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THE CURRENT STATUS AND RESEARCH PROGRESSION ON IMAGING EVALUATION OF HCC

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, which is a consequence of cirrhosis and develops mostly from patients with chronic liver disease. According to the EASL and EORTIC recommendations, diagnosis of HCC depends on the results of histopathological reports or imaging modalities. Diagnostic imaging of HCC plays an essential role in detecting, staging, prognosis, and treatment. The characteristic angiographic behavior of HCC nodules can be evaluated by using Doppler ultrasound, contrast-enhanced ultrasound (CEUS), contrast-enhanced computed tomography (CECT), and contrast-enhanced magnetic resonance imaging (CEMRI). Liver Imaging Reporting and Data System (LI-RADS) was created to standardize reporting and data collection. However, the use of LI-RADS in clinical practice is often mired by the lack of uniform terminology in reporting and the interpretation of the examination performed in the different centers or at different times. The objective of diagnostic imaging is to achieve early identification of the hepatic neoplasia for the possibility of curative therapies including local ablative, surgery or liver transplantation, and increase patient survival. Palliative therapies including transarterial chemoembolization (TACE), transarterial radio-embolization (TARE), or systematic therapy (administration of antiangiogenic drugs, sorafenib) have been frequently used according to HCC stages. The interpretation of the therapeutic response of HCC nodules was evaluated by using Modified Response Evaluation Criteria in Solid Tumors (mRECIST). These criteria are currently the gold standard for radiological response assessment as confirmed in the latest version of the EASL Guidelines. In this review, we aim to review the current imaging evaluation of Hepatocellular Carcinoma (HCC).

Keywords: Hepatocellular Carcinoma, Contrast-Enhanced Ultrasound, Contrast-Enhanced Magnetic Resonance Imaging, Focal Liver Nodule, Liver Imaging Reporting and Data System, Modified Response Evaluation Criteria in Solid Tumors.

ABBREVIATIONS

AASLD	:American Association for the study of Liver Disease
ADC	:Apparent Diffusion Coefficient
AFP	:Alpha Fetoprotein
APHE	:Arterial Phase Hyper enhancement
BCLC	:Barcelona Clinic Liver Cancer
CECT	:Contrast Enhanced Compute Tomography
CEMRI	:Contrast Enhanced Magnetic Resonance Imaging
CEUS	:Contrast Enhanced Ultrasound
CR	:Complete Response
DWI	:Diffuse Weighted Imaging
EASL	:European Association for the Study of Liver
EORTC	:European Organization for Research Treatment Of Cancer
EP	:Equilibrium phase
FLC	:Fibro Lamellar Carcinoma
FLLs	:Focal Liver Lesion
HAP	:Hepatic Arterial Phase
HBP	:Hepatobiliary Phase
HBV	:Hepatitis B Virus
HCC	:Hepatocellular Carcinoma
HCV	:Hepatitis C Virus
HU	:Hounsfield Unit
IR	:Incomplete Response
LI-RADS	:The Liver Imaging and Data System
mRECIST	:Modified Respond Evaluation Criteria in Solid Tumors
NAFLD	:Nonalcoholic Fatty Liver Disease
PET	:Positron Emission Tomography
PR	:Partial Response
PVP	:Portal Venous Phase
SD	:Stable Disease
TACE	:Trans arterial Chemoembolization
TARE	:Trans arterial Radioembolization
US	:Ultrasound
WHO	:World Health Organization

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INTRODUCTION

The cancer is a prevalent disease with an increasing number of patient's cancer-related deaths annually. The liver cancer is the sixth most common cancer and currently the second cause of cancer-related death worldwide. Liver cancer is the second most common cause of cancer-related mortality and morbidity in the world, amounting to 7% of all cancers [1-3]. Among liver cancer, hepatocellular carcinoma (HCC) is the most common primary liver cancer representing more than 90% of primary liver cancer. Around 90% of HCC develops in the situation of liver cirrhosis or advanced fibrosis. The probability of developing HCC increase with duration of liver cirrhosis and about 1/3 of patients with identified cirrhosis will HCC [4, 5]. The most predominant risk factors for the development of HCC are viral hepatitis, alcohol and nonalcoholic fatty liver disease (NAFLD). The others risk factors are gender (men), age after 40 years old, smoking, obesity, diabetes, the progression of liver cirrhosis, and its complication of liver cirrhosis [6-8]. There is the multiphase process in the progression of HCC in the cirrhotic liver including regenerative nodule, dysplastic nodule (low or high grade), HCC foci within a dysplastic nodule, the early form of HCC, and a mature form of HCC [9-11]. There are different forms and the most

commonly encountered form of HCC is a solitary tumor larger than 2cm in diameter [12]. The other form is small HCC with a diameter equal or smaller than 2cm seen as single HCC foci, and it has a good prognosis with over 90% of five-year survival if it was treated with complete resection or liver transplant [13]. The local invasiveness is infiltrative or tumor emboli within the portal vein system that facilitates intrahepatic metastasis [14, 15]. HCC is also characterized by a high degree of local invasiveness with potential to infiltrate in braches of the portal vein and less frequently biliary tracts to form abnormal arteriovenous connections and present with tumor emboli even in early stages of the disease that facilitate intrahepatic metastasis [16]. Around 10% of HCC develops in the unchanged liver parenchyma or the situation of non-cirrhotic patients. This HCC is often single, significantly larger and detected in the advanced stage [17, 18]. Moreover, one of the histological variants of primary liver cancer not associated with chronic liver disease is fibro lamellar carcinoma (FLC) that happened in youth-adult with average age 30 years old, no gender preference, accompanied by an increase in serum AFP and has a good prognosis [19]. Serum AFP is the most widely used tumor biomarker in the diagnosis of HCC. Serum AFP level < 20 ng/ml is considered normal and the cut-off value at the level 200 ng/ml is considered as malignancy. However, its value is often considered insufficient, and an increase of AFP levels in cirrhotic patients is non-specific for the development of HCC [20-25]. For the development of HCC, serum AFP levels are normal or increase only 10 to 20% of tumors in the early stage and maybe also seen in cases of advanced cirrhosis without HCC, exacerbation of HBV or HVC and in others neoplasms such as cholangiocarcinoma, gastric cancer, and germ cell tumors. Patients with early-stage of hepatocellular carcinoma (HCC) show a normal value of AFP value up to 40% [26-28]. According to EASL and EORTC recommendations, HCC surveillance, screening and follow up are suggested in the different group of patients such as non-cirrhotic patients with HBV infection and/or family history of HCC, advanced liver fibrotic patients with chronic HCV infection, cirrhotic patients with Child-Pugh A and B, and cirrhotic patients with Child-Pugh C and awaiting liver transplants [4, 5]. Diagnostic imaging for early detection of HCC is essential to reduce mortality in high-risk patients and ensure an effective treatment plan [29, 30]. In this review, we aim to describe and view all available imaging modality to detect and evaluate hepatocellular carcinoma (HCC).

Conventional Ultrasound (US)

Ultrasound (US) is a low cost, noninvasive imaging modality, widely available for the evaluation of liver parenchyma. The US with B-mode is used to evaluate the architecture modification, the lesion (the size, site, echogenicity) and its relationship with other hepatic structure [31, 32]. Doppler US is used to see the vascular pattern of the lesion (central or peripheral). The Doppler pattern of HCC shows rich arterial vascularization or the basket pattern surrounding the nodule with a high frequency >1 kHz and elevated resistive index >0.71 [33, 34]. The architecture modifications are a progressive increase of arterial flow inside newly formed tumor vessels called neo-angiogenesis and a decrease of normal flow in the portal vein and hepatic arteries. An arterio-portal fistula can be occasionally observed. The arterial neo-angiogenesis is considered a sign for the diagnosis of HCC [35-38]. Dissimilarity, there isn't vascularization or may show arterial vessels with a low frequency and a normal resistive index in macro regenerative nodule (RN) and dysplastic nodule (DN) [39]. Unfortunately, hemangioma and high grade dysplasia nodule may also present hyper arterial vascularization [40]. The combination of B-mode and Doppler was used to evaluate the architecture modification and vessel pattern. However, the efficacy for detection of HCC varies in cirrhotic patients (sensitivity 33 to 96% and specificity 90%) [41, 42].Small HCC foci < 2cm can be difficult for diagnosis in the presence of regenerative nodules in cirrhotic patients. Small HCC show typically as heterogeneous and hypoechoic lesion and some may shows as hyperechoic lesion due to inclusion of fatty tissue. Whereas, HCC >2cm shows as hypoechoic halo, blurred, poorly defined margins, and infiltration to surrounding parenchyma, portal vein, and its branches [43].

Contrast-Enhanced Ultrasound (CEUS)

Contrast Enhanced Ultrasound (CEUS), called micro bubbles enhanced US, is a new imaging technique that was used with a micro bubble contrast agent as the contrast material to show characteristic of liver tumor as well as real time continuous hemodynamic changes of liver tumor after injection [44, 45]. The blood supply of the liver is mainly from the portal vein (70 to 75%) and hepatic artery (25 to 30%) result in four phases of CEUS including three vascular phases and one post-vascular phase. CEUS is a real-time imaging modality with contrast enhancement showing in different phases such as arterial, portal venous, delayed, and post-vascular phases. Currently, three US contrast agents are commonly such as SonoVue, Definity/ Luminity, and Sonazoid. There three vascular phases for SonoVue, Definity/ Luminity. However, Sonazoid, a new contrast agent, has four-phase with additional post-vascular phase by the contrast agent being related in the liver and spleen due to the phagocytosis of Kupffer cell of the liver parenchyma [46]. CEUS contain several advantages such as safety for renal failure patients, good patient's compliance, better detection of arterial phase hyper-vascularity and washout in malignant tumor by its real time imaging capacity.US contrast agents are generally safe due to the absence of toxicity of heart, liver, kidney, and the incidence of allergy is low. It is not necessary to perform a laboratory test to assess liver or kidney function before the administration of these agents [47-50]. However, the current guideline suggests prudence when it will be used in patients with severe coronary artery disease [51]. The US contrast agents are administrated with a bolus injection 1 to 5ml followed by a flush of saline solution 5 to 10ml, and real-time CEUS examination is record as video clips with duration > 5min. After contrast agent injection, the duration is about 20 to 35s for arterial phase, 35 to 180s (3min) for portal venous phase, 4 to 6min for late phase, and 10 to 60min for post vascular phase [52-54]. Furthermore, CEUS is widely available and can be used to detect new liver nodules of HCC during its surveillance and evaluation [55]. In focal liver lesions (FLLs) with their level of enhancement in the late phase and post vascular phase [Figure1], CEUS comparable with CEMRI was shown as a higher efficacy modality to provide valuable information about the features of lesion and in differencing benign from malignancy. For malignant lesion, CEUS show as hypoechoic (hypo enhancing) to the surrounding liver parenchyma, while solid benign lesion shows as hyperechoic or isoechoic (hyper or iso enhancing) in the late and post vascular phase [56-60]. The probability of diagnosis HCC increases with nodules size. If nodule size < 1cm are rarely malignant, and ultrasound surveillance or follow up is sufficiently done around 3 to 4 months of intervals. On the contrary, if nodule size > 1cm is considered as high probability of being malignancy with 66% for nodule 1 to 2cm, 80% for nodule 2 to 3cm and 95% for nodule > 3cm [61].

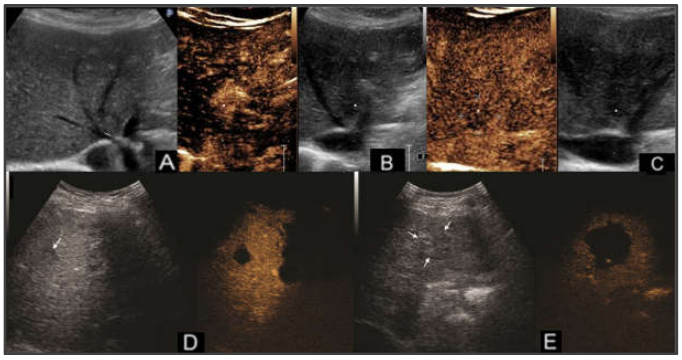

Figure1. CEUS Imaging of HCC

B-mode US (A), Hyper-enhancing in the arterial phase (B), Washout in the late phase (C), small HCC foci (D) and HCC>2 cm

Subsequently, if nodule is more than 1cm in diameter, additional imaging modality is required for the investigation [Figure5 and 6] [62-64].Early detection of HCC is essential for reducing tumor related mortality [65, 66]. The limitation of CEUS is that it was recently shown as lower sensitivity about 63% in early HCC [67]. Moreover, CEUS is impossible to scan the entire liver during arterial phase and difficult to detect HCC in some situation due to the inhomogeneous echo coarse parenchyma pattern of the cirrhotic liver [68]. The other limitations of CEUS are that the decreased detectability of deep lesion in the liver parenchyma, especially in steatosis, misinterpretation of the falciform ligament and surrounding fat as a focal liver nodule and impossibility to detect sub diaphragmatic lesion. Apart from these, another limitation of ultrasound contrast agents is its pharmacokinetic features for the use of CEUS examination in comparison to CT or MRI contrast agents. US contrast agents are the vascular space due to its blood pool agents, while contrast agents used in CT of MRI are extracellular space [69].

Contrasted-Enhanced Computed Tomography(CECT)

Contrasted-Enhanced Computed Tomography (CECT) is an imaging modality with the intravascular injection of iodine contrast agents. There are different phases including hepatic arterial phase (HAP), portal venous phase (PVP), equilibrium phase (EP) and delay phase with 40, 60, 180 and 600-900 seconds (10-15 minutes) respectively [Figure2]. In the early hepatic arterial phase, it can be performed for CT angiography reconstruction, while delay phase it can be delivered to detect lesions of the high content of fibrous tissue, for example, cholangiocarcinoma [70-72]. Iodine contrast agents are administered into the median cubical vein with a dose of 1 to 2.5 ml/kg and the rate of 3 to 4 ml/s. However, dose and rate may change depending on available equipment and the imaging protocol. In normal renal function, iodine contrast agents show a half-life time 1 to 2 hours [73]. Liver parenchyma contains its value of radiation attenuation coefficient from 50 to 60 Hounsfield Units (HU) [74, 75]. In non-enhanced CT, liver vessels show as hypodense in comparison to liver parenchyma. For liver tumor, by the decrease of glycogen and iron content, it shows as hypodense, while small HCC foci show as isodense (rarely as hyperdense) similar to the regenerative nodule and dysplastic nodule as a result of their high content of iron or copper [Table1] [76]. For CECT, large HCC shows typically as heterogeneous enhancement (regressive change of tumor) and strongly enhancement in the hepatic arterial phase [Figure2.E] (the enhancement of aorta 10 to 15s after injections of contrast agents) [77]. Washout pattern of contrast agent in portal vein phase (the phase of the strongest enhancement of liver parenchyma) and/ or equilibrium phrase is a typical feature or sign for the diagnosis of HCC [Figure2: G, H], with a specificity of 95 to 96% [76]. There is a better prognosis, if the tumor shows a pseudo-capsule pattern, clearly visible in the portal vein and equilibrium phase (prolonged enhancement) than in hepatic arterial phase. About 20% of HCC was presented as hypo vascular and poor enhancement than adjacent liver parenchyma in 3 phases of CECT (HAP, PVP, and EP) [78]. If this tumor doesn't meet the typical feature of HCC, liver biopsy is required. However, if liver biopsy can't verify the diagnosis, follow up by repeat imaging is recommended [Figure 5 and 6] [79].

Contrasted-Enhanced Magnetic Resonance Imaging (CEMRI)

A standard MRI protocol consists of 5 sequences including: 1-Pre-contrast and dynamic post-contrast T1W3D gradient echo sequences with fat-suppression, 2-Single/multiple shot fast spin-echo T2W sequences +/- fat-suppression, 3-In and out phase sequences, 4-Diffuse weighted imaging (DWI) and 5-Delayed post-contrast T1W sequence [80]. Paramagnetic Gadolinium Chelates are the most commonly used MRI contrast agents in everyday clinical practice with a recommended dose of 0.2 ml/kg (0.1mmol/kg), the flow rate of 2 to 3 ml/s and its half-life approximately 90 min [81]. Currently, there are two commercially available gadolinium-based hepatocyte-specific contrast agents including Gadoxetic Acid (10 to 20min, Gd-EOB-DTPA, USA) and GadobenateDimeglumine (60min, Gd-BOPTA, Italy) [82]. Contrast enhanced magnetic resonance imaging (CEMRI) is advantageous due to a higher contrast between the lesion and adjacent liver parenchyma and lack of exposure to ionizing radiation. In comparison to CECT, CEMRI shows similar enhancement pattern HCC with strong enhancement in the hepatic arterial phase and wash out in the following phases[83]. There are different enhancement patterns of HCC and others focal liver nodules showed in the table 1. In pre-contrast T1W3D gradient echo sequences with fat-suppression, small HCC shows as isointense to the adjacent liver parenchyma [Figure3]and large HCC shows as hypo intense. In single/multiple shot fast spin-echo T2W sequences +/- fat-suppression, small HCC foci show as hyper intense, while, regenerative nodules show as hypo intense due to iron deposit. The presence of intracellular fatty components may be quickly confirmed in phase and out of phase sequences[83]. Diffuse weighted imaging (DWI) is used to differentiate of tissue characteristic between benign and malignant, follow up the response of treatment and detection of recurrence. In DWI, lesions suspected of malignancy (restricted diffusion) shows as hyper intense and low values of ADC (Apparent Diffusion Coefficient). ADC (mm2/s) is a measure of water molecules motion that is larger when diffusion is unobstructed[84]. Delay post-contrast T1W sequence is used in hepatobiliary phase (HBP) with hepatocyte-specific contrast agents and HCC shows as hypo intense in comparison to the surrounding liver parenchyma, while arteriovenous shunts and/or focal nodule hepatic-like tumors show as isointense or hyper intense[85].

Positron Emission Tomography (PET)

Positron emission tomography (PET) has shown to be little diagnostic value because of its low sensitivity. It has proved beneficial in specific circumstance to listing patients with large HCC for liver transplantation, before major resections or when there is suspicion of an extra-hepatic neoplastic diffusion. In the last EASL guidelines 18F-deoxyglusose (FDG)-PET scan is not recommended for early diagnosis of HCC because of the high rate of false negative case but it seems to be of potential prognostic value. Therefore, it may facilitate the selection of patients for surgical resection or liver transplantation [4]. The role of PET scan in the evaluation of tumor response to TACE has been investigated. PET scan has shown to be little diagnostic value with respect to CECT and CEMRI for HCC in intermediate stage treated with TACE. Only under specific circumstances of a large intrahepatic tumor treated with yttrium90-

radioembolization PET scan show strong positivity and accuracy in early evaluation of tumor response [86].

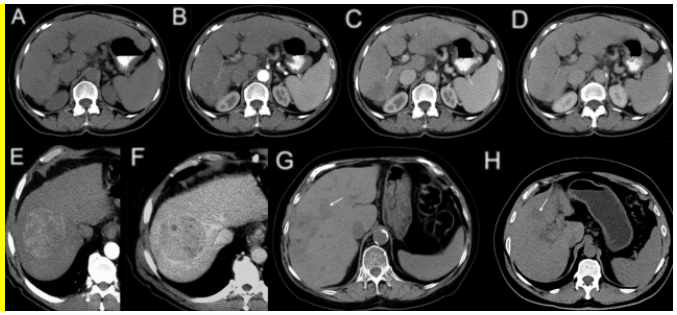

Figure2. CECT imaging of HCC

normal pre-contrast phase (A), normal hepatic arterial phase (B), normal portal venous phase (C), normal equilibrium phase (D), HCC in hepatic arterial phase (E) and portal phase (F), and hypodense HCC foci in non-enhanced CT (G and H)

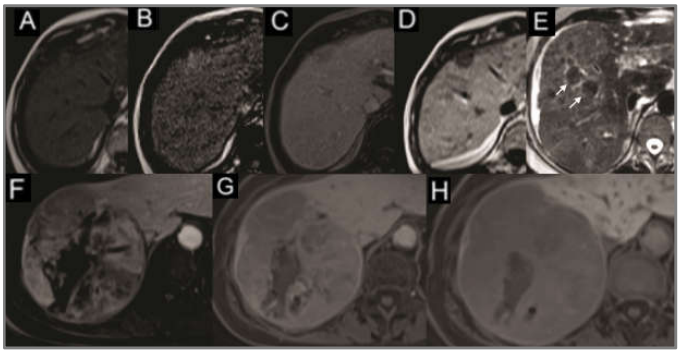

Figure3. CEMRI: Non-Enhanced Image (A); Small HCC in T1WI (with injection of hepatocyte-specific contrast agent) shows as slightly hyper intense in hepatic arterial phase (B), as hypo intense in equilibrium (C) and hepatobiliary phase (D); Regenerative nodules in T2WI (E); Large HCC of hepatic arterial phase in T1WI fat saturation shows heterogeneous enhancement of lesion and non-enhancing area of focal necrosis (F), Portal Venous Phase with subsequent washout of contrast agent (G) and Hepatobiliary Phase shows low signal intensity of lesion in comparison to adjacent liver parenchyma (H)

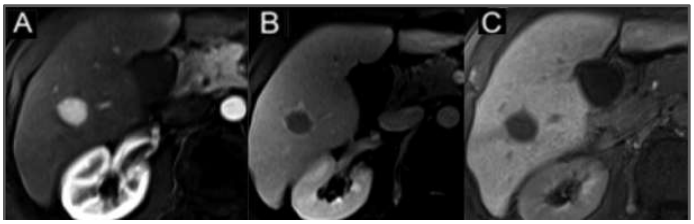

Figure4. CEMRI with hepatobilary specific contrast agent: Hepatic Arterial Phase shows homogenous marked arterial hyper enhancement of nodule (A); Transitional Phase shows washout of contrast agents of nodule with capsular enhancement (B); Hepatobiliary Phase shows marked hypo intensity of nodule relative to the liver parenchyma (C)

The Liver Imaging Reporting and Data System (LI-RADS)

The Liver Imaging and Data System (LI-RADS) is the standard examination report of the liver by using Ultrasound (US), contrast-enhanced ultrasound (CEUS), contrast-enhanced computed tomography (CECT) or contrast-enhanced magnetic resonance imaging (CEMRI) in high-risk patients. They provide information by evaluating important features including arterial phase hyper enhancement (APHE), size of the lesion, portal venous phase washout, enhancing capsule in portal venous/ delayed/ transitional phase and the speed of growth over a threshold. LI-RADS provide five categories such as LR1 (definitely benign), LR2 (probably benign), LR3 (intermediate of being probably malignant), LR-M (high probability of being malignant but not HCC), LR4 (probably HCC) and LR5 (definitely HCC) [Table 2 to 4]. These categories given and established by the American College of Radiology in 2011 and authenticate in many studies [87].

Treatment Response Assessment by Modified Response Evaluation Criteria in Solid Tumors (mRECIST)

Medical imaging plays an important role in diagnosis, prognosis and the assessment of the treatment response by loco regional or systemic treatment of HCC. In 2010, Response evaluation criteria in solid tumors (RECIST) and WHO criteria were suggested by EASL and AASLD to evaluate the treatment response of HCC. The application of RECIST is evaluated in the therapeutic response of HCC by measuring the longest diameter of HCC nodules. These criteria have been modified (mRECIST) by measuring only the vital tissue and considering the overall size of the necrotic portion of a treated nodule. Until 2012, mRECIST were recognized in EASL and EORTC Guidelines. Currently, mRECIST remain the gold standard for evaluation of therapeutic response as confirmed in the latest version of the Guideline of European Association for the Study of Liver (EASL) [4, 5, 88].Target Lesions are the clearly visible, measurable lesions with the typical sign of wash out and was measured the longest dimeter of their vital portion (tissue showing arterial hyper enhancement and venous/ delayed wash out) according to mRECIST. By comparison the size of vital portion before and after treatment, the possible therapeutic responses are complete response (CR), partial response (PR), progressive disease (PD) and stable disease (SD) [Table5].

Table1. Enhancement Pattern of the Focal Liver Nodule in CT and MRI

IMAGING FEATURE	AP SHUNTS	RN	LGDN	HGDN	HCC
NON-ENHANCED CT	Iso	Hyper	Hyper	Hyper	Hypo (Iso/ Hyper)
T1WI	Iso	Iso To Hyper	Iso To Hyper	Iso To Hyper	Hypo
T2WI	Iso	Hypo	Iso To Hyper	Iso	Hyper
DWI	Iso	Iso	Iso	Iso	Hyper
HAP(ENHANCEMENT)	Hyper	Iso	Iso	Hyper	Hyper
PVP(WASH-OUT)	None	None	None	None	Present+/ Pseudocapsule
HBP	Iso To Hyper	Iso To Hyper	Iso To Hyper	Iso	Hypo

Table2. US LI-RADS for Screening or Surveillance in High-Risk Patients of HCC

US CATEGORY	US-1 (NEGATIVE)	US-2 (SUB THRESHOLD)	US-3 (POSITIVE)
	-No observation -Definitely benign -No US evidence of HCC	-Observation of nodule <1cm -Not definitely benign -Short-term US surveillance	-Observation of nodule >1cm -Not definitely benign or new thrombus in vein -Multiphase contrast-enhanced imaging
US VISUALIZATION SCORE	**A (NO/ MINIMAL LIMITATION)**	**B (MODERATE LIMITATION)**	**C (SEVERE LIMITATION)**
	-Homo or minimally heterogeneous parenchyma -Minimal shadowing -Near entirely visualization of liver	-Moderate heterogeneous parenchyma -Moderate shadowing -Not visualization of some portions of -- liver or diaphragm	-Severely heterogeneous parenchyma -Severe shadowing -Not visualization of majority of liver (>50%) - Not visualization of majority of diaphragm (>50%)

Table3. CEUS LI-RADS for Diagnosis of HCC in High-Risk Patients

PRE-CONTRAST US	LR-NC	LR-TIV	LR-1	LR-2	LR-M	
	-Can't be categorized due to image degradation or omission	-Tumor in vein	-Definitely benign -Hemangioma (peripheral discontinuous globular)	-Probably benign	-Malignancy but not HCC specific (Rim in APHE, early <60s or marked washout)	
Arterial Phase Hyper enhancement (APHE)		**No APHE**			**APHE (Not rim or discontinuous globular)**	
Nodule Size (cm)		< 2cm	≥ 2cm		< 1cm	≥ 1cm
Washout (no of any type)		**LR-3**	**LR-3**		**LR-3**	**LR-4**
Washout (late and mild)		**LR-3**	**LR-4**		**LR-4**	**LR-5**

Table4. CECT/ CEMRI LI-RADS for Diagnosis and Treatment Response Assessment, (a) LR-4 if enhancing capsule or LR-5 if wash-out/ threshold growth

OBSERVATION	LR-NC	LR-TIV	LR-1	LR-2	LR-M	
	-Can't be categorized due to image degradation or omission	-Tumor in vein	-Definitely benign -Hemangioma (peripheral discontinuous globular)	-Probably benign	-Malignancy but not HCC specific (Rim in APHE, early <60s or marked washout)	
ARTERIAL PHASE HYPER ENHANCEMENT (APHE)		**NO APHE**		**APHE (NOT RIM)**		
Nodule Size (cm)		<2cm	≥2cm	<1cm	1-2cm	≥2cm
Additional Features:	None	**LR-3**	**LR-3**	**LR-3**	**LR-3**	**LR-4**
-Enhancing Capsule	1	**LR-3**	**LR-4**	**LR-4**	**LR-4 or LR-5 (a)**	**LR-5**
- Washout	≥2	**LR-4**	**LR-4**	**LR-4**	**LR-5**	**LR-5**
-Threshold Growth						
TREATMENT RESPONSE	**LR-NON EVALUABLE**		**LR-NONVIABLE**	**LR-EQUIVOCAL**	**LR-VIABLE**	
	-Can't be evaluated due to image degradation or omission		-No enhancement of treated lesion or -Expected enhancement pattern for specific treatment	-Atypical enhancementof treated lesion	-Nodular/ thick irregular tissue of treat lesion with any of the following: -Arterial phase enhancement - Washout -Enhancement similar to pretreatment	

Table5. Comparative Criteria between mRECIST and RECIST in HCC assessment

	RECIST	mRECIST for HCC
CR(complete Response)	Loss of all target lesions	Loss of arterial enhancement in all target lesions
PR (Partial Response)	Reduction at least a 30% in the sum of diameters of all target lesions by taking as reference in the baseline sum of the diameters of target lesions	Reduction at least a 30% in the sum of diameters of viable (enhancement in the arterial phase) target lesions by taking as reference in the baseline sum of the diameters of target lesions
SD(Stable Disease)	Non partial response and progressive disease	Non partial response and progressive disease
PD(Progressive Disease)	Rise in 20% in the sum of diameters of target lesions, by taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	Rise in 20% in the sum of diameters of viable (enhancing) target lesions, by taking as reference the smallest sum of the diameters of target lesions recorded since treatment started

While Non-target lesions are inconclusive measurable lesion with atypical sign of post contrast enhancement including intra hepatic lesions (infiltrative, poorly defined hyper enhancement and margin), malignant thrombosis, adenopathy, neoplastic ascites and numerous small diffuse lesions. Non-target lesions can be checked over time by observation on their absence/presence or their longest diameter measurement of the entire nodules according to RECIST. The possible responses of non-target lesion are a complete response (CR= loss of all non-target lesions), Incomplete response/ Stable disease (IR/ SD= persistence at least one of non-target lesion) and progressive disease (PD= the presence of a new lesion or the unequivocal worsening of at least one of the known non-target lesions). The overall response is achieved by the combination of two possible therapeutic response of the target and non-target lesion [Table6]. A good correlation between the objective therapeutic response evaluated with mRECIST and overall survival rate after loco regional or systemic therapies have been reported in subsequent publications [89, 90]. The measurement of the response rate after therapy in HCC has become a controversial issue and the application of mRECIST criteria in clinical practice is challenging because it is not rare to find HCC represented completely by non-target lesions (lesions which don't show the post-contrast enhanced features of HCC). In several studies, mRECIST reveal an improve prediction of treatment response and overall survival, but might be limited in some HCC patients, for example, advanced diffuse and/or non-arterial enhancing HCC [91-94].

Treatment Response Assessmentby Response Evaluation Criteria in Cancer of Liver (RECICL 2019)

The last version of the Response Evaluation Criteria in Cancer of the Liver (RECICL) was compiled, revised in 2018 and publish in 2019 (Version5). In recent years, treatment methods for HCC have changed greatly with the adoption of molecular targeted agents. Unlike cytotoxic anticancer drugs, molecular targeted agents both reduce the size of tumors and cause their necrosis due to their anti-angiogenic and anti-proliferative properties. In other words, there is now a greater need to establish proper evaluation criteria for tumor necrosis. In 2010, to make appropriate criteria for the assessment of therapeutic response, Lencioni et al. proposed a new version of RECIS 1.0 by considering the necrosis of tumors as a treatment response as know modified Response evaluation criteria in Solid Tumor (mRECIST). However, these criteria lacked accuracy because it used unidirectional measurements [95, 96]. In the 2015 revision (version 4), RECICL was modified to be an evaluation criteria applicable to all treatment methods by integrating the overall evaluation criteria of RECIST, making it applicable to extrahepatic lesions while conserving its features that are specific to HCC. Then, the 2018 revision of RECICL was created to add response evaluation criteria for intrahepatic cholangiocarcinoma and molecular targeted therapy by followed the revision process used for the 2015 version. The important revised points of the RECICL are patients (HCC or Cholangiocarcinoma), tumor maker (CEA, CA19.9), and the specific detail of target molecular therapy and evaluation timing of treatment response. The evaluation timing of treatment response including local ablation (immediately after ablation therapy to 2 weeks), TACE (1 to 3 months), systemic therapy (1 to 3 months) and radiation therapy (6 months). Many studies have revealed that tumor necrosis and tumor size reduction effects measured by RECICL or mRECIST are correlated with survival regardless of whether the patient received locoregional or systemic treatment, which makes evaluation with such criteria extremely important. To improve the accuracy of treatment response evaluation, RECICL can be considered more specific to HCC than mRECIST because it always uses bidirectional rather than unidirectional measurement [95-100]. The important goal of RECICL is to focus on the prognosis and the efficacy of various treatment methods, particularly loco-regional treatments, for target lesions by assessing correlation of the treatment effects and the overall response. Unlike systemic chemotherapy, the loco-regional treatment (by TACE or ablation therapy) is not carried out throughout the entire liver parenchyma and does not affect newly developed lesions in untreated areas of the liver. Hence, it shouldn't be changed the treatment method nor prognosis assessment criteria though a new target lesion appears in a different area of the liver parenchyma including multi-centric lesion, intrahepatic metastasis or recurrence. As a rule, CECT is carried out to assess treatment response in HCC or recurrent tumors by using RECICL, so tumors must be clearly visualized on the image as hyper vascular. Target lesions are all measurable lesions with two lesions per organ and a maximum of five lesions in total. However, if there are more than 3 lesions in the liver, three nodules should be included in the target lesions. The area of target lesions is calculated by multiplying and the sum of the areas in all target lesions is used as the baseline area and the length of the major axis by the maximum diameter crossing the major axis. All the remaining lesions are considered as non-target lesions[101, 102]. The tumor necrotic effect or the rate of tumor size reduction is calculated based on the size reduction or disappearance of arterial hyper enhancement of the hepatic nodule on CECT, CEMRI or CEUS. Based on the tumor size reduction observed within a predetermined period after treatment or the maximum tumor necrotic effect, the direct treatment effect or response on the target nodules are categorized into four categories [Table7].The treatment effect or response on target nodules is evaluated individually for up to a maximum of three lesions when multiple intrahepatic lesions are present.The Overall Treatment Response was evaluated based on the maximum response obtained over a period of time, 1 to 3 months after treatments (6 months after radiation therapy) [Table8].

Table6. Overall Treatment Response of HCC

Overall Response	Target Lesion	Non-Target Lesion	New Lesions
CR (Complete Response)	CR	CR	No
PR (Partial Response)	CR	IR (Incomplete Response) / SD	No
PR (Partial Response)	PR	Non-PD	No
SD (Stable Disease)	SD	Non-PD	No
PD (Progressive Disease)	PD	Any	Yes/ No
PD (Progressive Disease)	Any	PD	Yes/ No
PD (Progressive Disease)	Any	Any	Yes

Table7. Direct Treatment Response (RECICL)

Categories	Equivalent	Treatment Response Or Effect On The Target Hepatic Nodules
TE4	Complete Response (CR)	100% of Tumor Size Reduction or Tumor Necrosis TE4b: Tumor Necrotic Area is similar to the size of the Original Tumor TE4a: Tumor Necrotic Area is larger to the size of the Original Tumor
TE3	Partial Response (PR)	≥ 50% of Tumor Size Reduction or Tumor Necrosis
TE2	Stable Disease (SD)	The effect is neither TE3 nor TE1
TE1	Progressive Disease (PD)	≥ 50% of Tumor Size Enlargement (excluding the area of necrosis after treatment)

Table8. The overall Treatment (RECICL) obtained in the follow-up period

OVERALL TREATMENT RESPONSE	TARGET LESIONS	NON-TARGET LESIONS	NEW LESIONS
Complete Response (CR)	TE4	TE4	No
Partial Response (PR)	TE4 TE3	TE3 or TE2 TE4 or TE3 or TE2	No
Stable Disease (SD)	TE2	TE4 or TE3 or TE2	No
Progressive Disease (PD)	TE1 Any Any	Any TE1 Any	Yes or No Yes or No Yes

The Assessment of Atypical Non Hyper Vascular Hepatic Nodules

The transformation of a regenerative nodule of cirrhosis into dysplastic nodules involves a progressively reduced portal venous supply and a progressively increased arterial vascularization. Cell differentiation plays an important role in arterial hyper enhancement of HCCs Nodules [103]. A study that evaluated the enhancement pattern of HCC nodules by using CECT has found that the predominant enhancement patterns of HCC differ significantly in tumor size and cell differentiation. They found the arterial hyper enhancement in 75% of nodules 2 to 3 cm, 70% of nodules 1 to 2 cm and absent the arterial hyper enhancement in 46% of nodules < 1cm. They found the arterial hyper enhancement in 53% of well differentiated nodules, 79% of moderately differentiated nodules and 60% of poorly differentiated nodules. This study shows that large nodules are easily diagnosed and the main difficulty in diagnostic imaging of cirrhotic patients is the small hepatic nodules < 2cm (small hypo vascular nodules) as they frequently don't show the classical arterial hyper enhancement [104]. The hepatospecific contrast agents used in CEMRI has represented an important step towards the imaging diagnosis of small hypo vascular nodules in the delay hepatobiliary phase [Figure4]. A study in HCC by using CEMRI with hepatospecific contrast agent has found hypo intensity nodules in the hepatobiliary phase due to the lost capacity of intracellular uptake of the contrast agent, while the surrounding normal parenchyma remains strongly enhanced. These finding open a new scenario for the non-invasive diagnosis of atypical small hypo vascular nodules in the international guideline [105]. According to the algorithm of EASL-EORTC 2012 and 2018 for diagnosis of HCC in cirrhotic patients,the diagnostic imaging modalities of hepatic nodule vary depending on the size of hepatic nodules. Among three diagnosis contrast enhanced imaging including CEUS, CECT and CEMRI, if there is one positive typical imaging feature of HCC, then the diagnosis is HCC. However, if there is no typical imaging feature of HCC, repeating or changing to other imaging modalities and the liver biopsy were used to diagnosis and follow up these atypical nodules [Figure5 and 6]. The treatment of HCC depends on the stages including very early, early, intermediate, advance, and terminal stage which were modified by the BCLC system [Figure7].

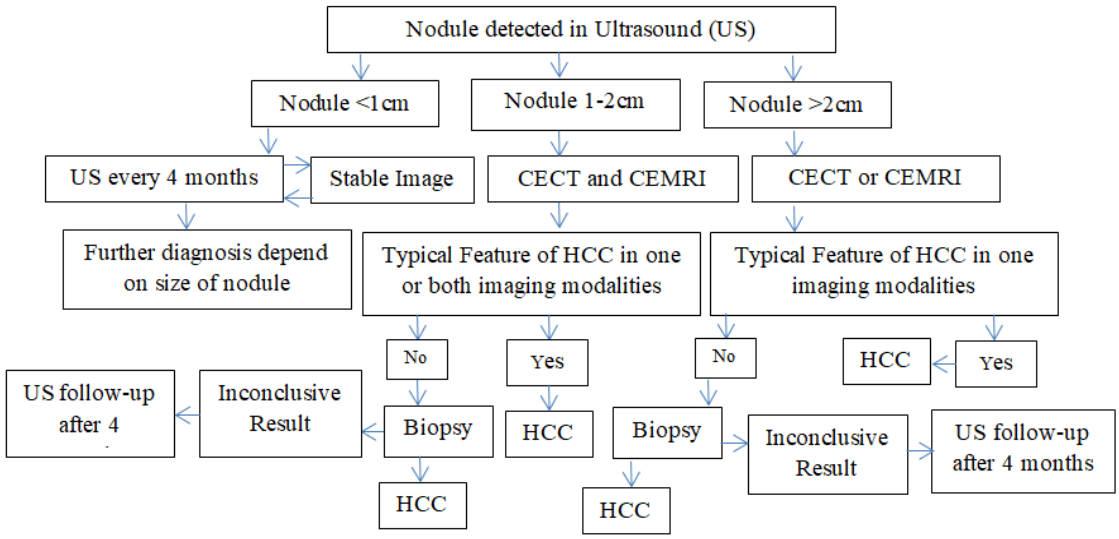

Figure5. Algorithm for Diagnosis of Hepatic Nodules of High Risk Patients (EASL-EORTC 2012)

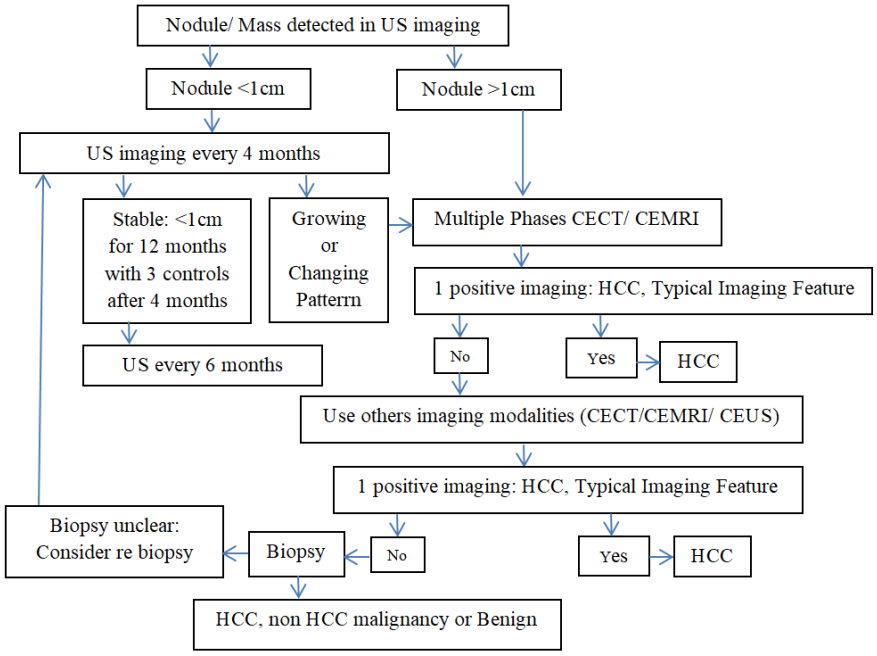

Figure6. Algorithm for HCC Diagnosis in Cirrhotic Patients (EASL-EORTC 2018)

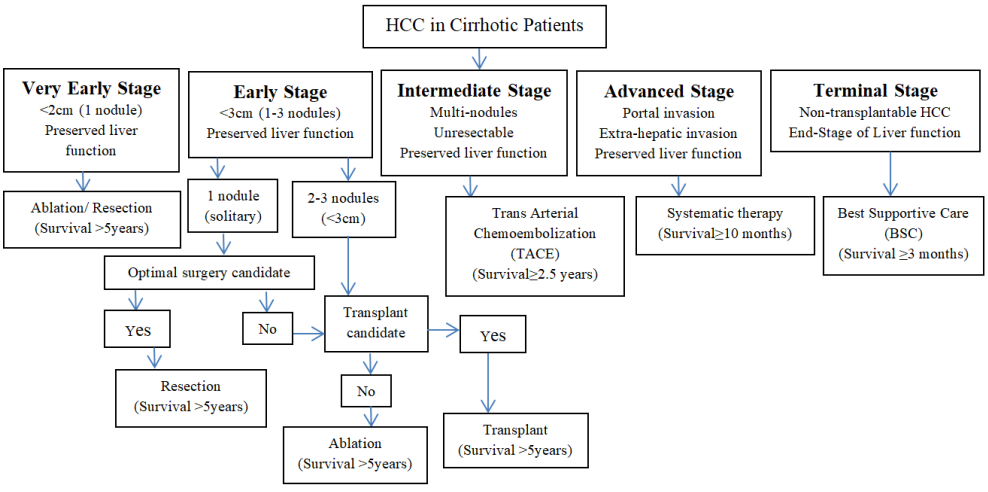

Figure7. HCC Staging and Treatment modified by BCLC (EASL-EORTC 2018

THE RESEARCH PROGRESSION AND FUTURE PERSPECTIVE

The computer aide diagnosis (CAD) program is, one of the most important research topics in the medical imaging and oncology, software for the recognition of the contrast features of the hepatic lesions to calculate the probability of being benign or malign based on LI-RADS criteria. The radiomic feature or texture analysis based on CEUS, CECT or CEMRI and integrated with development of artificial intelligence (AI) or Deep learning system (DLS) will possibly advance the interpretation and evaluation of the obtained medical images for diagnosis, prognosis and assessment the therapeutic effect in the near future.

CONCLUSION

Hepatocellular Carcinoma (HCC) is a multiphase process presented mostly in the cirrhotic liver including the r9egenerative nodules, dysplastic nodules (low or high grade), HCC foci within a dysplastic nodule, the early form of HCC, and a mature form of HCC. The Diagnostic imaging for early detection of HCC by contrast-enhanced imaging including the contrast enhanced US, contrast enhanced CT and contrast enhanced MRI are the important technique in high risk patients to reduce mortality rate and ensure an effective treatment plan. Liver Imaging Reporting and Data System (LI-RADS) were formed as a standard reporting and data collection in HCC diagnosis and treatment response. The interpretation of the therapeutic response of HCC nodules was evaluated by using Modified Response Evaluation Criteria in Solid Tumors (mRECIST) that was currently considered as the gold standard assessment confirmed in the latest version of the European Association for the Study of Liver (EASL). As the development of Computer-aided diagnosis program (CAD), the artificial intelligent (AI) or deep learning system (DLS), the interpretation of medical imaging in the radiomic feature or texture analysis will improve the diagnostic accuracy, limit diagnostic error and predict the treatment outcome.

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