. PET/CT scan is neither sufficient nor accurate for clinical staging of the primary lesion, and without evidence of distant metastases on contrast-enhanced cross-sectional imaging,

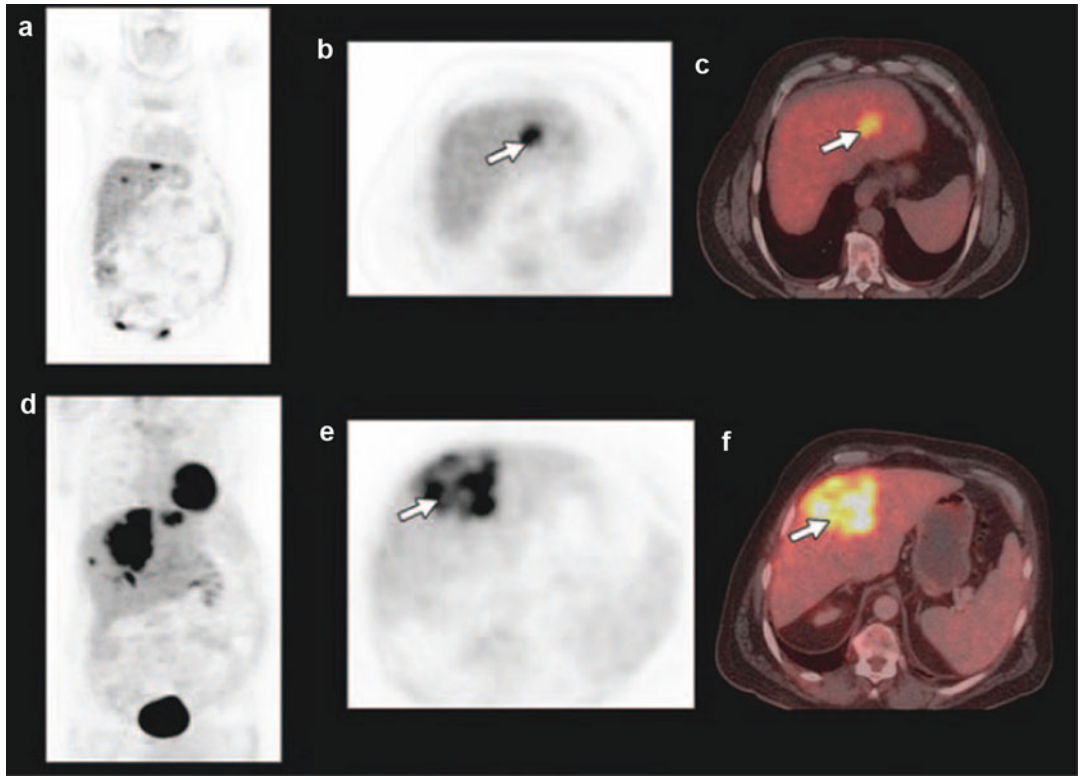

Fig. 1 71-year-old man with history of sigmoid colon cancer with surgical resection and chemotherapy for 6 months. (**a**) Patient's carcinoembryonic antigen levels started increasing after 6 months, and [^{18}F]FDG-PET/CT revealed hepatic metastasis. (**b**) Coronal PET shows two lesions (*arrow*) in segments 2 and 8. (**c**) Axial-fused PET/CT shows hypermetabolic lesion (*arrow*) in segment 2. (**d–f**) Patient underwent eight cycles of chemotherapy with FOLFOX-folinic acid, fluorouracil and oxaliplatin, and avastin, and subsequent PET-CT scans revealed progressive hepatic lesions (*arrow*, **e** and **f**) (Reprint with permission from Sacks A. et al. Value of PET-CT in the Management of Liver Metastases, Part 1. AJR Am J Roentgenol. 2011, Fig. 2, p. W259) [75]

the routine use of PET/CT is not justified. However, [^{18}F]FDG-PET scans are very accurate in detection of hepatic and extrahepatic disease. Pooled analysis from multiple studies demonstrates that the overall sensitivities of nonhelical CT, helical CT, 1.5-T MRI, and [^{18}F]FDG-PET in detecting liver metastases were 60.2%, 64.7%, 75.8%, and 94.6%, respectively [1]. Similar results were noted on a more recent analysis by Niekel et al., whereby the sensitivities of CT, MRI, and [^{18}F]FDG-PET were 83.6%, 88.2%, and 94.1%, respectively [2]. Similar sensitivity is noted for extrahepatic disease. A study by Kuehl et al. demonstrated an overall sensitivity of 95% for intrahepatic disease and 97% for extrahepatic disease [3].

Accurate staging of intrahepatic and extrahepatic disease is crucial in decision-making for these complex patients. A prospective study of patients with colorectal cancer metastatic to the liver demonstrated that a contrast-enhanced CT missed extrahepatic disease in one-third of the patients [4]. This number was reduced to 11% with the use of [^{18}F]FDG-PET scans. Similarly, another study reported that approximately one-third of the patients with a negative contrast-enhanced CT scan will have a positive finding on PET/CT scan [5]. [^{18}F]FDG-PET scans can be falsely positive in the setting of recent surgical resection or infection, and therefore, clinical correlation is vital when interpreting data from [^{18}F]FDG-PET scans.

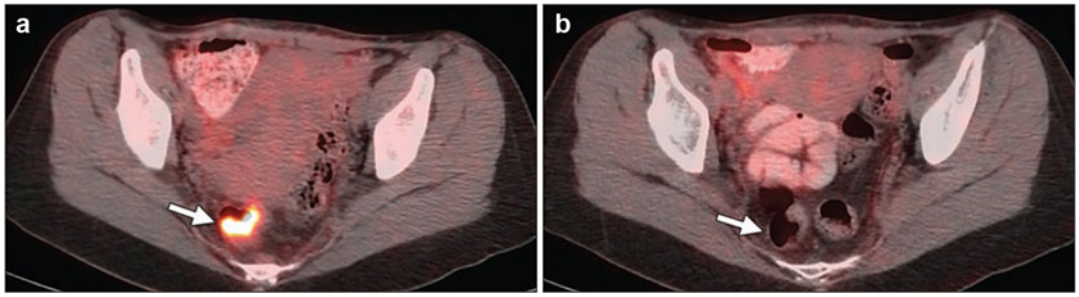

Fig. 2 [^{18}F]FDG PET/CT for initial staging and assessment of response to neoadjuvant therapy in 40-year-old woman with rectal adenocarcinoma. (**a**) Axial-fused PET/CT image obtained for initial staging shows metabolically active (standardized uptake value, 6.8) mass (*arrow*) in rectal wall. (**b**) Axial [^{18}F]FDG-PET/CT image obtained 3 months after staging PET/CT study (**a**) and after patient had undergone neoadjuvant chemotherapy shows lack of tracer uptake within rectal tumor (*arrow*), which suggests favorable response to therapy (Reprint with permission from Agarwal A. et al. FDG-PET-CT in the Management of Colorectal and Anal Cancers. AJR Am J Roentgenol. 2014, Fig. 2, p. 1116) [76]

In summary, PET/CT scans change the management choices in 30–40% of patients with colorectal liver metastases. The decision to obtain PET/CT scan preoperatively should be individualized. Patients with suspicious findings on contrast-enhanced CT or MRI or with extensive intrahepatic disease or those requiring extensive surgical resections with curative intent should be considered for an [^{18}F]FDG-PET scan.

b. Response to Therapies

Initial evidence supports the feasibility of PET scans in determining tumor response (Fig. 2). A study by Findlay et al. demonstrated that responsive lesions tend to grow slower at 5-week imaging intervals [6]. A recent meta-analysis of 15 studies with 867 patients demonstrated that a reduction in standardized uptake value (SUV) predicted overall survival. However, post-treatment SUV did not predict overall survival [7]. Additionally, [^{18}F]FDG-PET scans have been utilized increasingly to evaluate response to tumor-selective therapies such as radiofrequency or microwave ablation and selective radio- or trans-arterial chemoembolization.

[^{18}F]FDG-PET scans have the advantage of detecting metabolic response in a tumor that appears to be otherwise stable on cross-sectional imaging (Fig. 3). While several studies report the feasibility of this approach, whether a metabolic response is prognostic in these patients remains to be determined. Furthermore, neoadjuvant therapy lowers the sensitivity of [^{18}F]FDG-PET scans. A recent study reported a sensitivity of 65% for contrast-enhanced CT compared to 49% for [^{18}F]FDG-PET scan in detecting liver lesions after neoadjuvant chemotherapy [8]. For the same reason, there is no added value of [^{18}F]FDG-PET scan in detecting disappearing or vanishing liver metastases over a high-resolution contrast-enhanced CT or MRI.

c. Detecting Recurrence

Currently, National Comprehensive Cancer Network (NCCN) guidelines do not recommend routine use of PET/CT scans for surveillance, even in high-risk stage IV disease. This is likely the result of the lack of prospective studies that demonstrate the benefit of early detection of recurrence [9]. Theoretically, early detection would allow salvage curative resections, improving oncologic outcomes [10, 11]. A meta-analysis of 15 studies that included 510 patients demonstrated a 94% sensitivity and a 77.2% specificity of [^{18}F]FDG-PET scan in detecting recurrence for patients with rising CEA. This is more favorable than the sensitivity and specificity of contrast-enhanced CT scan at 51.3% and 90.2%, respectively [12], or that of plasma CEA levels alone, at 80% and 70%, respectively, in detecting recurrence [13]. Due to the unclear benefit of early

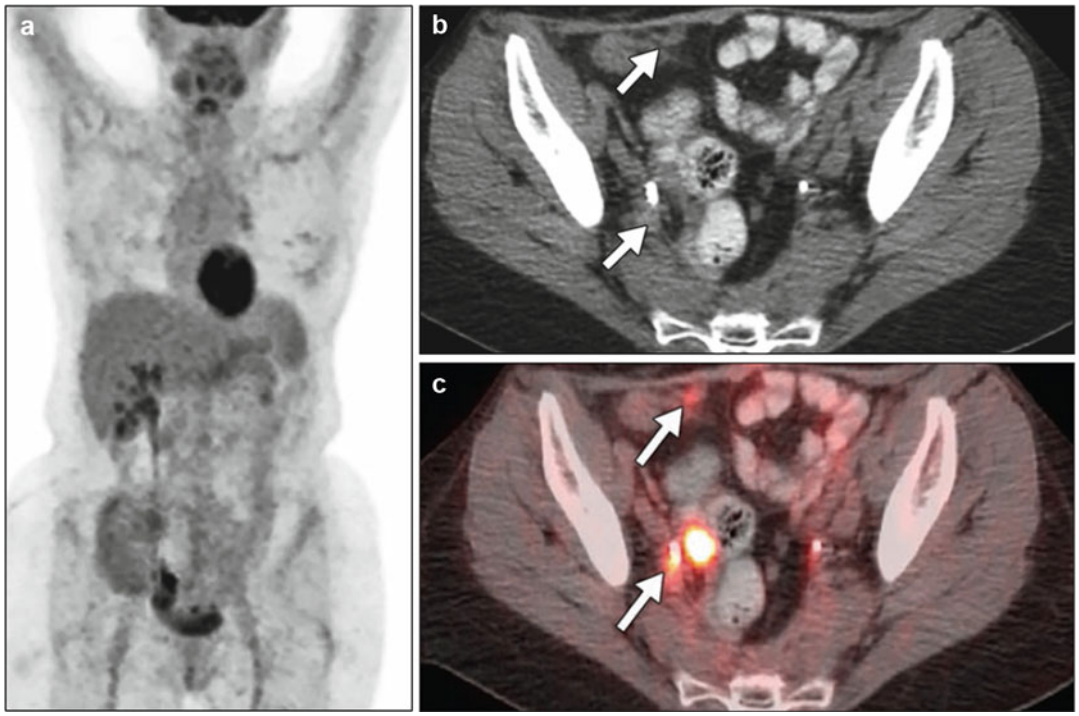

Fig. 3 Recurrence in 50-year-old woman with very low carcinoembryonic antigen (CEA) level who had undergone surgery and chemoradiation for treatment of adenocarcinoma of rectum. Patient underwent [^{18}F]FDG-PET/CT for restaging. (**a–c**) Anterior maximum intensity projection (**a**), axial CT (**b**), and fused PET/CT (**c**) images. Fused PET/CT image shows metabolically active (standardized uptake value, 10.02) malignant pelvic implants (*arrows*, **c**), whereas CT image shows ill-defined nonspecific soft tissue (*arrows*, **b**). CEA value at time of study was 1.8 ng/mL (Reprint with permission from Agarwal A. et al. FDG-PET-CT in the Management of Colorectal and Anal Cancers. AJR Am J Roentgenol. 2014, Fig. 5, p. 1117) [76]

detection on long-term survival and to the high cost of PET/CT scans, current consensus advises against the use of [^{18}F]FDG-PET scans for determining recurrence. However, an [^{18}F]FDG-PET scan should be considered in patients with continuously rising CEA over a 3-month interval with no visible disease on contrast-enhanced CT scan. We also consider [^{18}F]FDG-PET scan in CEA nonproducers who have suspicious findings for metastases on routine cross-sectional imaging.

Neuroendocrine Metastases

Neuroendocrine tumors (NETs) are rare with an incidence of 1.9–5.7 cases per 100,000 [14]. The majority of gastric, appendiceal, and rectal NETs are local. However, 65–95% of enteropancreatic NETs present with liver metastases [15, 16]. Liver metastases are the single most important prognostic determinant for patients with NETs. Morphologic combined with functional imaging plays an important role in diagnosis, determining resectability, and monitoring response to therapy and recurrence of liver metastases from NETs. However, the rarity of NETs makes it challenging to perform large prospective studies.

^{123}I-labeled noradrenalin analog metaiodobenzylguanidine (MIBG), ^{111}In-diethylenetriaminepentaacetic acid-octreotide somatostatin receptor scintigraphy (^{111}In-SRS), and [^{18}F]FDG-PET remain the most commonly used modalities for evaluating liver metastases from NETs. In a head-to-head comparison of the three modalities in a large prospective study of 96 patients, the overall sensitivity of ^{111}In-SRS, ^{123}I-MIBG scintigraphy, and [^{18}F]FDG-PET was 89%, 52%, and 58%,

respectively [17]. ^{111}In-SRS also exceeded ^{123}I-MIBG scintigraphy and [^{18}F]FDG-PET based on the number of lesions detected (393, 185, and 225, respectively). However, the sensitivity of [^{18}F]FDG-PET (92%) exceeded that of both ^{111}In-SRS (69%) and ^{123}I-MIBG scintigraphy (46%) for tumors with a proliferation index above 15%.

^{111}In-SRS relies on somatostatin receptor expression in NETs, which is seen in 60–90% of these tumors. Of these, 85% of NETs express somatostatin receptor subtype 2. There have been several attempts to improve on the ^{111}In-SRS introduced in 1990s, and the true benefit of these newer agents remains to be seen. Early experience with ^{68}Ga-labeled somatostatin analogues (DOTATOC, DOTATATE, or DOTANOC) suggests a lower cost and higher sensitivity in comparison to ^{111}In-SRS. Similarly, ^{64}Cu-DOTATATE somatostatin receptor scintigraphy was noted to be more sensitive than ^{111}In-SRS detecting additional lesions in 43% of the patients evaluated. Other radiotracers that have been used for functional imaging include ^{18}F-DOPA PET and [^{11}C]5-hydroxy-tryptophan ([^{11}C]5-HTP) PET. The role of these tracers and their comparative effectiveness remains to be studied [18].

In summary, we recommend that additional imaging should be strongly considered in patients with liver metastases from NETs on cross-sectional imaging to evaluate the true burden of disease and to determine resectability. ^{68}Ga-SRS appears to be more sensitive and cheaper than ^{111}In-SRS and should be utilized whenever available for low Ki67 (<15%) tumors. [^{18}F]FDG-PET should be preferred in evaluating tumors with high Ki67 (≥15%). Whether nuclear medicine imaging changes management over conventional morphologic imaging with high-resolution CT or MRI remains to be evaluated.

Primary Tumors

Hepatocellular Carcinoma

Hepatoma, also commonly referred to as hepatocellular carcinoma (HCC), is a neoplasm that arises from hepatic cells. Being one of the most common tumors worldwide, HCC is the fifth most frequent type of cancer, and it is the third most lethal [19, 20]. Due to the prevalence of hepatitis B or C infections in Asia compared to other world regions and to the expansion of hepatitis C infection in the USA, HCC cases are on the rise [21, 22]. Some patients with HCC still present normal liver function and may have a localized lesion when diagnosed; although those may be treated with partial resection, the 5-year survival rate is only 60–70% [23, 24]. Therapy for unresectable patients may require liver transplantation, although the majority of patients with HCC resort to nonoperative approaches, due to high-risk factors, including nonlocalized multiple intrahepatic lesions, extensive vascular invasion, or extrahepatic metastasis [25]. These therapeutic options include transcatheter arterial chemoembolization (TACE) and transcatheter arterial infusion chemotherapy (TAI) (Fig. 4).

Due to the complexity of HCC management, accurate staging of HCC is crucial in order to define treatment strategy. Conventional imaging modalities, including multiphase contrast-enhanced CT or MR imaging, are the current gold standard, with HCC tumors classically demonstrating late arterial enhancement with portal venous washout, obviating the need for tissue diagnosis. However, CT and MR scans frequently detect lesions that cannot be further defined, introducing uncertainty about the diagnosis or disease extent. Similarly, the therapeutic response of HCC to nonoperative therapy is usually assessed by conventional imaging modalities on the basis of changes in tumor size [26].

However, such criteria based on conventional imaging modalities have inherent limitation for accurate assessment of therapeutic response and tumor viability. Radiotracer imaging with or without concurrent high-resolution cross-sectional imaging provides a promising strategy to (i) improve our ability to detect subclinical disease, (ii) provide a functional insight into the behavior of tumors (i.e., glucose utilization), and (iii) probe molecular characteristics by utilizing targeted radiotracers. Each of these applications is reviewed below.

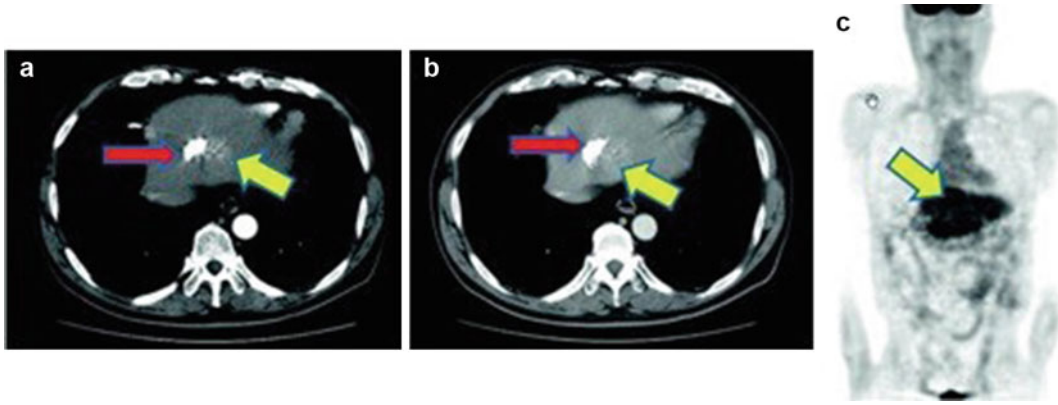

Fig. 4 A hepatoma recurrence after arterial chemoembolization. Contrast-enhanced CT at both arterial and portal phase shows a slight enhancement as suspected viable recurrent hepatoma, and a high [^{18}F]FDG accumulation is coincident with this stain (**a**–**c**; *large arrows*). [^{18}F]FDG-PET is to easily visualize viable hepatoma if the high-density area at CT image is difficult to distinguish with post-hemoembolized change (**a**, **b**; *small arrows*) [77]

a. 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG)
The most common and widely available radiotracer for imaging [^{18}F]FDG has been investigated in patients with hepatocellular carcinomas [27, 28]. While [^{18}F]FDG-PET is considered as a sensitive modality to assess tumor viability and tumor detection for a multitude of histologies, its ability to detect hepatocellular carcinoma lesions within the liver is low [28–33]. Relatively low [^{18}F]FDG accumulation in liver cells is due to the presence of cytosolic glucose-6-phosphatase (G-6-Pase) which converts [^{18}F]FDG-6-P back to [^{18}F]FDG, which allows the tracer to diffuse out of liver cells [34, 35]. Moreover, well-differentiated HCCs demonstrate similar metabolic characteristics as adjacent liver tissue, making it very difficult to identify tumor lesions within the liver (Figs. 5 and 6) [34–36].

At present, the use of [^{18}F]FDG-PET scans for routine local staging and surveillance is not recommended. The overall sensitivity of [^{18}F]FDG-PET/CT in detecting HCC within the liver suffers, with a reported range of 50–65%. For this reason, [^{18}F]FDG-PET has been determined to be insufficiently sensitive to diagnose primary HCC. A study by Khan et al. found that the sensitivity of [^{18}F]FDG-PET in the diagnosis of HCC was 55%, compared with 90% for contrast-enhanced CT [31]. Another report, by Wudel et al. involving one of the largest series of [^{18}F]FDG-PET for HCC ($n = 91$), reported that the sensitivity of [^{18}F]FDG-PET for detection of HCC was 64% [37]. To improve the sensitivity of [^{18}F]FDG-PET to detect HCC, investigators have suggested a 2–3-h delay between [^{18}F]FDG injection and imaging instead of the conventional 1-h delay between injection and imaging [38]. The delayed [^{18}F]FDG-PET may differentiate HCC lesions showing persistent [^{18}F]FDG uptake from normal liver tissue with gradual washout of [^{18}F]FDG [38].

Seminal work by Torizuka et al. demonstrated that [^{18}F]FDG uptake in HCC directly correlates with the degree of differentiation of these tumors, with higher grade tumors demonstrating on average a twofold uptake increase compared to low-grade tumors [39]. Further, a recent study demonstrated that SUV ratios (SUV ratio of hepatoma to adjacent liver) directly correlates with tumor doubling time, providing important prognostic information that allows prediction of overall survival when adjusted for tumor size [40]. The role of [^{18}F]FDG-PET scans as a component of clinical prognostication tool remains to be further tested and validated.

With growing experience in the utilization of [^{18}F]FDG-PET scans in patients with HCC, another application has come to light. Limited, small sample studies demonstrate the superiority

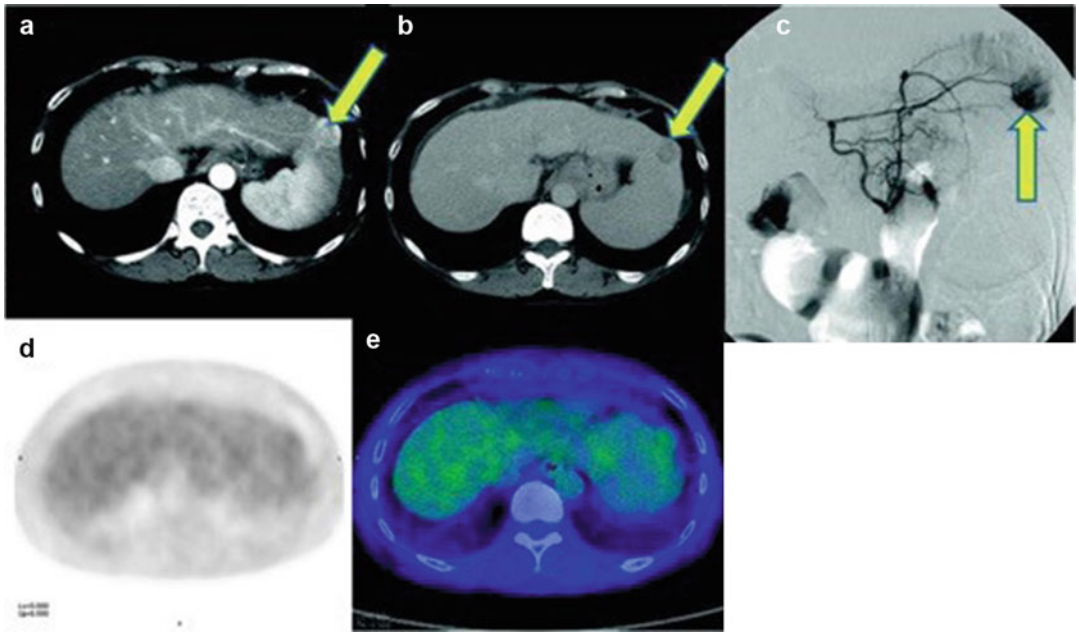

Fig. 5 *Normoglycolytic hepatoma*. Multiphase contrast-enhanced CT shows a tumor lesion, which has rich arterial perfusion but poor portal perfusion in left lobe (**a**, **b**; *yellow arrows*). Arterial angiography also shows early intense stain at same point (**c**; *yellow arrow*). These findings mean a typical classical hepatoma. However, PET/CT images do show only a normal [^{18}F]FDG accumulation on hepatoma (**d**, **e**) [77]

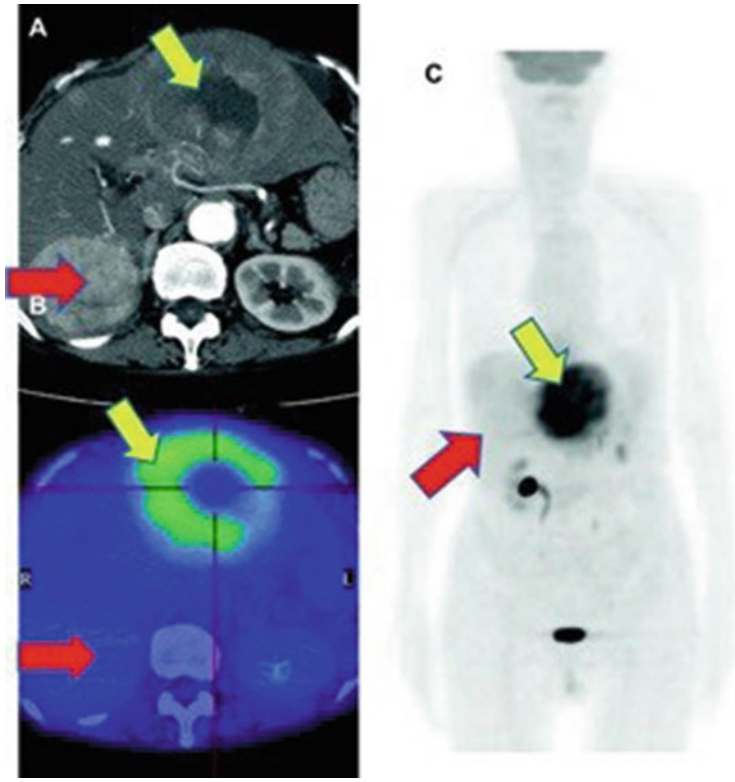

Fig. 6 *Synchronous double hepatomas*. Contrast-enhanced CT at arterial phase showed two of intrahepatic tumors. The heterogeneously stained tumor in the left lobe shows intense but heterogeneous accumulation of [^{18}F]FDG (**a**–**c**; *yellow arrows*). The other homogenously stained tumor in the right lobe shows [^{18}F]FDG normoaccumulation (**a**–**c**; *red arrows*). Both tumors were biopsied and proved that left-lobe hepatoma was poorly differentiated, but right-lobe one was well differentiated [77]

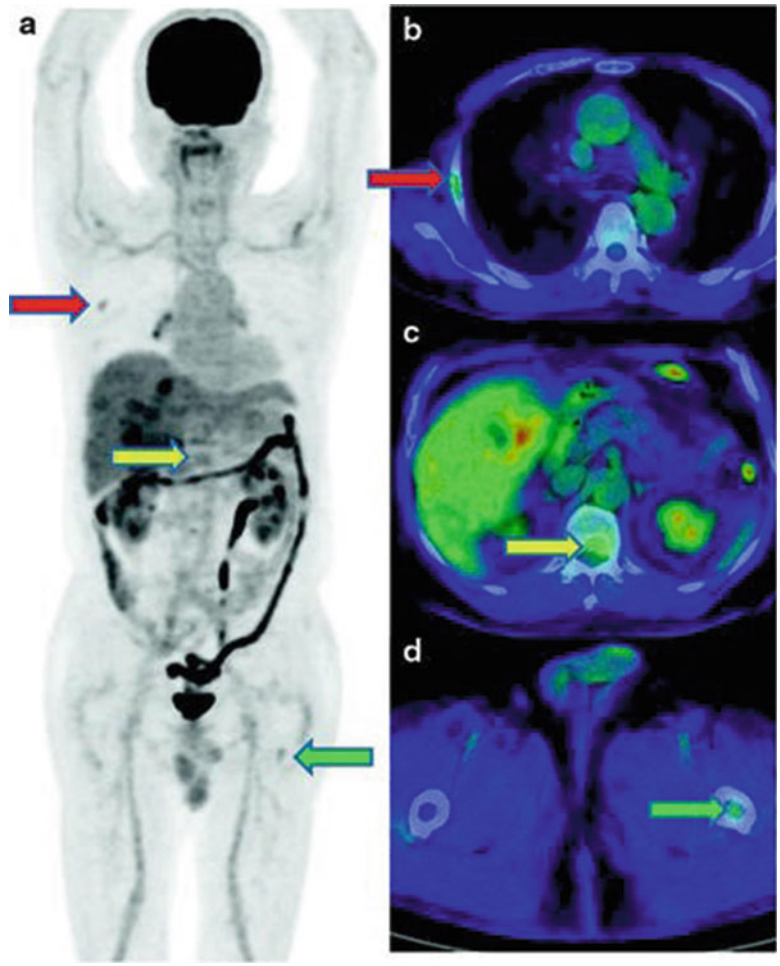

Fig. 7 *Multiple osseous metastases*. Slight [^{18}F]FDG accumulations are shown at the right thorax (**a**; *red arrow*), back (**a**; *yellow arrow*), and left femur (**c**; *green arrow*) on PET image. Fusion images disclose that these are, respectively, costal (**b**; *red arrow*), vertebral (**c**; *yellow arrow*), and femoral (**d**; *green arrow*) bone metastasis [77]

of detecting extrahepatic metastases with [^{18}F]FDG-PET scans in comparison to conventional MRI or CT (Figs. 7 and 8) [41]. In one study, 24 out of 87 patients with HCC had extrahepatic disease detectable by [^{18}F]FDG-PET [42]. Extrahepatic metastases in 10 out of the 24 patients were missed on conventional CT and MRI scans. The higher sensitivity of the [^{18}F]FDG-PET scan to detect metastatic disease versus localized disease is largely attributable to the higher grade of metastatic lesions. In particular, [^{18}F]FDG-PET scans are by far superior in the detection of bone metastases from HCC (sensitivity 83.3%, specificity 86.1%), in comparison to CT scan (sensitivity 41.6%, specificity 94.5%) and bone scintigraphy (sensitivity 52.7%, specificity 83.3%) [43].

Accurate assessment of treatment monitoring and outcome is another important role of [^{18}F]FDG-PET [29, 39, 44–46]. When the [^{18}F]FDG uptake in the lesion was higher or similar to the activity in the surrounding tissue, the presence of residual tumor was seen on histological confirmation. On the other hand, reduced [^{18}F]FDG uptake in the lesion makes it unlikely that there is residual tumor after TACE treatment [47, 48]. Similar findings have been reported in detecting local tumor progression following radiofrequency ablation of HCC. Kim et al. reported that, in HCC patients treated with

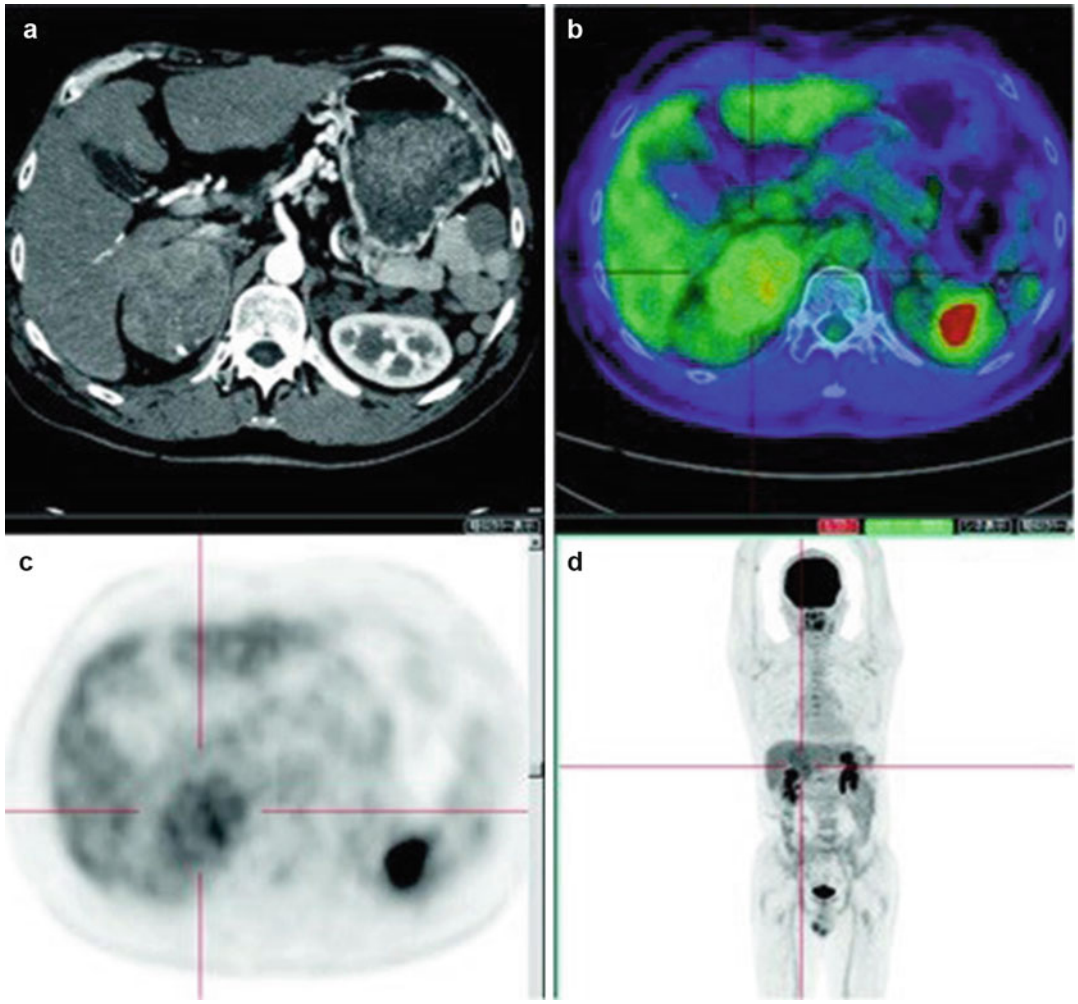

Fig. 8 *An adrenal metastasis of hepatoma*. A male with history of HCC therapy with AFP elevation but no intrahepatic recurrence. Contrast-enhanced CT at arterial phase shows early enhance on right enlarged adrenal gland (**a**). [^{18}F]FDG-PET/CT shows moderate hyperglycolysis at adrenal gland, so resection of this tumor disclosed metastatic hepatoma of adrenal gland (**b**). [^{18}F]FDG accumulation is slight and heterogeneous as well as general findings of hepatoma on PET (**c**, **d**) [77]

chemoradiation therapy, low [^{18}F]FDG uptake was associated with longer progression-free survival (PFS) and overall survival (OS) and that the high [^{18}F]FDG uptake group was more likely to have extrahepatic metastasis within 6 months [49].

b. [^{11}C]Acetate

To overcome the limited uptake and retention of [^{18}F]FDG in well-differentiated HCCs within the liver parenchyma, alternative radiotracers have been used. One such agent, [^{11}C]acetate, has been widely investigated with or without [^{18}F]FDG. Acetate, or acetic acid, is a molecule quickly picked up by cells and converted into acetyl-CoA by acetyl-CoA synthetase [50]. Acetyl-CoA feeds into the tricarboxylic acid cycle and it is utilized for cellular energy production. Alternatively, acetyl-CoA is an important substrate of anabolic pathways that lead to the synthesis of cholesterol, fatty acids, or amino acids. Tumor cells that overexpress fatty acid

synthetase or acetyl-CoA carboxylase generate [^{11}C]-labeled fatty acids and cholesterol, which are rapidly incorporated into the tumor cell membranes allowing for detection of tumor using [^{11}C]acetate-PET scans [50].

One of the first studies utilizing [^{11}C]acetate-PET scans in detecting HCC within the liver by Ho et al. included 39 patients with HCC [51]. Concurrent [^{18}F]FDG-PET scans were performed for comparison. Dual radiotracer imaging proved to be complimentary with a sensitivity of 98% and specificity of 86%. Well-differentiated lesions preferentially accumulate [^{11}C]acetate, whereas poorly differentiated lesions accumulate [^{18}F]FDG. A similar but considerably prospective study by Park et al. incorporated patients with localized as well as distant disease (n=90) [52]. [^{11}C]Acetate-PET offered superior sensitivity (75.4%) compared to [^{18}F]FDG-PET (60.9%). Dual-tracer imaging had a combined sensitivity of 82.7%. Of note, the ability to detect lesions by dual-tracer imaging is highly dependent on tumor size. For instance, tumors less than 2 cm are detected with a sensitivity of ~30% by combined radiotracer imaging.

The use of [^{11}C]acetate-PET in determining response to treatment remains to be studied. A feasibility study of [^{11}C]acetate in the monitoring of treatment response following Radiotherapy in patients with hepatocellular carcinoma is currently underway (NCT02549755). In conclusion, the early experience with dual-tracer PET imaging is very encouraging. More studies are needed to determine the utility of this modality in diagnosis, staging, surveillance, and response to therapy.

c. Tracers in Development

Targeted radiotracers hold the promise of enhanced sensitivity and specificity. Additionally, next-generation radiotracers could provide functional insight into the behavior of HCCs. This information can be crucial in selecting therapies as well as in assessing response to therapies. A recent study evaluated glypican 3-targeted [^{89}Zr] PET imaging for HCC [53]. Glypican 3 is expressed on the cell surface of up to 80% of HCCs, making it a suitable imaging target. Using this immune probe, tumors as small as 1 mm could be accurately identified in small animal studies with excellent specificity. Another study demonstrated that mouse extrahepatic hepatoma could be visualized by PET using copper-64 chloride as a tracer, based on increased copper uptake mediated by mouse copper transporter 1 (mCtr1). There was relatively less ^{64}Cu uptake in the hepatoma compared to the liver due to the presence of mCtr1 in normal liver cells. Choline is one of the components of phosphatidylcholine, an essential element of phospholipids in the cell membrane. HCC has significantly higher choline content than normal liver tissue. A prospective study aimed to compare the diagnostic performance of ^{18}F-fluorocholine and [^{18}F]FDG for detecting and staging hepatocellular carcinoma (HCC) in patients with chronic liver disease and suspected liver nodules [54]. This study demonstrated that ^{18}F-fluorocholine was significantly more sensitive (94%) than [^{18}F]FDG (59%) at detecting HCC, particularly in well-differentiated forms. The combined modality was thought to be superior.

In conclusion, [^{18}F]FDG-PET scan is inferior to multiphase CT or MRI in assessing true burden of hepatic disease. Liver HCC lesions that appear [^{18}F]FDG-avid tend to be poorly differentiated. Further, [^{18}F]FDG-PET can be considered in ruling out extrahepatic disease in patients undergoing transplantation or in analyzing burden of disease prior to systemic therapies. [^{11}C]Acetate scans are complimentary to [^{18}F]FDG-PET scans, and dual-tracer PET scans are expected to be more widely adapted in clinical practice as clinical experience accumulates. Development of targeted and functional radiotracers in proof-of-concept studies highlights the potential of these agents as promising tools in treatment of hepatocellular carcinomas.

Cholangiocarcinoma

Cholangiocarcinoma is a neoplasm that arises from cholangiocytes, the epithelial cells lining

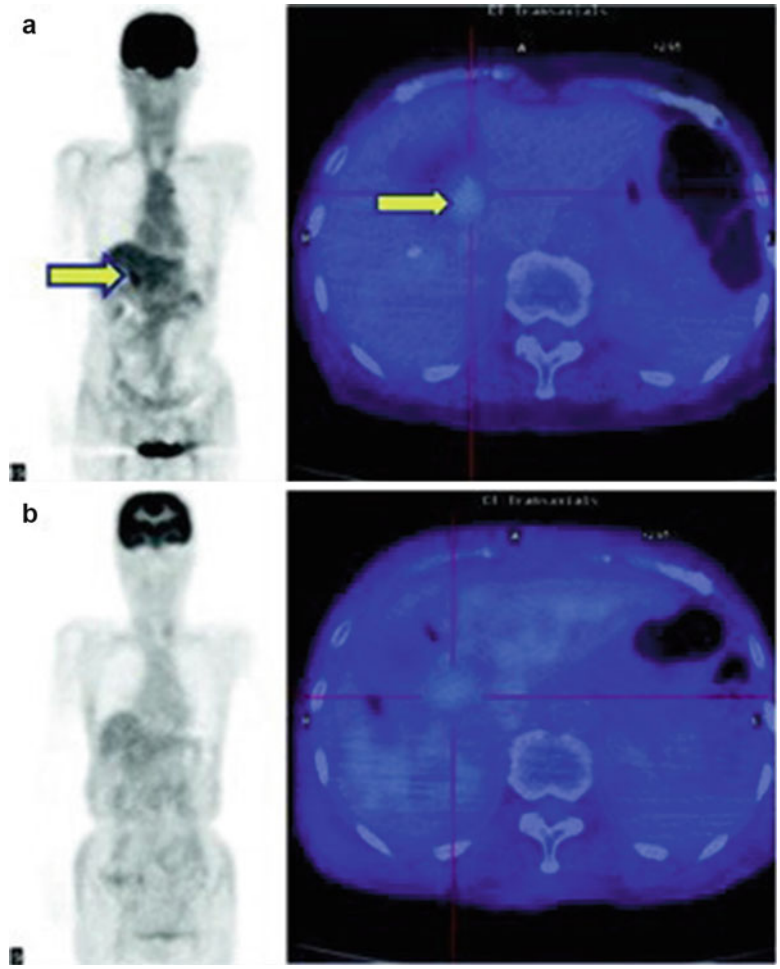

Fig. 9 Therapy monitor imaging of unresectable Klatskin tumor. [^{18}F]FDG abnormally accumulates primary tumor at hepatic hilum (**a**, **b**; *yellow arrows*). After external radiation (44 Gy) and brachytherapy (12 Gy) with concurrent hepatic arterial infusion (AI) together, [^{18}F]FDG accumulation became indistinct [77]

the bile ducts. The majority of lesions are adenocarcinoma. Carcinoma of the extrahepatic biliary tract is defined by the location of the tumor into Klatskin (hilar) tumor (Fig. 9), hepatic bile duct, common bile duct tumor, gallbladder cancer, and ampulla of Vater cancer [55]. Histopathological characterization of extrahepatic biliary cancer divides lesions into moderately differentiated, poorly differentiated, or undifferentiated adenocarcinoma [56]. Carcinoma of extrahepatic biliary tract is histopathologically divided into mass-forming (nodular), periductal-infiltrating (sclerosing), and intraductal (papillary) type (Fig. 10) [56]. These histopathological difference classifications give a great deal of influences at the situation using the radiological diagnosis. Although mass-forming types show vertical progression, while periductal-infiltrating lesions show horizontal progression, both of them progress invasively into surrounding structures. However, intraductal type including mucin-producing tumor progresses horizontally but noninvasively (Figs. 9 and 10) [56, 57].

In the USA, it is estimated that there have been 9760 new cases of cholangiocarcinoma in 2010 and 3320 deaths (ACS Cancer Facts 2010). Its incidence is annually 1–2 per 100,000 in the western world [58]. This rate is rising around the world, while in Japan the rate is decreasing in the twenty-first century. The annual number of deaths due to extrahepatic biliary cancer was

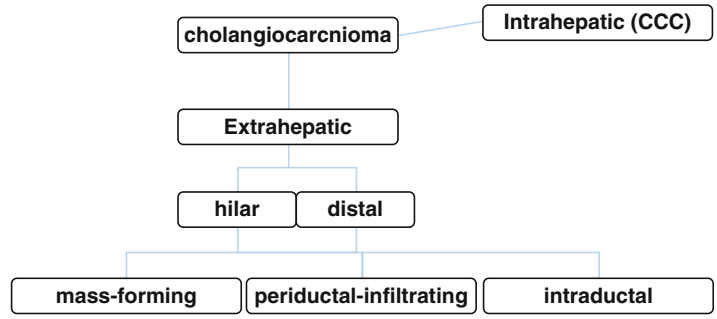

Fig. 10 Classification of cholangiocarcinoma [77]

about 3600 people in the USA. Statistics show that the 60s are the most frequent age, and the frequency in men is about twice than in women. Several known risk factors are described for cholangiocarcinoma, including primary sclerosing cholangitis [PSC, often associated with ulcerative colitis], Caroli's congenital abnormalities of the biliary tree (Caroli's disease syndrome, congenital hepatic fibrosis, and choledochal cysts), parasitic biliary infection (e.g., liver fluke, *Clonorchis*), and chronic typhoid fever [59]. It is thought that a long-term inflammation of the biliary tract or abnormal choledocholithiasis influences carcinogenesis, but there are a lot of unknown molecular carcinogenic processes [60].

The first clinical symptom is often painless jaundice, sometimes accompanied by pruritus, weight loss, and fever. Abdominal pain may occur in 30–50% of patients. Patients often have advanced disease at the time of diagnosis. In general, cholangiocarcinoma have a poor prognosis because complete resection is the only curative treatment. The 5-year survival rate after curative resection is still low (26–51%) [61]. For unresectable disease, chemotherapy with gemcitabine and cisplatin provides marginal benefit in overall survival [62].

Patients with cholangiocarcinoma typically present with painless jaundice that prompts an ultrasound (US) of the liver. Biliary dilation and elevated bilirubin necessitates multimodality imaging with endoscopic retrograde cholangiography, endoscopic US, and high-resolution triple-phase (arterial, venous, and delayed venous) contrast-enhanced cross-sectional imaging (CT or MRI). This provides adequate information to assess resectability of cholangiocarcinoma. Pathologic diagnosis is based on brushings and cytology. Often, surgical resection is warranted based on imaging findings in the absence of tissue diagnosis.

The role of [^{18}F]FDG-PET scan for imaging of biliary cancers is evolving (Figs. 11, 12, 13, and 14). Small, mostly retrospective series report a sensitivity ranging 91–95% for intrahepatic cholangiocarcinoma and 55–83% for extrahepatic cholangiocarcinoma [63–66]. Further, the diagnostic accuracy is higher for larger mass-forming lesions than periductal-infiltrating tumors. For instance, Anderson et al. reported that mass-forming or intraductally progressive (volume) type showed a higher proportion of patients with [^{18}F]FDG accumulation (17/20 patients) compared to the periductal-infiltrating (thin) type, which was found to be [^{18}F]FDG-positive in only 2/11 patients [63].

Obstructive jaundice typically leads to bactibilia, and some degree of cholangitis is usually present [57]. The utility of [^{18}F]FDG-PET scan is therefore limited by the high positive rates in the setting of acute cholangitis. It is also important to distinguish biliary cancer from autoimmune IgG_4-related cholangitis. As such, IgG_4-related disease is characterized by high serum IgG_4 concentrations and sclerosing inflammation (involving the parotid gland, pancreas, bile duct, and so on) with numerous IgG_4-positive plasma cells. However, [^{18}F]FDG-PET cannot help distinguish the two entities as autoimmune IgG_4-related cholangitis readily accumulates [^{18}F]FDG as well (Fig. 15). Involvement of multiple organs and elevated serum IgG_4

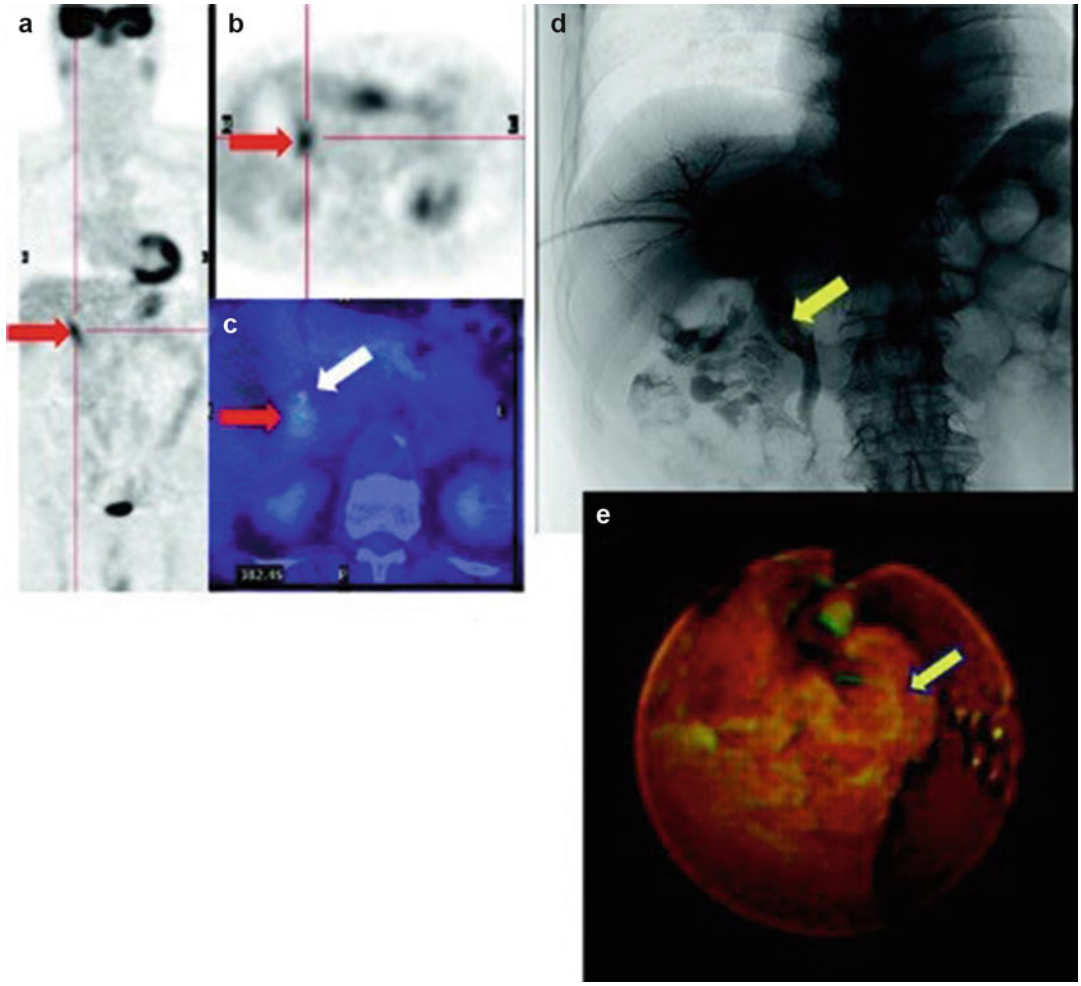

Fig. 11 Pretherapeutic extrahepatic bile duct (common bile duct) cancer. [^{18}F]FDG abnormally accumulates in the common bile duct (**a**–**c**; *red arrows*). And fusion image clearly discloses a local relationship between tumor and replaced drainage tube (**c**; *white arrow*). Cholangiography shows a filling defect on the dilated common bile duct (**d**; *yellow arrow*), and PTCS finding is mass-forming tumor (**e**; *yellow arrow*) [77]

should raise suspicion for autoimmune cholangitis rather than cholangiocarcinoma. Definitive diagnosis is only possible after surgical resection.

a. Preoperative Staging and Resectability
   Kim et al. analyzed their experience with 94 cholangiocarcinoma cases [65]. They reported a sensitivity of 95% for [^{18}F]FDG-PET/CT versus 100% for MRI/MRCP. High-resolution cross-sectional imaging provides vital information on the relationship of the tumor to the porta hepatic vasculature, allowing accurate assessment of resectability. [^{18}F]FDG-PET scan does not improve on this assessment given its low resolution. Accurate diagnosis of lymph node involvement is of clinical value for accurate staging in each patient. Again, [^{18}F]FDG-PET may have limited value for this purpose due to limited spatial resolution. One of the major limitations is that lymph node involvement is mainly seen in the adjacent areas of the primary tumor, therefore making it rather difficult to separate the lymph node lesion, without the use of PET/CT from the primary lesion by relatively low-resolution PET. In addition, it is rather difficult to

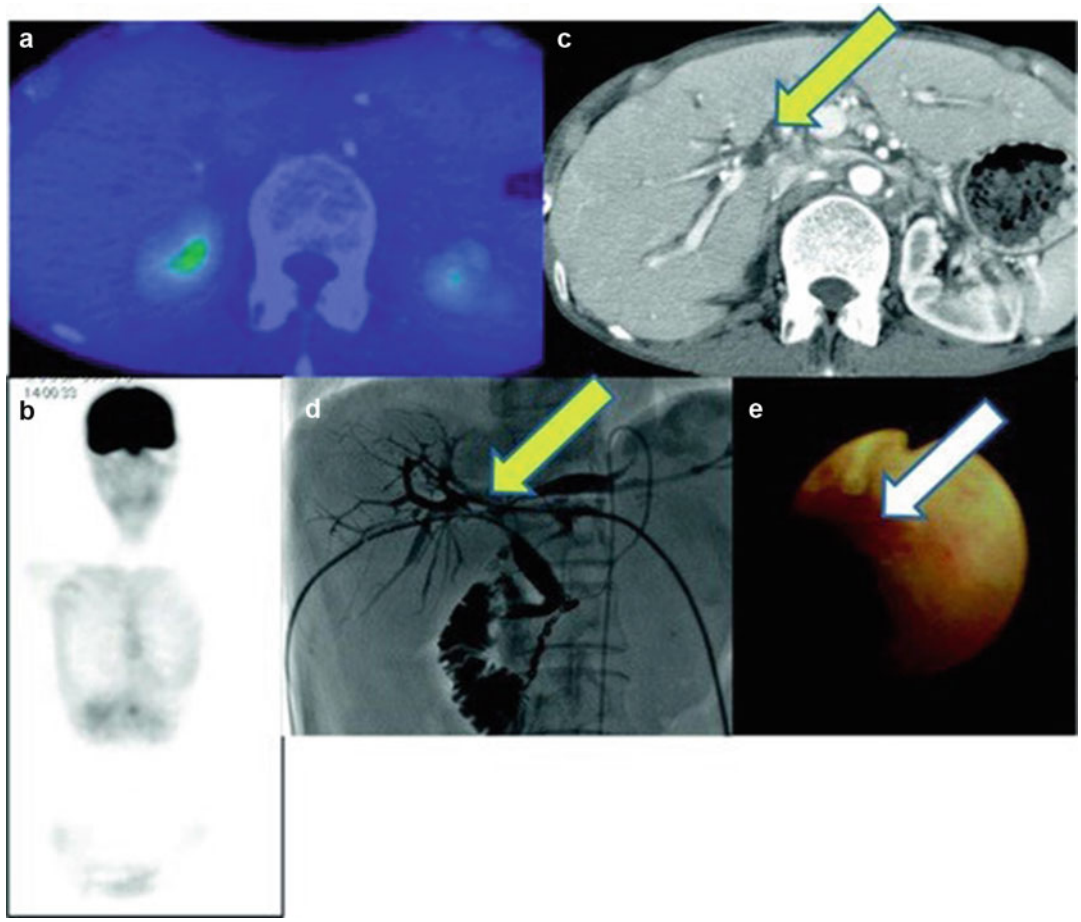

Fig. 12 Pretherapeutic Klatskin tumor. PET/CT does not show abnormal [^{18}F]FDG accumulation (**a**, **b**). Contrast-enhanced CT and cholangiography shows multiple filling defects (**c**, **d**; *yellow arrows*) because of tumor in hilum. PTCS shows focal mucosal redness (**e**; *white arrow*). Biopsy specimen proved periductal-infiltrating-type adenocarcinoma [77]

differentiate malignant invasion from the accompanied benign inflammatory lesions, which are often seen in biliary tracts. On the other hand, [^{18}F]FDG-PET has a high diagnostic value for detecting distant lymph node involvement, where previous reports showed a wide range of sensitivity (12–50%), specificity (80–100%), and overall accuracy (69–77%) [67]. However, among those, the relatively high specificity may prove to be of clinical value in identifying distant nodal involvement, as these patients are unlikely to benefit from aggressive surgical resection. It is estimated that [^{18}F]FDG-PET scans change patient management in 16–30% of patients with cholangiocarcinoma.

b. Detection of Recurrence

Patients with cholangiocarcinomas are currently evaluated by contrast-enhanced cross-sectional imaging for surveillance. A recent multicenter retrospective study in 50 patients with posttreatment surveillance of biliary cancer in Japan indicated that [^{18}F]FDG-PET provided high sensitivity (86%), specificity (91%), and overall accuracy (88%) for detecting tumor recurrence [68]. In addition, the [^{18}F]FDG-PET findings resulted in a change in management of 10 of the 50 patients

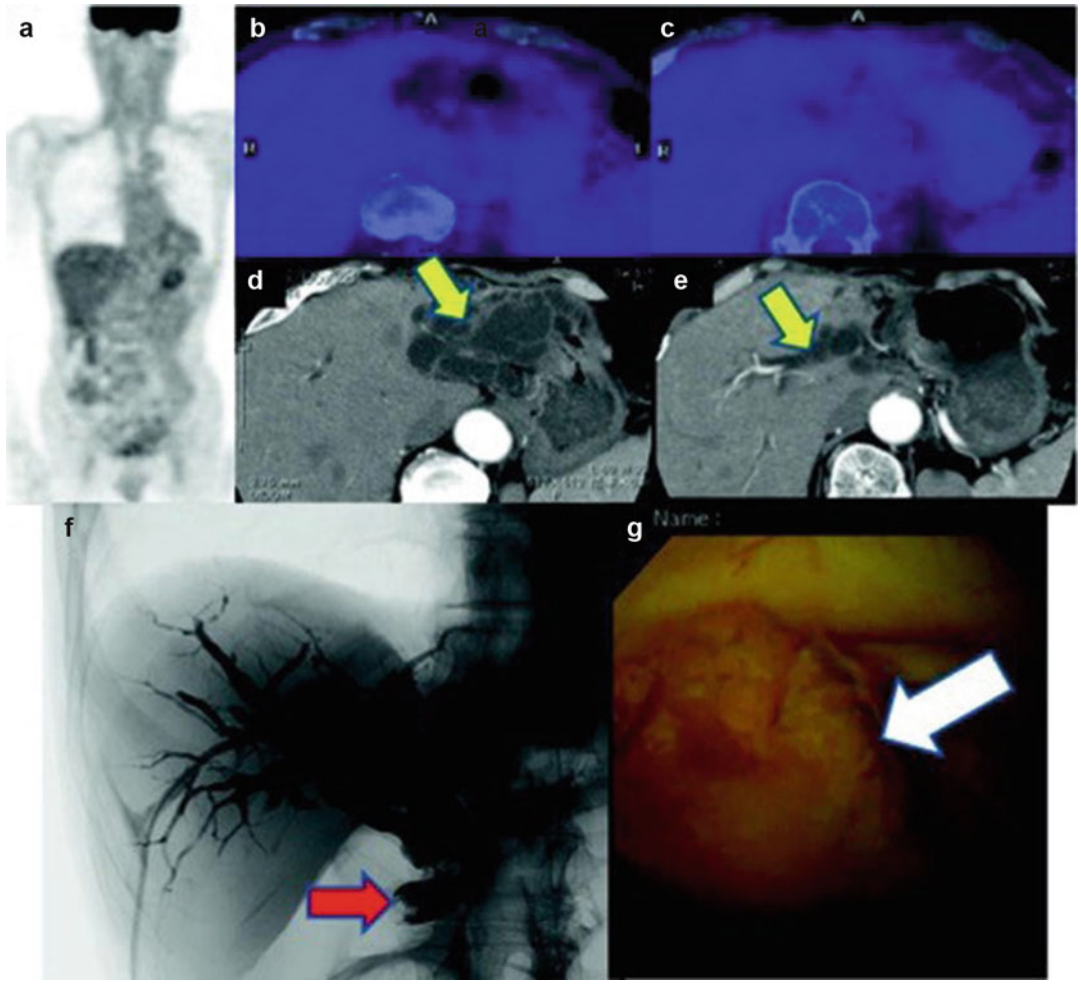

Fig. 13 Mucin-producing extrahepatic bile duct tumor. PET/CT does not show abnormal [^{18}F]FDG accumulation (**a**–**c**). Contrast-enhanced CT shows bile duct dilatation in bilateral lobe (**d**, **e**; *yellow arrows*). Cholangiography shows extra- and intrahepatic biliary dilatation and filling defect at lower common bile duct (**f**; *red arrow*). PTCS shows focal mucosal redness (**g**; *white arrow*). Biopsy specimen proved papillary-type, mucin-producing adenocarcinoma [77]

(20%) by initiating an unplanned treatment strategy ($n = 7$), by obviating the need for planned diagnostic procedures ($n = 2$), and by changing the treatment planning ($n = 1$) [68]. These multicenter studies confirmed the value of PET in patients with bile duct cancer after operation.

c. Risk Stratification

There are a number of established criteria for assessing prognosis of patients with bile duct cancer, including tumor histology and staging. Most of criteria may come from the findings during or after operation. PET and PET/CT may have a potential for selecting high-risk patients on the basis of tissue characterization. Furukawa et al. studied 69 patients with bile duct cancer [69]. These investigators found the [^{18}F]FDG uptake as a significant prognostic indicator. Those with SUV_{max} of higher than 6.3 on [^{18}F]FDG-PET were in the poor prognostic group, with a 3-year survival rate of 44.1%, whereas those with SUV_{max} of 6.3 or

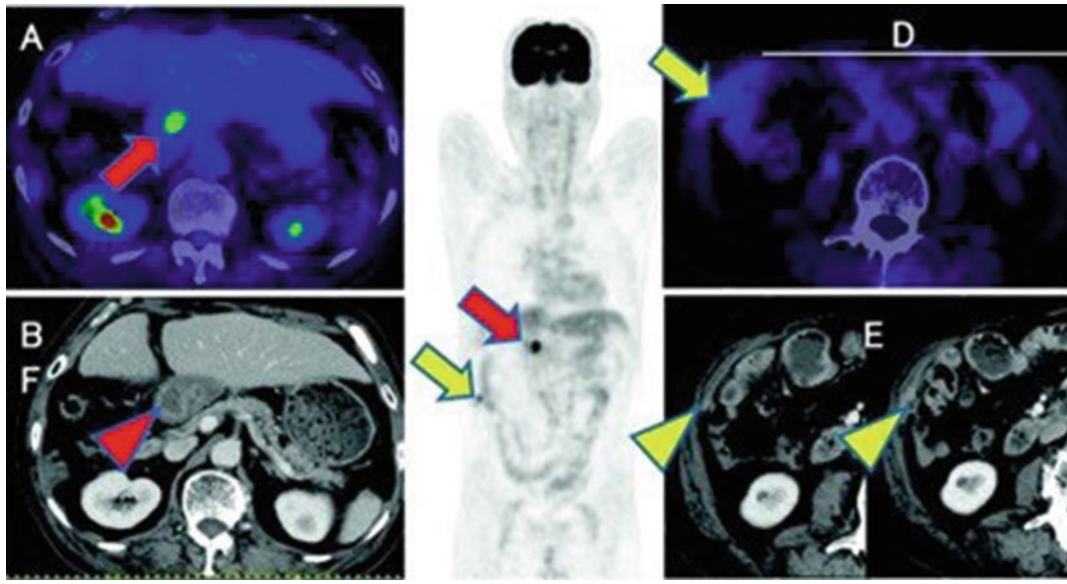

Fig. 14 Postoperative common bile duct cancer patient with CA19–9 elevation. Abnormal [^{18}F]FDG accumulations are shown at hepatic hilum (**a**, **c**; *red arrows*) and intra-abdominal space (**c**, **d**; *yellow arrows*). So these are highly suspected recurrent lesions including local recurrence and peritoneal dissemination. Coincidently, contrast-enhanced CT shows choledochojejunostomized wall (**b**; *red arrowhead*) and peritoneal small and increasing enhanced nodule (**e**, **f**; *yellow arrowheads*). But it is difficult to differentiate anastomosis and recurrence [77]

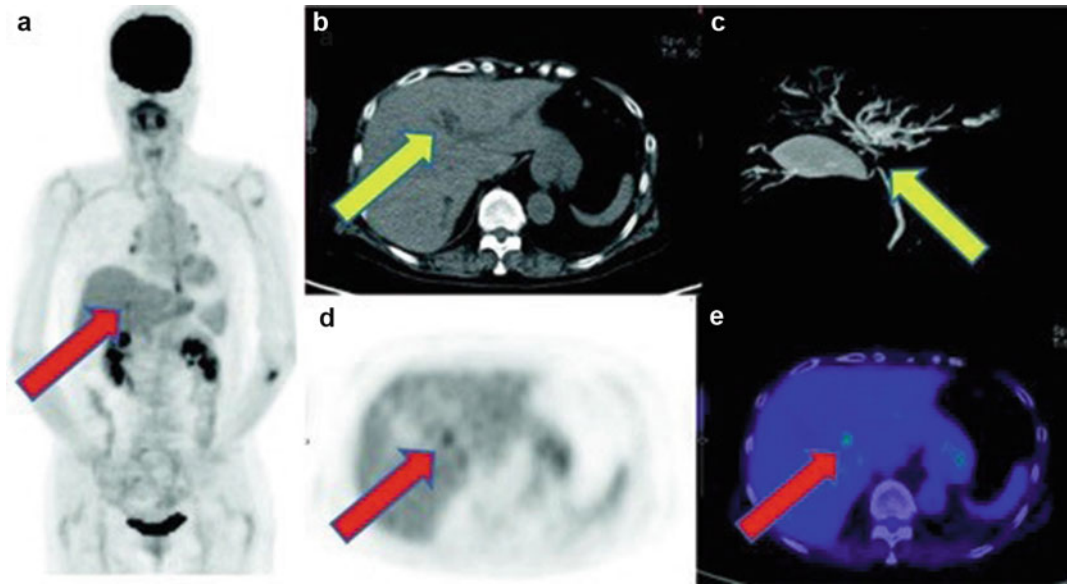

Fig. 15 IgG_4-related sclerosing cholangitis. Non-contrast CT and MRCP show intrahepatic bile duct dilatation due to hepatic hilar severe stenosis (**b**, **c**; *yellow arrows*). [^{18}F] FDG accumulates on the point of hepatic hilum (**a**, **d**, **e**; *red arrows*). But biopsy specimen proved no carcinoma cell but sclerosis cholangitis with plasmacyte and lymphocyte infiltration. His serum IgG_4 level was so high that IgG_4-related disease was confirmed [77]

less on [^{18}F]FDG-PET were in the better prognostic group, with a 3-year survival rate of 74.3% ($P = 0.012$). Kitamura et al. studied 73 patients with extrahepatic bile duct cancers to show SUV_{max} value of 5.7 as a significant cutoff point to differentiate poor prognosis from good prognosis subgroups [70]. They showed [^{18}F]FDG uptake value as an independent significant prognostic indicator on multivariate analysis.

Gallbladder Carcinoma

Gallbladder cancer (GBC) is a rare neoplasm that arises from the mucosal lining of the gallbladder. The American Cancer Society estimates approximately 10,000 cases of biliary origin cancers are diagnosed each year. Half of these originate in the gallbladder. Chronic inflammation is thought to be the main etiology in a majority of patients. For instance, the presence of gallstones increases the risk of GBC up to fivefold and predates the development of GBC in 75% of patients. Other causes of chronic inflammation predisposing to GBC can be autoimmune, i.e., primary sclerosing cholangitis and ulcerative colitis, or infectious, i.e., *Salmonella typhi* and *S. paratyphi*, liver flukes, and *Helicobacter pylori*. Genetic factors that may contribute are under active investigation. This hypothesis is based in the observation that the incidence of GBC is increased in certain genetic syndromes such as Gardner syndrome, neurofibromatosis type 1, and hereditary nonpolyposis colon cancer. The incidence of GBC in the USA has been decreasing since 1973. Internationally, a high incidence of GBC is noted in South America (Chile, Columbia, Peru, Bolivia, and Ecuador), South Asia (India), and East Asia (Korea and Japan).

Symptomatology occurs late in the course of the disease. Approximately 50% of patients have nodal disease at diagnosis. Increasingly, patients are incidentally discovered to have gallbladder cancer after a "routine" cholecystectomy for biliary colic or acute cholecystitis. Surgical resection is the only potentially curative treatment. Extent of surgical resection and resectability depends on accurate radiologic staging. A high-quality, contrast-enhanced cross-sectional imaging modality (CT or MRI) is the current standard. The role of PET scan is not clearly established for GBC and is not routinely recommended in the USA. However, mounting evidence from small studies may change this recommendation. The accuracy and utility of [^{18}F]FDG-PET in detecting regional and distant metastases in an otherwise resectable patient is discussed below. In addition, we discuss the role of [^{18}F]FDG-PET in the management of recurrent disease and the novel approaches being developed.

Preoperative PET/CT scans have been evaluated through small institutional experiences. The majority of these studies combine patients with GBC and cholangiocarcinoma, making it difficult to draw meaningful conclusions (Fig. 16). Butte et al. investigated 32 patients with incidental GBC following laparoscopic cholecystectomy [71]. While 13 patients had negative PET/CT results, 9 refused further resection, and only 1 of the 4 patients was resected, having residual disease on operative exploration. PET/CT changed management in 12 out of 32 patients (38%) demonstrating unexpected disseminated disease in 10 patients and localized resectable disease in 2 patients. Corvera et al. studied 31 patients with gallbladder cancer within their published series [66]. They demonstrated a sensitivity of 86% and a specificity of 50% for detection of the primary tumor, and a sensitivity of 87% and specificity of 89% for detection of nodal/distant disease, respectively. This resulted in a change in treatment for seven (23%) patients.

Shukla et al. evaluated the role of PET/CT in 24 patients with incidental gallbladder cancer prior to radical resection [72]. They demonstrated that PET/CT predicted resectability with a sensitivity of 100% but was not significantly superior to conventional CT. PET/CT demonstrated residual disease with a sensitivity of 28.5% and with a specificity of 80.9%. These results may have changed clinical management for two patients. One of the largest series analyzed data from 100 patients at a single institution [73]. Sixty-three patients were incidentally discovered to have GBC. In 73 patients, the PET/CT was concordant with contrast-enhanced imaging and did

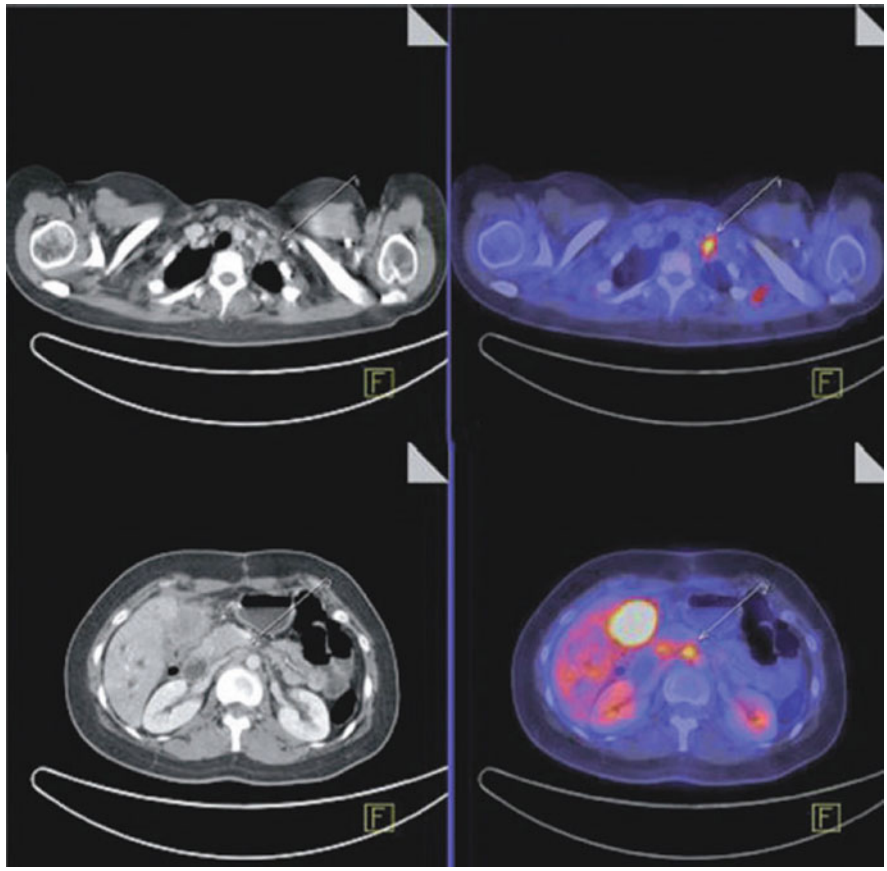

Fig. 16 An example of an [^{18}F]FDG PET/CT which showed evidence (positive finding) of disseminated disease (*arrow*) in a patient who was diagnosed with an incidental gallbladder carcinoma after cholecystectomy (Reprint with permission from Butte JM. et al. The role of PET/CT in patients with incidental gallbladder cancer. HPB. 2009, Fig. 3, p. 588) [71]

not add any information. In 3 patients, PET/CT detected metastatic disease not suspected on contrast-enhanced CT alone. In 12 patients, the CT scan was suspicious for locally advanced disease, and PET/CT helped confirm distant nodal disease (11 patients) or T4 disease (1 patient). Further, in two patients, CT was suspicious for distant metastases, but PET/CT ruled out that possibility, changing treatment choice. Taken together, PET/CT changed decision-making for 17 patients (17%). Improvement in conventional imaging has mitigated the benefit of PET/CT scans in recent years, with older studies reporting a higher proportion of patients where PET/CT appeared to change decision-making. The sensitivity of PET/CT in detecting distant metastases is 57%. This poor sensitivity is mainly because peritoneal disease tends to be less [^{18}F]FDG-avid (sensitivity 28%) versus nodal disease (70%). Given these results, routine preoperative [^{18}F] FDG-PET/CT is not recommended. A PET/CT scan may help prevent a potentially morbid operation in patients with suspicious nodal or distant lesions on cross-sectional imaging. False-positive result in these patients is thought to be low (specificity ~97–100%). Nonetheless, it must be kept in mind that equivocal or unexpected PET findings may prompt additional biopsies.

Kumar et al. evaluated the role of PET/CT in detecting recurrent GBC in 49 patients [74]. These investigators demonstrated a sensitivity and specificity of 97.6% and 90%, respectively, for

detecting recurrent disease. PET/CT was shown to be more specific than conventional imaging (100% vs. 50%) and resulted in a change in management for five patients (20%). More studies are needed to establish the role of PET/CT in recurrent GBC. The cost and resource utilization of unnecessary biopsies for false-positive findings needs to be investigated further.

In conclusion, [^{18}F]FDG-PET appears to be complimentary rather than definitive in many patients with GBC, and its role is limited in patients with negative CT/MRI and T1 disease. While the routine use of PET/CT in GBC is probably not cost effective, we believe that PET should be used when there are suspicious findings on CT/MRI, such as large tumors or questionable nodes. [^{18}F]FDG PET/CT should not be the imaging modality of choice when peritoneal-only disease is suspected as the sensitivity is low. Diagnostic laparoscopy has a higher yield in these patients.

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