SPECIAL ARTICLE

Clinical Decision Making and Research in Hepatocellular Carcinoma: Pivotal Role of Imaging Techniques

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Imaging techniques are a key tool for clinical decision making in the evaluation of patients with liver tumors. The development of ultrasound (US), computed tomography (CT), and magnetic resonance (MR) has allowed the detection and diagnosis of liver tumors at an asymptomatic stage, and this has modified their diagnostic approach and treatment.[1] Indeed, some of the effective therapies are image guided. Furthermore, evaluation of treatment and follow-up are done through imaging. Hence, understanding of the information provided by imaging techniques is critical for the clinician in charge of liver cancer patients.

Three major scenarios frame the clinical problem. The more common is formed by healthy individuals without liver disease and no previous cancer. Most will be diagnosed with a benign condition. Patients with a history of cancer should be suspected to present with metastases, whereas those with underlying liver disease should be considered at risk of liver cancer. In most, this will correspond to hepatocellular carcinoma (HCC), but occurrence of intrahepatic cholangiocarcinoma (ICC) is also increasing.[2] This review summarizes the current knowledge about the use of imaging techniques for the diagnosis of primary liver cancer and the evaluation of treatment efficacy.

Diagnosis of HCC and Staging

HCC is the leading cause of death in patients with cirrhosis.[1] It emerges as a small nodule composed of well-differentiated hepatocytes and progresses at a heterogeneous rate into a larger nodule.[3] Most small nodules appear hypoechoic at US, but some are hyperechogenic because of microsteatosis that may disappear upon progression.[3] Major angiogenesis resulting in arterial vascularization occurs between 10 and 20 mm. Differentiation is lost with progression, and this is paralleled by an increasing prevalence of microvascular invasion and satellite lesion.[3] Though some HCCs <20 mm may lack arterialization, most HCCs >20 mm are intensely hypervascular. This provides the specific diagnostic profile (i.e., intense contrast uptake in the arterial phase, followed by contrast washout in the delayed venous phase) at dynamic imaging by CT/MR.[1] Decreased contrast uptake in the delayed venous phase without arterial uptake is not an accurate criteria and should not be registered as washout. The accuracy of the "wash-in wash-out" profile has been validated,[4-6] and HCC in the setting of liver cirrhosis might be diagnosed both by imaging and biopsy.[1] Contrast-enhanced US (CEUS) may also recognize arterial uptake and washout, but this has also been described in ICC patients.[7] Hence, the clinical effectiveness of CEUS has been impaired, because whatever its pattern, it would always be followed by CT or MR. These secure the diagnosis and simultaneously evaluate tumor extent.

Screening for HCC by US in the population at risk aims to detect the tumor <20 mm.[1] Data about tumor-volume doubling time suggest 6 months as the optimal screening interval. This was also used in the

Abbreviations: CEUS, contrast-enhanced ultrasound; CR, complete response; CT, computed tomography; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; MR, magnetic resonance; mRECIST, modified Response Evaluation Criteria in Solid Tumors; MRI, magnetic resonance imaging; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; RFS, recurrence-free survival; RR, response rate; TTP, time to progression; US, ultrasound; TTUP, time to untreatable progression.

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trial that showed survival benefit through surveillance.[8] A shorter interval provides no benefit and merely increases the number of nodules <10 mm.[9] These are unfeasible to diagnose and may even vanish during follow-up. Hence, when a detected nodule is <10 mm, it is recommended to monitor evolution until detecting growth.[1] In addition, because of their slow progression rate, any intervention would probably incur more harm than benefit, leading to overdiagnosis.[10] This concept is well known in prostate cancer and may also apply to patients with HCCs <10 mm.

The diagnostic approach should be engaged in settings with extensive expertise both for image and pathology interpretation. Distinction between high-grade dysplasia and HCC requires the recognition of subtle changes suggestive of malignancy.[11] Immunohistochemical staining for glypican 3, heat shock protein 70, glutamine synthetase, and clathrin heavy chain may reinforce HCC diagnosis,[12,13] but frequently, more than one tissue sampling is needed. In addition, nodule location or clotting disorders may prevent biopsy. This has primed the development of imaging criteria. Up to 60%-70% of HCCs of 10-20 mm may be diagnosed by imaging with a >99% specificity.[4-6] A 100% specificity for minute nodules is also not reached by biopsy, because there is not full concordance by different hepatopathologists examining the same specimen.[11] Diagnostic capacity by imaging is not improved by lipiodol staining after injection through angiography because of false negatives and false positives.[14] New functional imaging techniques, such as diffusion magnetic resonance imaging (MRI), have not allowed a full distinction of HCC from other hepatic lesions.[15] Positron-emission tomography has no value for diagnosis,[16] and major advancements may come from organ-specific contrasts.[17,18] Those would be taken up by benign hepatocytes and not by malignant nodules. As a consequence, they would be able to characterize atypical nodules or those minute vascular spots that are just recognized during the arterial phase. Robust studies with pathology correlation are missing to rule out uptake in small, well-differentiated HCC or the existence of false positives resulting from other entities. If specificity is proven, the current risk of under- and overstaging would be reduced.

Treatment of HCC: Assessment of Efficacy and Follow-up

Cost-effective treatment requires an individualized assessment, so that each patient receives the option that better balances expected benefit with risks.[19] The Barcelona Clinic Liver Cancer treatment strategy[20] addresses this need by linking stage with preferred first-line option. In brief, patients at an early stage are considered for resection, transplantation, and ablation. Patients with intermediate stage (i.e., multifocal tumor without cancer symptoms and/or vascular invasion/extrahepatic spread) are candidates for chemoembolization, if cirrhosis is compensated. Patients with advanced stage or those failing previous options are candidates for sorafenib, if liver function is preserved. Finally, end-stage patients (i.e., heavily impaired liver function with HCC exceeding transplant criteria or heavily impaired physical condition) receive symptomatic care. Background for outcome prediction and treatment selection has been reviewed elsewhere.[20] Here, we discuss how to evaluate treatment efficacy and treatment failure and/or progression during follow-up.

Surgical Resection and Transplantation

There is no controversy about their evaluation. All known tumor sites should be removed and have the patient classified as R0. This corresponds to complete response (CR) in oncology.[21,22] Trials to prevent recurrence may confirm R0 by imaging techniques (i.e., CT/MRI) at inclusion, but in practice, the standard is to establish follow-up examinations every 3-6 months, and the techniques include US, CT, and MR. No evidence-based policy can be recommended.

Locoregional Therapies

Their efficacy assessment is more controversial. They aim to necrose tumor tissue, and this is not captured by measuring tumor size according to the oncology Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[23,24] Tumor necrosis is identified by the absence of contrast uptake within the tumor at imaging. Ablation aims to achieve complete necrosis and thus CR. Residual contrast uptake reflects failure and the need to consider treatment repetition or transition to other therapy. The clinical effectiveness of imaging techniques to assess initial treatment success differs according to tumor size. In HCCs <20 mm, the rate of CR is high[25,26] and any assessment early after therapy may be misleading because of inflammatory changes.[27] Larger tumors are less likely to be completely ablated in one session, and periprocedural CEUS may identify the nonablated areas that need another insertion targeting the untreated sector. CEUS beyond 1 month may confirm CR or detect residual disease, deserving a final ablation attempt.[27] CT or MR are more effective for follow-up monitoring

Table 1. HCC Target Lesion Response by RECIST and mRECIST

RECIST	mRECIST for HCC
CR = disappearance of all target lesions	CR = disappearance of all target lesions or disappearance of any intratumoral arterial enhancement in all target lesions
PR = at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	PR = at least a 30% decrease in the sum of diameters of viable (enhancing) target lesions, taking as reference the baseline sum of the diameters of target lesions (Enhancement in the arterial phase reflects viable tumor tissue)
SD = any cases that do not qualify for either partial response or progressive disease	SD = any cases that do not qualify for either partial response or progressive disease
PD = an increase of at least 20% in the sum of the diameters of target lesions recorded since treatment started	PD = an increase of at least 20% in the sum of the diameters of viable target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started (Enhancement in the arterial phase reflects viable tumor tissue)

Malignant portal vein thrombosis cannot be used as target lesion.

Modified from Lencioni R, Llovet JM. Modified RECIST (mRECIST) in hepatocellular carcinoma. Semin Liver Dis 2010;30:52-60.[23]

Abbreviations: HCC, hepatocellular carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

beyond 1 month: They will confirm CR and detect tumor recurrence. This is as frequent as after surgical resection (>70% at 5 years), and how to register it is discussed below.

Assessment of chemoembolization is also challenging. Necrosis is also estimated by the absence of contrast uptake, but the rate of CR is lower. Residual disease is frequent, and this has led to the proposing of a system to measure the amount of tumor necrosis according to the extent of residual viable tissue by summing the length of the remnant viable parts.[23,28] This parallels the definitions of conventional RECIST and is presented as modified RECIST (Table 1).[28] Extensive necrosis by chemoembolization correlates with outcome,[29,30] but several aspects need validation. There is risk of overestimation of the necrosis extent, as also happens with ablation. Some patients classified as CR have residual disease at the time of explant, if resected or transplanted.[31-33] This risk may vary according to the agent used for vessel obstruction. Thus, comparison of the response rate (RR) between different technologies may be not be reliable. Evaluation of radioembolization is more controversial. Tumor necrosis is achieved after several months, and the optimal timing for assessment needs to be ascertained.[30,34] Lipiodol uptake and retention has been used as a surrogate of necrosis, but studies in transplanted patients show that there is risk of major response overestimation.[33]

Two of the critical issues in chemoembolization are (1) when treatment should be repeated (until achieving CR, at regular intervals or on demand) and (2) when it should be cancelled. CR is not achieved in a large proportion of cases. In addition, whatever degree of necrosis is obtained, the tumor will regain vascularization during follow-up and/or show an increase in the remnant viable area. In our positive trial,[29] we performed two treatment sessions at baseline, then repeated chemoembolization every 6 months. Other investigators apply a more intense schedule, but the absence of survival benefit, in some studies, may be caused by the fact that the antitumoral efficacy of intensive retreatment is counterbalanced by a negative effect in liver function. This stresses the need to define when treatment is no longer to be repeated.

In oncology, progression is seen as treatment failure, and a common parameter to describe treatment efficacy is time to progression (TTP). This is not the case in locoregional treatment. Progression (i.e., either regrowth of initially treated tumor sites or appearance of a new intrahepatic nodule) may be successfully treated and the disease may be again kept under control. If progression is major (e.g., extrahepatic spread and vascular invasion), retreatment may be of no benefit and survival may be impaired.[35] Thus, in this setting, the patient should be considered for a second-line therapy. Hence, it is clinically obvious that the term progression needs to be refined to become a valid surrogate of outcome. This justifies the novel concept of "untreatable progression" (Fig. 1), defined by progression associated with a profile that prevents retreatment or, by this failing, to induce an objective response. Untreatable progression includes major progression (e.g., massive liver involvement, extrahepatic spread, and vascular invasion), but also minor intrahepatic progression with impaired liver function and performance status that contraindicate treatment. Accordingly, chemoembolization should not be repeated in

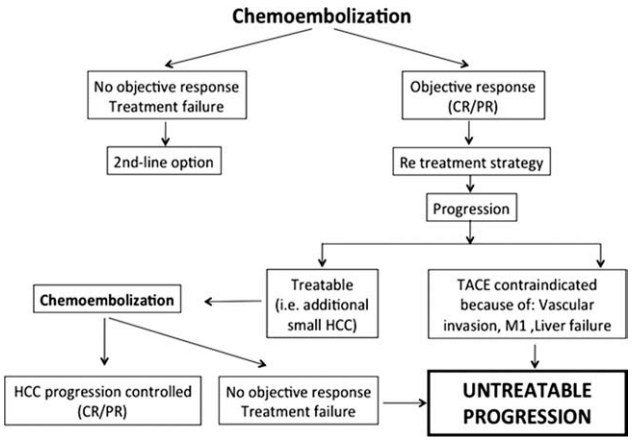

Fig. 1. Diagram to define untreatable tumor progression according to the potential to retreat and achieve disease control or failure to do so. The concept is valid for surgery and locoregional treatment.

the following situations: (1) when it fails to achieve significant necrosis after two treatment sessions; (2) when follow-up treatment fails to induce significant tumor necrosis of progressed tumor sites; and (3) when the evaluation of the patient with progression prevents safe retreatment. The first option indicates treatment failure, and the second options should be registered as untreatable progression and its occurrence during follow-up is time to untreatable progression (TTUP).

Systemic Treatment

Tumor-burden reduction has been the backbone of the evaluation of systemic agents.[21,22] Rate of objective response (including complete and partial) was used to capture promising efficacy signals of novel agents before phase III trials. This approach may have discarded agents that, though not reducing tumor mass, could have had a benefit on survival by delaying tumor progression and death. This possibility has been proven with sorafenib, an oral multikinase inhibitor. In the initial phase II study,[36] the rate of objective responses was marginal, but the observed TTP became the background for the design of the phase III trials that had survival as endpoint.[37,38] Interestingly, treatment was not interrupted at the time of progression. This already took into account that progression may be a heterogeneous event, as already mentioned, and that its detection by follow-up imaging may not always reflect treatment failure.

The demonstration that a beneficial effect could be achieved without tumor reduction has primed the research of functional imaging that would capture the effects of drugs in tumor tissue. Antiangiogenics induce changes in tumor vascularization, and this may be identified by parameters such as blood flow, blood volume, permeability perfusion, or K-trans value.[39,40] To date, there are no data to support the use of these techniques to define whether a drug has any efficacy or whether it fails. Assessment of the reduction of tumor density after contrast administration aiming to reproduce the Choi criteria for gastrointestinal stromal tumors[41] has not provided useful criteria for HCC.

It is important to note that even if antiangiogenics may decrease tumor density upon contrast administration, this should not be taken as tumor necrosis. This is recognized by no increase in tumor enhancement after intravenous contrast administration (Fig. 2). Thus, a mere reduction in enhancement just reflects a hypovascular HCC profile and should not be wrongly registered as partial response or CR.

Time to Progression

As mentioned above, tumor progression is a critical event. Despite all limitations, it has become the

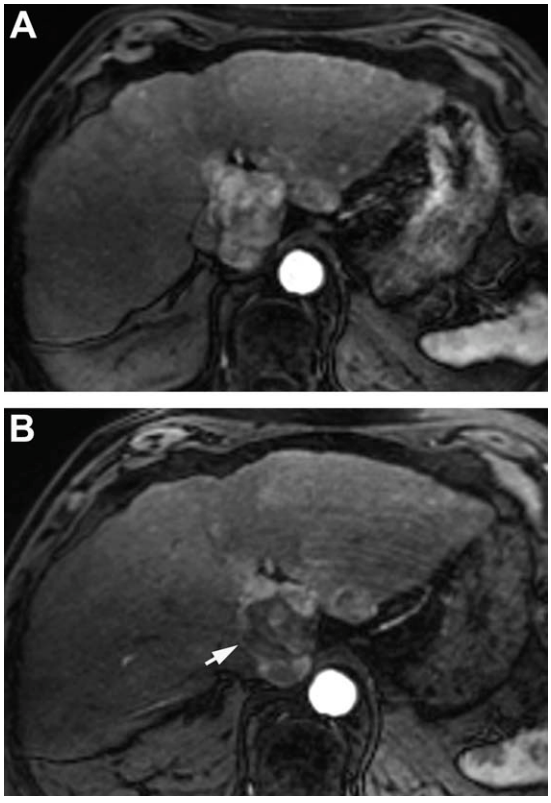

Fig. 2. Reduction in arterial contrast uptake during antiangiogenic therapy can not be registered as necrosis. Panel A: Highly vascularised HCC located in the caudate lobe. According to clinical staging the patient corresponded to BCLC stage C and treatment with sorafenib was initiated at full dose (800 mg /day). Panel B: The contrast uptake in the arterial phase has been significantly reduced. This can not be registered as necrosis as contrast still reaches tumor tissue. Necrosis can be registered if there is no contrast uptake at all (the arrow points at a tiny necrotic spot that does not qualify as a partial response even if necrosis is taken into account).

Fig. 3. Detection of HCC recurrence after surgical resection. This series of images shows the evolution of a nodule detected during follow-up and how it would be registered as a new tumor site according to conventional RECIST or as per mRECIST.[23,28] Panel A represents the non-contrast CT scan phase without an evident nodule. During the arterial phase (panel B) it is feasible to identify a 10 mm nodule located in the left hepatic lobe. Panel C exposes the pattern at the equilibrium phase where no washout is evidenced. According to conventional RECIST, this could be registered as tumor recurrence (or progression if treated by ablation/chemoembolization or with systemic therapy). By contrast, to register it as such using mRECIST it is needed to follow-up the patient until detecting the appearance of washout. At that point the new tumor site is confirmed. Panel D shows that after 6 months, the nodule has grown and still exhibitis intense contrast uptake in the arterial phase, while also showing washout in the equilibrium phase (panel E). Time of recurrence/progression is that of first detection with both systems, but if follow-up would not have been there because of trial design, it would have been impossible to properly evaluate the data according to mRECIST as some recurrences would never be confirmed.

recommended endpoint for the early assessment of novel agents.[28] Hence, proper criteria to register its occurrence are mandatory for optimal practice and research.

Conventional RECIST is not fully reliable for this purpose in HCC patients. The imaging follow-up protocol of the sorafenib phase III trials already incorporated several amendments. Ascites or pleural effusion should not be registered as disease progression unless malignant origin was proven by pathology. Presence of slightly enlarged lymph nodes can be observed in cirrhosis of any etiology.[42,43] Thus, malignant involvement would not be declared until growth beyond 2 cm.

Modified RECIST (mRECIST) was developed to take into account tumor necrosis such as that which occurs during chemoembolization and radiofrequency ablation. However, whether mRECIST can be

extrapolated to targeted therapy or not has not been validated. Changes in arterial perfusion of HCC target lesions do occur with targeted therapy, but complete necrosis is uncommon. Whether quantitative changes in arterial perfusion equate to a less aggressive tumor biology or a therapeutic response remains unclear. Until mRECIST has been verified to correlate with overall survival in HCC, its utilization as an endpoint in targeted therapy remains questionable.

In addition, a pitfall of RECIST relates to the definition of hypervascular intrahepatic foci not fulfilling the pattern of HCC. These are common in cirrhotics and portal hypertension, and in HCC patients, they will likely correspond to new HCC sites.[44] However, until these nonspecific nodules are confirmed by growth or by development of a typical HCC pattern, they should not be registered as progression. These concepts were ultimately the basis for the mRECIST proposal.[28] Although in conventional RECIST new nodules >10 mm would be classified as progression with the potential risk of wrongly registering regenerative or dysplasic nodules as new tumor sites, mRECIST indicates that such nonspecific nodules require follow-up to detect growth or development of the diagnostic imaging profile. If ultimately classified as malignant, the time of progression is that of first detection (Fig. 3). Retrospective assessments using mRECIST in studies conducted under conventional RECIST are at risk of major bias, because the absence of follow-up of those patients classified as progressing by RECIST would not have the needed follow-up to properly classify them by mRECIST. As a result, TTP would be overestimated, because some of the recurrences that would be ultimately confirmed are no longer in the analysis.

Some investigators propose progression-free survival (PFS) as an optimal tool, but this is an unreliable endpoint. There is no proof of correlation between PFS and survival. Indeed, in the recent trial comparing sunitinib versus sorafenib, survival under sorafenib was significantly better, whereas PFS was not different.[45] This failure of PFS to reflect survival has also recently been shown for breast cancer treated with bevacizumab.[46] The same consideration may be applied to the use of recurrence-free survival (RFS) in treatment to prevent recurrence after resection or ablation. There is no proof of correlation between RFS and survival, and differences in RFS may be the result of its composite nature that implies a mix of death caused by cancer and deaths resulting from the progressive liver disease.[1] As a result, regulatory agencies base their decisions for registration on a positive result in survival, whereas the other endpoints (e.g., RR, TTP, TTUP, and PFS) are mere suggestions that may prove correct in predicting survival benefit.

In summary, imaging techniques are a central tool in clinical decision making. Any team willing to provide state-of-the-art clinical care and engage in research should secure the active involvement of expert radiologists. If such commitment is not in place, quality of care will be suboptimal, and the advances provided by technology will not be properly implemented for the benefit of the patients and the cost-effective use of the expensive resources needed in cancer management.

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