World Journal of Radiology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4329/wjr.v7.i7.157

World J Radiol 2015 July 28; 7(7): 157-169
ISSN 1949-8470 (online)

REVIEW

Non-invasive diagnostic imaging of colorectal liver metastases

Pier Paolo Mainenti, Federica Romano, Laura Pizzuti, Sabrina Segreto, Giovanni Storto, Lorenzo Mannelli, Massimo Imbriaco, Luigi Camera, Simone Maurea

Pier Paolo Mainenti, Laura Pizzuti, IBB CNR, 80145 Naples, Italy

Federica Romano, Sabrina Segreto, Massimo Imbriaco, Luigi Camera, Simone Maurea, Advanced Biomedical Science Department, Radiology Section, University of Naples "Federico II", 80145 Naples, Italy

Giovanni Storto, IRCCS, CROB, 85028 Rionero in Vulture, Italy

Lorenzo Mannelli, Radiology Department, Memorial Sloan-Kettering Cancer Center, New York, NY 10022, United States

Author contributions: All authors contributed to this paper.

Conflict-of-interest statement: The review has not been published before, is not under consideration for publication elsewhere and its publication has been approved by all co-authors. All the authors do not have any conflicting interests (including but not limited to commercial, personal, political, intellectual, or religious interests) related to the manuscript.

Correspondence to: Pier Paolo Mainenti, MD, IBB CNR, Via De Amicis, 95, 80145 Naples,
Italy. pierpamainenti@hotmail.com
Telephone: +39-081-7613060
Fax: +39-081-7616013

Received: January 28, 2015
Peer-review started: January 29, 2015
First decision: April 27, 2015
Revised: May 10, 2015
Accepted: June 1, 2015

Article in press: June 2, 2015
Published online: July 28, 2015

Abstract

Colorectal cancer is one of the few malignant tumors in which synchronous or metachronous liver metastases [colorectal liver metastases (CRLMs)] may be treated with surgery. It has been demonstrated that resection of CRLMs improves the long-term prognosis. On the other hand, patients with un-resectable CRLMs may benefit from chemotherapy alone or in addition to liver-directed therapies. The choice of the most appropriate therapeutic management of CRLMs depends mostly on the diagnostic imaging. Nowadays, multiple non-invasive imaging modalities are available and those have a pivotal role in the workup of patients with CRLMs. Although extensive research has been performed with regards to the diagnostic performance of ultrasonography, computed tomography, positron emission tomography and magnetic resonance for the detection of CRLMs, the optimal imaging strategies for staging and follow up are still to be established. This largely due to the progressive technological and pharmacological advances which are constantly improving the accuracy of each imaging modality. This review describes the non-invasive imaging approaches of CRLMs reporting the technical features, the clinical indications, the advantages and the potential limitations of each modality, as well as including some information on the development of new imaging modalities, the role of new contrast media and the feasibility of using parametric image analysis as diagnostic marker of presence of CRLMs.

Key words: Advances in imaging; Colorectal cancer; Liver metastases

Core tip: The present review describes the non invasive imaging approaches of colorectal liver metastases colorectal liver metastases (CRLMs) reporting the technical features, the clinical indications, the advantages and the potential limitations of each modality [ultrasonography, computed tomography (CT); magnetic resonance imaging (MRI), positron emission tomography (PET)/CT, PET/MRI] as well as including some information on the development of new imaging modalities, the role of new contrast media and the feasibility of using parametric image analysis as diagnostic marker of presence of CRLMs.

Mainenti PP, Romano F, Pizzuti L, Segreto S, Storto G, Mannelli L, Imbriaco M, Camera L, Maurea S. Non-invasive diagnostic imaging of colorectal liver metastases. *World J Radiol* 2015; 7(7): 157-169 Available from: URL: http://www.wjgnet.com/1949-8470/full/v7/i7/157.htm DOI: http://dx.doi.org/10.4329/wjr.v7.i7.157

INTRODUCTION

Annually over 130000 new cases of colorectal cancer (CRC) are diagnosed in the United States, representing the third most common cancer in both men and women, with more than 50000 deaths each year[1].

Liver metastases are detected approximately in up to 20%-25% of patients with CRC at the time of diagnosis[2]. The 5-year cumulative rate of metachronous colorectal liver metastases [colorectal liver metastases (CRLMs)] is reported to be 15%[2]. Overall, approximately 50% of patients with CRC will develop liver metastases[3].

CRC is one of the few malignant tumors in which synchronous or metachronous liver metastases may be treated with surgery. CRLMs are resectable in about 20%-30% of the cases[4] with a 5-year survival of about 50%-60% in comparison to a survival of less than 5% of patients with CRLMs not amenable to liver surgery[5].

In patients who are not suitable candidates for surgery, chemotherapy alone or in addition to local hepatic treatments, such as intrahepatic arterial infusion chemotherapy or radiofrequency ablation or laser therapy or cryotherapy, may be performed. These treatments options have been shown to increase survival, too[6-11].

Common to any therapy is the need for pretreatment anatomic planning to assess feasibility and avoid injury to adjacent structures such as vasculature, biliary ducts and surrounding organs.

The surgical criteria, which permit to select the candidates for liver resection, are represented by the size of the lesion, number and location with respect to anatomic landmarks of the CRLMs, as well as the number of segments involved, the volume of the remaining liver and the general clinical parameters[6,7]. Metastases can be completely resected if at least 2 adjacent liver segments can be spared and if the future liver remnant is at least 20% of total pre-resection liver volume[8] in patients with normal liver function and more than 40% in patients with reduced liver function[12,13].

Moreover anatomic variants of hepatic arteries, biliary tree and portal venous system need to be excluded because the surgical resection may be problematic, and thus additional surgery steps may be required[14].

Obviously, diagnostic imaging plays a crucial role in selecting the more appropriate therapy for patients with CRLMs, by detecting the lesions, determining the resectability and assessing the response to treatments.

Even though many non invasive imaging modalities are now available and effective in detection and follow up of CRLMs, such as ultrasonography (US), computed tomography (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI), each offering some advantages as disadvantages over the others, the optimal imaging strategy in patients with CRLMs have still to be designed.

The lack of a worldwide well defined CRLMs imaging protocol is in part due to continuous and rapid technological and pharmacological developments which are progressively improving the performance of each imaging modality.

This review describes the non-invasive imaging approaches of CRLMs reporting the technical features, the clinical indications, the advantages and the potential limitations of each modality, as well as including some information on the development of new imaging modalities, the role of new contrast media and the feasibility of using parametric image analysis as diagnostic marker of presence of CRLMs.

US

Because of its non-invasive character, low cost, no radiation exposure, good patient acceptance and widespread availability, US is often the first choice for screening patients with malignancy and/or suspected liver lesions, and it is widely used in the evaluation of liver metastases[15-19].

In particular, the sensitivity of US for CRLMs detection is variable ranging from 50% to 76%[17,20]; however US sensitivity depends mostly on the size of the lesion and it can be as low as 20% if liver lesions are less than 10 mm[15,16]. Despite of this limitation, in daily practice, US plays still a clinical role in distinguishing two different groups of patients with liver metastases: (1) patients with diffuse metastases who are no longer eligible for curative treatment; and (2) patients without metastases or a very limited number of them. Further diagnostic investigation with tomographic imaging is mandatory for the patients of the group 2 to define the correct therapeutic management.

During the last few years, the contrast-enhanced ultrasound (CEUS) has progressively gained a huge role in the evaluation of liver lesions, improving detection and characterization of both primary or secondary liver lesions[21-28]. The added role of CEUS compared to the baseline US (b-US) has been observed for CRLMs detection, too[29]. A few studies have shown a

significantly better sensitivity of CEUS *vs* b-US in the identification of CRLMs measuring less than 10 mm; moreover CEUS should replace b-US for the detection of CRLMs in patients being treated with neoadjuvant systemic chemotherapy[30-33].

Westwood *et al*[29] in their recent meta-analysis of 19 studies on liver CEUS with Sonovue stated that CEUS shows a similar performance to liver CT and MRI in the characterization of incidentally detected focal liver lesions with lower costs respect to MRI and it may be adequate to rule out CRLMs; in particular, similarly to CT and MRI even with CEUS the CRLMs are better detected in post-contrast portal and late phases[31].

Nevertheless some limitations of CEUS need to be considered. CEUS presents still low sensitivity for very small focal liver lesions (< 5 mm), due to the low spatial resolution, and thus very small CRLMs might be missed[29]. In addition, CEUS does not go beyond certain limitations of the US examinations, like the difficulty in the evaluation of the sub-diaphragmatic liver or the interposition of the intestine, and above all the notable weakness of being operator dependent. Moreover liver steatosis and fibrosis are an important limitation that can increase the possibility of missing deep seated metastases[34]. Finally, another aspect to consider is that CEUS does not offer comprehensive information for surgical planning as both CT and MRI do. Bolondi *et al*[35] report that even if the use of CEUS is largely accepted in clinical practice its role in the diagnostic algorithm of liver lesions has not yet been established.

Beyond the scope of the present review because of the invasive approach, the following US technique merit to be mentioned: the US-guided percutaneous biopsy which allow characterizing indeterminate hepatic lesions and the intra-operative ultra-sonography which offer the highest accuracy rates in CRLMs detection[36,37].

MULTIDETECTOR CT

Multidetector CT MDCT is considered the imaging modality of choice for CRC staging and follow up, because it provides excellent coverage of the entire chest/abdomen/pelvis offering a global one session staging. Nevertheless up to 25% of CRLMs may be missed[38]. The current MDCT devices enable high spatial resolution studies of the entire liver generating slice thickness $\leqslant$ 1 mm and isotropic pixel sizes and, thus, allowing high quality reformatted multiplanar (MPR) and volumetric three-dimensional rendering (3D VR) reconstructions. The resulting high definition images define accurately the main features of each lesion, as the sizes, the margins, the segmental spatial distribution, the relation with the vascular and biliary structure, and the volume of the remaining liver.

The additional diagnostic value of using thin collimation in the detection of hepatic lesions is debated. Some authors have demonstrated that the use of a thinner section thickness (*i.e.*, 2.5 mm *vs* $\geqslant$ 5 mm slice thickness) at CT improves the detection of hepatic lesions[39], as well as, the accuracy of 16-MDCT using a 1.5 mm collimation might be superior to previous CT techniques in differentiating between hepatic metastases and hepatic cysts[40]. On the contrary, other authors reported that image reconstruction with MDCT at collimations less than 5 mm did not improve sensitivity in the detection of hepatic metastases 1.5 cm or smaller[41], as well as, a slice thickness $\leqslant$ 1 mm does not improve hepatic lesion detection and it provides a significant increase of image noise[42]. As a result of the above information, a CRLMs protocol scanning of 2-4 mm of collimation may be recommended.

The value of unenhanced scans lies mainly in the characterization of small lesions as being solid or cystic or in the identification of calcified CRLMs. About the contrast-enhanced (ce) scanning protocol, the venous phase is well recognized as the optimal timing to detect CRLMs. Arterial and equilibrium phase CT have no incremental value compared to hepatic venous phase MDCT in the detection of CRLMs, as a result a multiphasic scanning protocol implies an unjustified additional radiation exposure[43,44]. Moreover the single portal venous phase contrast enhanced MDCT (ce-MDCT) scanning protocol enables accurate preoperative assessment of the local CRC staging (T and N), too[45].

The performance of MDCT in the CRLMs detection is variable showing unsatisfactory sensitivity and specificity values for lesions < 10 mm[46] or in presence of fatty liver which is often a consequence of chemotherapy[47]. Furthermore, incidental findings such as small hemangiomas and cysts measuring less than 10 mm in size can be difficult to differentiate from metastases because of volume averaging[48,49].

Contrast medium allergies as well as renal impairment may limit the use of the ce-CT; however they do not represent absolute contraindications because of the possibility of a supporting therapy.

MRI

Currently, MRI represents the most accurate modality for evaluating CRLMs; it provides anatomic details and has a high detection rate, even for lesions smaller than 10 mm[38,48-51].

The recent technological advances (high magnetic field strength > 1 T, high gradients, parallel imaging techniques, fast dynamic sequences, breath-hold sequences) have improved the liver application of MRI increasing the signal-to-noise ratio, the contrast-to-noise ratio (CNR), the spatial resolution and the image quality as well as reducing the scan times.

The unenhanced standard MRI protocol for detecting and characterizing focal liver lesions includes both T1- and T2-weighted images. For T1-weighted imaging, the in-phase and opposed-phase gradient-recalled echo (GRE) sequences are acquired to assess the presence of parenchymal fatty infiltration or focal sparing of diffuse fatty infiltration. For T2-weighted imaging, the turbo-spin echo (TSE) or the fast spin echo without and with

fat suppression are preferred over the single-shot TSE pulse sequences, because the latter do not offer an optimal soft tissue contrast. For detection of focal lesions a TE of approximately 80-100 ms is adopted, however a heavily T2-weighted sequences with a time of echo of approximately 160-180 ms may help in differentiation between solid and non-solid lesions (*e.g.*, metastasis/HCC *vs* haemangioma/cyst)[52-54].

Recent clinically important advances in MRI include the addition of diffusion-weighted imaging (DWI). DWI is a functional technique that looks at the Brownian motion of water in tissues. In biological tissues, the Brownian motion is restricted by interactions with cell membranes and macromolecules on a microscopic level as well as it is modified by any architectural tissue changes[55]. Increased tissue cellularity observed in tumors restricts Brownian motion, which can be quantified by calculation of the apparent diffusion coefficient (ADC) on derived ADC parametric maps. Of note, ADC has been shown to be inversely correlated with tumor cellularity and it can be considered a quantitative biomarker parameter of pathology. Metastases tend to restrict diffusion and the addition of DWI to the standard liver MRI protocol improves sensitivity and specificity for lesion detection and characterization[56-58]. The added value of DWI is even more evident in the detection of CRLMs $\leqslant$ 1 cm with sensitivity of 92% compared to 71% of late phase hepato-biliary contrast agent MRI[59]. Hence, these sequences are now routinely included in a liver MRI protocols.

Successively, the contrast-enhanced sequences are performed. Three different groups of MRI contrast agents for hepatic imaging are available: the non-specific extracellular gadolinium chelates, the organs-specific (reticulo-endothelial) and the liver-specific intracellular (hepato-biliary) contrast agents.

Non-specific gadolinium chelates

Extracellular gadolinium chelates are the contrast agent more frequently used for MRI. Several agents with similar properties are on the market, including gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany), Gd-DTPA-BMA (Omniscan®, GE Healthcare, Chalfont St. Giles, United Kingdom) and Gd-DOTA (Dotarem, Guerbet, Aulnay-sous-Bois, France).

Non-specific extracellular gadolinium chelates have pharmacokinetics similar to those of iodinated contrast agents and are excreted almost exclusively by passive glomerular filtration through the kidneys. Because of their small size, gadolinium chelates are rapidly cleared from the intravascular space into the extracellular interstitial space according to the concentration difference of the contrast agent between the two compartments. The transfer of the molecules occurs in the opposite direction, when the concentration gradient inverts[60].

About the contrast-enhanced scanning protocol, the T1-weighted 3D-GRE breath hold (BH) sequences are obtained during the arterial, portal venous phase and the equilibrium phase. The following considerations have to be reported about the differences between MRI and CT contrast-enhanced scanning protocol: the exposure to ionizing radiation suggests to use single phase CT protocol and to reserve multiphasic studies only when really necessary; although the MRI of the liver is the most accurate modality for detecting CRLMs, in the clinical practice it is frequently used after a staging whole-body ce-MDCT to solve problems of differential diagnosis; that is why a multiphasic MRI liver protocol may be necessary to characterize correctly a liver lesion defined as undetermined at ce-MDCT.

Gadolinium-based contrast agents may cause collateral effects, such as acute non-renal adverse reactions (*e.g.*, anaphylactoid reactions), acute renal adverse reactions (*e.g.*, contrast induced nephropathy), delayed adverse reactions [nephrogenic systemic fibrosis (NSF)] and problems at the site of injection (*e.g.*, local necrosis)[60]. NSF is a rare potentially fatal disease that has been observed in patients with severe renal insufficiency exposed to gadolinium contrast agent. To prevent the risk of NSF it is suggested to avoid the intravenous (*iv*) administration of gadolinium contrast agents in patients who have a glomerular filtration rate lower than 30 mL/min per 1.73 m^2 as well as in those who are on dialysis or have acutely renal impairment. This point represents a recommendation rather than an absolute contraindication.

Reticulo-endothelial contrast agents

All reticuloendothelial system (RES) agents are super-paramagnetic iron oxide-based contrast agents (SPIO). SPIO particles are taken up by RES cells of the normal liver parenchyma, the spleen and the lymph nodes. They shorten T2 and T2* relaxation times resulting in a loss of signal intensity in normal liver parenchyma. On the opposite, malignant liver lesions do not have a substantial number of RES cells and appear as hyperintense lesions with distinct borders in contrast to the hypointense liver parenchyma after application of SPIO on T2-weighted MRI.

Although SPIO agents have showed high accuracy in the detection of liver lesions[40,61-64], hepatocyte-specific contrast agents are preferred to these molecules in clinical practice[65].

Hepato-biliary contrast agents

Hepatobiliary agents represent a heterogeneous group of paramagnetic molecules of which a fraction is taken up by hepatocytes and excreted into the bile. On T1 weighted images, lesions not containing hepatocytes are hypointense to the surrounding enhanced parenchyma during the hepato-biliary phase (HBP). Presently, the hepatobiliary agents actually available are mangafodipir trisodium (MT, Teslascan®, GE Healthcare), godobenate dimeglumine (Gd-BOPTA, Multihance®, Bracco) and gadoxetic acid (Gd-EOB-DTPA, Primovist®, Schering).

MT has limited assessment of vascular structures due to its inability to be administered as a bolus. Gd-BOPTA and Gd-EOB-DTPA show biphasic liver enhancement

with an early vascular and extracellular phase allowing arterial, portal venous and equilibrium phase and a delayed HBP with a peak to 20-40 min for Gd-EOB-DTPA and 60-90 min for Gd-BOPTA. The advantages of the Gd-EOB-DTPA over Gd-BOPTA are the higher biliary excretion approximately close to the 50% of the delivered dose respect to 3%-5%, the high relaxivity, the earlier onset and the longer duration of contrast, which facilitates imaging and image quality[65,66].

HBP improves the sensitivity of MRI in the detection of CRLMs[59]. In addition hepatocyte-specific contrast agents allow detection of the "disappearing liver metastases"[13], which mimic a complete response to neoadjuvant chemotherapy leading to a mismatch between imaging response and true pathological complete response. A false complete imaging response is more often observed with CT and PET-CT[67], while the current data suggest that MRI with hepato-biliary contrast agents represent the most appropriate imaging modality for assessment of patients with CRLMs treated with neoadjuvant chemotherapy[68].

Despite of the great ability of MRI in detection of CRLMs, above all with the introduction of DWI and HBP, this modality still presents some limitations in patients who have difficulty holding their breath. Motion artefacts can heavily degrade images especially in dynamic acquisitions. Different sequences can be performed to study dynamic and HBP such as volumetric interpolated BH examination (Siemens Healthcare, Erlangen, Germany), liver acquisition with acceleration volume acquisition (GE Healthcare, Waukesha, Wis), or enhanced high-resolution isotropic volume excitation (Philips Healthcare, Best, the Netherlands) or respiratory-triggered T1-WI, this latter independent from patient's collaboration[69]. Recently Yoon *et al*[70] have evaluated in a large number of patients the image quality and diagnostic performance in evaluation of focal liver lesions of the respiratory-triggered 3D T1W-GRE sequence compared to standard BH T1W-GRE in HBP. Their results demonstrate that in no-collaborative patients respiratory-triggered 3D T1W-GRE images showed clearer liver margins and intrahepatic vascular structures as well as better image quality, so providing a better diagnostic performance. Overall image quality of respiratory-triggered 3D T1W-GRE was also better than that of BH T1W-GRE in patients with sufficient breath-holding capacity (n = 309, 3.96 ± 0.88, 3.81 ± 0.6, respectively, $P < 0.001$).

^{18}F-FDG-PET AND ^{18}F-FDG-PET/CT

^{18}F-FDG-PET is the most sensitive non-invasive imaging modality for the detection of CRLMs on a per patient basis[15,38,49,50]; however PET is limited by the low spatial resolution, the lack of clear anatomic landmarks, and the physiological uptake of the parenchyma which can mask small hepatic lesions. As a result, the detection of CRLMs by ^{18}F-FDG-PET is directly related to the size of the liver metastases: 14% of hepatic lesions ⩽ 15 mm[71] and 5%-36% of hepatic lesion ⩽ 10 mm[72-74] were identified by ^{18}F-FDG-PET.

Therefore, to overcome the above limitations, PET has been combined with CT to realize the hybrid modality PET/CT. This combination provides simultaneous functional and anatomic diagnostic information. The combination of PET with CT improves the distinction of physiological ^{18}F-FDG uptake from pathology and also aids the localization of metastases within the segmental anatomy of the liver, but does not overcome the intrinsic limits of PET modality such as the poor spatial resolution or the inaccurate identification of small non-hyper-metabolic lesions. That is why performing the CT of the PET/CT examination with the administration of *iv* iodinated contrast medium improves the performance of the PET/CT modality. ^{18}F-FDG-PET/ce-CT increases significantly the detection of CRLMs compared with ^{18}FDG-PET/CT[75].

^{18}F-FDG-PET does not require breath holding during acquisition, thus respiratory movements may reduce conspicuity of small liver lesions with potential errors in the detection of focal sub-diaphragmatic ^{18}F-FDG uptakes and respiratory phase mismatch between the PET and CT data. Revheim *et al*[76] have recently investigated the added role of two tailored ^{18}F-FDG-PET liver protocols [prolonged liver acquisition time (PL-PET) and repeated breath-hold respiratory gated liver acquisition (RGL-PET)] to a standard whole body (sWB) ^{18}F-FDG-PET/CT protocol to improve detection of CRLMs. The PL-PET protocol lasted 8 min and covered the liver with two bed positions, while patients of the RGL-PET protocol were asked to alternate breaths and BHs for 10 min. The addition of tailored liver-specific ^{18}F-FDG PET protocols to sWB-PET scan improved the detection of CRLMs compared to sWB-PET alone; more lesions were detected and a higher CRLMs SUV max was measured, with a substantial reduction of the background noise related to physiologic liver uptake.

The role of PET/CT in CRLMs is yet evolving. Due to the high cost and an additional radiation exposure, ^{18}F-FDG-PET/CT is reserved for the detection of occult extra-hepatic disease in patients with CRLMs amenable of surgical resection to avoid the morbidity of a futile invasive therapy[77].

Moreover further clinical roles of ^{18}F-FDG-PET/CT may be the following: (1) identification of the primary colorectal neoplasm and evaluation of its local extent[78,79]; (2) after a curative resection, the detection of local or distant recurrence of the disease[80] as well as solving ambiguous cases of unexplained CEA rise without conventional radiological explanation and in their prognostic stratification[81]; and (3) metabolic monitoring of the tumor response to the therapy[82].

^{18}F-FDG-PET/MRI

As stated above, both PET and CT show a few limitations in the evaluation of liver lesions; recently PET/MRI has been proposed as an alternative hybrid imaging modality.

Because of the great sensitivity of MRI in recognizing small liver metastases, its combination with the metabolic data obtained by PET may lead to an improved diagnostic accuracy.

Nowadays, the role of PET-MRI in evaluating CRLMs is becoming a topic of major interest, however at present insufficient data is available because hybrid devices are present in few highly specialized centers.

Recent studies have enrolled patients with CRLMs to evaluate the performance of PET-MRI[83-85]. Drzezga *et al*[85] compared PET/CT and PET-MRI in 32 oncologic patients, four of those had CRC and with seven liver lesions. Overall conclusion of this study was that PET/MRI was comparable to PET/CT. Quick *et al*[86] studied 80 patients who underwent a double-scanning protocol with PET/ MRI and PET/CT with 195 tracer-avid lesions and rated image quality. Their results show that integrated PET/MR hybrid imaging is feasible in clinical setting with similar detection rates as those of PET/CT. Partovi *et al*[87] and Kershah *et al*[88] investigated the role of PET/MRI in 120 patients with various primary neoplasms (13 CRCs) who underwent double-scanning protocol with PET/MR and PET/CT in a sequential design following a single-tracer injection of FDG. They observed that hybrid PET-MRI imaging led to a better diagnostic confidence in the characterization of focal liver lesions, taking advantage from the synergic evaluation of ADC and SUVmax. Nielsen *et al*[89] investigated the possible role of PET/MRI in evaluation of therapeutic response in twenty patients with CRLMs treated with radiofrequency or microwave ablation. The sensitivity of MRI in detecting small intrahepatic lesions combined with the ability of ^{18}F-FDG-PET to visualize enhanced metabolism at the ablation site suggests that ^{18}F-FDG-PET/MRI could potentially improve the accuracy of early detection of progressive disease, and thus allow swifter and more effective decision-making regarding appropriate treatment.

NON-CONVENTIONAL PARAMETRIC IMAGING OF CRLMs

This section is dedicated to morphological and functional liver parametric imaging proposed for detecting occult CRLMs and predicting which patients are at risk to develop metachronous liver disease. At present, the real role of parametric images has to be further investigated, as a result they are not routinely performed in the diagnostic clinical management of patients with CRC.

Different studies[90,91] have focused on methods targeting liver perfusion to individuate occult CRLMs before they become overt on morphological imaging. Changes of liver hemodynamics may indeed be related to the presence of occult liver metastases and may also predict the development of metachronous ones. It is well known that the liver receives a dual blood supply from the portal and systemic circulation. Normally in healthy subjects approximately two thirds of this blood supply is carried by the portal vein and one third by the common hepatic artery. During the onset of liver metastases this relation changes because of the increase of arterial blood flow (arterialization) and decrease of portal venous inflow[92].

Imaging can allow recognizing and quantifying these perfusional changes occurring in the liver microvasculature even before any visible morphological signs. For this purpose, doppler perfusion index (DPI) is an US measure of the ratio of arterial hepatic blood flow to total hepatic blood flow[93,94]. Kopljar *et al*[95] compared two different groups with and without liver metastases and observed that patients with liver metastases showed greater DPI determined by increased arterial hepatic blood flow associated to a smaller portal cross-sectional area portal blood flow. The strong operator dependence of the technique represents the major limit of this method.

Perfusion CT allows evaluation hepatic hemodynamic changes and provides quantitative perfusional data useful for the precocious detection of liver metastases[96]. However, to produce reliable enhancement curves the perfusion CT necessitates of multiple high temporal resolution acquisitions after administration of *iv* contrast medium, this leads to radiation overexposure; moreover the breathing cycle can cause severe motion and distortion artifacts[97].

Thanks to the lack of ionizing exposure, perfusion MRI seems to be more promising as a reliable tool for the evaluation of focal and global perfusion indexes[98]. The perfusion parameters evaluated with dynamic contrast-enhanced MRI are essentially represented by Ktrans (volume transfer constant) and Kep (rate constant). Ktrans is the rate constant of contrast agent transfer from the plasma compartment into the extracellular extravascular space, whereas Kep is the rate constant of contrast agent that escape from the extracellular extravascular space back into the plasma compartment. De Bruyne *et al*[99] found that a decrease in Ktrans of more than 40% after bevacizumab-containing chemotherapy was associated with better progression-free survival. Further investigations are needed to understand the real role of perfusion MRI in CRLMs.

Different authors[100-103] have investigated the role of CT texture analysis (TA) to identify the early changes in liver texture heralding the possible presence of occult liver micro-metastases. Texture analysis does not require any additional phase and it can be easily obtained from routinely acquired clinical CT data. This technique is based on the assumption that presence of liver occult lesions can be suspected by the amount of spatial heterogeneity on CT which can be assessed quantifying the texture parameters. These parameters go beyond human visual evaluation and include as main explored values the brightness (quantitative measurement of the mean grey level intensity), entropy (grade of inhomogeneity) and uniformity (distribution of grey levels). As different studies are investigating the potential role of TA, it is debated which is the more appropriate CT phase to analyze. Ganeshan *et al*[100] applied TA to non-

contrast enhanced CT scan of patients with CRC showing significant changes of TA parameters in the non diseased part of the liver of patients with CRLMs compared to those without. Similar results are reached even using TA on routinely acquired portal phase images[101-103]. The exact reasons to explain the relationship between an altered texture in apparently disease-free liver areas and the presence of occult micro-metastases or the development of metachronous live metastases are not quite clear. Probably the alterations of texture features are related to subtle tumor-induced structural and/or hemodynamic changes.

As it has been well demonstrated that the presence of micro-metastasis is related to subtle changes in liver hemodynamics, some authors are investigating the role of blood oxygenation level dependent MRI in early detection of CRLMs. Barash *et al*[104,105] evaluated in mice the pathological changes in liver perfusion assessing the hemodynamic response imaging (HRI), a method that involves hypercapnic challenge with brief inhalation of 5% CO_2 followed by hyperoxic challenge with brief inhalation of carbogen. They demonstrated that during CO_2 enrichment there is an increase in portal flow compared to arterial hepatic flow, and that the higher deoxyhemoglobin levels produced a decrease in fMRI signal intensity. Conversely hyperoxia signifies vascular density and tissue perfusion. Edrei *et al*[106,107] more recently applied this method to demonstrate in a mouse model the early hemodynamic changes that occur in CRLMs, and their modification with advance of liver involvement. The HRI method showed enhanced sensitivity for small CRLM (1-2 mm) detection compared with ce-MRI (82% *vs* 38%, respectively) as well as it demonstrated hemodynamic changes occurring during CRLMs antiangiogenic treatment.

DETECTION OF CRLMs: WHICH IS THE MOST ACCURATE MODALITY?

A huge literature is available about the performances of each imaging modality in the evaluation of CRLMs; as a consequence, we will describe mostly the data of meta-analysis reports in this section.

Kinkel *et al*[15] performed a meta-analysis including papers published between 1985 and 2000 and concluded that, at equivalent specificity ($\geqslant$ 85%), ^{18}F-FDG-PET (90%; CI: 80, 97) is the most sensitive non invasive imaging modality compared to US (55%; CI: 41, 68), CT (72%; CI: 63, 80) and MR (76%; CI: 57, 91) for the detection of hepatic metastases from colorectal, gastric and esophageal cancers on a patient basis.

Bipat *et al*[49] performed a meta-analysis including papers published between 1990 and 2003 and concluded that ^{18}F-FDG-PET is the most sensitive diagnostic tool for the detection of hepatic metastases from CRC on a per patient basis, but not on a per lesion basis. On a per patient basis, the sensitivity of CT, MR, ^{18}F-FDG-PET were 64% (CI: 55, 72), 65% (CI: 58, 70) and 76% (CI: 61, 86), respectively. For lesion of 1 cm or larger SPIO-enhanced MRI was the most accurate modality.

Niekel *et al*[38] performed a meta-analysis including papers published between 1990 and 2010 and concluded that, MRI is the preferred fist-line modality for evaluating CRLMs in patients who have not previously undergone therapy; it provides anatomic details and has a high detection rate for lesions smaller than 10 mm. ^{18}F-FDG-PET can be used as the second line-modality because it is valuable in the evaluation of extra-hepatic disease. The role of ^{18}F-FDG-PET/CT was not clear owing the small number of studies. At equivalent specificity, the sensitivity of CT, MR and ^{18}F-FDG-PET was 75% (CI: 69, 79), 80% (CI: 75, 62) and 81% (CI: 66, 91), respectively, on a per lesion basis, and 84% (CI: 67, 93), 88% (CI: 65, 97) and 94% (CI: 92, 96), respectively, on a per patient basis.

van Kessel *et al*[68] performed a meta-analysis including papers published between 2005 and 2011 and concluded that, MRI is the most appropriate imaging modality for preoperative assessment of patients with CRLMs treated with neoadjuvant chemotherapy. The sensitivity of CT, MRI, ^{18}F-FDG-PET and ^{18}F-FDG-PET/CT were 70% (CI: 47, 62), 86% (CI: 70, 94), 54% (CI: 47, 62) and 52% (CI: 38, 65), respectively, on a per patient basis.

Seo *et al*[108] reported the comparison of Gd-EOB-DTPA-MRI and ^{18}F-FDG-PET/ce-CT in 68 patients with 103 CRLMs and concluded that Gd-EOB-DTPA-MRI is more accurate than ^{18}F-FDG-PET/ce-CT, especially for detection of small ($\leqslant$ 1 cm) lesions. The sensitivity, the specificity, the positive and negative predictive values on a patients basis were 100%, 71%, 97% and 100% respectively for Gd-EOB-DTPA-MRI, and 93%, 71%, 97% and 57% respectively for ^{18}F-FDG-PET/ce-CT.

Muhi *et al*[109] reported the comparison of ce-CT, ce-US, SPIO-MRI and Gd-EOB-DTPA-MRI in 111 patients with CRC, 46 of whom presented 112 hepatic metastases. The sensitivity of ce-US, ce-CT, SPIO-MRI and Gd-EOB-DTPA-MRI, was 73%, 63%, 80% and 95%, respectively, considering all the lesions, and 41%, 26%, 63% and 92%, respectively, considering the lesions $\leqslant$ 10 mm. The sensitivity of MRI was significantly better than the other modalities. Although the sensitivity of Gd-EOB-DTPA-MRI was superior to that of SPIO-MRI especially for lesions $\leqslant$ 10 mm, the difference was not statistically significant. No significant differences in positive predictive value were disclosed between any of the images sets for all the lesions, lesions > 1 cm and lesions $\leqslant$ 1 cm.

Berger-Kulemann *et al*[47] evaluated the performance of ce-MDCT and gadoxetic acid enhanced MRI in the detection of CRLMs in patients with diffuse fatty infiltration of the liver. MDCT identified 49 (72%) and MRI 66 (97%) of 68 lesions confirmed by hystopathology. Statistical analysis showed that the MRI was superior to MDCT with a significant difference considering all the lesions ($P < 0.001$) and small lesions ($\leqslant$ 1 cm; $P < 0.001$), while there was no-significant difference between

the two modalities in the detection of lesions > 1 cm.

Zech *et al*[110] reported that Gd-EOB-DTPA-MRI can lead to cost savings respect to extracellular-contrast-medium-MRI by improving pre-operative planning, reducing additional imaging and decreasing intra-operative changes.

Chen *et al*[111] performed a meta-analysis including 13 papers published between 2011 and 2012 (6/13 papers dealt with CRLMs) and concluded that, Gd-EOB-DTPA-MRI presents high sensitivity (93%; CI: 90, 95) and specificity (95%; CI: 91, 97) for detection of CRLMs.

Maffione *et al*[112] have evaluated the diagnostic performance of ^{18}F-FDG PET and PET/CT for staging liver metastases in patients with CRC including in their meta-analysis studies published from 2004 to 2014. They conclude that ^{18}F-FDG-PET/CT is highly accurate for the detection of CRLMs on a per-patient basis (pooled sensitivity and specificity of 93%) while on a per-lesion basis results were lower (pooled sensitivity and specificity of 60% and 79%). Comparing PET with different imaging modalities their results show that PET had a lower sensitivity than MRI and CT on a per-patient basis (93%, 100% and 98%) and a per-lesion basis (66%, 89% and 79%). In contrast, PET appeared more specific than MRI and CT (86%, 81% and 67%).

Maas *et al*[80] published a meta-analysis comparing PET, PET-CT and CT for whole body staging in patients with suspected recurrence of CRC. The Authors found PET and PET-CT to have the highest diagnostic performance with an area under the curve of 0.94 for both PET and PET-CT compared to 0.83 for CT scan. PET/CT appears as the whole body technique of choice because of its greater ability respect to CT to identify extra-hepatic and additional sites of disease and also for the detection of local recurrence.

MANAGEMENT OF CRLMS: WHICH IMAGING PROTOCOL?

The main clinical scenarios to be managed in patients with CRLMs are the following: (1) detection of liver metastases as part of global staging of newly diagnosed CRC; and (2) pre-surgical planning of CRLMs resection; c) surveillance/monitoring of treatment response of the CRLMs.

Although the optimal imaging strategy is not well established, yet, we will suggest a diagnostic algorithm for each clinical scenario underscoring in part information just reported above.

Detection of CRLMs of newly diagnosed CRC

ce-CT is currently regarded as the standard for one session whole-body staging, including the liver, for initially diagnosed CRC patients. However, as stated above, ce-CT may miss up to 25% of CRLMs also using a multiphasic acquisition protocol and its performance worsens in presence of hepatic steatosis[47]. Furthermore, ce-CT shows limitations in characterizing small (< 1 cm) hypoattenuating lesions, which may be defined as indeterminate or "too-small-to-characterize" (TSCT)[46].

Currently, liver MRI is increasingly used to evaluate CRLMs. The higher accuracy of MRI in comparison with CT and PET/CT for detection of CRLMs, especially for lesions < 1 cm, has been just largely mentioned in the previous section. However, it is unclear which CRC patients should receive liver MRI in addition to standard staging CT. Recently, Han *et al*[113] have investigated the clinical impact of liver MRI in staging evaluation of newly diagnosed CRC patients in three ce-CT groups of patients: (1) patients who demonstrate diminutive indeterminate hypoattenuating TSCT lesions; (2) patients with metastasis-negative hepatic findings; and (3) suspicious or non-TSCT indeterminate lesions. The Authors concluded that liver MRI provides little benefit for detecting synchronous CRLMs in the groups 1 and 2, while it has a significant impact in the group 3. Moreover in the setting of hepatic steatosis, MRI with hepato-biliary contrast agents is superior to ce-MDCT in detecting CRLMs[47].

Both US and PET/CT play a marginal role. As stated above, US may be used to identify patients with diffuse liver metastases who may not need further hepatic diagnostic investigation, whereas PET/CT show a high performance in identifying patients with liver metastases.

Pre-surgical planning of CRLMs resection

The current National Comprehensive Cancer Network (NCCN) guidelines state that liver MRI can be consider to further evaluate patients diagnosed with potentially resectable CRLMs on CT[114]. This recommendation takes into account the fact that liver MRI is most reliable in defining the number, the size and the location of CRLMs, may detect additional CRLMs that are undiagnosed on CT and therefore may change the treatment plan. Moreover it provides information about the volume of the future liver remnant, of the biliary ductal system and of the hepatic parenchyma, such as steatosis, iron deposition, fibrosis, that may impair liver function.

ce-MDCT and ce-MRI angiography have shown similar performance for preoperative hepatic vascular anatomic evaluation[115], however CT may have some advantages over MRI as rapid acquisition, less susceptibility to motion, thin collimation, which assure excellent MPR and 3D images. ce-MDCT may be preferred to ce-MRI angiography in situations where detailed vascular information is necessary prior to complex hepatic resection.

^{18}F-FDG-PET/CT may be recommended for the detection of occult extra-hepatic disease prior of CRLMs surgical resection to avoid not useful invasive treatment.

Surveillance/monitoring of the treatment response of the CRLMs

As diagnostic imaging can help identify the best therapeutic strategy for treatment of CRLMs, equally it plays a key role in assessing response to treatment.

The criteria for monitoring CRLMs response to chemotherapy are the response evaluation criteria in solid tumors, which consist of a simple single dimension measurement of tumor size with efficacy determined by tumor shrinkage[116]. In the evaluation of patients with CRLMs treated with chemotherapy, ce-MRI should be preferred to both ce-MDCT and ^{18}F-FDG-PET/CT for the following reasons: (1) the steatosis induced by chemotherapy decreases the liver-to-lesion contrast, hindering the detection and delineation of the lesions on ce-MDCT; and (2) the necrosis, the reduction of the size of the lesions and the decrease in metabolic activity of cancer cells hamper the diagnostic performance of ^{18}F-FDGPET/CT; it is still not clear if the disappearance of metabolic activity of a lesion can be considered a complete response[117,118]. Today, MRI with DWI and liver specific contrast agents provide the most sensitive tool for detecting CRLMs in patients who have undergone neoadjuvant chemotherapy.

After systemic or local therapy, the change in size of the CRLMs may not be representative of a response, because the initial post-treatment examinations often fail to demonstrate shrinkage of the tumor. In such cases radiologists can misinterpret a slight increase in size of a recently treated lesion as tumor progression, whereas it is often sign of early response to anti-angiogenic treatment. The CT "pseudo-progression" is defined as the increase in size of a lesion after treatment associated with a reduction of attenuation, due to intra-lesional edema, together with a decrease in the tumor markers[119]. In these instances, the evaluation of changes in size and enhancement of the lesion as well as following the lesion up over time, preferably using the same modality, helps determine the efficacy of the treatment[120].

After a local hepatic treatment, the current NCCN guidelines[114] suggest surveillance imaging with CT or MRI every 3-6 mo for 2 years, then every 6 mo for 3-5 years. The NCCN guidelines do not recommend PET/CT for assessing treatment response, because of false-negative (necrotic lesions) and false-positive (inflammation and surgery) results may occur.

CONCLUSION

Several imaging techniques are available in management of CRLMs.

US plays a marginal role due to the operator-dependence, the lack of panoramic view and the low sensitivity for lesions < 10 mm. US may select patients with diffuse secondary liver involvement who do not benefit of further hepatic imaging.

Actually, ce-MDCT is the preferred imaging modality for initial global staging, allowing also an optimal pre-treatment planning for curative CRLMs resection.

MRI provides additional information respect to ce-MDCT when suspicious or non-TSCT indeterminate hepatic lesions are present on ce-MDCT, in presence of hepatic steatosis or in the post-chemotherapy liver evaluation.

^{18}F-FDG-PET/CT may be proposed to detect occult extra-hepatic disease prior of CRLMs resection to avoid inappropriate surgical treatment.

^{18}F-PET-MRI may represent the future elective diagnostic tool because it combines the high accuracy for CRLMs detection of MRI with the high performance of extra-hepatic metastases evaluation of PET.

Non-conventional parametric imaging may play a future role for detecting occult CRLMs and predicting which patients are at risk to develop metachronous liver disease, but these techniques have to be further investigated.

REFERENCES

1 **American Cancer Society**. Cancer Facts & Figures 2014. Atlanta: American Cancer Society, 2014. [Accessed 2014 Jan 21]. Available from: URL: http://www.cancer.org/research/cancerfactsstatistics/index

2 **Manfredi S**, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg* 2006; **244**: 254-259 [PMID: 16858188 DOI: 10.1097/01.sla.0000217629.94941.cf]

3 **Kanas GP**, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, Alexander DD, Choti MA, Poston G. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol* 2012; **4**: 283-301 [PMID: 23152705 DOI: 10.2147/CLEP.S34285]

4 **Simmonds PC**, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. *Br J Cancer* 2006; **94**: 982-999 [PMID: 16538219 DOI: 10.1038/sj.bjc.6603033]

5 **Tzeng CW**, Aloia TA. Colorectal liver metastases. *J Gastrointest Surg* 2013; **17**: 195-201; quiz p.201-202 [PMID: 23054896 DOI: 10.1007/s11605-012-2022-3]

6 **Fong Y**, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, Marrero AM, Prasad M, Blumgart LH, Brennan MF. Liver resection for colorectal metastases. *J Clin Oncol* 1997; **15**: 938-946 [PMID: 9060531]

7 **Nakamura S**, Suzuki S, Baba S. Resection of liver metastases of colorectal carcinoma. *World J Surg* 1997; **21**: 741-747 [PMID: 9276706 DOI: 10.1007/s002689900300]

8 **Alberts SR**, Poston GJ. Treatment advances in liver-limited metastatic colorectal cancer. *Clin Colorectal Cancer* 2011; **10**: 258-265 [PMID: 21820974 DOI: 10.1016/j.clcc.2011.06.008]

9 **Tanada M**, Saeki T, Takashima S, Mogami H, Hyoudou I, Jinno K. [Intrahepatic arterial infusion chemotherapy for the colon cancer patients with liver metastases--a comparison of arterial embolization chemotherapy versus continuous arterial infusion chemotherapy]. *Gan To Kagaku Ryoho* 1996; **23**: 1440-1442 [PMID: 8854774]

10 **Dodd GD**, Soulen MC, Kane RA, Livraghi T, Lees WR, Yamashita Y, Gillams AR, Karahan OI, Rhim H. Minimally invasive treatment of malignant hepatic tumors: at the threshold of a major breakthrough. *Radiographics* 2000; **20**: 9-27 [PMID: 10682768 DOI: 10.1148/radiographics.20.1.g00ja019]

11 **Ruers T**, Bleichrodt RP. Treatment of liver metastases, an update on the possibilities and results. *Eur J Cancer* 2002; **38**: 1023-1033 [PMID: 11978527]

12 **Clavien PA**, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. *N Engl J Med* 2007; **356**: 1545-1559 [PMID: 17429086]

13 **Shah KN**, Clary BM. Selection of Patients with Colorectal/Liver Metastases for Surgical Intervention: Current Issues and Challenges. *Curr Surg Rep* 2014; **2**: 1-7 [DOI: 10.1007/s40137-014-0065-y]

14 **Catalano OA**, Singh AH, Uppot RN, Hahn PF, Ferrone CR, Sahani

DV. Vascular and biliary variants in the liver: implications for liver surgery. *Radiographics* 2008; **28**: 359-378 [PMID: 18349445 DOI: 10.1148/rg.282075099]

15 **Kinkel K**, Lu Y, Both M, Warren RS, Thoeni RF. Detection of hepatic metastases from cancers of the gastrointestinal tract by using noninvasive imaging methods (US, CT, MR imaging, PET): a meta-analysis. *Radiology* 2002; **224**: 748-756 [PMID: 12202709 DOI: 10.1148/radiol.2243011362]

16 **Wernecke K**, Rummeny E, Bongartz G, Vassallo P, Kivelitz D, Wiesmann W, Peters PE, Reers B, Reiser M, Pircher W. Detection of hepatic masses in patients with carcinoma: comparative sensitivities of sonography, CT, and MR imaging. *AJR Am J Roentgenol* 1991; **157**: 731-739 [PMID: 1892027 DOI: 10.2214/ajr.157.4.1892027]

17 **Glover C**, Douse P, Kane P, Karani J, Meire H, Mohammadtaghi S, Allen-Mersh TG. Accuracy of investigations for asymptomatic colorectal liver metastases. *Dis Colon Rectum* 2002; **45**: 476-484 [PMID: 12006929]

18 **Clarke MP**, Kane RA, Steele G, Hamilton ES, Ravikumar TS, Onik G, Clouse ME. Prospective comparison of preoperative imaging and intraoperative ultrasonography in the detection of liver tumors. *Surgery* 1989; **106**: 849-855 [PMID: 2554519]

19 **Ohlsson B**, Tranberg KG, Lundstedt C, Ekberg H, Hederström E. Detection of hepatic metastases in colorectal cancer: a prospective study of laboratory and imaging methods. *Eur J Surg* 1993; **159**: 275-281 [PMID: 8103361]

20 **Ong KO**, Leen E. Radiological staging of colorectal liver metastases. *Surg Oncol* 2007; **16**: 7-14 [PMID: 17499498]

21 **Albrecht T**, Hohmann J, Oldenburg A, Skrok J, Wolf KJ. Detection and characterisation of liver metastases. *Eur Radiol* 2004; **14** Suppl 8: P25-P33 [PMID: 15700330]

22 **Albrecht T**, Hoffmann CW, Schmitz SA, Schettler S, Overberg A, Germer CT, Wolf KJ. Phase-inversion sonography during the liver-specific late phase of contrast enhancement: improved detection of liver metastases. *AJR Am J Roentgenol* 2001; **176**: 1191-1198 [PMID: 11312180 DOI: 10.2214/ajr.176.5.1761191]

23 **Albrecht T**, Blomley MJ, Burns PN, Wilson S, Harvey CJ, Leen E, Claudon M, Calliada F, Correas JM, LaFortune M, Campani R, Hoffmann CW, Cosgrove DO, LeFevre F. Improved detection of hepatic metastases with pulse-inversion US during the liver-specific phase of SHU 508A: multicenter study. *Radiology* 2003; **227**: 361-370 [PMID: 12649417 DOI: 10.1148/radiol.2272011833]

24 **Esteban JM**, Mollá MA, Tomás C, Maldonado L. Improved detection of liver metastases with contrast-enhanced wideband harmonic imaging: comparison with CT findings. *Eur J Ultrasound* 2002; **15**: 119-126 [PMID: 12423737 DOI: 10.1016/S0929-8266(02)00032-0]

25 **Quaia E**, D'Onofrio M, Palumbo A, Rossi S, Bruni S, Cova M. Comparison of contrast-enhanced ultrasonography versus baseline ultrasound and contrast-enhanced computed tomography in metastatic disease of the liver: diagnostic performance and confidence. *Eur Radiol* 2006; **16**: 1599-1609 [PMID: 16552507 DOI: 10.1007/s00330-006-0192-7]

26 **Dalla Palma L**, Bertolotto M, Quaia E, Locatelli M. Detection of liver metastases with pulse inversion harmonic imaging: preliminary results. *Eur Radiol* 1999; **9** Suppl 3: S382-S387 [PMID: 10602934 DOI: 10.1007/PL00014079]

27 **Celli N**, Gaiani S, Piscaglia F, Zironi G, Camaggi V, Leoni S, Righini R, Bolondi L. Characterization of liver lesions by real-time contrast-enhanced ultrasonography. *Eur J Gastroenterol Hepatol* 2007; **19**: 3-14 [PMID: 17206071 DOI: 10.1097/01.meg.0000250585.53608.3c]

28 **Larsen LP**, Rosenkilde M, Christensen H, Bang N, Bolvig L, Christiansen T, Laurberg S. The value of contrast enhanced ultrasonography in detection of liver metastases from colorectal cancer: a prospective double-blinded study. *Eur J Radiol* 2007; **62**: 302-307 [PMID: 17194561 DOI: 10.1016/j.ejrad.2006.11.033]

29 **Westwood M**, Joore M, Grutters J, Redekop K, Armstrong N, Lee K, Gloy V, Raatz H, Misso K, Severens J, Kleijnen J. Contrast-enhanced ultrasound using SonoVue® (sulphur hexafluoride microbubbles) compared with contrast-enhanced computed tomography and contrast-enhanced magnetic resonance imaging for the characterisation of focal liver lesions and detection of liver metastases: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2013; **17**: 1-243 [PMID: 23611316 DOI: 10.3310/hta17160]

30 **Rafaelsen SR**, Jakobsen A. Contrast-enhanced ultrasound vs multidetector-computed tomography for detecting liver metastases in colorectal cancer: a prospective, blinded, patient-by-patient analysis. *Colorectal Dis* 2011; **13**: 420-425 [PMID: 20412096 DOI: 10.1111/j.1463-1318.2010.02288.x]

31 **Cantisani V**, Ricci P, Erturk M, Pagliara E, Drudi F, Calliada F, Mortele K, D'Ambrosio U, Marigliano C, Catalano C, Marin D, Di Seri M, Longo F, Passariello R. Detection of hepatic metastases from colorectal cancer: prospective evaluation of gray scale US versus SonoVue® low mechanical index real time-enhanced US as compared with multidetector-CT or Gd-BOPTA-MRI. *Ultraschall Med* 2010; **31**: 500-505 [PMID: 20408122 DOI: 10.1055/s-0028-1109751]

32 **Larsen LP**, Rosenkilde M, Christensen H, Bang N, Bolvig L, Christiansen T, Laurberg S. Can contrast-enhanced ultrasonography replace multidetector-computed tomography in the detection of liver metastases from colorectal cancer? *Eur J Radiol* 2009; **69**: 308-313 [PMID: 18068925 DOI: 10.1016/j.ejrad.2007.10.023]

33 **Konopke R**, Bunk A, Kersting S. Contrast-enhanced ultrasonography in patients with colorectal liver metastases after chemotherapy. *Ultraschall Med* 2008; **29** Suppl 4: S203-S209 [PMID: 18833498 DOI: 10.1055/s-2008-1027795]

34 **Cantisani V**, Grazhdani H, Fioravanti C, Rosignuolo M, Calliada F, Messineo D, Bernieri MG, Redler A, Catalano C, D'Ambrosio F. Liver metastases: Contrast-enhanced ultrasound compared with computed tomography and magnetic resonance. *World J Gastroenterol* 2014; **20**: 9998-10007 [PMID: 25110428 DOI: 10.3748/wjg.v20.i29.9998]

35 **Bolondi L**. The appropriate allocation of CEUS in the diagnostic algorithm of liver lesions: a debated issue. *Ultrasound Med Biol* 2013; **39**: 183-185 [PMID: 23140590]

36 **Choti MA**, Sitzmann JV, Tiburi MF, Sumetchotimetha W, Rangsin R, Schulick RD, Lillemoe KD, Yeo CJ, Cameron JL. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg* 2002; **235**: 759-766 [PMID: 12035031]

37 **Rojas Llimpe FL**, Di Fabio F, Ercolani G, Giampalma E, Cappelli A, Serra C, Castellucci P, D'Errico A, Golfieri R, Pinna AD, Pinto C. Imaging in resectable colorectal liver metastasis patients with or without preoperative chemotherapy: results of the PROMETEO-01 study. *Br J Cancer* 2014; **111**: 667-673 [PMID: 24983362 DOI: 10.1038/bjc.2014.351]

38 **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; **257**: 674-684 [PMID: 20829538 DOI: 10.1148/radiol.10100729]

39 **Weg N**, Scheer MR, Gabor MP. Liver lesions: improved detection with dual-detector-array CT and routine 2.5-mm thin collimation. *Radiology* 1998; **209**: 417-426 [PMID: 9807568]

40 **Kim YK**, Ko SW, Hwang SB, Kim CS, Yu HC. Detection and characterization of liver metastases: 16-slice multidetector computed tomography versus superparamagnetic iron oxide-enhanced magnetic resonance imaging. *Eur Radiol* 2006; **16**: 1337-1345 [PMID: 16453115 DOI: 10.1007/s00330-005-0140-y]

41 **Haider MA**, Amitai MM, Rappaport DC, O'Malley ME, Hanbidge AE, Redston M, Lockwood GA, Gallinger S. Multi-detector row helical CT in preoperative assessment of small (< or = 1.5 cm) liver metastases: is thinner collimation better? *Radiology* 2002; **225**: 137-142 [PMID: 12354997 DOI: 10.1148/radiol.2251011225]

42 **Kulinna C**, Helmberger T, Kessler M, Reiser M. [Improvement in diagnosis of liver metastases with the multi-detector CT]. *Radiologe* 2001; **41**: 16-23 [PMID: 11220094 DOI: 10.1007/s001170050923]

43 **Ch'en IY**, Katz DS, Jeffrey RB, Daniel BL, Li KC, Beaulieu CF, Mindelzun RE, Yao D, Olcott EW. Do arterial phase helical CT images improve detection or characterization of colorectal liver

metastases? *J Comput Assist Tomogr* 2011; **21**: 391-397 [PMID: 9135646 DOI: 10.1097/00004728-199705000-00010]

44 **Wicherts DA**, de Haas RJ, van Kessel CS, Bisschops RH, Takahara T, van Hillegersberg R, Bipat S, Rinkes IH, van Leeuwen MS. Incremental value of arterial and equilibrium phase compared to hepatic venous phase CT in the preoperative staging of colorectal liver metastases: an evaluation with different reference standards. *Eur J Radiol* 2011; **77**: 305-311 [PMID: 19695807 DOI: 10.1016/j.ejrad.2009.07.026]

45 **Mainenti PP**, Cirillo LC, Camera L, Persico F, Cantalupo T, Pace L, De Palma GD, Persico G, Salvatore M. Accuracy of single phase contrast enhanced multidetector CT colonography in the preoperative staging of colo-rectal cancer. *Eur J Radiol* 2006; **60**: 453-459 [PMID: 16965883 DOI: 10.1016/j.ejrad.2006.08.001]

46 **Bajpai SK**, Sahani D. Recent progress in imaging of colorectal cancer liver metastases. *Curr Colorectal Cancer Rep* 2009; **5**: 99-107 [DOI: 10.1007/s11888-009-0015-8]

47 **Berger-Kulemann V**, Schima W, Baroud S, Koelblinger C, Kaczirek K, Gruenberger T, Schindl M, Maresch J, Weber M, Ba-Ssalamah A. Gadoxetic acid-enhanced 3.0 T MR imaging versus multidetector-row CT in the detection of colorectal metastases in fatty liver using intraoperative ultrasound and histopathology as a standard of reference. *Eur J Surg Oncol* 2012; **38**: 670-676 [PMID: 22652037 DOI: 10.1016/j.ejso.2012.05.004]

48 **Bipat S**, Niekel MC, Comans EF, Nio CY, Bemelman WA, Verhoef C, Stoker J. Imaging modalities for the staging of patients with colorectal cancer. *Neth J Med* 2012; **70**: 26-34 [PMID: 22271811]

49 **Bipat S**, van Leeuwen MS, Comans EF, Pijl ME, Bossuyt PM, Zwinderman AH, Stoker J. Colorectal liver metastases: CT, MR imaging, and PET for diagnosis--meta-analysis. *Radiology* 2005; **237**: 123-131 [PMID: 16100087 DOI: 10.1148/radiol.2371042060]

50 **Mainenti PP**, Mancini M, Mainolfi C, Camera L, Maurea S, Manchia A, Tanga M, Persico F, Addeo P, D'Antonio D, Speranza A, Bucci L, Persico G, Pace L, Salvatore M. Detection of colorectal liver metastases: prospective comparison of contrast enhanced US, multidetector CT, PET/CT, and 1.5 Tesla MR with extracellular and reticulo-endothelial cell specific contrast agents. *Abdom Imaging* 2010; **35**: 511-521 [PMID: 19562412 DOI: 10.1007/s00261-009-9555-2]

51 **Blyth S**, Blakeborough A, Peterson M, Cameron IC, Majeed AW. Sensitivity of magnetic resonance imaging in the detection of colorectal liver metastases. *Ann R Coll Surg Engl* 2008; **90**: 25-28 [PMID: 18201494 DOI: 10.1308/003588408X242303]

52 **Schima W**, Saini S, Echeverri JA, Hahn PF, Harisinghani M, Mueller PR. Focal liver lesions: characterization with conventional spin-echo versus fast spin-echo T2-weighted MR imaging. *Radiology* 1997; **202**: 389-393 [PMID: 9015063]

53 **Bennett GL**, Petersein A, Mayo-Smith WW, Hahn PF, Schima W, Saini S. Addition of gadolinium chelates to heavily T2-weighted MR imaging: limited role in differentiating hepatic hemangiomas from metastases. *AJR Am J Roentgenol* 2000; **174**: 477-485 [PMID: 10658728 DOI: 10.2214/ajr.174.2.1740477]

54 **Cittadini G**, Santacroce E, Giasotto V, Rescinito G. [Focal liver lesions: characterization with quantitative analysis of T2 relaxation time in TSE sequence with double echo time]. *Radiol Med* 2004; **107**: 166-173 [PMID: 15031682]

55 **Patterson DM**, Padhani AR, Collins DJ. Technology insight: water diffusion MRI--a potential new biomarker of response to cancer therapy. *Nat Clin Pract Oncol* 2008; **5**: 220-233 [PMID: 18301415 DOI: 10.1038/ncponc1073]

56 **Bruegel M**, Holzapfel K, Gaa J, Woertler K, Waldt S, Kiefer B, Stemmer A, Ganter C, Rummeny EJ. Characterization of focal liver lesions by ADC measurements using a respiratory triggered diffusion-weighted single-shot echo-planar MR imaging technique. *Eur Radiol* 2008; **18**: 477-485 [PMID: 17960390 DOI: 10.1007/s00330-007-0785-9]

57 **Parikh T**, Drew SJ, Lee VS, Wong S, Hecht EM, Babb JS, Taouli B. Focal liver lesion detection and characterization with diffusion-weighted MR imaging: comparison with standard breath-hold T2-weighted imaging. *Radiology* 2008; **246**: 812-822 [PMID: 18223123 DOI: 10.1148/radiol.2463070432]

58 **Kenis C**, Deckers F, De Foer B, Van Mieghem F, Van Laere S, Pouillon M. Diagnosis of liver metastases: can diffusion-weighted imaging (DWI) be used as a stand alone sequence? *Eur J Radiol* 2012; **81**: 1016-1023 [PMID: 21377305 DOI: 10.1016/j.ejrad.2011.02.019]

59 **Löwenthal D**, Zeile M, Lim WY, Wybranski C, Fischbach F, Wieners G, Pech M, Kropf S, Ricke J, Dudeck O. Detection and characterisation of focal liver lesions in colorectal carcinoma patients: comparison of diffusion-weighted and Gd-EOB-DTPA enhanced MR imaging. *Eur Radiol* 2011; **21**: 832-840 [PMID: 20886339 DOI: 10.1007/s00330-010-1977-2]

60 **Bellin MF**, Van Der Molen AJ. Extracellular gadolinium-based contrast media: an overview. *Eur J Radiol* 2008; **66**: 160-167 [PMID: 18358659 DOI: 10.1016/j.ejrad.2008.01.023]

61 **del Frate C**, Bazzocchi M, Mortele KJ, Zuiani C, Londero V, Como G, Zanardi R, Ros PR. Detection of liver metastases: comparison of gadobenate dimeglumine-enhanced and ferumoxides-enhanced MR imaging examinations. *Radiology* 2002; **225**: 766-772 [PMID: 12461259 DOI: 10.1148/radiol.2253011854]

62 **Ward J**, Robinson PJ, Guthrie JA, Downing S, Wilson D, Lodge JP, Prasad KR, Toogood GJ, Wyatt JI. Liver metastases in candidates for hepatic resection: comparison of helical CT and gadolinium- and SPIO-enhanced MR imaging. *Radiology* 2005; **237**: 170-180 [PMID: 16126930 DOI: 10.1148/radiol.2371041444]

63 **Kim YK**, Lee JM, Kim CS, Chung GH, Kim CY, Kim IH. Detection of liver metastases: gadobenate dimeglumine-enhanced three-dimensional dynamic phases and one-hour delayed phase MR imaging versus superparamagnetic iron oxide-enhanced MR imaging. *Eur Radiol* 2005; **15**: 220-228 [PMID: 15624108 DOI: 10.1007/s00330-004-2570-3]

64 **Maurea S**, Mainenti PP, Tambasco A, Imbriaco M, Mollica C, Laccetti E, Camera L, Liuzzi R, Salvatore M. Diagnostic accuracy of MR imaging to identify and characterize focal liver lesions: comparison between gadolinium and superparamagnetic iron oxide contrast media. *Quant Imaging Med Surg* 2014; **4**: 181-189 [PMID: 24914419 DOI: 10.3978/j.issn.2223-4292.2014.01.02]

65 **Hamm B**, Staks T, Mühler A, Bollow M, Taupitz M, Frenzel T, Wolf KJ, Weinmann HJ, Lange L. Phase I clinical evaluation of Gd-EOB-DTPA as a hepatobiliary MR contrast agent: safety, pharmacokinetics, and MR imaging. *Radiology* 1995; **195**: 785-792 [PMID: 7754011]

66 **Dahlström N**, Persson A, Albiin N, Smedby O, Brismar TB. Contrast-enhanced magnetic resonance cholangiography with Gd-BOPTA and Gd-EOB-DTPA in healthy subjects. *Acta Radiol* 2007; **48**: 362-368 [PMID: 17453513 DOI: 10.1080/02841850701196922]

67 **Auer RC**, White RR, Kemeny NE, Schwartz LH, Shia J, Blumgart LH, Dematteo RP, Fong Y, Jarnagin WR, D'Angelica MI. Predictors of a true complete response among disappearing liver metastases from colorectal cancer after chemotherapy. *Cancer* 2010; **116**: 1502-1509 [PMID: 20120032 DOI: 10.1002/cncr.24912]

68 **van Kessel CS**, Buckens CF, van den Bosch MA, van Leeuwen MS, van Hillegersberg R, Verkooijen HM. Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. *Ann Surg Oncol* 2012; **19**: 2805-2813 [PMID: 22396005 DOI: 10.1245/s10434-012-2300-z]

69 **Tran PV**, Jhaveri KS. Comparison of high spatial resolution respiratory triggered inversion recovery-prepared spoiled gradient echo sequence with standard breathhold T1 sequence MRI of the liver using gadoxetic acid. *J Magn Reson Imaging* 2013; **37**: 700-706 [PMID: 23335396 DOI: 10.1002/jmri.23864]

70 **Yoon JH**, Lee JM, Lee ES, Baek J, Lee S, Iwadate Y, Han JK, Choi BI. Navigated three-dimensional T1-weighted gradient-echo sequence for gadoxetic acid liver magnetic resonance imaging in patients with limited breath-holding capacity. *Abdom Imaging* 2015; **40**: 278-288 [PMID: 25112454]

71 **Ruers TJ**, Langenhoff BS, Neeleman N, Jager GJ, Strijk S, Wobbes T, Corstens FH, Oyen WJ. Value of positron emission tomography with [F-18]fluorodeoxyglucose in patients with

colorectal liver metastases: a prospective study. *J Clin Oncol* 2002; **20**: 388-395 [PMID: 11786565 DOI: 10.1200/JCO.20.2.388]

72 **Rappeport ED**, Loft A, Berthelsen AK, von der Recke P, Larsen PN, Mogensen AM, Wettergren A, Rasmussen A, Hillingsoe J, Kirkegaard P, Thomsen C. Contrast-enhanced FDG-PET/CT vs. SPIO-enhanced MRI vs. FDG-PET vs. CT in patients with liver metastases from colorectal cancer: a prospective study with intraoperative confirmation. *Acta Radiol* 2007; **48**: 369-378 [PMID: 17453514 DOI: 10.1080/02841850701294560]

73 **Fong Y**, Saldinger PF, Akhurst T, Macapinlac H, Yeung H, Finn RD, Cohen A, Kemeny N, Blumgart LH, Larson SM. Utility of 18F-FDG positron emission tomography scanning on selection of patients for resection of hepatic colorectal metastases. *Am J Surg* 1999; **178**: 282-287 [PMID: 10587184 DOI: 10.1016/S0002-9610(99)00187-7]

74 **Sahani DV**, Kalva SP, Fischman AJ, Kadavigere R, Blake M, Hahn PF, Saini S. Detection of liver metastases from adenocarcinoma of the colon and pancreas: comparison of mangafodipir trisodium-enhanced liver MRI and whole-body FDG PET. *AJR Am J Roentgenol* 2005; **185**: 239-246 [PMID: 15972430 DOI: 10.2214/ajr.185.1.01850239]

75 **Badiee S**, Franc BL, Webb EM, Chu B, Hawkins RA, Coakley F, Singer L. Role of IV iodinated contrast material in 18F-FDG PET/CT of liver metastases. *AJR Am J Roentgenol* 2008; **191**: 1436-1439 [PMID: 18941082 DOI: 10.2214/AJR.07.3750]

76 **Revheim ME**, Haugvik SP, Johnsrud K, Mathisen Ø, Fjeld JG, Skretting A. Respiratory gated and prolonged acquisition 18F-FDG PET improve preoperative assessment of colorectal liver metastases. *Acta Radiol* 2015; **56**: 397-403 [PMID: 24682406 DOI: 10.1177/0284185114529563]

77 **Ruers TJ**, Wiering B, van der Sijp JR, Roumen RM, de Jong KP, Comans EF, Pruim J, Dekker HM, Krabbe PF, Oyen WJ. Improved selection of patients for hepatic surgery of colorectal liver metastases with (18)F-FDG PET: a randomized study. *J Nucl Med* 2009; **50**: 1036-1041 [PMID: 19525451 DOI: 10.2967/jnumed.109.063040]

78 **Mainenti PP**, Salvatore B, D'Antonio D, De Falco T, De Palma GD, D'Armiento FP, Bucci L, Pace L, Salvatore M. PET/CT colonography in patients with colorectal polyps: a feasibility study. *Eur J Nucl Med Mol Imaging* 2007; **34**: 1594-1603 [PMID: 17492447 DOI: 10.1007/s00259-007-0422-5]

79 **Mainenti PP**, Iodice D, Segreto S, Storto G, Magliulo M, De Palma GD, Salvatore M, Pace L. Colorectal cancer and 18FDG-PET/CT: what about adding the T to the N parameter in loco-regional staging? *World J Gastroenterol* 2011; **17**: 1427-1433 [PMID: 21472100 DOI: 10.3748/wjg.v17.i11.1427]

80 **Maas M**, Rutten IJ, Nelemans PJ, Lambregts DM, Cappendijk VC, Beets GL, Beets-Tan RG. What is the most accurate whole-body imaging modality for assessment of local and distant recurrent disease in colorectal cancer? A meta-analysis : imaging for recurrent colorectal cancer. *Eur J Nucl Med Mol Imaging* 2011; **38**: 1560-1571 [PMID: 21468765 DOI: 10.1007/s00259-011-1785-1]

81 **Giacomobono S**, Gallicchio R, Capacchione D, Nardelli A, Gattozzi D, Lettini G, Molinari L, Mainenti P, Cammarota A, Storto G. F-18 FDG PET/CT in the assessment of patients with unexplained CEA rise after surgical curative resection for colorectal cancer. *Int J Colorectal Dis* 2013; **28**: 1699-1705 [PMID: 23846517 DOI: 10.1007/s00384-013-1747-0]

82 **Storto G**, Nicolai E, Salvatore M. [18F]FDG-PET-CT for early monitoring of tumor response: when and why. *Q J Nucl Med Mol Imaging* 2009; **53**: 167-180 [PMID: 19293765]

83 **Partovi S**, Kohan A, Gaeta C, Rubbert C, Vercher-Conejero JL, Jones RS, O'Donnell JK, Wojtylak P, Faulhaber P. Image quality assessment of automatic three-segment MR attenuation correction vs. CT attenuation correction. *Am J Nucl Med Mol Imaging* 2013; **3**: 291-299 [PMID: 23638340]

84 **Schwenzer NF**, Schmidt H, Claussen CD. Whole-body MR/PET: applications in abdominal imaging. *Abdom Imaging* 2012; **37**: 20-28 [PMID: 22002195 DOI: 10.1007/s00261-011-9809-7]

85 **Drzezga A**, Souvatzoglou M, Eiber M, Beer AJ, Fürst S, Martinez-Möller A, Nekolla SG, Ziegler S, Ganter C, Rummeny EJ, Schwaiger M. First clinical experience with integrated whole-body PET/MR: comparison to PET/CT in patients with oncologic diagnoses. *J Nucl Med* 2012; **53**: 845-855 [PMID: 22534830 DOI: 10.2967/jnumed.111.098608]

86 **Quick HH**, von Gall C, Zeilinger M, Wiesmüller M, Braun H, Ziegler S, Kuwert T, Uder M, Dörfler A, Kalender WA, Lell M. Integrated whole-body PET/MR hybrid imaging: clinical experience. *Invest Radiol* 2013; **48**: 280-289 [PMID: 23442775 DOI: 10.1097/RLI.0b013e3182845a08]

87 **Partovi S**, Kohan A, Paspulati RM, Ros PR, Herrmann KA. PET/MRI in Colorectal cancer. In: Carrio I, Ros P. PET/MRI Methodology and Clinical Applications. *Springer* 2014; 7: 95-108

88 **Kershah S**, Partovi S, Traughber BJ, Muzic RF, Schluchter MD, O'Donnell JK, Faulhaber P. Comparison of standardized uptake values in normal structures between PET/CT and PET/MRI in an oncology patient population. *Mol Imaging Biol* 2013; **15**: 776-785 [PMID: 23632951 DOI: 10.1007/s11307-013-0629-8]

89 **Nielsen K**, Scheffer HJ, Pieters IC, van Tilborg AA, van Waesberghe JH, Oprea-Lager DE, Meijerink MR, Kazemier G, Hoekstra OS, Schreurs HW, Sietses C, Meijer S, Comans EF, van den Tol PM. The use of PET-MRI in the follow-up after radiofrequency- and microwave ablation of colorectal liver metastases. *BMC Med Imaging* 2014; **14**: 27 [PMID: 25103913 DOI: 10.1186/1471-2342-14-27]

90 **Sheafor DH**, Killius JS, Paulson EK, DeLong DM, Foti AM, Nelson RC. Hepatic parenchymal enhancement during triple-phase helical CT: can it be used to predict which patients with breast cancer will develop hepatic metastases? *Radiology* 2000; **214**: 875-880 [PMID: 10715061]

91 **Miles KA**, Colyvas K, Griffiths MR, Bunce IH. Colon cancer: risk stratification using hepatic perfusion CT. *Eur Radiol* 2004; **14** (Suppl 2): 129

92 **Ridge JA**, Bading JR, Gelbard AS, Benua RS, Daly JM. Perfusion of colorectal hepatic metastases. Relative distribution of flow from the hepatic artery and portal vein. *Cancer* 1987; **59**: 1547-1553 [PMID: 3828954]

93 **Leen E**, Goldberg JA, Robertson J, Sutherland GR, McArdle CS. The use of duplex sonography in the detection of colorectal hepatic metastases. *Br J Cancer* 1991; **63**: 323-325 [PMID: 1997115]

94 **Leen E**, Goldberg JA, Robertson J, Sutherland GR, Hemingway DM, Cooke TG, McArdle CS. Detection of hepatic metastases using duplex/color Doppler sonography. *Ann Surg* 1991; **214**: 599-604 [PMID: 1953113]

95 **Kopljar M**, Brkljacic B, Doko M, Horzic M. Nature of Doppler perfusion index changes in patients with colorectal cancer liver metastases. *J Ultrasound Med* 2004; **23**: 1295-1300 [PMID: 15448318]

96 **Anzidei M**, Napoli A, Zaccagna F, Cartocci G, Saba L, Menichini G, Cavallo Marincola B, Marotta E, Di Mare L, Catalano C, Passariello R. Liver metastases from colorectal cancer treated with conventional and antiangiogenetic chemotherapy: evaluation with liver computed tomography perfusion and magnetic resonance diffusion-weighted imaging. *J Comput Assist Tomogr* 2011; **35**: 690-696 [PMID: 22082538 DOI: 10.1097/RCT.0b013e318230d905]

97 **Meijerink MR**, van Waesberghe JH, van der Weide L, van den Tol P, Meijer S, van Kuijk C. Total-liver-volume perfusion CT using 3-D image fusion to improve detection and characterization of liver metastases. *Eur Radiol* 2008; **18**: 2345-2354 [PMID: 18491094 DOI: 10.1007/s00330-008-0996-8]

98 **Kanematsu M**, Goshima S, Watanabe H, Kondo H, Kawada H, Noda Y, Moriyama N. Diffusion/perfusion MR imaging of the liver: practice, challenges, and future. *Magn Reson Med Sci* 2012; **11**: 151-161 [PMID: 23037559]

99 **De Bruyne S**, Van Damme N, Smeets P, Ferdinande L, Ceelen W, Mertens J, Van de Wiele C, Troisi R, Libbrecht L, Laurent S, Geboes K, Peeters M. 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; **106**: 1926-1933 [PMID: 22596235 DOI: 10.1038/bjc.2012.184]

100 **Ganeshan B**, Miles KA, Young RC, Chatwin CR. Texture analysis

in non-contrast enhanced CT: impact of malignancy on texture in apparently disease-free areas of the liver. *Eur J Radiol* 2009; **70**: 101-110 [PMID: 18242909 DOI: 10.1016/j.ejrad.2007.12.005]

101 **Miles KA**, Ganeshan B, Griffiths MR, Young RC, Chatwin CR. Colorectal cancer: texture analysis of portal phase hepatic CT images as a potential marker of survival. *Radiology* 2009; **250**: 444-452 [PMID: 19164695 DOI: 10.1148/radiol.2502071879]

102 **Rao SX**, Lambregts DM, Schnerr RS, van Ommen W, van Nijnatten TJ, Martens MH, Heijnen LA, Backes WH, Verhoef C, Zeng MS, Beets GL, Beets-Tan RG. Whole-liver CT texture analysis in colorectal cancer: Does the presence of liver metastases affect the texture of the remaining liver? *United European Gastroenterol J* 2014; **2**: 530-538 [PMID: 25452849 DOI: 10.1177/2050640614552463]

103 **Ganeshan B**, Miles KA. Quantifying tumour heterogeneity with CT. *Cancer Imaging* 2013; **13**: 140-149 [PMID: 23545171 DOI: 10.1102/1470-7330.2013.0015]

104 **Barash H**, Gross E, Edrei Y, Pappo O, Spira G, Vlodavsky I, Galun E, Matot I, Abramovitch R. Functional magnetic resonance imaging monitoring of pathological changes in rodent livers during hyperoxia and hypercapnia. *Hepatology* 2008; **48**: 1232-1241 [PMID: 18629804 DOI: 10.1002/hep.22394]

105 **Barash H**, Gross E, Matot I, Edrei Y, Tsarfaty G, Spira G, Vlodavsky I, Galun E, Abramovitch R. Functional MR imaging during hypercapnia and hyperoxia: noninvasive tool for monitoring changes in liver perfusion and hemodynamics in a rat model. *Radiology* 2007; **243**: 727-735 [PMID: 17463135]

106 **Edrei Y**, Gross E, Corchia N, Tsarfaty G, Galun E, Pappo O, Abramovitch R. Vascular profile characterization of liver tumors by magnetic resonance imaging using hemodynamic response imaging in mice. *Neoplasia* 2011; **13**: 244-253 [PMID: 21390187]

107 **Edrei Y**, Freiman M, Sklair-Levy M, Tsarfaty G, Gross E, Joskowicz L, Abramovitch R. Quantitative functional MRI biomarkers improved early detection of colorectal liver metastases. *J Magn Reson Imaging* 2014; **39**: 1246-1253 [PMID: 24006217 DOI: 10.1002/jmri.24270]

108 **Seo HJ**, Kim MJ, Lee JD, Chung WS, Kim YE. Gadoxetate disodium-enhanced magnetic resonance imaging versus contrast-enhanced 18F-fluorodeoxyglucose positron emission tomography/computed tomography for the detection of colorectal liver metastases. *Invest Radiol* 2011; **46**: 548-555 [PMID: 21577131 DOI: 10.1097/RLI.0b013e31821a2163]

109 **Muhi A**, Ichikawa T, Motosugi U, Sou H, Nakajima H, Sano K, Sano M, Kato S, Kitamura T, Fatima Z, Fukushima K, Iino H, Mori Y, Fujii H, Araki T. Diagnosis of colorectal hepatic metastases: comparison of contrast-enhanced CT, contrast-enhanced US, superparamagnetic iron oxide-enhanced MRI, and gadoxetic acid-enhanced MRI. *J Magn Reson Imaging* 2011; **34**: 326-335 [PMID: 21780227 DOI: 10.1002/jmri.22613]

110 **Zech CJ**, Grazioli L, Jonas E, Ekman M, Niebecker R, Gschwend S, Breuer J, Jönsson L, Kienbaum S. Health-economic evaluation of three imaging strategies in patients with suspected colorectal liver metastases: Gd-EOB-DTPA-enhanced MRI vs. extracellular contrast media-enhanced MRI and 3-phase MDCT in Germany, Italy and Sweden. *Eur Radiol* 2009; **19** Suppl 3: S753-S763 [PMID: 19484243 DOI: 10.1007/s00330-009-1432-4]

111 **Chen L**, Zhang J, Zhang L, Bao J, Liu C, Xia Y, Huang X, Wang J. Meta-analysis of gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced magnetic resonance imaging for the detection of liver metastases. *PLoS One* 2012; **7**: e48681 [PMID: 23144927 DOI: 10.1371/journal.pone.0048681]

112 **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; **42**: 152-163 [PMID: 25319712 DOI: 10.1007/s00259-014-2930-4]

113 **Han K**, Park SH, Kim KW, Kim HJ, Lee SS, Kim JC, Yu CS, Lim SB, Joo YS, Kim AY, Ha HK. Use of liver magnetic resonance imaging after standard staging abdominopelvic computed tomography to evaluate newly diagnosed colorectal cancer patients. *Ann Surg* 2015; **261**: 480-486 [PMID: 24866542]

114 National Comprehensive Cancer Network Oncologic Guidelines. Colon cancer. Version 2. 2012. Available from: URL: http://nccn.org

115 **Sahani D**, Mehta A, Blake M, Prasad S, Harris G, Saini S. Preoperative hepatic vascular evaluation with CT and MR angiography: implications for surgery. *Radiographics* 2004; **24**: 1367-1380 [PMID: 15371614 DOI: 10.1148/rg.245035224]

116 **Therasse P**, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205-216 [PMID: 10655437 DOI: 10.1093/jnci/92.3.205]

117 **Catenacci DV**, Kozloff M, Kindler HL, Polite B. Personalized colon cancer care in 2010. *Semin Oncol* 2011; **38**: 284-308 [PMID: 21421118]

118 **Chibaudel B**, Maindrault-Goebel F, Lledo G, Mineur L, André T, Bennamoun M, Mabro M, Artru P, Carola E, Flesch M, Dupuis O, Colin P, Larsen AK, Afchain P, Tournigand C, Louvet C, de Gramont A. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. *J Clin Oncol* 2009; **27**: 5727-5733 [PMID: 19786657 DOI: 10.1200/JCO.2009.23.4344]

119 **Chung WS**, Park MS, Shin SJ, Baek SE, Kim YE, Choi JY, Kim MJ. Response evaluation in patients with colorectal liver metastases: RECIST version 1.1 versus modified CT criteria. *AJR Am J Roentgenol* 2012; **199**: 809-815 [PMID: 22997372]

120 **Schima W**, Ba-Ssalamah A, Kurtaran A, Schindl M, Gruenberger T. Post-treatment imaging of liver tumours. *Cancer Imaging* 2007; **7** Spec No A: S28-S36 [PMID: 17921098 DOI: 10.1102/1470-7330.2007.9047]

P- Reviewer: Kita K **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com