Review

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Functional imaging in liver tumours

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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.

Keywords: Liver; Tumours; Metastases; Imaging.

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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 work-up 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 (LM), 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

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Key point

Functional imaging assesses *in vivo* physiological parameters of tissues, and may be used in tumour detection, characterisation, treatment selection and follow-up.

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, ^{68}Ga-radiolabelled somatostatin analogues; ^{68}Ga-DOTATOC, [^{68}Ga-DOTA^{0},Tyr^{3}] octreotide; ^{68}Ga-DOTANOC, [^{68}Ga-DOTA,1-Nal^{3}]octreotide; ^{68}Ga-DOTATATE, [^{68}Ga-DOTA^{0}, Tyr^{3}]octreotate).

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 min after injection. With gadobenate dimeglumine, around 5% is taken-up, and the hepatobiliary phase is obtained 1–3 h 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 min 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 CE 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, whilst that of CT is 68–91% [13–16]. Indeed, the diagnostic performance is strongly related to tumour size. The sensitivity for large HCC (>2 cm), 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].

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