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Post-treatment imaging of liver tumours

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Abstract

In the past few years, great improvements have been made to achieve local tumour control of primary liver malignancies and liver metastases. For hepatocellular carcinoma (HCC), transarterial chemoembolisation (TACE) and tumour ablation techniques, including percutaneous ethanol injection (PEI), radiofrequency ablation (RF), and laser-induced interstitial thermotherapy (LITT) have been developed. For colorectal liver metastases, surgery is still the standard technique in localised disease, although percutaneous RF ablation has gained considerable acceptance. In patients with widespread disease, chemotherapy with new drugs offers improved survival. Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are the modalities of choice to evaluate treatment response. The present review demonstrates imaging findings of complete and incomplete tumour control after intervention as well as the imaging spectrum of complications. Imaging guidelines according to the World Health Organization and Response Evaluation Criteria In Solid Tumors (RECIST) for assessment of chemotherapy response are presented.

Keywords: *Liver; Metastasis; hepatocellular carcinoma (HCC); magnetic resonance imaging (MRI); computed tomography (CT).*

Introduction

The liver is the second most common site of metastatic spread of epithelial cancers, especially in primary malignancies of the gastrointestinal tract. Liver metastases are approximately ten times more common than primary malignant tumours of the liver, which comprise hepatocellular carcinoma (HCC), cholangiocellular carcinoma (CCC), and rare tumours such as angiosarcoma, haemangioendothelioma, etc. Nowadays a wide array of efficient (and quite often competing) therapeutic alternatives is available: new anticancer drugs, surgical resection techniques for advanced disease, and interventional-radiological procedures for tumour destruction.

Radiologic assessment is the cornerstone to evaluate the success of any tumour therapy in the liver. It is used to evaluate local tumour control or tumour recurrence after surgical resection, tumour ablation, and transarterial chemoembolisation procedures[1–3]. During chemotherapy radiologic assessment of tumour burden is used as an objective confirmation of tumour response[4].

In clinical practice and as required in chemotherapeutic drug trials, contrast-enhanced computed tomography (CT) is the most often used imaging modality because of its availability, robustness, and the ability to scan the abdomen and chest in one setting. Contrast-enhanced magnetic resonance imaging (MRI) plays a role in tumour assessment of patients with a contraindication to the intravenous application of iodine contrast material. Due to its superior contrast resolution, MRI is also helpful in the assessment of tumour response of HCC patients, especially after chemoembolisation. Ultrasound (with intravenous contrast material) may be used in selected cases for the follow-up of patients after tumour evaluation[5], although its operator dependency limits its widespread use for serial follow-up of tumours.

The present review summarises the current use of imaging modalities for assessment of tumour therapy response in the liver. It describes the current guidelines according to the World Health Organization (WHO) for bi-dimensional tumour assessment and the Response Evaluation Criteria In Solid Tumors (RECIST) criteria

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for uni-dimensional assessment of tumour response[6–8]. The imaging appearance of complete and incomplete local tumour control and tumour recurrence are presented.

Hepatocellular carcinoma

To date, hepatic resection and liver transplantation are considered the most effective treatment options for hepatocellular carcinoma (HCC). However, only a minority of HCC patients may undergo surgery, because advanced disease with multifocal tumour spread or gross vascular invasion, extrahepatic tumour spread or inadequate functional liver reserve related to co-existent cirrhosis precludes successful surgery. Thus, palliative treatment in patients with irresectable HCC, such as transarterial chemoembolisation (TACE) and tumour ablation techniques, such as percutaneous ethanol injection (PEI), radiofrequency ablation (RFA) and laser-induced interstitial thermo-therapy (LITT) are treatment options for patients with advanced disease. It is the task of these treatment modalities to provide local tumour control. Patients with residual or locally recurrent tumour after treatment or patients with development of new tumours may undergo repetitive treatment. Cross-sectional imaging is of key importance to detect residual tumour or tumour regrowth at the periphery.

Tumour ablation

Contrast-enhanced multiphasic helical or multi-detector CT (MDCT) are widely used in the evaluation of HCC patients after local tumour treatment. Acquisition of an unenhanced scan is of major importance in patients with treated HCC lesions. Successfully treated (i.e. necrotic) lesions appear in general as low-density areas (sometimes with gas bubbles) (Fig. 1) with a thin rim of contrast enhancement in the arterial and portal venous phase, which may represent granulation tissue. Moreover, subsegmental peripheral hyperaemia may be seen adjacent to HCC lesion post-tumour ablation. In contrast, residual tumour after incomplete tumour ablation may display focal or nodular peripheral enhancement in the arterial or portal venous phase. Sometimes comparison of the pre- and post-treatment CT scan may help in the confident diagnosis of residual tumour post-treatment: side-by-side analysis shows whether the size of necrosis shown in the post-treatment scan actually covers completely the tumour seen on the pre-contrast scan.

At MRI, necrosis post-tumour ablation may show low signal intensity on T2-weighted images and high signal intensity on T1-weighted images due to coagulation necrosis. To detect residual tumour, or tumour recurrence, gadolinium-enhanced dynamic T1-weighted gradient recalled echo (GRE) pulse sequences are mandatory. Only non-specific gadolinium chelates will reliably show perfusion of vital tumour, whereas liver-specific contrast agents, by nature of their accumulation in 'healthy' liver tissue, cannot reliably differentiate between vital and necrotic tumour. T2-weighted turbo spin echo (TSE) images are also helpful in the detection of residual or recurrent tumour, because the vital tumour is hyperintense to necrosis. Cystic necrosis of tumour may also display hyperintensity on T2-weighted images, which can be further characterised by gadolinium-enhanced T1-weighted imaging[9].

Chemoembolisation

For chemo-embolisation of HCC, a chemotherapeutic agent is most often mixed with iodised oil (lipiodol). The distribution and the degree of lipiodol uptake within HCC provides information about the extent of tumour necrosis. However, the high attenuation of

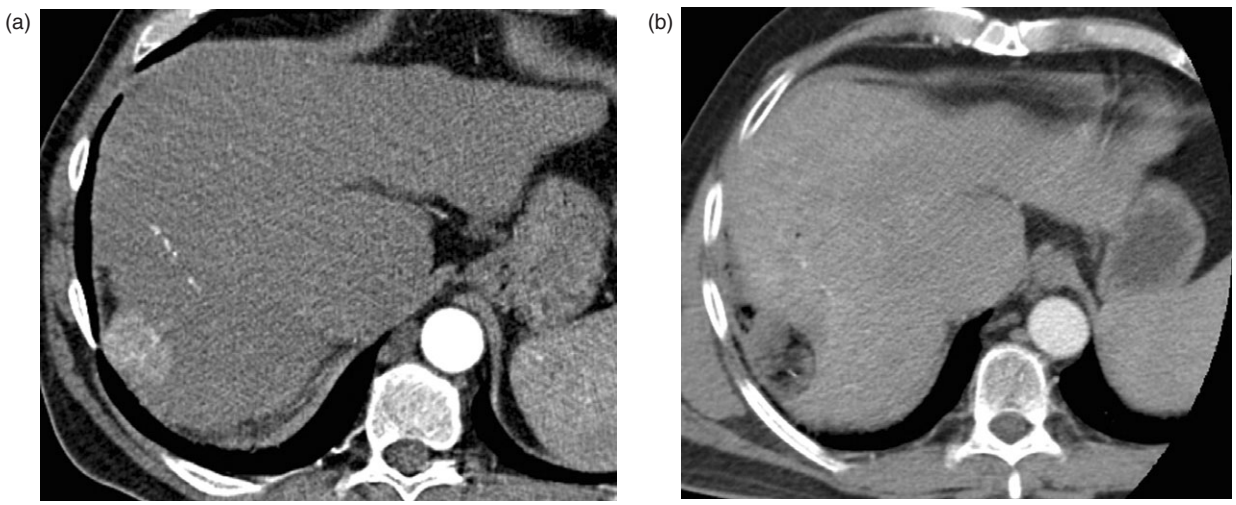

Figure 1 **Successful percutaneous ethanol instillation (PEI) of HCC. (a) Contrast-enhanced MDCT shows a subcapsular HCC in segment 7. (b) Contrast-enhanced MDCT immediately during PEI shows tumour necrosis slightly larger than the original tumour; there is no residual tumour seen.**

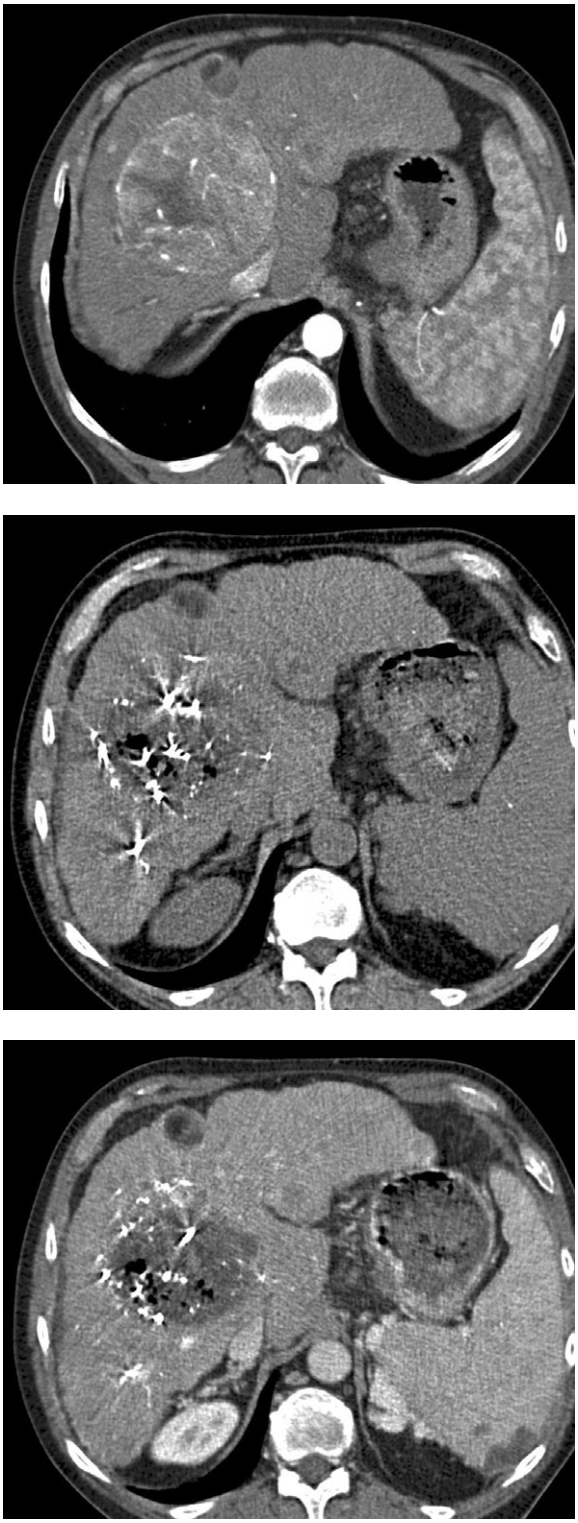

Figure 2 **Successful TACE of HCC. (a) Contrast-enhanced MDCT shows a large encapsulated HCC, which is hypervascular in the arterial phase. There is also a smaller lesion in segment 4 present. (b) After successful chemo-embolisation of the large tumour, unenhanced CT demonstrate lipiodol in the tumour bed. There are also gas bubbles present due to tumour necrosis. (c) Contrast-enhanced MDCT shows no residual tumour. The smaller lesion in segment 4 is not treated.**

lipiodol on unenhanced CT scans makes it difficult to find residual or recurrent tumour at contrast-enhanced CT scans. As long as subtraction techniques of enhanced and contrast-enhanced CT scans are not widely available, critical side-by-side assessment of unenhanced and contrast-enhanced CT scans is the standard technique to find HCC recurrence (Fig. 2). Focal wash-out of lipiodol during follow-up also suggests the presence of viable tumour in the respective area.

Many authors consider MR imaging very valuable and superior to CT in the evaluation of HCC after TACE, because lipiodol deposition in the tumours does not interfere with the signal intensity of T1-weighted and T2-weighted MR images. Similar to the follow-up after local tumour ablation, gadolinium-enhanced dynamic T1-weighted GRE pulse sequences are most sensitive for the detection of tumour recurrence in the arterial phase. Dynamic multiphasic scanning is recommended, because in the equilibrium phase vital tumour parts may be as hypointense as necrotic areas. In our institution, after TACE of tumour ablation treatment, early follow-up (either contrast-enhanced MDCT or MRI) are performed at 3 weeks post-treatment. Depending on the results, patients may undergo repetitive treatment or serial follow-up at 3-month intervals.

Recently, a study assessed the value of contrast-enhanced multi-phasic CT in the determination of completeness of tumour response after therapy[3]. In their study, histologic evaluation of explanted liver specimens after transplantation was performed, which showed that the positive predictive value of contrast-enhanced CT in determination of compete tumour response was only 69%. HCC deemed to be treated 'completely' at contrast-enhanced CT had a tumour necrosis rate of $99.4 \pm 19.2\%$, with a range of 40–100% growth at histopathology. The authors conclude that due to the inaccuracy of contrast-enhanced CT to assess complete tumour response, regular follow-up examination after treatment is mandatory to detect early recurrence before widespread progression[3].

TACE is not without complications. Inadvertent embolisation of the cystic artery or visceral branches may induce inflammation and necrosis. The two most common sites of complications include the gallbladder with necrotising cholecystitis post-therapy and pancreatitis (Fig. 3).

Metastases

A variety of extrahepatic primary malignancies tend to spread to the liver via the arterial or portal venous blood supply to seed metastases. The liver is a favourable environment for metastatic cells to grow. The liver as the site of metastatic spread limits the prognosis of patients. In general, imaging methods are used for the detection of liver metastases. Different imaging modalities may yield a wide range of results for accuracy regarding

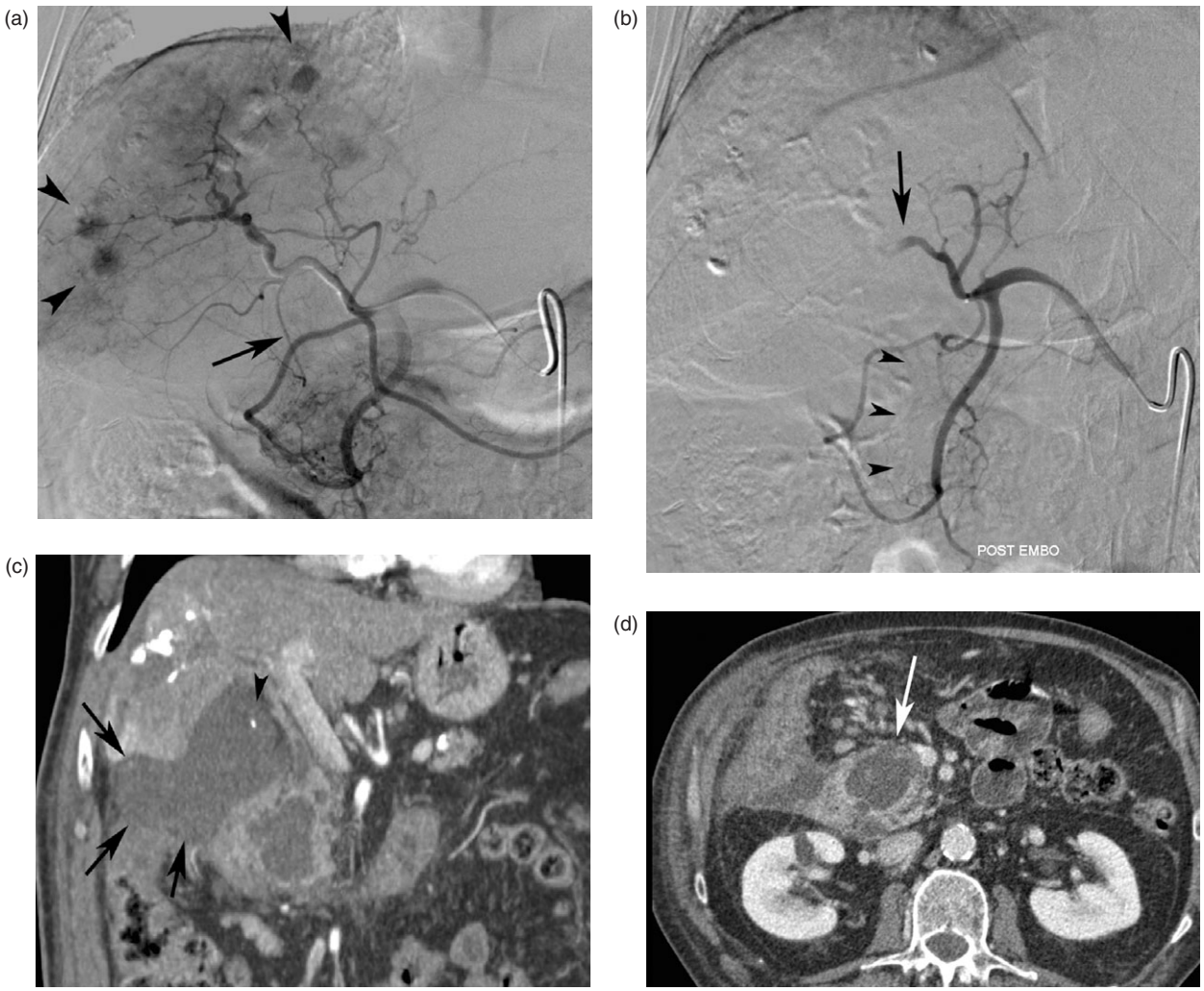

Figure 3 **Complications of TACE. (a) Selective digital subtraction angiography (DSA) shows tumour staining of multicentric HCC in the liver (arrowheads). The cystic artery is also depicted (arrow). (b) After embolisation with backflow of embolisation material (not shown), not only the right hepatic artery (arrow) but also the cystic artery is occluded. There is also devascularisation of the pancreatic head (arrowheads). (c) Subsequent contrast-enhanced MDCT in coronal plane demonstrates embolisation material in the gallbladder wall (arrowhead) and a large abscess due to cholecystitis with contained gallbladder perforation (arrows). There is also a 'cystic mass' present in the pancreatic head. Note the lipiodol in the right hepatic lobe. (d) The axial CT image demonstrates better post-embolisation necrotising pancreatitis with liquefaction of the pancreatic head (arrow).**

the detection of liver metastases, depending on the spatial resolution and the imaging contrast[10,11]. Transabdominal ultrasound and contrast-enhanced CT are used for detection or exclusion of liver metastases. Since the vast majority of patients with liver metastases are not amenable to liver surgery, systemic chemotherapy is the therapy of choice in chemotherapy-sensitive tumours.

Surgery

In contrast, patients with a limited number of colorectal liver metastases may benefit from surgical resection, as has been shown by several studies[12,13]. In these patients, contrast enhanced CT and/or MRI are used to define the tumour burden prior to resection and for follow-up to detect tumour recurrence. With modern surgical techniques, local tumour recurrence at the resection site is rare nowadays[14] (Fig. 4). A 5-year survival rate of up to 40% may be achieved with curative resection of colorectal liver metastases[12,13,15,16]. However, tumour recurrence remote from the resection site due to development of new metastases or growth of micrometastases, which have not found at the initial resection, may be seen.

Tumour ablation

Although surgical resection is considered treatment for patients with resectable liver metastases, radiofrequency

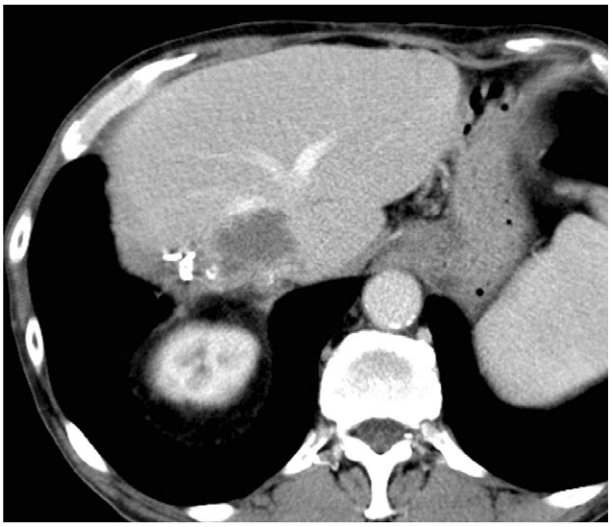

Figure 4 **Tumour recurrence after surgical resection of liver metastases. Contrast-enhanced CT shows the resection plane with surgical clips. There is tumour in the liver adjacent to the resection plane.**

(RF) ablation has shown great promise as an alternative for patients who refuse surgery or in whom surgery resection is contra-indicated for medical reasons. Moreover, RF ablation has shown success in attempted reduction of tumour burden in patients with locally irresectable disease. Initial results were quite optimistic on the rate of successful and complete necrosis of metastases or HCC, as shown by post-treatment CT or ultrasound (US) scans[17–20]. However, routine imagine surveillance will identify a high rate of tumour recurrence at the treatment site and remotely due to development of new metastases[21]. Chopra *et al.*[21] showed local intrahepatic tumour recurrence in 73% of patients and remote intrahepatic recurrence due to new tumours in 45% of patients with liver metastases (Fig. 5). Moreover, 40% of patients developed extrahepatic tumour recurrence[21]. Local intrahepatic tumour recurrence appeared in three patterns: nodular, halo, or gross enlargement. Nodular and gross hepatic recurrence of colorectal metastases tend to be hypovascular in the arterial phase and are not well discernible. In the portal venous phase, these areas of vital tumour tend to display better lesion contrast towards areas of tumour necrosis and towards normal liver parenchyma. Halo type of tumour recurrence is usually observed in patients with primary incomplete tumour response, where a thick rim of vital tumour is not ablated. This progressively thickening rim of tumour can be differentiated from the 1–2 mm thick halo of hyperenhancement due to granulation tissue and hyperaemia around a successfully ablated tumour.

Chemotherapy

In patients with liver metastases not treated by surgery or local tumour therapy, contrast-enhanced CT is used to monitor disease progression or regression after chemotherapy. The World Health Organization (WHO) guidelines define bi-dimensional tumour measurement. According to the guidelines, tumour size is assessed by multiplying the longest diameter in the axial plane by its perpendicular diameter on the same slice. Multiplication of tumour diameters yields a cross product of tumour, which has to be assessed on the pre-and post-treatment scans. WHO guidelines categorise tumour response to treatment into four different categories. Complete response (CR) indicates completed tumour disappearance, partial response (PR) indicates >50% reduction in cross product of tumour, disease progression (DP) indicates >25% increase in cross product. Stable disease (SD) represents tumour response between the categories of PR and DP, representing <50% reduction to <25% increase. However, a weakness of the WHO guidelines is the effort needed for manual bi-dimensional tumour measurement of several target lesions, a technique which is also shown to be prone to a high inter-rater variability. In 2000, the Response Evaluation Criteria in Solid Tumors (RECIST) criteria were developed, which define uni-dimensional tumour measurement for oncologic evaluation[6] (Figs. 6 and 7). In these guidelines a minimum diameter of target lesions was defined, which should be double the CT slice thickness to allow accurate representation of the lesion diameter on CT without partial volume averaging[22]. RECIST defines a maximum of five target lesions per organ and a total of 10 target lesions per evaluation. Target lesions must be clearly definable and measurable and fulfil the minimum size criteria, as defined above. Non-target lesions are those lesions that do not fulfil the size criteria and lesions that cannot be accurately measured, such as lymphangiosis, pleural effusion, and ascites.

Studies have compared individual patient's response to tumour treatment using bi-dimensional (WHO) and uni-dimensional (RECIST) criteria, which showed that uni-dimensional tumour measurements are equivalent to those obtained by bi-dimensional criteria[6]. In a study on 86 breast cancer patients, Prasad *et al.*[7] showed that uni-dimensional and bi-dimensional measurement techniques were concordant in 76/86 patients. In five patients, response assessment was improved using uni-dimensional criteria and in another five patients the response was worth using uni-dimensional guidelines. However, one limitation of the study is the selection of patients with single target lesions to eliminate the confounding influence of a variable number of lesions in different organs.

Recently, Mazumdar *et al.*[8] challenged the assessment of tumour response as measured by RECIST. In their study the percentage of overall disagreement between WHO and RECIST criteria was found to be 14–20%. Patients categorized by WHO criteria as progressive disease would fall into a different category by using RECIST criteria in 32–35% of cases. This means that using RECIST criteria would result in an

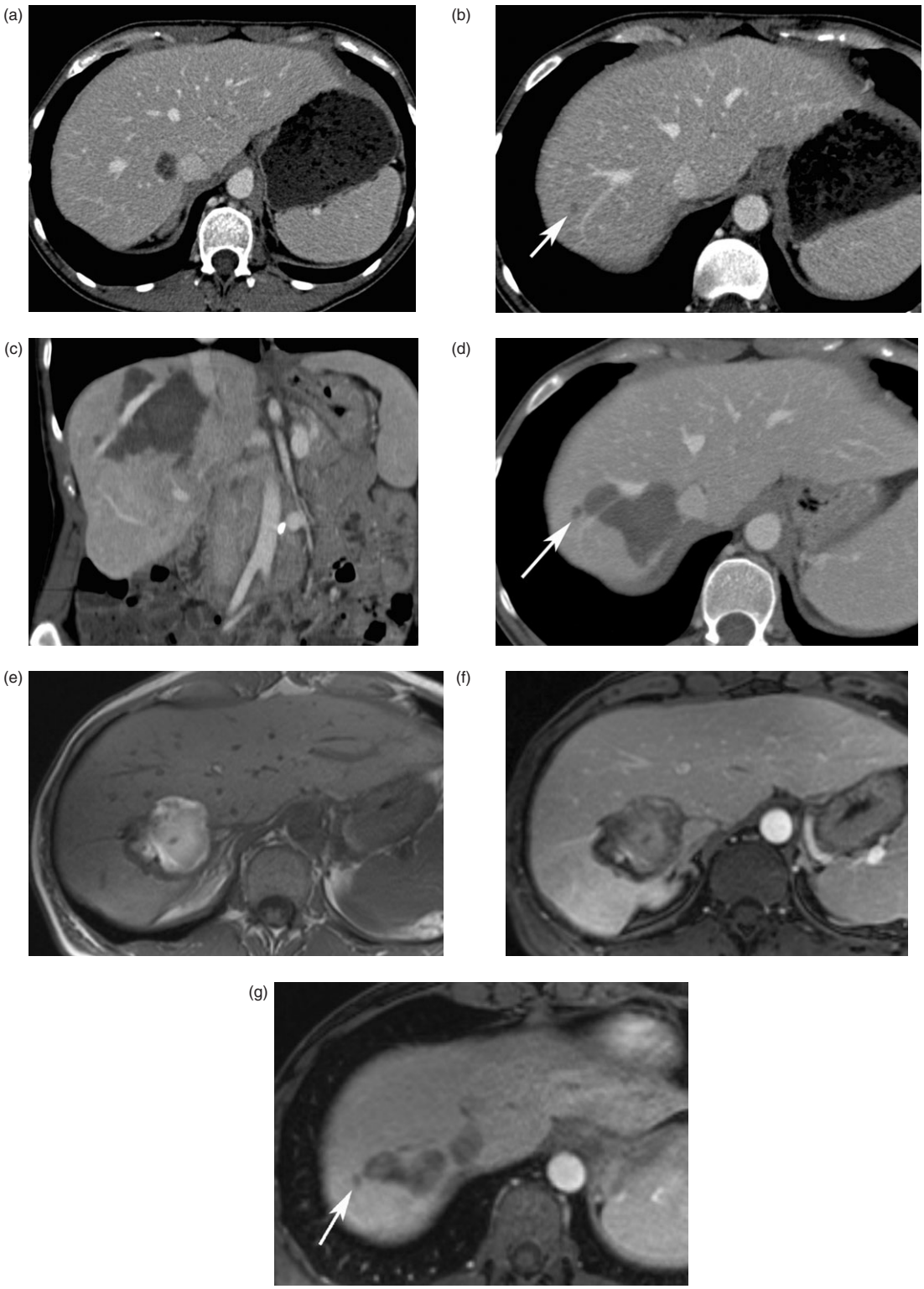

Figure 5 **Incomplete radiofrequency ablation of two metastases. (a) Contrast-enhanced MDCT shows a metastasis in segment 7/8 adjacent to the inferior vena cava (IVC). (b) There is also a tiny metastasis in segment 7 present (arrow). (c) After RF ablation, there is a large necrosis present in the right lobe, adjacent to the IVC and the right hepatic vein. (d) Axial contrast-enhanced MDCT shows the complete necrosis of the larger metastases adjacent to the IVC. However, necrosis seems not to extend to the smaller lesion in the periphery (arrow). (e) Unenhanced T1-weighted GRE MR image shows the typical appearance of a coagulation necrosis after RFA. (f) Contrast-enhanced T1-weighted GRE MR image does not show contrast-enhancement, indicative of complete ablation of the larger metastasis. (g) However, contrast-enhanced T1-weighted GRE MR image shows that the necrosis does not extend to the smaller metastasis (arrow), which subsequently grew.**

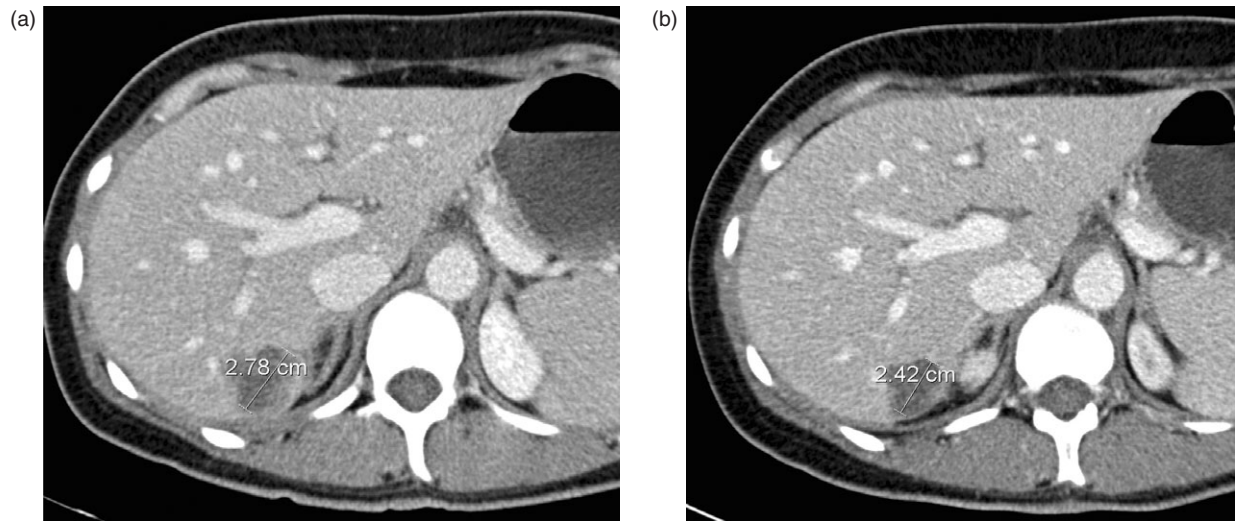

Figure 6 **Chemotherapy of liver metastases: Stable disease. (a) Pre-treatment MDCT shows a metastasis in the right lobe. (b) After three cycles of chemotherapy, there is minimal shrinkage of the lesion, which does not fulfil the criteria of disease regression. Tumour response was categorised as stable disease.**

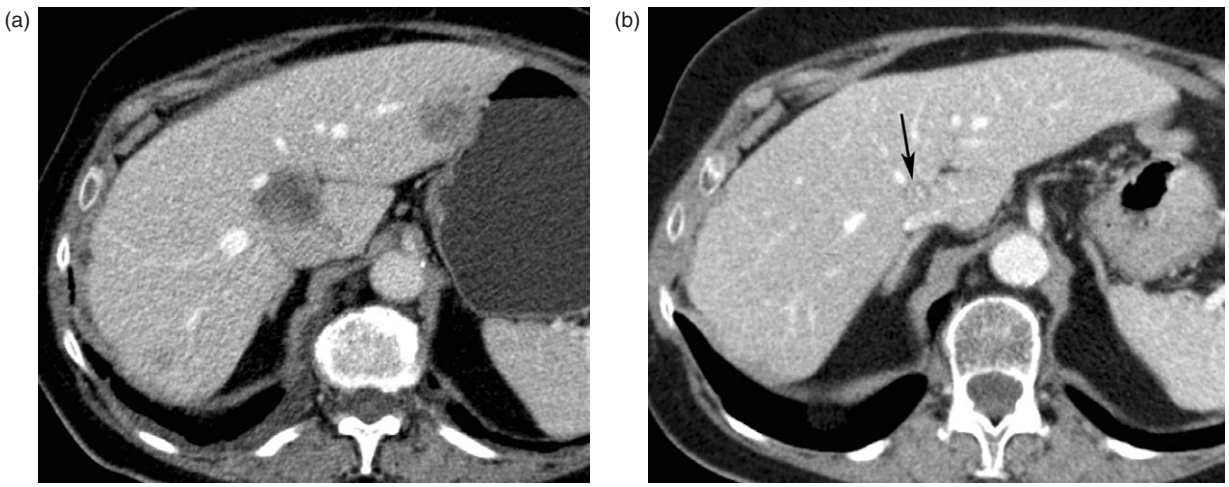

Figure 7 **Chemotherapy of liver metastases: partial response. (a) Pre-treatment MDCT shows 3 liver metastases in both lobes. (b) Post-treatment MDCT shows near-complete response. Only a small residual tumour at the venous confluence is present (arrow).**

apparently lower rate of disease progression in clinical oncology trials. This could be problematic if recent trials of new chemotherapeutic drugs using RECIST criteria are compared to the results of 'historic' studies, which were performed under the guidelines of the WHO criteria[8].

Recently, the value of dynamic contrast-enhanced MRI to assess tumour response to anti-angiogenesis drugs was described[23]. Dynamic contrast-enhanced MRI may be used to study the pathophysiology of tumours by measuring the microvascular density of the tumour and vascular permeability. In the study of Morgan *et al.*[23] chemotherapy responders showed a reduction in tumour perfusion after the first dose of chemotherapy within 26–33 h. These results suggest that dynamic contrast-enhanced MRI may serve as a more precise biomarker to monitor pharmacological response to angiogenesis inhibitors than measurements of tumour diameter.

Cholangiocarcinoma (CCC)

For these tumours, surgical resection is the only curative treatment offered; it has been shown to be effective in large series. Assessment of resectability of hilar CCC (Klatskin tumour) has to focus on the assessment of

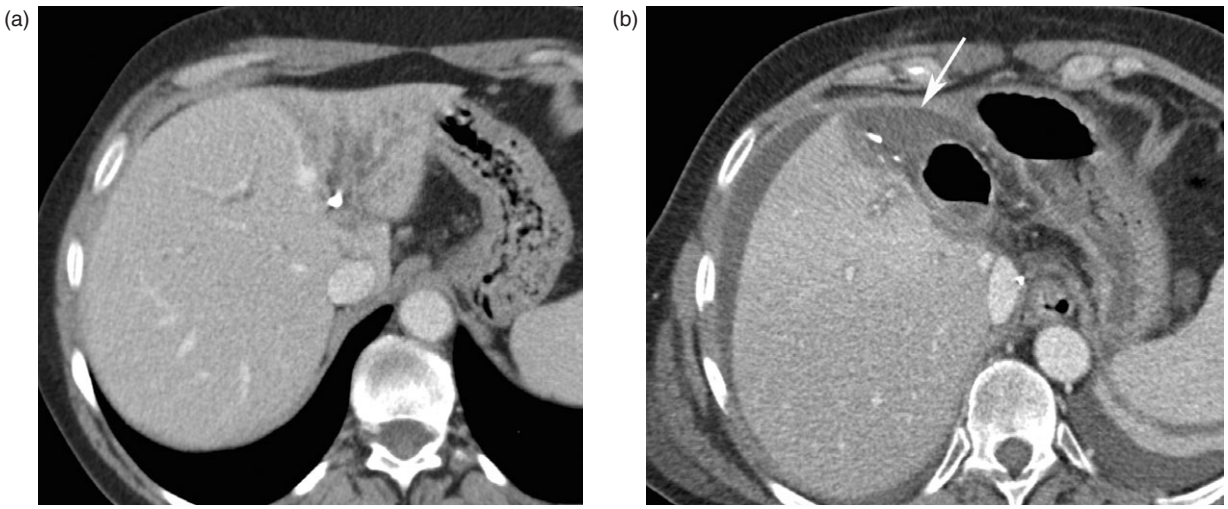

Figure 8 **Biloma after CCC resection. (a) Pre-operative CT shows Klatskin tumour with shrinkage of the left lobe. There is a biliary plastic stent in situ. (b) After left hemihepatectomy there is a fluid collection adjacent to the resection plane (arrow) and around the liver. Insufficiency of the bilio-digestive anastomosis was subsequently found.**

portal vein and hepatic artery invasion and involvement of the secondary biliary ducts, as cholangiocarcinoma tend to grow along these structures. At surgery, radical resection may involve resection of the portal vein bifurcation and extension of the surgical margin to the periphery with several biliary anastomoses involved to achieve a histologically clear (R0) margin. Complex biliary reconstruction bears the risk of development of anastomotic insufficiency with biloma formation (Fig. 8). The tendency of CCC to infiltrate along the bile ducts and neurovascular structures increases the risk of local tumour recurrence. Although contrast-enhanced CT is not a very sensitive technique for early detection of recurrence, development of biliary duct dilatation or soft tissue thickening at the hilum at follow-up raises the suspicion of tumour recurrence. For intrahepatic cholangiocarcinoma, the same CT rules as for detection of metastasis recurrence apply.

In summary, contrast-enhanced multi-phasic MDCT and MRI are the most precise tools to assess tumour response to therapy. In patients with treated liver metastases, MDCT has the advantage of an increased scan range to monitor liver disease and extrahepatic disease. Contrast-enhanced perfusion MRI has the potential to serve as a very sensitive biomarker to assess tumour response to the new angiogenesis inhibitor drugs.

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