Functional imaging in liver tumours

Maxime Ronot [1,2,3], Ashley Kieran Clift [4], Valérie Vilgrain [1,2,3], Andrea Frilling [4]

1. Department of Radiology, APHP, University Hospitals Paris Nord Val de Seine, Beaujon, Clichy, Hauts-de-Seine, France
2. University Paris Diderot, Sorbonne Paris Cité, Paris, France
3. INSERM U1149, centre de recherche biomédicale Bichat-Beaujon, CRB3, Paris, France
4. Department of Surgery and Cancer, Imperial College London, London, UK

Corresponding author: Valérie Vilgrain

Radiology Department, Beaujon Hospital

100, Bd du Général Leclerc, 92110 – Clichy

valerie.vilgrain@aphp.fr

+33 1 4087 55 66

Key words: liver, tumours, metastases, imaging

Abbreviations: DW (diffusion weighted), MRI (magnetic resonance imaging), CE (contrast enhanced), US (ultrasound), CT (computed tomography), PET (positron emission tomography), HCC (hepatocellular carcinoma), MFC (mass-forming cholangiocarcinoma), OATP (organic anionic transporting polypeptides), MRPs (multidrug resistance proteins), Gd-BOPTA (Gadobendate dimeglumine), Gd-EOD-OTPA (Gadoxetic acid), ADC (apparent diffusion coefficient), ^{18}F-FDG (^{18}F-fluorodeoxyglucose), ^{18}F-FLT (^{18}F-fluorothymidine), LM (liver metastases), CRC (colorectal carcinoma), NET (neuroendocrine tumours), CR (colorectal), NE (neuroendocrine), NEC (neuroendocrine carcinoma), SIRT (selective internal radiotherapy), PRRT (peptide receptor radionuclide therapy), G (grade), SSTR (somatostatin receptor), GLP-1R (glucagon like peptide-1 receptor), ^{18}F-DOPA (6-^{18}F-L-3,4-dihydroxyphenylalanine), ^{11}C-5-HTP (β-[^{11}C]-5-hydroxy-L-

tryptophan), SPECT (single positron emission computed tomography), SRS (somatostatin receptor scintigraphy), SSAs (somatostatin analogues), ^{68}Ga-SSAs (68Ga-radiolabelled somatostatin analogues), ^{68}Ga-DOTATOC ([68Ga-DOTA^{0},Tyr3]octreotide), ^{68}Ga-DOTANOC ([^{68}Ga-DOTA,1-Nal^{3}]octreotide), ^{68}Ga-DOTATATE ([^{68}Ga-DOTA^{0},Tyr^{3}]octreotate).

Word count: 4,873

Number of figures: 5 Number of tables: 1

Conflict of interest: none

Financial support disclosure: none

Authors contributions: Review of the literature and data extraction: MR, AKC

Drafting of the manuscript: MR, AKC

Review of the manuscript and amendments: VV, AF

Final approval: MR, AKC, VV, AF

Summary:

Functional imaging encompasses techniques capable of assessing physiological parameters of tissues, and offers useful clinical information in addition to that obtained from morphological imaging. Such techniques may include magnetic resonance imaging with diffusion-weighted sequences or hepatobiliary contrast agents, perfusion imaging, or molecular imaging with radiolabelled tracers. The liver is of major importance in oncological practice; not only is hepatocellular carcinoma one of the malignancies with steadily rising incidence worldwide, but hepatic metastases are regularly observed with a range of solid neoplasms. Within the realm of hepatic oncology, different functional imaging modalities may occupy pivotal roles in lesion characterisation, treatment selection and follow-up, depending on tumour size and type. In this review, we characterise the major forms of functional

imaging, discuss their current application to the management of patients with common primary and secondary liver tumours, and anticipate future developments within this field.

Key points:

- Functional imaging assesses *in vivo* physiological parameters of tissues, and may be used in tumour detection, characterisation, treatment selection and follow-up
- The combination of MRI with diffusion-weighted sequences and hepatobiliary contrast agents play a central role in the detection and characterisation of cirrhosis-related focal liver lesions
- The role of perfusion imaging is limited, but data are encouraging regarding future clinical utility in assessing the effects of loco-regional and systemic therapies.
- MRI with diffusion-weighted sequences and hepatobiliary MR contrast agents are the most accurate modality for characterising and detecting colorectal and neuroendocrine liver metastases
- Molecular imaging with radiolabelled somatostatin analogues represents the gold-standard imaging approach for the majority of neuroendocrine tumours

Introduction

The term ‘functional imaging’ refers to a collection of techniques providing information regarding the physiological properties of tissues. In the field of liver oncology, functional imaging may be used for tumour detection and characterisation, selection of treatment, monitoring of treatment response and patient follow-up. These techniques do not compete with morphological imaging workup but may yield additional information.

Four main functional modalities are utilised in liver tumour imaging: diffusion-weighted (DW) magnetic resonance imaging (MRI) is sensitive to the Brownian motion of water molecules, and is considered as a marker of tissue cellularity and microarchitecture[1] ; perfusion imaging using contrast-enhanced (CE) ultrasound (US), computed tomography (CT) or MRI provides information about tissue microcirculation or the movement of water and solutes[2,3] ; imaging of the hepatocellular function using hepatospecific MR contrast agents [4,5]; and nuclear metabolic imaging using positron emission tomography (PET)/CT with targeted radiotracers to assess specific metabolic pathways. Some are currently included in routine practice, such as DW-MRI and hepatospecific MR contrast agents, some may be used in specific settings (nuclear metabolic imaging), and finally others are still restricted to research settings (perfusion imaging).

Here, we provide an overview of functional imaging methods. Thereafter, we review the role of functional imaging techniques in the commonest primary liver tumours, i.e. hepatocellular carcinoma (HCC) and mass-forming cholangiocarcinoma (MFC), as well as in the most clinically relevant types of liver metastases, including those of colorectal and neuroendocrine origins.

Functional imaging methods

Imaging hepatocellular function: hepatobiliary MR contrast agents

Hepatobiliary MR contrast agents are gadolinium chelates that are taken up by functioning hepatocytes. Their internalisation is mediated by organic anionic transporting polypeptides (OATP) expressed on the sinusoidal membrane of functional hepatocytes [6]. Subsequently, 50% of the contrast agent is excreted into the biliary canals through multidrug resistance-associated proteins (MRPs) [5,7]. The level of expression of these proteins is significantly decreased in impaired hepatocytes. As a consequence, these contrast agents are accurate markers of hepatocellular function.

Hepatospecific CE MR sequences are T1-weighted, and are obtained when the liver and the bile ducts are markedly enhanced. On these images, non-hepatocellular tumours, tumours containing impaired hepatocytes, and also vessels or cysts appear black. Currently, two hepatobiliary MR contrast agents are commercially available: gadobenate dimeglumine or Gd-BOPTA (Multihance, Bracco Imaging) and gadoxetate disodium also called gadoxetic acid or Gd-EOB-DTPA (Primovist / Eovist, Bayer). The latter is the most frequently used worldwide because 50% of the injected dose is rapidly taken-up by hepatocytes, allowing for acquisition of the "hepatobiliary phase" 20 minutes after injection. With gadobenate dimeglumine, around 5% is taken up, and the hepatobiliary phase is obtained 1-3 hours after injection. Due to the rapid entry of Gd-EOB-DTPA into hepatocytes, classical features of liver tumours are modified on sequences classically referred to as delayed phase sequences (3-5 minutes after injection). Indeed, these images combine the extracellular and intrahepatocellular components of the contrast agent and are best defined as transitional phase images [8]. This is not observed with Gd-BOPTA.

Imaging tissue cellularity and architecture: diffusion-weighted MRI

DW MRI is a technique based on the random mobility of protons in tissues. In highly cellular tissues such as tumours, the diffusion of water protons is restricted. Thus, both qualitative (signal intensity) and quantitative (apparent-diffusion coefficient [ADC]) variables reflect tissue cellularity and cellular membrane integrity [1]. 'Diffusion restriction' refers to a tumour signal intensity that is higher than that of the surrounding liver on high b value DW MR images, corresponding to low ADC values on quantitative maps. DW MRI with a mono-exponential model is now part of the routine MR protocol for liver diseases. A more refined approach, referred to as the intravoxel incoherent motion (IVIM) theory allows the separation of pure molecular diffusion parameters from perfusion-related diffusion parameters within a tissue [9].

Imaging tumour microvasculature: perfusion imaging

Perfusion imaging provides information about tissue microcirculation or the movement of water and solutes at levels far below the spatial resolution of conventional imaging techniques. Thus, perfusion imaging is not the dynamic, qualitative analysis commonly obtained with tissue enhancement, but a quantitative extraction of physiological perfusion parameters of the liver. It requires the injection of a tracer and the acquisition by rapid temporal sampling of signal intensity/time curves that provide information on variations in tracer concentrations over time. The physiological parameters are extracted from these curves by adjusting them to mathematical perfusion models. Various imaging techniques can be used: CEUS, CT (perfusion CT), or MRI (commonly named dynamic CE MRI).

Imaging tumour metabolism: PET

In routine oncologic imaging, metabolic imaging is mostly based on gluconeogenesis. Indeed, gluconeogenesis is increased in most malignant tissues, and can be visualized using ^{18}F-fluorodeoxyglucose (^{18}F-FDG). Recently, several other tracers have been developed for imaging different malignancies: ^{18}F-fluorothymidine (^{18}F-FLT) has been validated as a specific biomarker of proliferation, ^{11}C- or ^{18}F-acetate and ^{11}C- or ^{18}F-choline as indicators of tumour growth or invasiveness.

Primary Liver Tumours

Primary liver tumours are a group of malignancies derived from various liver cells. The most frequent is HCC, accounting for 85-90% of all primary liver tumours. It is the sixth most common malignancy worldwide and the second most common cause of cancer-related mortality [10]. Cholangiocarcinoma is the second most common primary liver tumour and derives from the bile ducts. It is classically classified into extrahepatic (80-90%) and intrahepatic (5-10%) types. Intrahepatic cholangiocarcinoma can present as mass-forming (so called 'peripheral type'), or more rarely as periductal-infiltrating, or intraductal growing tumours [11].

HCC and MFC present with variable imaging features depending on their extension and biological behaviour. In daily practice however, the detection, characterisation and follow-up of these lesions rely on morphological features assessed on contrast-enhanced imaging techniques, mostly CT and MRI. The hallmarks of HCC are the association of hypervascularity on the arterial phase and washout on the portal venous and/or delayed phases [12]. MFCs appear as focal lesions with various degrees of peripheral hypervascularity, and progressive contrast uptake due to their fibrous stroma [11].

Based on morphological criteria, the sensitivity of MRI for the diagnosis of HCC is 77-100% using extracellular contrast agents, while that of CT is 68-91% [13–16]. Indeed, the diagnostic performance is strongly related to tumour size. The sensitivity for large HCC (> 2cm), is close to 100% for both

imaging techniques, but drops to around 45-80% (MRI) and 40-75% (CT) for 1-2 cm lesions and is lower in HCCs < 1 cm [17,18].

Added value of hepatobiliary MR contrast agents in primary liver tumours

Loss of hepatocellular function occurs early during the carcinogenesis of liver tumours, often prior to the tumour neoangiogenesis which predicates lesion hypervascularity. Consequently, most HCCs appear hypointense during the hepatobiliary phase[19] while most non-HCC, cirrhosis–associated regenerative or dysplastic nodules appear iso- or hyperintense. A recent meta-analysis focusing on the diagnostic performance of MRI for diagnosing HCC up to 2cm has shown that Gd-EOB-DTPA MRI had significantly increased sensitivity compared to extracellular contrast agent MRI (92% and 67%, respectively) [20]. The high contrast between the background liver and hypointense lesions in the hepatobiliary phase explains why some early HCCs are only visible on this sequence [21]. Kim et al showed that the use of Gd-EOB-DTPA MRI may also result in increased overall survival of patients with early-stage lesions showing additional HCC nodules in 16% of patients diagnosed with a single-nodular HCC by multiphasic CT [22]. This explains why Korean and Japanese guidelines recommend the use of Gd-EOB-DTPA MRI as first line imaging for the diagnosis of HCC [23,24]. Nevertheless, the specificity of diagnosing HCC using Gd-EOB-DTPA MRI with transitional or hepatobiliary phases seems to be lower than with extracellular MR contrast agents. To keep the specificity high when using Gd-EOB-DTPA MRI, washout should be determined on the portal venous phase alone [25]. This may explain why extracellular contrast MR agents are still recommended in Western guidelines [13,14].

The optimum circumstances for utilising the additional information yielded by hepatobiliary MR contrast agents should be considered. When HCC harbour the typical enhancement pattern, hypointensity during the hepatobiliary phase is almost always observed, limiting its added value [26]. Therefore, Gd-EOB-DTPA MRI appears to be most useful in atypical HCC (i.e. lacking hypervascularity or washout during the portal venous or delayed phases). Interestingly, hypovascular

HCCs are hypointense on hepatobiliary phase in 96% of cases [26]. Such hypovascular, hypointense lesions are challenging because not all of them correspond to HCC at the time of imaging, and around one third may eventually progress to hypervascular HCC over a period of 12-18 months [27–29]. In this setting, ancillary findings such as hyperintensity on DW- or on T2-weighted MR sequences have been shown to be associated with early HCC [30,31].

Data are scarcer regarding the added value of hepatospecific MR contrast agents in MFC. Typically using Gd-EOB-DTPA MRI, most MFCs show a thin peripheral rim with internal heterogeneous enhancement during the dynamic phase and hypointensity on the hepatobiliary phase [32]. This peculiar enhancement on dynamic sequences may help differentiating small HCCs from MFCs [33]. It has also been shown that the hepatobiliary phase demonstrates increased lesion conspicuity and better delineation of daughter nodules and intrahepatic metastasis [32].

Added value of diffusion-weighted MRI in primary liver tumours

Most HCC (80%) are hyperintense on high b value DW MR sequences [34]. The addition of DW sequences to MRI examinations increases the detection rate of HCC and helps characterise small lesions [35,36]. DW MR sequences are most useful in HCCs smaller than 2cm when classical morphological criteria are not met; CE and DW images may increase the sensitivity for diagnosing HCC up to 85% [36,37]. Hyperintensity on DW MRI has been recently endorsed by the liver imaging reporting and data system (Li-Rads) recently introduced by the American College of Radiology [38] as an ancillary feature for the non-invasive diagnosis of HCC. DW MRI has also been demonstrated to increase the detection of small MFCs, with better conspicuity when compared to other MR sequences [39]. DW MRI has also been evaluated in assessing tumour differentiation – ADC values are decreased in moderately- or poorly-differentiated HCCs compared to well-differentiated HCC, and also correlate with microvascular invasion, presence of progenitor cell markers, and early recurrence after resection [40]. However, these data have not been applied to routine practice because individual values are still a

matter of ongoing investigation. DW MRI may also help differentiate tumoural venous invasion from bland thrombus [41].

If the qualitative evaluation of DW images is mostly used for tumour detection and characterisation, the quantitative approach has mostly been studied to assess tumour response to various treatments. Pre-clinical and clinical studies have shown that ADC measurements could indicate the degree of tumour necrosis in HCCs treated with loco-regional therapy as necrotic tissue shows higher ADC values than viable tissue [42–47]. Interestingly, these alterations can be observed as early as one week after the treatment, thus helping predict further response [48–50]. Several teams have also investigated the role of the pre-treatment ADC value in predicting tumour response. Although these series are preliminary, tumour ADC obtained before transarterial chemoembolisation or radioembolisation can be used to predict tumour response and patient survival [51–53]. Similar results have been reported with MFC treated with intra-arterial therapy [54].

Added value of perfusion imaging in primary liver tumours

Several studies have investigated the ability of perfusion imaging to characterise HCC in patients with cirrhosis. Arterial hepatic blood flow and hepatic perfusion index have been found to be higher, while the portal venous hepatic blood flow was significantly lower in HCC compared to liver parenchyma [55–57], suggesting that perfusion techniques can provide quantitative information about tumour-related angiogenesis. Thus, analysis of perfusion maps might increase the sensitivity for detection of HCC [58]. Perfusion parameters (evaluated by perfusion CT) were also shown to correlate with tumour differentiation, with well-differentiated HCC having significantly higher perfusion values than other grades [59].

Perfusion studies of loco-regional treatment of liver tumours, especially HCC provide limited additional information during and after percutaneous microwave or radiofrequency ablation because morphological imaging criteria are sufficiently reliable for assessing tumour response and recurrence

[60,61]. One perfusion CT study suggested that analysis of blood volume was useful for detecting recurrence in contact with ablation zones [62], but these results have not been validated.

More studies have been published regarding the role of perfusion imaging (using either perfusion CT or dynamic CE MRI) to assess the efficacy of intra-arterial therapy. Animal studies have shown that early changes in perfusion parameters (at 1 week) are observed after transarterial chemoembolisation in treated compared to untreated areas [63–65]. Similar results have been observed in humans, i.e. the ability to detect tumour residues following transarterial chemoembolisation [55,66–69]. Pre-treatment perfusion parameters before transarterial chemoembolisation have been shown to predict progression free-survival, independently of tumour size and number of lesions [70].

In patients treated with targeted therapies, perfusion parameters (using either CT or MR) decrease early and significantly in responders when compared to non-responders. Higher baseline perfusion values are also observed in patients in whom the disease was controlled [71–73]. French teams also reported that standardized quantitative CEUS could predict tumour progression [74–76]. This technique is not based on pharmacokinetic models allowing for the extraction of quantitative perfusion parameters. It is based on the descriptive but quantitative analysis of intensity-time enhancement curves.

Added value of metabolic imaging in primary liver tumours

Most published studies have used ^{18}F-FDG. The sensitivity of PET using ^{18}F-FDG is low (approximately 50%), especially for small and/or well-differentiated HCCs [77]. Overall, around 30–50% of all HCC are missed [78], explaining why ^{18}F-FDG PET is not routinely used in the management of HCC. Nevertheless, ^{18}F-FDG uptake is mostly observed in high-grade HCCs, thus providing potentially interesting information regarding tumour biology [79,80]. Indeed, some teams use ^{18}F-FDG PET for patient selection before liver transplantation, with promising results [81]. Other indications include detection of extrahepatic disease with a reported 83 % sensitivity for supra-centimetre extrahepatic metastases [82], or diagnosis of recurrent HCC especially in patients with poorly-differentiated HCC [83]. MFCs has been reported to be highly FDG avid [84], with 84-94% sensitivity and

79-100% specificity [85,86]. Nevertheless, there are limited data available on the influence of PET/CT imaging for the management of MFC [84], and this examination is not routinely performed by most teams.

Published data with other radiotracers is limited, and most studies have compared alternative tracers to ^{18}F-FDG PET only. In all cases, tracers are metabolised in normal hepatocytes, resulting in high background uptake, limiting their utility. Choline has been the most studied tracer. Various studies have shown that ^{11}C-choline and ^{18}F-choline have increased uptake in moderately differentiated HCC, but lower uptake in poorly differentiated lesions. A recent meta-analysis reported a detection rate of 84% [87], significantly higher than that of ^{18}F-FDG [88]. Finally, ^{11}C-acetate showed an encouraging sensitivity of 75% for detecting HCC, but decreased to 32% in HCC smaller than 2 cm [89].

Secondary liver tumours

The dual blood supply of the liver from the portal venous system and hepatic artery, and the sinusoidal cytoarchitecture of the liver parenchyma with its vessel fenestrations both favour the invasion of circulating tumour cells for establishing metastatic foci. Liver metastases (LM) occur in approximately 50% of patients with colorectal carcinoma (CRC) [90], and in approximately 10% of all cases of breast cancer [91]. Depending on primary tumour site and grade, LM may occur in up to 95% of patients with neuroendocrine tumours (NET) [92]. If liver biopsies is often performed for tumor characterization, the apparition of focal liver lesions showing typical imaging features with or without elevated tumor markers in patients with a pathologically proven primary cancer with a pathologically proven primary cancer do not require a pathological proof of liver metastases. Advances in the management of LM with surgical and non-surgical modalities underscore the importance of their morphologic and functional characterisation as they play crucial roles in staging and thus treatment selection. Furthermore, assessment of extra-hepatic disease triggers treatment decisions for LM.

Meticulous characterisation of colorectal (CR) LM is essential for optimal treatment selection. Whilst chemotherapy is the mainstay of CRLM treatment, modern onco-surgical techniques for controlling CRLM have been associated with 5-year survival rates of up to 58% with two-stage hepatectomy [93], compared to as low as 5% for those with disease not amenable for resection[94]. Accurate imaging information on extent of tumour burden, intrahepatic anatomy and topography including calculation of future liver remnant is pre-requisite for advanced surgical planning [95].

Hepatic metastases from NET are often small (<10mm) with a bilobar distribution, with morphological imaging underestimating true hepatic disease burden by at least 50% as compared to meticulous pathological examination [96]. Various therapeutic strategies may be employed in the management of neuroendocrine liver metastases, including resection, transplantation, trans-arterial or percutaneous liver-directed modalities including SIRT, peptide receptor radionuclide therapy (PRRT) [92], and medical treatment with targeted drugs or chemotherapy. Treatment of neuroendocrine (NE) LM is often multimodal, with therapy planning underpinned by accurate radiological interrogation of hepatic disease. Neuroendocrine LM are classically described as hypervascular lesions. This is partly true as they indeed tend to be more vascularised than LM from other, commoner primary tumours, yet hypovascular NE LM are relatively common. The technique for MRI of NE LM should incorporate T1, T2 and CE sequences.

Added value of hepatobiliary contrast and diffusion-weighted MRI in secondary liver tumours

Magnetic resonance imaging with diffusion-weighted sequences and hepatobiliary contrast agents are extremely useful modalities for lesion characterisation. A recent meta-analysis [97] of 39 studies (1989 patients, 3854 metastases) compared hepatobiliary contrast enhanced MRI with DW MRI in detecting CRLM. This demonstrated per-lesion sensitivity estimates for DW-, gadoxetic acid-enhanced MRI, and the combined sequence for detecting CRLM of 87.1%, 90.6% and 95.5%, respectively. Gadoxetic acid-enhanced MRI and the combined sequence were significantly more sensitive than DW MRI

($p=0.0001$ and $p<0.0001$, respectively), with combined sequence imaging in turn significantly more sensitive than gadoxetic acid-enhanced MRI ($p<0.0001$). Similar results were observed in studies comparing these 3 techniques simultaneously. The combination of DW and CE MR sequences provides the optimal sensitivity for CRLM. Experience with DW MRI in NE LM is relatively restricted, although existing data are promising: DW MRI possesses a higher sensitivity than T2 MRI and dynamic MRI [98] in NE LM characterisation, and has been used to evaluate response to treatment with transarterial chemoembolisation [99] and SIRT [100] although these roles are not yet routine.

Added value of perfusion imaging in secondary liver tumours

Perfusion imaging has been analysed in the context of assessing the response of CRLM to treatment with combined targeted and cytotoxic therapies. A significantly higher baseline vascular permeability was reported in responders to such treatment, as was a significant decrease after 6 weeks of treatment [101]. Furthermore, improved progression-free survival has been demonstrated in those with reductions of >40% in the transfer constant on dynamic CE MRI [102]. Regarding SIRT, significant differences in arterial perfusion have been identified between responders and non-responders on pre-treatment CT perfusion imaging [103], with higher perfusion associated with a significantly improved 1-year survival. Experience with perfusion imaging in NE LM is limited, although the existing data are consistent with those obtained in CRLM [104].

Added value of molecular imaging in colorectal liver metastases

Three recent systematic reviews/meta-analyses have compared imaging CRLM with PET and morphological modalities [105–107]. Although the number of studies directly comparing these modalities is low, it appears that CT and MRI possess higher sensitivity than PET in per-lesion and per-patient bases. Nevertheless, PET may be more specific and is capable of altering initial management plans in 24% of patients on average [107], with noted power in detecting extra-hepatic deposits and thus impact

on selection for hepatectomy. However, prospective studies have not demonstrated survival benefit of including PET in the radiological work-up for CRLM [108,109].

The use of ^{18}F-FDG PET for monitoring of chemotherapy is not recommended [110,111], a notable consideration given that the mainstay of metastatic CRC treatment is cytotoxic chemotherapy. Indeed, the optimal modalities for assessing CRLM patients treated with neoadjuvant chemotherapeutics are CE or DW MRI [110]. For non-surgical patients the albeit limited data suggests that ^{18}F-FDG PET and ^{18}F-FDG PET/CT are useful for evaluating response of CRLM after treatment with SIRT [112]. Early metabolic response, defined as >50% reduction of liver-to-tumour ratio on ^{18}F-FDG PET may correlate with survival post-SIRT and aid adaptation of management to tumour response [113]. Furthermore, ^{18}F-FDG PET/CT-derived factors such as functional tumour volume and total lesion glycolysis have been demonstrated to be significant prognosticators for patient survival following SIRT in small cohorts [112]. Hybrid ^{18}F-FDG PET/MRI has been shown to possess higher accuracy in the diagnosis of LM in a number of reports either in mixed cohorts [114,115] or in exclusively CRC cohorts [116] however further studies specific to CRLM are required.

Added value of molecular imaging in neuroendocrine liver metastases

The molecular imaging repertoire for NET encompasses an array of radiotracers. Selection is dependent on tumour grade (G) and availability. Based on Ki67 index, NET may be classified as G1 (Ki67 ≤2%), G2 (Ki67 3-20%) and G3 (Ki67 >20%, neuroendocrine carcinoma [NEC]) [117]. Radiotracers may exploit the observation that G1/2 NET commonly express somatostatin receptors (SSTRs) on their cell membranes, most commonly SSTR2. Such SSTR-targeted imaging includes SSTR scintigraphy (SRS) with the radioligand [^{111}In-DTPA^{0}]octreotide (OctreoScan), or SSTR PET using somatostatin analogues (SSAs) radiolabelled with the positron emitters Gallium-68 (^{68}Ga), or Copper-64 (^{64}Cu). Functional SSTR-targeted imaging is the ideal modality capable of ascertaining the suitability of PRRT as a treatment strategy. Recently developed tracers include radioligands with high affinity for glucagon-like peptide-1 receptors (GLP-1R), mostly utilised in single photon emission

computed tomography (SPECT)/CT for the localisation of occult insulinoma, which typically have lower expression of SSTRs [118] and are often challenging to localise. GLP-1R based imaging has been shown to guide surgical decision and enable parenchyma-sparring pancreatic resections [119].

Alternatively, tumour cell metabolism may be targeted; ^{18}F-FDG is useful in imaging NEC or poorly-differentiated NET. Other tracers that target neuroendocrine cell amine precursor uptake and metabolism are available for NET, including 6-^{18}F-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) and β-[^{11}C]-5-hydroxy-L-tryptophan (^{11}C-5-HTP).

Globally, OctreoScan is the most widely utilised imaging modality for NET, and is typically combined with SPECT or SPECT/CT to optimise lesion localisation and characterisation [120]. Imaging may be done at 24hr and 48hr post-injection, due to a half-life of 2.8days. To avert potential competition at SSTRs between radiolabelled analogues and therapeutic SSAs and thus image degradation, it has been posited that short-acting SSAs and long-acting SSAs be temporarily discontinued for at 24hr and 3-6weeks before SRS, respectively, although this is debated [121,122]. Primary tumour localisation rates with OctreoScan have been reported to be as low as 37% [123] in recent studies, although its performance in detecting liver metastases appears better, with sensitivities from 49.3% [124] to 91% being reported [125]. However, one study by Dromain and colleagues [124] demonstrated MRI as superior to CT and SRS in detecting NE LM. The predominant limiting factors for SRS in detecting neuroendocrine liver metastases appear to be tumour size [123], relatively high tracer uptake in the liver due to hepatocyte SSTR expression, and hepatic and renal tracer excretion [126]. Technetium-99 (^{99m}Tc) labelled SSAs, such as ^{99m}Tc-EDDA/HYNIC-Tyr^3-octreotide (^{99m}Tc-EDDA/HYNIC-TOC), which is alternatively known as ^{99m}Tc-Tecktroyd are mostly used in Eastern Europe.

Functional imaging with ^{68}Ga-radiolabelled SSAs (^{68}Ga-SSAs) is restricted mostly to specialist European centres at present. Currently available ^{68}Ga-SSAs include: [68Ga-DOTA^0,Tyr3]octreotide (^{68}Ga-DOTATOC), [^{68}Ga-DOTA,1-Nal^3]octreotide (^{68}Ga-DOTANOC) and [^{68}Ga-DOTA^0,Tyr^3]octreotate (^{68}Ga-DOTATATE), which possess comparable sensitivities and specificities [127]. However, ^{68}Ga-SSA PET is increasingly expected to become the global gold standard by virtue of

its improved lesion detection capabilities as compared to SRS [128,129] and CT/MRI [130,131] with obvious ramifications on informing treatment strategies [131,132], as well as reported cost-effectiveness [133]. Molecular imaging with ^{68}Ga-SSA PET plays a major role in the selection of patients for PRRT and their personalised management [134]. Recent studies have suggested that the combination of ^{68}Ga-DOTA PET and MRI with [135–137] or without [138] contrast is an optimal imaging strategy for gastroenteropancreatic NE LM, with the two modalities providing complementary information regarding the state of disease intrinsic to the liver.

Despite the overall improved capabilities of ^{68}Ga-SSA PET over morphological imaging in assessing disease stage, even SSTR-targeted imaging has been shown to underestimate true disease burden, particularly sub-centimetre lesions such as miliary liver metastases. A group from Copenhagen recently developed the novel tracer ^{64}Cu-DOTATATE which can identify liver metastases that ^{111}In-DTPA SRS cannot [139], although there have been no studies comparing ^{64}Cu-DOTATATE PET with ^{68}Ga-DOTATATE PET.

The glucose analogue ^{18}F-FDG is limited to the imaging of NEC and poorly-differentiated NET. On a per-patient basis, ^{18}F-FDG PET has inferior sensitivity compared to both SRS [140] and ^{68}Ga-SSA PET [141]. However, a correlation between higher tumour grade and ^{18}F-FDG uptake has been demonstrated in NET [142]. Clinical experience with ^{11}C-5-HTP PET in NET is mostly confined to Dutch and Swedish centres, arguably due to the complexities of tracer synthesis. Contrastingly, ^{18}F-DOPA is more widely available due to implementation in functional neurological imaging, and targets NET amine metabolism. Both ^{18}F-DOPA and ^{11}C-5-HTP may be alternative or problem-solving modalities in tumours negative on SSTR imaging. The study of Koopmans et al [143] compared these against CT and SRS in both enteric and pancreatic islet cell tumours. For LM from enteric tumours, ^{18}F-DOPA PET/CT significantly out-performed ^{11}C-5-HTP PET/CT (sensitivities 100% and 91%, respectively); whereas for metastases from pancreatic NET, ^{11}C-5-HTP PET/CT significantly out-performed ^{18}F-DOPA PET/CT (sensitivities 96% and 86%, respectively). Whilst the data directly comparing ^{68}Ga-SSA PET and ^{18}F-DOPA PET are limited, it appears that the former detects more liver lesions than the latter [144,145].

Interestingly, SSTR-antagonists such as ^{111}In-DOTA-BASS have emerged as a promising novel approach. These have displayed higher, prolonged retention in tumours and predicated improved imaging quality compared to ^{111}In-pentreotide scans in small patient series [146]. Early evidence also suggests a potential role for ^{89}Zr-labelled bevacizumab in assessing NET treatment response to everolimus [147].

Added role of molecular imaging in non-colorectal, non-neuroendocrine liver metastases

Although functional imaging does not exert much influence on the assessment of locoregional disease in pancreatic cancer, studies have demonstrated appreciable effects of PET/CT in detecting metastatic deposits. A recent meta-analysis of the use of ^{18}F-FDG PET in pancreatic cancer [148] demonstrated pooled sensitivity and specificity values of 67% and 96%, respectively, for LM. Unsurprisingly, combined PET/CT was significantly more sensitive than PET alone in pancreatic LM evaluation (82% vs. 67%). Not to be used as a stand-alone modality, studies have demonstrated the effect of PET as an add-on to morphological imaging in altering initial management plans for up to 26% of patients based on its power in detecting distant disease [149] [150].

Whilst occupying limited roles in radiologically assessing oesophageal carcinomas due to low sensitivity (18-100%) and resolution limits [151], PET has clinically useful accuracy in pre-operatively detecting distant metastases. The meta-analysis of van Vliet et al. [152] demonstrated a sensitivity and specificity of PET of 71% and 93%, respectively, vs. 52% and 91% for CT, respectively. Furthermore, PET has been shown to alter strategies in approximately one third of patients [153,154]. Nevertheless, data specifically pertaining to PET for oesophageal LM is scarce, likely due to the limited impact that LM specifically exert on management strategies, as distant metastases of any site preclude a curative surgical approach in oesophageal carcinoma, and the repertoire of therapies for such disease is limited to cytotoxic and molecularly-targeted therapies and not inclusive of liver-targeted modalities.

Limitations and realistic clinical use of functional imaging techniques

Functional imaging techniques are widely performed for various purposes, yet some are routinely used, while others remain restricted to the field of clinical of pre-clinical research. This is mostly due to the strength and limitations that each technique individually bears.

Most techniques are used as *qualitative rather than quantitative* tools because they provide valuable information about tumor tissue. Diffusion-weighted imaging is now well established and validated as a cellularity/architecture biomarker, hepatospecific MR contrast agents are accurate biomarkers of the hepatocellular functions, and molecular imaging of tumor biology. This illustrates the difference between *functional imaging* and *quantitative imaging.* They all suffer from limitations (technical, clinical, biological, etc). Regarding diffusion-weighted imaging, reproducibility and sequence standardization need to be further improved. The use of hepatospecific contrast agents requires clinical validation in specific clinical context. Molecular imaging is limited either by a lack of tracer uptake (for instance in HCC), or the lack of validation or evidence that its use positively impact patients' outcome (for instance in cholangiocarcinoma and colorectal liver metastases). Nevertheless, and interestingly, these limitations do not prevent from using these functional imaging technique either routinely and worldwide (diffusion-weighted imaging and hepatospecific MR contrast agents), or in more selected cases (molecular imaging).

Perfusion imaging is different because it is not used in clinical practice due to major technical limitations: lack of standardization of acquisition protocols, mathematical models, and post-processing. This leads to a high variability and to the difficulty to replicate and compare results issues from different vendors and teams.

Concluding perspectives

Functional imaging offers useful clinical information as alterations in parameters such as tumour perfusion and cellular metabolic activity often precede – and are thus observed earlier than – morphological changes evident on conventional imaging.

For the commonest primary liver tumours, HCC and MFC, functional imaging plays central roles in radiological work-up. Particular examples include the delineation between HCC and non-HCC cirrhotic nodules on MRI with hepatobiliary contrast agents based on lesion signal intensity, and also the increased detection of HCC with the addition of DW sequences. Whilst experience with perfusion imaging is relatively limited, the data are encouraging regarding future clinical utility in assessing the effects of loco-regional and systemic therapies. Whilst molecular imaging with ^{18}F-FDG PET has been used by some centres in patient selection for liver transplantation for HCC, and also for imaging of MFC, these indications are not widely acknowledged.

Whilst CE CT is typically employed as the first-step staging modality in primary colorectal cancer, CE and DW MRI are typically regarded as the gold-standard in the diagnostic work-up of patients with CRLM due to their high accuracy of lesion detection. The data regarding ^{18}F-FDG PET as an add-on modality for CRLM is conflicting across studies. Whilst some studies suggest a favourable effect on patient selection for hepatectomy by virtue of its capabilities in detecting extra-hepatic disease, the clinical role for this functional modality is yet to be established.

Molecular SSTR-targeted imaging represents the gold-standard imaging approach in the majority of cases of metastatic NET. Whilst ^{68}Ga-SSA PET/CT is seemingly the most accurate (established) molecular tracer with a sensitivity of 82-100% and a specificity of 67-100% [155], its availability is limited. The archetypal oncological imaging radiotracer ^{18}F-FDG is limited to imaging high-grade NET. Novel tracers including those targeting GLP-1 receptors represent useful advances in tumour type-specific imaging in this heterogeneous family of neoplasms.

Data regarding functional imaging of LM from other primary tumour types is limited, arguably mostly attributable to the lack of specific, LM-targeted therapies for such tumours and thus futility of extensive functional characterisation of hepatic disease.

With expansions in the armamentarium for the management of liver tumours, functional imaging may play key roles in treatment selection and assessing disease response during the treatment journey, for example, as is evident in the preliminary reports discussed above. The recent realisation of PET/MRI hybrid scanners [114] and the introduction of radiomics – comprehensive quantification of tumour phenotypes by applying a large number of quantitative features from imaging, [156] represent exciting prospects in liver tumour imaging.

References

1 Taouli B, Koh D-M. Diffusion-weighted MR imaging of the liver. *Radiology*. 2010 Jan; **254**: 47–66.

2 Ronot M, Lambert S, Daire J-L, Lagadec M, Doblas S, Garteiser P, *et al.* Can we justify not doing liver perfusion imaging in 2013? *Diagn Interv Imaging*. 2013 Dec; **94**: 1323–1336.

3 Van Beers BE, Doblas S, Sinkus R. New acquisition techniques: fields of application. *Abdom Imaging*. 2012 Apr; **37**: 155–163.

4 Van Beers BE, Pastor CM, Hussain HK. Primovist, Eovist: what to expect? *J Hepatol*. 2012 Aug; **57**: 421–429.

5 Vilgrain V, Van Beers BE, Pastor CM. Insights into the diagnosis of hepatocellular carcinomas with hepatobiliary MRI. *J Hepatol*. 2015 Nov 26;

6 Kitao A, Matsui O, Yoneda N, Kozaka K, Shinmura R, Koda W, *et al.* The uptake transporter OATP8 expression decreases during multistep hepatocarcinogenesis: correlation with gadoxetic acid enhanced MR imaging. *Eur Radiol*. 2011 Oct; **21**: 2056–2066.

7 Kitao A, Zen Y, Matsui O, Gabata T, Kobayashi S, Koda W, *et al.* Hepatocellular carcinoma: signal intensity at gadoxetic acid-enhanced MR Imaging--correlation with molecular transporters and histopathologic features. *Radiology*. 2010 Sep; **256**: 817–826.

8 Nakamura Y, Toyota N, Date S, Oda S, Namimoto T, Yamashita Y, *et al.* Clinical significance

of the transitional phase at gadoxetate disodium-enhanced hepatic MRI for the diagnosis of hepatocellular carcinoma: preliminary results. *J Comput Assist Tomogr*. Jan; **35**: 723–727.

9 Le Bihan D, Breton E, Lallemand D, Aubin ML, Vignaud J, Laval-Jeantet M. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. *Radiology*. 1988 Aug; **168**: 497–505.

10 http://globocan.iarc.fr/Default.aspx Last accessed June 20, 2016

11 Bridgewater J, Galle PR, Khan SA, Llovet JM, Park J-W, Patel T, *et al.* Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol*. 2014 Jun; **60**: 1268–1289.

12 Ronot M, Vilgrain V. Hepatocellular carcinoma: diagnostic criteria by imaging techniques. *Best Pract Res Clin Gastroenterol*. 2014 Oct; **28**: 795–812.

13 EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2012 Apr; **56**: 908–943.

14 Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011 Mar; **53**: 1020–1022.

15 Rimola J, Forner A, Tremosini S, Reig M, Vilana R, Bianchi L, *et al.* Non-invasive diagnosis of hepatocellular carcinoma ≤ 2 cm in cirrhosis. Diagnostic accuracy assessing fat, capsule and signal intensity at dynamic MRI. *J Hepatol*. 2012 Jun; **56**: 1317–1323.

16 Sersté T, Barrau V, Ozenne V, Vullierme M-P, Bedossa P, Farges O, *et al.* Accuracy and disagreement of computed tomography and magnetic resonance imaging for the diagnosis of small hepatocellular carcinoma and dysplastic nodules: role of biopsy. *Hepatology*. 2012 Mar; **55**: 800–806.

17 Rode A, Bancel B, Douek P, Chevallier M, Vilgrain V, Picaud G, *et al.* Small nodule detection in cirrhotic livers: evaluation with US, spiral CT, and MRI and correlation with pathologic examination of explanted liver. *J Comput Assist Tomogr*. Jan; **25**: 327–336.

18 Kim YK, Kim CS, Chung GH, Han Y-M, Lee SY, Chon S Bin, *et al.* Comparison of gadobenate dimeglumine-enhanced dynamic MRI and 16-MDCT for the detection of hepatocellular carcinoma. *AJR Am J Roentgenol*. 2006 Jan; **186**: 149–157.

19 Sano K, Ichikawa T, Motosugi U, Sou H, Muhi AM, Matsuda M, *et al.* Imaging study of early hepatocellular carcinoma: usefulness of gadoxetic acid-enhanced MR imaging. *Radiology*. 2011 Dec; **261**: 834–844.

20 Kierans AS, Kang SK, Rosenkrantz AB. The Diagnostic Performance of Dynamic Contrast-enhanced MR Imaging for Detection of Small Hepatocellular Carcinoma Measuring Up to 2 cm: A Meta-Analysis. *Radiology*. 2016 Jan; **278**: 82–94.

21 Kim M-J, Lee M, Choi J-Y, Park YN. Imaging features of small hepatocellular carcinomas with microvascular invasion on gadoxetic acid-enhanced MR imaging. *Eur J Radiol*. 2012 Oct; **81**: 2507–2512.

22 Kim H-D, Lim Y-S, Han S, An J, Kim G-A, Kim SY, *et al.* Evaluation of early-stage hepatocellular carcinoma by magnetic resonance imaging with gadoxetic acid detects additional lesions and increases overall survival. *Gastroenterology*. 2015 Jun; **148**: 1371–1382.

23 2014 KLCSG-NCC Korea Practice Guideline for the Management of Hepatocellular Carcinoma. *Gut Liver*. 2015 May 23; **9**: 267–317.

24 Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, *et al.* JSH Consensus-Based Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma: 2014 Update by the Liver Cancer Study Group of Japan. *Liver cancer*. 2014 Oct; **3**: 458–468.

25 Joo I, Lee JM, Lee DH, Jeon JH, Han JK, Choi BI. Noninvasive diagnosis of hepatocellular carcinoma on gadoxetic acid-enhanced MRI: can hypointensity on the hepatobiliary phase be used as an alternative to washout? *Eur Radiol*. 2015 Oct; **25**: 2859–2868.

26 Choi JW, Lee JM, Kim SJ, Yoon J-H, Baek JH, Han JK, *et al.* Hepatocellular carcinoma:

imaging patterns on gadoxetic acid-enhanced MR Images and their value as an imaging biomarker. *Radiology*. 2013 Jun; **267**: 776–786.

27 Hyodo T, Murakami T, Imai Y, Okada M, Hori M, Kagawa Y, *et al.* Hypovascular nodules in patients with chronic liver disease: risk factors for development of hypervascular hepatocellular carcinoma. *Radiology*. 2013 Feb; **266**: 480–490.

28 Motosugi U, Ichikawa T, Sano K, Sou H, Onohara K, Muhi A, *et al.* Outcome of hypovascular hepatic nodules revealing no gadoxetic acid uptake in patients with chronic liver disease. *J Magn Reson Imaging*. 2011 Jul; **34**: 88–94.

29 Akai H, Matsuda I, Kiryu S, Tajima T, Takao H, Watanabe Y, *et al.* Fate of hypointense lesions on Gd-EOB-DTPA-enhanced magnetic resonance imaging. *Eur J Radiol*. 2012 Nov; **81**: 2973–2977.

30 Lee MH, Kim SH, Park MJ, Park CK, Rhim H. Gadoxetic acid-enhanced hepatobiliary phase MRI and high-b-value diffusion-weighted imaging to distinguish well-differentiated hepatocellular carcinomas from benign nodules in patients with chronic liver disease. *AJR Am J Roentgenol*. 2011 Nov; **197**: W868–W875.

31 Hwang J, Kim YK, Jeong WK, Choi D, Rhim H, Lee WJ. Nonhypervascular Hypointense Nodules at Gadoxetic Acid-enhanced MR Imaging in Chronic Liver Disease: Diffusion-weighted Imaging for Characterization. *Radiology*. 2015 Oct; **277**: 309.

32 Kang Y, Lee JM, Kim SH, Han JK, Choi BI. Intrahepatic mass-forming cholangiocarcinoma: enhancement patterns on gadoxetic acid-enhanced MR images. *Radiology*. 2012 Sep; **264**: 751–760.

33 Kim R, Lee JM, Shin C-I, Lee ES, Yoon JH, Joo I, *et al.* Differentiation of intrahepatic mass-forming cholangiocarcinoma from hepatocellular carcinoma on gadoxetic acid-enhanced liver MR imaging. *Eur Radiol*. 2015 Sep 15;

34 Wu L-M, Xu J-R, Lu Q, Hua J, Chen J, Hu J. A pooled analysis of diffusion-weighted imaging

in the diagnosis of hepatocellular carcinoma in chronic liver diseases. *J Gastroenterol Hepatol*. 2013 Feb; **28**: 227–234.

35 Vandecaveye V, De Keyzer F, Verslype C, Op de Beeck K, Komuta M, Topal B, *et al.* Diffusion-weighted MRI provides additional value to conventional dynamic contrast-enhanced MRI for detection of hepatocellular carcinoma. *Eur Radiol*. 2009 Oct; **19**: 2456–2466.

36 Piana G, Trinquart L, Meskine N, Barrau V, Beers B Van, Vilgrain V. New MR imaging criteria with a diffusion-weighted sequence for the diagnosis of hepatocellular carcinoma in chronic liver diseases. *J Hepatol*. 2011 Jul; **55**: 126–132.

37 Park M-S, Kim S, Patel J, Hajdu CH, Do RKG, Mannelli L, *et al.* Hepatocellular carcinoma: detection with diffusion-weighted versus contrast-enhanced magnetic resonance imaging in pretransplant patients. *Hepatology*. 2012 Jul; **56**: 140–148.

38 Liver Imaging Reporting and Data System (LI-RADS) - American College of Radiology [Internet]. [cited 2016 Jan 7]. Available from: http://www.acr.org/Quality-Safety/Resources/LIRADS

39 Fattach H El, Dohan A, Guerrache Y, Dautry R, Boudiaf M, Hoeffel C, *et al.* Intrahepatic and hilar mass-forming cholangiocarcinoma: Qualitative and quantitative evaluation with diffusion-weighted MR imaging. *Eur J Radiol*. 2015 Aug; **84**: 1444–1451.

40 Nakanishi M, Chuma M, Hige S, Omatsu T, Yokoo H, Nakanishi K, *et al.* Relationship between diffusion-weighted magnetic resonance imaging and histological tumor grading of hepatocellular carcinoma. *Ann Surg Oncol*. 2012 Apr; **19**: 1302–1309.

41 Catalano OA, Choy G, Zhu A, Hahn PF, Sahani D V. Differentiation of malignant thrombus from bland thrombus of the portal vein in patients with hepatocellular carcinoma: application of diffusion-weighted MR imaging. *Radiology*. 2010 Jan; **254**: 154–162.

42 Mannelli L, Kim S, Hajdu CH, Babb JS, Clark TWI, Taouli B. Assessment of tumor necrosis of hepatocellular carcinoma after chemoembolization: diffusion-weighted and contrast-

enhanced MRI with histopathologic correlation of the explanted liver. *AJR Am J Roentgenol*. 2009 Oct; **193**: 1044–1052.

43 Namimoto T, Yamashita Y, Sumi S, Tang Y, Takahashi M. Focal liver masses: characterization with diffusion-weighted echo-planar MR imaging. *Radiology*. 1997 Sep; **204**: 739–744.

44 Bonekamp S, Li Z, Geschwind J-FH, Halappa VG, Corona-Villalobos CP, Reyes D, *et al.* Unresectable hepatocellular carcinoma: MR imaging after intraarterial therapy. Part I. Identification and validation of volumetric functional response criteria. *Radiology*. 2013 Aug; **268**: 420–430.

45 Bonekamp S, Jolepalem P, Lazo M, Gulsun MA, Kiraly AP, Kamel IR. Hepatocellular carcinoma: response to TACE assessed with semiautomated volumetric and functional analysis of diffusion-weighted and contrast-enhanced MR imaging data. *Radiology*. 2011 Sep; **260**: 752–761.

46 Bonekamp S, Halappa VG, Geschwind J-FH, Li Z, Corona-Villalobos CP, Reyes D, *et al.* Unresectable hepatocellular carcinoma: MR imaging after intraarterial therapy. Part II. Response stratification using volumetric functional criteria after intraarterial therapy. *Radiology*. 2013 Aug; **268**: 431–439.

47 Yuan Z, Zhang J, Yang H, Ye X-D, Xu L-C, Li W-T. Diffusion-Weighted MR Imaging of Hepatocellular Carcinoma: Current Value in Clinical Evaluation of Tumor Response to Locoregional Treatment. *J Vasc Interv Radiol*. 2016 Jan; **27**: 20–30.

48 Kamel IR, Liapi E, Reyes DK, Zahurak M, Bluemke DA, Geschwind J-FH. Unresectable hepatocellular carcinoma: serial early vascular and cellular changes after transarterial chemoembolization as detected with MR imaging. *Radiology*. 2009 Feb; **250**: 466–473.

49 Chen C-Y, Li C-W, Kuo Y-T, Jaw T-S, Wu D-K, Jao J-C, *et al.* Early response of hepatocellular carcinoma to transcatheter arterial chemoembolization: choline levels and MR diffusion constants--initial experience. *Radiology*. 2006 May; **239**: 448–456.

50 Chung JC, Naik NK, Lewandowski RJ, Deng J, Mulcahy MF, Kulik LM, *et al.* Diffusion-weighted magnetic resonance imaging to predict response of hepatocellular carcinoma to chemoembolization. *World J Gastroenterol*. 2010 Jul 7; **16**: 3161–3167.

51 Mannelli L, Kim S, Hajdu CH, Babb JS, Taouli B. Serial diffusion-weighted MRI in patients with hepatocellular carcinoma: Prediction and assessment of response to transarterial chemoembolization. Preliminary experience. *Eur J Radiol*. 2013 Apr; **82**: 577–582.

52 Dong S, Ye X-D, Yuan Z, Xu L-C, Xiao X-S. Relationship of apparent diffusion coefficient to survival for patients with unresectable primary hepatocellular carcinoma after chemoembolization. *Eur J Radiol*. 2012 Mar; **81**: 472–477.

53 Kokabi N, Camacho JC, Xing M, Qiu D, Kitajima H, Mittal PK, *et al.* Apparent diffusion coefficient quantification as an early imaging biomarker of response and predictor of survival following yttrium-90 radioembolization for unresectable infiltrative hepatocellular carcinoma with portal vein thrombosis. *Abdom Imaging*. 2014 Oct; **39**: 969–978.

54 Halappa VG, Bonekamp S, Corona-Villalobos CP, Li Z, Mensa M, Reyes D, *et al.* Intrahepatic cholangiocarcinoma treated with local-regional therapy: quantitative volumetric apparent diffusion coefficient maps for assessment of tumor response. *Radiology*. 2012 Jul; **264**: 285–294.

55 Taouli B, Johnson RS, Hajdu CH, Oei MTH, Merad M, Yee H, *et al.* Hepatocellular carcinoma: perfusion quantification with dynamic contrast-enhanced MRI. *AJR Am J Roentgenol*. 2013 Oct; **201**: 795–800.

56 Ippolito D, Sironi S, Pozzi M, Antolini L, Ratti L, Meloni F, *et al.* Perfusion computed tomographic assessment of early hepatocellular carcinoma in cirrhotic liver disease: initial observations. *J Comput Assist Tomogr*. Jan; **32**: 855–858.

57 Ippolito D, Sironi S, Pozzi M, Antolini L, Ratti L, Alberzoni C, *et al.* Hepatocellular carcinoma in cirrhotic liver disease: functional computed tomography with perfusion imaging in the assessment of tumor vascularization. *Acad Radiol*. 2008 Jul; **15**: 919–927.

58 Fischer MA, Kartalis N, Grigoriadis A, Loizou L, Stål P, Leidner B, *et al.* Perfusion computed tomography for detection of hepatocellular carcinoma in patients with liver cirrhosis. *Eur Radiol*. 2015 Nov; **25**: 3123–3132.

59 Sahani D V, Holalkere N-S, Mueller PR, Zhu AX. Advanced hepatocellular carcinoma: CT perfusion of liver and tumor tissue--initial experience. *Radiology*. 2007 Jun; **243**: 736–743.

60 Chopra S, Dodd GD, Chintapalli KN, Leyendecker JR, Karahan OI, Rhim H. Tumor recurrence after radiofrequency thermal ablation of hepatic tumors: spectrum of findings on dual-phase contrast-enhanced CT. *AJR Am J Roentgenol*. 2001 Aug; **177**: 381–387.

61 Forner A, Ayuso C, Varela M, Rimola J, Hessheimer AJ, de Lope CR, *et al.* Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? *Cancer*. 2009 Feb 1; **115**: 616–623.

62 Meijerink MR, van Waesberghe JHTM, van der Weide L, van den Tol P, Meijer S, Comans EF, *et al.* Early detection of local RFA site recurrence using total liver volume perfusion CT initial experience. *Acad Radiol*. 2009 Oct; **16**: 1215–1222.

63 Choi SH, Chung JW, Kim H-C, Kim H-C, Baek JH, Park CM, *et al.* The role of perfusion CT as a follow-up modality after transcatheter arterial chemoembolization: an experimental study in a rabbit model. *Invest Radiol*. 2010 Jul; **45**: 427–436.

64 Wang D, Bangash AK, Rhee TK, Woloschak GE, Paunesku T, Salem R, *et al.* Liver tumors: monitoring embolization in rabbits with VX2 tumors--transcatheter intraarterial first-pass perfusion MR imaging. *Radiology*. 2007 Oct; **245**: 130–139.

65 Braren R, Altomonte J, Settles M, Neff F, Esposito I, Ebert O, *et al.* Validation of preclinical multiparametric imaging for prediction of necrosis in hepatocellular carcinoma after embolization. *J Hepatol*. 2011 Nov; **55**: 1034–1040.

66 Ippolito D, Bonaffini P-A, Ratti L, Antolini L, Corso R, Fazio F, *et al.* Hepatocellular carcinoma treated with transarterial chemoembolization: dynamic perfusion-CT in the

assessment of residual tumor. *World J Gastroenterol*. 2010 Dec 21; **16**: 5993–6000.

67 Larson AC, Wang D, Atassi B, Sato KT, Ryu RK, Lewandowski RJ, *et al.* Transcatheter intraarterial perfusion: MR monitoring of chemoembolization for hepatocellular carcinoma--feasibility of initial clinical translation. *Radiology*. 2008 Mar; **246**: 964–971.

68 Gaba RC, Wang D, Lewandowski RJ, Ryu RK, Sato KT, Kulik LM, *et al.* Four-dimensional transcatheter intraarterial perfusion MR imaging for monitoring chemoembolization of hepatocellular carcinoma: preliminary results. *J Vasc Interv Radiol*. 2008 Nov; **19**: 1589–1595.

69 Wang D, Jin B, Lewandowski RJ, Ryu RK, Sato KT, Mulcahy MF, *et al.* Quantitative 4D transcatheter intraarterial perfusion MRI for monitoring chemoembolization of hepatocellular carcinoma. *J Magn Reson Imaging*. 2010 May; **31**: 1106–1116.

70 Michielsen K, De Keyzer F, Verslype C, Dymarkowski S, van Malenstein H, Oyen R, *et al.* Pretreatment DCE-MRI for prediction of PFS in patients with inoperable HCC treated with TACE. *Cancer Imaging.* 2011 Jan 1; **11**: S114–S114.

71 Hsu C-Y, Shen Y-C, Yu C-W, Hsu C, Hu F-C, Hsu C-H, *et al.* Dynamic contrast-enhanced magnetic resonance imaging biomarkers predict survival and response in hepatocellular carcinoma patients treated with sorafenib and metronomic tegafur/uracil. *J Hepatol*. 2011 Oct; **55**: 858–865.

72 Zhu AX, Sahani D V, Duda DG, di Tomaso E, Ancukiewicz M, Catalano OA, *et al.* Efficacy, safety, and potential biomarkers of sunitinib monotherapy in advanced hepatocellular carcinoma: a phase II study. *J Clin Oncol*. 2009 Jun 20; **27**: 3027–3035.

73 Sahani D V, Jiang T, Hayano K, Duda DG, Catalano OA, Ancukiewicz M, *et al.* Magnetic resonance imaging biomarkers in hepatocellular carcinoma: association with response and circulating biomarkers after sunitinib therapy. *J Hematol Oncol*. 2013 Jan; **6**: 51.

74 Lassau N, Chapotot L, Benatsou B, Vilgrain V, Kind M, Lacroix J, *et al.* Standardization of dynamic contrast-enhanced ultrasound for the evaluation of antiangiogenic therapies: the

French multicenter Support for Innovative and Expensive Techniques Study. *Invest Radiol*. 2012 Dec; **47**: 711–716.

75 Frampas E, Lassau N, Zappa M, Vullierme M-P, Koscielny S, Vilgrain V. Advanced Hepatocellular Carcinoma: early evaluation of response to targeted therapy and prognostic value of Perfusion CT and Dynamic Contrast Enhanced-Ultrasound. Preliminary results. *Eur J Radiol*. 2013 May; **82**: e205–e211.

76 Lassau N, Bonastre J, Kind M, Vilgrain V, Lacroix J, Cuinet M, *et al.* Validation of dynamic contrast-enhanced ultrasound in predicting outcomes of antiangiogenic therapy for solid tumors: the French multicenter support for innovative and expensive techniques study. *Invest Radiol*. 2014 Dec; **49**: 794–800.

77 Ho C, Chen S, Yeung DWC, Cheng TKC. Dual-tracer PET/CT imaging in evaluation of metastatic hepatocellular carcinoma. *J Nucl Med*. 2007 Jun; **48**: 902–909.

78 Hennedige T, Venkatesh SK. Imaging of hepatocellular carcinoma: diagnosis, staging and treatment monitoring. *Cancer Imaging*. 2013 Jan; **12**: 530–547.

79 Torizuka T, Tamaki N, Inokuma T, Magata Y, Sasayama S, Yonekura Y, *et al.* In vivo assessment of glucose metabolism in hepatocellular carcinoma with FDG-PET. *J Nucl Med*. 1995 Oct; **36**: 1811–1817.

80 Seo S, Hatano E, Higashi T, Hara T, Tada M, Tamaki N, *et al.* Fluorine-18 fluorodeoxyglucose positron emission tomography predicts tumor differentiation, P-glycoprotein expression, and outcome after resection in hepatocellular carcinoma. *Clin Cancer Res*. 2007 Jan 15; **13**: 427–433.

81 Hong G, Suh K-S, Suh S, Yoo T, Kim H, Park M-S, *et al.* Preoperative Alpha-fetoprotein and (18)F-FDG PET Predict Tumor Recurrence better than Milan Criteria in Living Donor Liver Transplantation. *J Hepatol*. 2015 Nov 30;

82 Sugiyama M, Sakahara H, Torizuka T, Kanno T, Nakamura F, Futatsubashi M, *et al.* 18F-FDG

PET in the detection of extrahepatic metastases from hepatocellular carcinoma. *J Gastroenterol*. 2004 Oct; **39**: 961–968.

83 Lin C-Y, Chen J-H, Liang J-A, Lin C-C, Jeng L-B, Kao C-H. 18F-FDG PET or PET/CT for detecting extrahepatic metastases or recurrent hepatocellular carcinoma: a systematic review and meta-analysis. *Eur J Radiol*. 2012 Sep; **81**: 2417–2422.

84 Jiang L, Tan H, Panje CM, Yu H, Xiu Y, Shi H. Role of 18F-FDG PET/CT Imaging in Intrahepatic Cholangiocarcinoma. *Clin Nucl Med*. 2016 Jan; **41**: 1–7.

85 Jadvar H, Henderson RW, Conti PS. [F-18]fluorodeoxyglucose positron emission tomography and positron emission tomography: computed tomography in recurrent and metastatic cholangiocarcinoma. *J Comput Assist Tomogr*. Jan; **31**: 223–228.

86 Kim JY, Kim M-H, Lee TY, Hwang CY, Kim JS, Yun S-C, *et al.* Clinical role of 18F-FDG PET-CT in suspected and potentially operable cholangiocarcinoma: a prospective study compared with conventional imaging. *Am J Gastroenterol*. 2008 May; **103**: 1145–1151.

87 Bertagna F, Bertoli M, Bosio G, Biasiotto G, Sadeghi R, Giubbini R, *et al.* Diagnostic role of radiolabelled choline PET or PET/CT in hepatocellular carcinoma: a systematic review and meta-analysis. *Hepatol Int*. 2014 Oct; **8**: 493–500.

88 Talbot J-N, Fartoux L, Balogova S, Nataf V, Kerrou K, Gutman F, *et al.* Detection of hepatocellular carcinoma with PET/CT: a prospective comparison of 18F-fluorocholine and 18F-FDG in patients with cirrhosis or chronic liver disease. *J Nucl Med*. 2010 Nov; **51**: 1699–1706.

89 Park J-W, Kim JH, Kim SK, Kang KW, Park KW, Choi J-I, *et al.* A prospective evaluation of 18F-FDG and 11C-acetate PET/CT for detection of primary and metastatic hepatocellular carcinoma. *J Nucl Med*. 2008 Dec; **49**: 1912–1921.

90 Taylor A, Langeberg W, Mowat F, Alexander D, Choti M, Poston G. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin*

Epidemiol. 2012 Nov; **4**: 283.

91 Page AJ, Weiss MJ, Pawlik TM. Surgical management of noncolorectal cancer liver metastases. *Cancer*. 2014 Oct 15; **120**: 3111–3121.

92 Frilling A, Modlin IM, Kidd M, Russell C, Breitenstein S, Salem R, *et al.* Recommendations for management of patients with neuroendocrine liver metastases. *Lancet Oncol*. 2014 Jan; **15**: e8–e21.

93 Brouquet A, Abdalla EK, Kopetz S, Garrett CR, Overman MJ, Eng C, *et al.* High survival rate after two-stage resection of advanced colorectal liver metastases: response-based selection and complete resection define outcome. *J Clin Oncol*. 2011 Mar 10; **29**: 1083–1090.

94 Tzeng C-WD, Aloia TA. Colorectal liver metastases. *J Gastrointest Surg*. 2013 Jan; **17**: 195–201; quiz p.201–202.

95 Radtke A, Sotiropoulos GC, Molmenti EP, Schroeder T, Peitgen HO, Frilling A, *et al.* Computer-assisted surgery planning for complex liver resections: when is it helpful? A single-center experience over an 8-year period. *Ann Surg*. 2010 Nov; **252**: 876–883.

96 Elias D, Lefevre JH, Duvillard P, Goéré D, Dromain C, Dumont F, *et al.* Hepatic metastases from neuroendocrine tumors with a 'thin slice' pathological examination: they are many more than you think... *Ann Surg*. 2010 Feb; **251**: 307–310.

97 Vilgrain V, Esvan M, Ronot M, Caumont-Prim A, Aube C, Chatellier G. A meta-analysis of diffusion-weighted and gadoxetic acid-enhanced MR imaging for the detection of colorectal liver metastases. *Eur Radiol*. 2016;

98 d'Assignies G, Fina P, Bruno O, Vullierme M-P, Tubach F, Paradis V, *et al.* High sensitivity of diffusion-weighted MR imaging for the detection of liver metastases from neuroendocrine tumors: comparison with T2-weighted and dynamic gadolinium-enhanced MR imaging. *Radiology*. 2013 Aug; **268**: 390–399.

99 Liapi E, Geschwind J-F, Vossen JA, Buijs M, Georgiades CS, Bluemke DA, *et al.* Functional

MRI evaluation of tumor response in patients with neuroendocrine hepatic metastasis treated with transcatheter arterial chemoembolization. *AJR Am J Roentgenol*. 2008 Jan; **190**: 67–73.

100 Kukuk GM, Mürtz P, Träber F, Meyer C, Ullrich J, Gieseke J, *et al.* Diffusion-weighted imaging with acquisition of three b-values for response evaluation of neuroendocrine liver metastases undergoing selective internal radiotherapy. *Eur Radiol*. 2014 Feb; **24**: 267–276.

101 Coenegrachts K, Bols A, Haspeslagh M, Rigauts H. Prediction and monitoring of treatment effect using T1-weighted dynamic contrast-enhanced magnetic resonance imaging in colorectal liver metastases: potential of whole tumour ROI and selective ROI analysis. *Eur J Radiol*. 2012 Dec; **81**: 3870–3876.

102 De Bruyne S, Van Damme N, Smeets P, Ferdinande L, Ceelen W, Mertens J, *et al.* Value of DCE-MRI and FDG-PET/CT in the prediction of response to preoperative chemotherapy with bevacizumab for colorectal liver metastases. *Br J Cancer*. 2012 Jun 5; **106**: 1926–1933.

103 Morsbach F, Pfammatter T, Reiner CS, Fischer MA, Sah B-R, Winklhofer S, *et al.* Computed tomographic perfusion imaging for the prediction of response and survival to transarterial radioembolization of liver metastases. *Invest Radiol*. 2013 Nov; **48**: 787–794.

104 Miyazaki K, Orton MR, Davidson RL, d'Arcy JA, Lewington V, Koh TS, *et al.* Neuroendocrine tumor liver metastases: use of dynamic contrast-enhanced MR imaging to monitor and predict radiolabeled octreotide therapy response. *Radiology*. 2012 Apr; **263**: 139–148.

105 Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology*. 2010 Dec; **257**: 674–684.

106 Patel S, McCall M, Ohinmaa A, Bigam D, Dryden DM. Positron emission tomography/computed tomographic scans compared to computed tomographic scans for detecting colorectal liver metastases: a systematic review. *Ann Surg*. 2011 Apr; **253**: 666–671.

107 Maffione AM, Lopci E, Bluemel C, Giammarile F, Herrmann K, Rubello D. Diagnostic accuracy and impact on management of (18)F-FDG PET and PET/CT in colorectal liver metastasis: a meta-analysis and systematic review. *Eur J Nucl Med Mol Imaging*. 2015 Jan; **42**: 152–163.

108 Ruers TJM, Wiering B, van der Sijp JRM, Roumen RM, de Jong KP, Comans EFI, *et al.* Improved selection of patients for hepatic surgery of colorectal liver metastases with (18)F-FDG PET: a randomized study. *J Nucl Med*. 2009 Jul; **50**: 1036–1041.

109 Moulton C-A, Gu C-S, Law CH, Tandan VR, Hart R, Quan D, *et al.* Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial. *JAMA*. 2014 May 14; **311**: 1863–1869.

110 van Kessel CS, Buckens CFM, van den Bosch MAAJ, van Leeuwen MS, van Hillegersberg R, Verkooijen HM. Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. *Ann Surg Oncol*. 2012 Sep; **19**: 2805–2813.

111 Glazer ES, Beaty K, Abdalla EK, Vauthey JN, Curley SA. Effectiveness of positron emission tomography for predicting chemotherapy response in colorectal cancer liver metastases. *Arch Surg*. 2010 Apr; **145**: 340–345; discussion 345.

112 Annunziata S, Treglia G, Caldarella C, Galiandro F. The role of 18F-FDG-PET and PET/CT in patients with colorectal liver metastases undergoing selective internal radiation therapy with yttrium-90: a first evidence-based review. *ScientificWorldJournal*. 2014 Jan; **2014**: 879469.

113 Sabet A, Meyer C, Aouf A, Sabet A, Ghamari S, Pieper CC, *et al.* Early post-treatment FDG PET predicts survival after 90Y microsphere radioembolization in liver-dominant metastatic colorectal cancer. *Eur J Nucl Med Mol Imaging*. 2015 Mar; **42**: 370–376.

114 Beiderwellen K, Geraldo L, Ruhlmann V, Heusch P, Gomez B, Nensa F, *et al.* Accuracy of [18F]FDG PET/MRI for the Detection of Liver Metastases. *PLoS One*. 2015 Jan; **10**: e0137285.

115 Reiner CS, Stolzmann P, Husmann L, Burger IA, Hüllner MW, Schaefer NG, *et al.* Protocol requirements and diagnostic value of PET/MR imaging for liver metastasis detection. *Eur J Nucl Med Mol Imaging*. 2014 Apr; **41**: 649–658.

116 Brendle C, Schwenzer NF, Rempp H, Schmidt H, Pfannenberg C, la Fougère C, *et al.* Assessment of metastatic colorectal cancer with hybrid imaging: comparison of reading performance using different combinations of anatomical and functional imaging techniques in PET/MRI and PET/CT in a short case series. *Eur J Nucl Med Mol Imaging*. 2015 Jul 31;

117 Rindi G, Klöppel G, Couvelard A, Komminoth P, Körner M, Lopes JM, *et al.* TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch*. 2007 Oct; **451**: 757–762.

118 Christ E, Wild D, Ederer S, Béhé M, Nicolas G, Caplin ME, *et al.* Glucagon-like peptide-1 receptor imaging for the localisation of insulinomas: a prospective multicentre imaging study. *lancet Diabetes Endocrinol*. 2013 Oct; **1**: 115–122.

119 Wenning AS, Kirchner P, Antwi K, Fani M, Wild D, Christ E, *et al.* Preoperative Glucagon-like peptide-1 receptor imaging reduces surgical trauma and pancreatic tissue loss in insulinoma patients: a report of three cases. *Patient Saf Surg*. 2015 Jan; **9**: 23.

120 van Essen M, Sundin A, Krenning EP, Kwekkeboom DJ. Neuroendocrine tumours: the role of imaging for diagnosis and therapy. *Nat Rev Endocrinol*. 2014 Feb; **10**: 102–114.

121 Balon HR, Brown TLY, Goldsmith SJ, Silberstein EB, Krenning EP, Lang O, *et al.* The SNM practice guideline for somatostatin receptor scintigraphy 2.0. *J Nucl Med Technol*. 2011 Dec; **39**: 317–324.

122 Bombardieri E, Ambrosini V, Aktolun C, Baum RP, Bishof-Delaloye A, Del Vecchio S, *et al.* 111In-pentetreotide scintigraphy: procedure guidelines for tumour imaging. *Eur J Nucl Med Mol Imaging*. 2010 Jul; **37**: 1441–1448.

123 Maxwell JE, Sherman SK, Menda Y, Wang D, O'Dorisio TM, Howe JR. Limitations of

somatostatin scintigraphy in primary small bowel neuroendocrine tumors. *J Surg Res*. 2014 Aug; **190**: 548–553.

124 Dromain C, de Baere T, Lumbroso J, Caillet H, Laplanche A, Boige V, *et al.* Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. *J Clin Oncol*. 2005 Jan 1; **23**: 70–78.

125 Shi W, Johnston CF, Buchanan KD, Ferguson WR, Laird JD, Crothers JG, *et al.* Localization of neuroendocrine tumours with [111In] DTPA-octreotide scintigraphy (Octreoscan): a comparative study with CT and MR imaging. *QJM*. 1998 Apr; **91**: 295–301.

126 Kwekkeboom DJ, Kam BL, van Essen M, Teunissen JJM, van Eijck CHJ, Valkema R, *et al.* Somatostatin-receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. *Endocr Relat Cancer*. 2010 Mar; **17**: R53–R73.

127 Johnbeck CB, Knigge U, Kjær A. PET tracers for somatostatin receptor imaging of neuroendocrine tumors: current status and review of the literature. *Future Oncol*. 2014 Nov; **10**: 2259–2277.

128 Geijer H, Breimer LH. Somatostatin receptor PET/CT in neuroendocrine tumours: update on systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging*. 2013 Oct; **40**: 1770–1780.

129 Gabriel M, Decristoforo C, Kendler D, Dobrozemsky G, Heute D, Uprimny C, *et al.* 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. *J Nucl Med*. 2007 May; **48**: 508–518.

130 Ambrosini V, Campana D, Bodei L, Nanni C, Castellucci P, Allegri V, *et al.* 68Ga-DOTANOC PET/CT clinical impact in patients with neuroendocrine tumors. *J Nucl Med*. 2010 May; **51**: 669–673.

131 Frilling A, Sotiropoulos GC, Radtke A, Malago M, Bockisch A, Kuehl H, *et al.* The impact of 68Ga-DOTATOC positron emission tomography/computed tomography on the multimodal

management of patients with neuroendocrine tumors. *Ann Surg*. 2010 Nov; **252**: 850–856.

132 Ruf J, Heuck F, Schiefer J, Denecke T, Elgeti F, Pascher A, *et al.* Impact of Multiphase 68Ga-DOTATOC-PET/CT on therapy management in patients with neuroendocrine tumors. *Neuroendocrinology*. 2010 Jan; **91**: 101–109.

133 Schreiter NF, Brenner W, Nogami M, Buchert R, Huppertz A, Pape U-F, *et al.* Cost comparison of 111In-DTPA-octreotide scintigraphy and 68Ga-DOTATOC PET/CT for staging enteropancreatic neuroendocrine tumours. *Eur J Nucl Med Mol Imaging*. 2012 Jan; **39**: 72–82.

134 Baum RP, Kulkarni HR. THERANOSTICS: From Molecular Imaging Using Ga-68 Labeled Tracers and PET/CT to Personalized Radionuclide Therapy - The Bad Berka Experience. *Theranostics*. 2012 Jan; **2**: 437–447.

135 Hope TA, Pampaloni MH, Nakakura E, VanBrocklin H, Slater J, Jivan S, *et al.* Simultaneous (68)Ga-DOTA-TOC PET/MRI with gadoxetate disodium in patients with neuroendocrine tumor. *Abdom Imaging*. 2015 Aug; **40**: 1432–1440.

136 Armbruster M, Sourbron S, Haug A, Zech CJ, Ingrisch M, Auernhammer CJ, *et al.* Evaluation of neuroendocrine liver metastases: a comparison of dynamic contrast-enhanced magnetic resonance imaging and positron emission tomography/computed tomography. *Invest Radiol*. 2014 Jan; **49**: 7–14.

137 Armbruster M, Zech CJ, Sourbron S, Ceelen F, Auernhammer CJ, Rist C, *et al.* Diagnostic accuracy of dynamic gadoxetic-acid-enhanced MRI and PET/CT compared in patients with liver metastases from neuroendocrine neoplasms. *J Magn Reson Imaging*. 2014 Aug; **40**: 457–466.

138 Flechsig P, Zechmann CM, Schreiweis J, Kratochwil C, Rath D, Schwartz LH, *et al.* Qualitative and quantitative image analysis of CT and MR imaging in patients with neuroendocrine liver metastases in comparison to (68)Ga-DOTATOC PET. *Eur J Radiol*. 2015 Aug; **84**: 1593–1600.

139 Pfeifer A, Bardram Johnbeck C, Knigge U, Mortensen J, Oturai P, Loft A, *et al.* Clinical PET imaging of neuroendocrine tumors using 64Cu-DOTA-Tyr3-octreotate. *J Nucl Med*. 2013 May 1; **54**: 1854 – .

140 Binderup T, Knigge U, Loft A, Mortensen J, Pfeifer A, Federspiel B, *et al.* Functional imaging of neuroendocrine tumors: a head-to-head comparison of somatostatin receptor scintigraphy, 123I-MIBG scintigraphy, and 18F-FDG PET. *J Nucl Med*. 2010 May; **51**: 704–712.

141 Naswa N, Sharma P, Gupta SK, Karunanithi S, Reddy RM, Patnecha M, *et al.* Dual tracer functional imaging of gastroenteropancreatic neuroendocrine tumors using 68Ga-DOTA-NOC PET-CT and 18F-FDG PET-CT: competitive or complimentary? *Clin Nucl Med*. 2014 Jan; **39**: e27–e34.

142 Binderup T, Knigge U, Loft A, Federspiel B, Kjaer A. 18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. *Clin Cancer Res*. 2010 Feb 1; **16**: 978–985.

143 Koopmans KP, Neels OC, Kema IP, Elsinga PH, Sluiter WJ, Vanghillewe K, *et al.* Improved staging of patients with carcinoid and islet cell tumors with 18F-dihydroxy-phenyl-alanine and 11C-5-hydroxy-tryptophan positron emission tomography. *J Clin Oncol*. 2008 Mar 20; **26**: 1489–1495.

144 Ambrosini V, Tomassetti P, Castellucci P, Campana D, Montini G, Rubello D, *et al.* Comparison between 68Ga-DOTA-NOC and 18F-DOPA PET for the detection of gastro-entero-pancreatic and lung neuro-endocrine tumours. *Eur J Nucl Med Mol Imaging*. 2008 Aug; **35**: 1431–1438.

145 Haug A, Auernhammer CJ, Wängler B, Tiling R, Schmidt G, Göke B, *et al.* Intraindividual comparison of 68Ga-DOTA-TATE and 18F-DOPA PET in patients with well-differentiated metastatic neuroendocrine tumours. *Eur J Nucl Med Mol Imaging*. 2009 May; **36**: 765–770.

146 Wild D, Fani M, Behe M, Brink I, Rivier JEF, Reubi JC, *et al.* First clinical evidence that imaging with somatostatin receptor antagonists is feasible. *J Nucl Med*. 2011 Sep; **52**: 1412–

1417.

147 van Asselt SJ, Oosting SF, Brouwers AH, Bongaerts AHH, de Jong JR, Lub-de Hooge MN, *et al.* Everolimus Reduces (89)Zr-Bevacizumab Tumor Uptake in Patients with Neuroendocrine Tumors. *J Nucl Med.* 2014 Jul; **55**: 1087–1092.

148 Wang Z, Chen J-Q, Liu J-L, Qin X-G, Huang Y. FDG-PET in diagnosis, staging and prognosis of pancreatic carcinoma: a meta-analysis. *World J Gastroenterol*. 2013 Aug 7; **19**: 4808–4817.

149 Kauhanen SP, Komar G, Seppänen MP, Dean KI, Minn HR, Kajander SA, *et al.* A prospective diagnostic accuracy study of 18F-fluorodeoxyglucose positron emission tomography/computed tomography, multidetector row computed tomography, and magnetic resonance imaging in primary diagnosis and staging of pancreatic cancer. *Ann Surg*. 2009 Dec; **250**: 957–963.

150 Burge ME, O'Rourke N, Cavallucci D, Bryant R, Francesconi A, Houston K, *et al.* A prospective study of the impact of fluorodeoxyglucose positron emission tomography with concurrent non-contrast CT scanning on the management of operable pancreatic and peri-ampullary cancers. *HPB (Oxford)*. 2015 Jul; **17**: 624–631.

151 Dai T, Popa E, Shah MA. The role of ^{18}F-FDG PET imaging in upper gastrointestinal malignancies. *Curr Treat Options Oncol*. 2014 Sep; **15**: 351–364.

152 van Vliet EPM, Heijenbrok-Kal MH, Hunink MGM, Kuipers EJ, Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis. *Br J Cancer*. 2008 Feb 12; **98**: 547–557.

153 Chatterton BE, Ho Shon I, Baldey A, Lenzo N, Patrikeos A, Kelley B, *et al.* Positron emission tomography changes management and prognostic stratification in patients with oesophageal cancer: results of a multicentre prospective study. *Eur J Nucl Med Mol Imaging*. 2008 Oct 18; **36**: 354–361.

154 Barber TW, Duong CP, Leong T, Bressel M, Drummond EG, Hicks RJ. 18F-FDG PET/CT has

a high impact on patient management and provides powerful prognostic stratification in the primary staging of esophageal cancer: a prospective study with mature survival data. *J Nucl Med*. 2012 Jun; **53**: 864–871.

155 Breeman WAP, de Blois E, Sze Chan H, Konijnenberg M, Kwekkeboom DJ, Krenning EP. (68)Ga-labeled DOTA-peptides and (68)Ga-labeled radiopharmaceuticals for positron emission tomography: current status of research, clinical applications, and future perspectives. *Semin Nucl Med*. 2011 Jul; **41**: 314–321.

156 Aerts HJWL, Velazquez ER, Leijenaar RTH, Parmar C, Grossmann P, Cavalho S, *et al.* Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. *Nat Commun*. 2014 Jan; **5**: 4006.

157 Bodei L, Sundin A, Kidd M, Prasad V, Modlin IM. The status of neuroendocrine tumor imaging: from darkness to light? *Neuroendocrinology*. 2015 Jan; **101**: 1–17.

	^{111}In-pentetreotide	^{68}Ga-SSA	^{18}F-DOPA	^{11}C-5-HTP	^{18}FDG
Technical considerations	Whole-body imaging Somatostatin receptor-targeted Poor resolution for <10mm lesions 2D planar imaging, with 3D SPECT. May combine with CT 2-4 day process Widely used, approved by FDA/EMA	Whole-body imaging Somatostatin receptor-targeted Higher resolution (4-6mm) Hybrid systems with CT and MRI 1 day process Mostly restricted to European centres	Whole-body imaging Images neuroendocrine cell metabolism Higher resolution (4-6mm) May combine with CT 1 day process Utilised for neurological imaging	Whole-body imaging Images neuroendocrine cell metabolism Higher resolution (4-6mm) May combine with CT 1 day process Restricted to research centres	Whole-body imaging Images tumour cell metabolism Higher resolution (4-6mm) Hybrid systems with CT and MRI 1 day process Widely utilised for other cancers
Clinical considerations	Tumour localisation, staging, restaging, therapy selection Sensitivity for LM 49.3-91% Poor sensitivity for insulinoma	Tumour localisation, staging, restaging, therapy selection Sensitivity for LM 82-100% High sensitivity for most primary types	Tumour localisation, staging, re-staging, tumour metabolism Sensitivity for LM appears inferior to ^{68}Ga-SSA High sensitivity for small bowel NET	Tumour localisation, staging, re-staging, tumour metabolism Limited data High sensitivity for pancreatic NET	Prognostic marker (not fully validated) Sensitivity for NET 58% Poor sensitivity for well-differentiated/lower-grade NET. Higher sensitivity for poorly-differentiated/high-grade NET/NEC

Table 1. Technical and clinical considerations of molecular imaging with the most widely used radiotracers for neuroendocrine tumours. FDA = Food and Drug Administration, EMA = European Medicines Agency, CT = computed tomography, MRI = magnetic resonance imaging, SPECT = single photon emission CT, LM = liver metastases, NET = neuroendocrine tumours, NEC = neuroendocrine carcinomas. Adapted from [157].

Figure legends

Fig. 1. Perfusion imaging in hepatocellular carcinoma. (A) Example of perfusion parametric maps (total perfusion, hepatic perfusion index, mean transit time and regional blood volume) obtained from a patient with hepatocellular carcinoma 7 days after the initiation of sorafenib treatment. Perfusion parameters were extracted using a non-linear least square fit on a dual-input one-compartment model including two delays (arterial and portal). (B) The lesion was located in the dome of the liver. Comparison between the lesion (upper part) and the surrounding liver (lower part). The lesion showed a significant total perfusion decrease, with significant hepatic perfusion index and mean transit time increase consistent with a tumoural response to the treatment.

Fig. 2. Hepatobiliary contrast MRI in typical unifocal hepatoceullar carcinoma in a 55 year old-female with HBV and HIV infection. Gd-EOB-DTPA enhanced MR imaging showed a supracentimetric hypervascular lesion located in the left liver lobe (A) with washout on portal venous phase images (B), allowing for the non-invasive diagnosis of HCC. On the hepatobiliary phase images acquired 20 minutes after the injection (C) the lesion showed marked signal hypointensity, consistent with the presence of impaired hepatocytes.

Fig. 3. Diffusion-weighted MRI in intrahepatic cholangiocarcinoma in a 57 year-old male. The lesion was located in the posterior part of the right liver lobe. The patient was initially referred for a right hepatectomy. On contrast enhanced MR imaging after injection of extracellular contrast-agent, the portal venous phase images showed a heterogeneous lesion, with a central necrotic area, and peripheral enhancement, consistent with the fibrous stroma of the tumour (B). The left liver lobe was unremarkable (B). On diffusion-weighted images, the conspicuity of the main lesion is better (C), and several infracentimetric nodules are visible in the left lobe (D). These lesions were proven to be intrahepatic distant metastasis, and led to a change in the management of the patient.

Fig 4. Comparison of CT and ^{68}Ga-DOTATATE PET/CT in a patient with pulmonary NET. (A) Axial CT of liver. (B) Axial PET image of liver. (C) Fused PET/CT demonstrates involvement of liver, pancreatic tail and several abdominal lymph nodes not otherwise evident on morphological imaging. (D) Maximum intensity projection of ^{68}Ga-DOTATATE uptake, also demonstrating radiotracer uptake in left-sided metastatic supra-clavicular lymph nodes.

Fig 5. Identification of primary NET, hepatic and extra-hepatic metastases on ^{68}Ga-DOTATATE PET/CT. (A) Uptake corresponding to primary pancreatic NET. (B) Bilobar neuroendocrine liver metastases. (C) Identification of a small, solitary bone metastasis not evident on morphological imaging.