Overview and Current Status Of Contrast-Enhanced Imaging in Assessing Diagnosis Of HCC after TACE

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Abstract*— Hepatocellular carcinoma (HCC) is the fifth most common cancer and a principal cause of cancer-related deaths approximately one-third of cancer-related deaths worldwide. HCC appears on the background of a cirrhotic liver. The treatment strategies have been considerable developed during the last 30 years; the stage of HCC and the underlying liver function determine the therapeutic option and management of diseases. Transarterial chemoembolization (TACE) is considered the best treatment option of HCC nodules not suitable for curative treatment including surgery and liver transplantation. Moreover, the modified Response Evaluation Criteria in Solid Tumors (mRECIST) is vital to determine the degree of tumor necrosis. If there is a tumor with partial necrosis, retreatment or additional treatment including ethanol injection, radiofrequency ablation, and microwave or HIFU ablation may be performed to achieve complete necrosis after TACE. Different Imaging modalities used to evaluate the treatment response to TACE include contrast-enhanced computed tomography (CECT), contrast-enhanced ultrasound (CEUS), and contrast-enhanced magnetic resonance imaging (CEMRI). CECT has been commonly used as the standard imaging modality to evaluate the treatment response of HCC after TACE. However, several studies have reported a weak diagnostic performance of CECT for the assessing diagnosis of residual tumors after cTACE. In DEB-TACE, the half-life of doxorubicin is normally a long time that is why a very assessment of treatment response after treatment could be appropriate and the degree of tumor necrosis could be underestimated. The purpose of this current study was to perform a systematic review of the literature to present the ability of contrast-enhanced imaging to evaluate treatment response of HCC after TACE. The current available contrast-enhanced imaging modalities (CEUS, CECT, and CEMRI) and new CEUS techniques will be discussed to their advantages based on currently available literature and our experience in contrast-enhanced imaging. Of all available imaging modalities including CECT and CEMRI, CEUS is a valuable imaging modality to assess the treatment response of HCC after TACE, especially the conventional TACE and may provide comparable sensitivity and other benefits to CECT. As the result of new techniques and software, contrast-enhanced imaging may have their advantages in assessing diagnosis of HCC treatment response. The perspectives of contrast-enhanced imaging in clinical practice are promising and the development of new contrast agents, as well as new software for analyzing images, will gradually evolve. This will create new prospects for characterizing hepatic lesions and assessing the treatment response of HCC after TACE.

***Keywords*— Contrast-enhanced Ultrasound, Contrast-enhanced Computed Tomography, Contrast-enhanced Magnetic Resonance Imaging, Hepatocellular Carcinoma, Trans arterial Chemoembolization**

***Abbreviation*—**

AASLD	:	The American Association for the Study of Liver Diseases
CEUS	:	Contrast-enhanced Ultrasound
CECT	:	Contrast-enhanced Computed Tomography
CEMRI	:	Contrast-enhanced Magnetic Resonance Imaging
DEB-TACE	:	Trans-arterial Chemoembolization
2DCEUS	:	2 dimensional contrast-enhanced Ultrasound
3DCEUS	:	3 dimensional contrast-enhanced Ultrasound
HIFU	:	High Intensity Focus Ultrasound
HCC	:	Hepatocellular Carcinoma
mRECIST	:	The modified Response Evaluation Criteria in Solid Tumors
TACE	:	Trans-arterial Chemoembolization
TIC	:	Time Intensity Curve
WHO	:	World Health Organization

INTRODUCTION

Hepatocellular carcinoma (HCC), ranked as the fifth most common cancer by the World Health Organization (WHO), is a principal cause of cancer-related deaths and responsible for approximately one-third of cancer-related deaths worldwide. HCC is the most common primary neoplasia of the liver and the majority of HCC appears on the background of a cirrhotic liver. During the last 30 years, the development of therapeutic strategies has been remarkable done and there is a significant advancement in the management of the disease. However, patient survival has not improved as greatly as for many other tumors because HCC is not diagnosed until the disease is already at intermediate or even advanced stage of HCC. In these circumstances, the stage of HCC and the underling liver function determine the therapeutic option and management of disease [1-4]. Many new treatment techniques are currently available for the management of HCC patients. Of these treatment's options, trans arterial chemoembolization (TACE) is considered the best treatment option of HCC nodules not suitable for curative treatment option including resection or liver transplantation. Nowadays TACE is considered as an effective treatment option and has become the standard

treatment option of HCC in patients with preserved liver function, no evidence of vascular invasion or extra-hepatic spread, and no cancer-related symptoms. Moreover, with the advancement of technical and chemoembolization agents, this therapeutic method has been currently used to assessing diagnose the viable HCC or the treatment response of HCC after TACE [5-8]. In TACE protocol, iodized oil (lipiodol) is delivered to intra-arterials of the tumor and after TACE procedure, complete necrosis is definitely an independent prognostic factor of patient survival. Therefore, assessing diagnosis with imaging and the modified Response Evaluation Criteria in Solid Tumors (mRECIST) is important to determine the complete necrosis. In cases of partial necrosis a new TACE session or additional treatment including ethanol injection, radiofrequency ablation, and microwave or HIFU ablation may be performed in order to achieve complete necrosis [9-14]. Different Imaging modalities used to evaluate the treatment response to TACE include contrast-enhanced computed tomography (CECT), contrast-enhanced ultrasound (CEUS), and contrast-enhanced magnetic resonance imaging (CEMRI). CECT has been commonly used as the standard imaging modality to evaluate the treatment response of HCC after TACE; however, this imaging technique has some disadvantages. One of the most important disadvantages is the overestimation of tumor response and recent studies recommended that the assessment of the treatment response generally have to be performed 1 month or more after TACE. To overcome this limitation, many studies have focused on other alternative imaging option; especially CEUS with second generation of contrast agent (SonoVue) was considered a valuable imaging modality to assess HCC after treatment [15-19]. CEUS is less affected by lipiodol retention that is useful for the assessing diagnosis of treatment response after TACE. Furthermore, advantages of CEUS are reproducibility, high temporal resolution, the absence of radiation and high safety. Therefore, CEUS is suitable for patients with allergy to iodine or renal failure. However, several studies have reported varying results when comparing CEUS with CECT. Based on the diagnosis algorithm of the American Association for the Study of Liver Diseases (AASLD), CEUS is not recommended anymore for diagnosis of HCC because it can be false positive with cholangiocarcinoma. However, based on experience of operator, CEUS is widely used in the diagnosis of HCC and the combination of CEUS and CECT or CEMR are cost-effective for diagnosis of small HCC [20-24]. It is possible that a decrease the rate of partial necrosis stands for increase patient survival and an early assessment is very important because it may allow detection of areas not covered by the treatment which will need retreatment or additional treatment in order to achieve a complete necrosis of tumor. With the use of CEUS to evaluate HCC after TACE, the second insertion could be performed during the procedure. Therefore, the same operator uses the same equipment and could evaluate the efficacy of treatment and additional treatment such as ablation. By using this method, there is a decrease the rate of partial necrosis in treated HCCs from 16% to 3.8%. Even though CECT is considered the gold standard for assessment of HCC treatment response, many authors have recommended that CEUS should be the first imaging modality to assess the initial treatment response at 1 month and CECT or CEMRI should be reserved for follow-up of treatment response at 3 months [25, 26]. The purpose of this current study was to perform a systematic review of the literature to present the ability of contras-enhanced imaging to evaluate treatment response of HCC after TACE. The current available contrast-enhanced imaging modalities (CEUS, CECT and CEMRI) and new CEUS techniques will be discussed to its advantage based on current available literature and our experience in contrast-enhanced imaging.

CEUS with mRECIST to evaluate HCC after TACE

An accurate assessment of therapeutic response is important to judge whether it is complete or non-complete treatment response as the result of different treatment options as a suitable alternative to surgery in patients with HCC including loco-regional and systemic therapies. The rate of tumor necrosis after TACE significantly increases patient survival and residual viable tumor needs additional treatment. 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) [12, 27, 28] [Table1]. Since 2008, Modified Response Evaluation Criteria in Solid Tumors (mRECIST) was used to assessing diagnosis the treatment response of HCC after loco regional (TACE, ablation) or systemic therapy (anti-angiogenetic treatments). It is based on unidimensional measurement of the hyper arterial enhancement parts of treated target tumors. Some studies recommended that mRECIST is able to predict the overall survival of HCC patients treated by TACE or Sorafenib; CECT and CEMRI are the standard imaging modalities with mRECIST to assess the treatment response after TACE. In the last recent year, CEUS is more reliable than CECT and was used with mRCIST to assess HCC after TACE. Effective TACE was detected by CEUS as previous hyper arterial enhancement becomes no enhancement after treatment. Study has reported that treatment response group had longer mean survival than non-response group (37.1 months vs 10.9 months) let to validate mRECIST using with CEUS as an assessing diagnosis and reliable prognostic tool of HCC after TACE. The use of CEUS with the second generation of contrast agent (SonoVue) may increase specificity for discerning viable and non-viable HCC after TACE. Complete tumor necrosis or complete response (negative enhancement) is defined as no enhancement of tumors compared with previous hyper arterial enhancement before

treatment, while the surrounding hepatic parenchyma was filled with enhancement signals. Incomplete tumor necrosis or incomplete response (positive enhancement) is defined as strong contrast enhancement appearing within the tumor and interpreted as viable tumor in treated nodules. No response is defined as the enhancement of the whole nodules (rare). In another rare case, a partial or total infarct of a liver segment may be detected [29-33]. The early HCC diagnosis offers better outcomes of treatment; however, there is currently no consensus regarding which is the best time interval for CEUS to be performed after TACE. Hence, earlier diagnosis of incomplete treatment response or incomplete tumor necrosis after TACE could increase the patient survival. Study has reported that the result of CEUS 1 week after TACE was consistent with that of CECT 2 months after treatment. To assess viable or residual tumor blood flow after TACE, another study has reported that the result of CEUS performed more than two day after TACE is similar to the reliable result of CECT or CEMRI 3 months after TACE [34, 35]. The use of intra-procedural CEUS during DEB-TACE has been reported that 50% of the degree of complete tumor necrosis was underestimated and there are few studies about the possible role for intra-procedural CEUS. By using DEB-TACE, the underestimated degree of complete tumor necrosis may be the reason that the time to progression of tumor necrosis takes place during days or weeks after this treatment procedure [36]. Intra-procedural CEUS with intra-arterial ultrasound contrast agent injection may also help in finding extrahepatic tumor-feeding arteries. Intra-arterial application of SonoVue using the placed intra-arterial catheter is able to diagnose and locate additional hepatic lesions in patients with HCC, not detectable in the other applied imaging modalities. These findings had a direct impact on patient management in almost two-thirds of all cases. However, the manufacturer does not indicate this route of administration, and further safety data are required before clinical translation. Although the number of patients was limited in both studies, there is some evidence to support the use of intra-procedural CEUS [37, 38].

CEUS compared with CECT and CEMRI

The assessing and diagnostic performance of CEUS, CECT and CEMRI in detecting viable HCC at 4 and 12 weeks after TACE have been recently studied and reported by using the results of CEMRI at 12 weeks as reference standard. The result of this study shows that the sensitivity of CEUS (4week), CECT (4week), and CEMI (4week) are 100%, 50% and 50%, respectively. According to above mentioned study, the assessing diagnosis performance of CEUS 1 to 4 weeks after conventional TACE (cTACE) is similar to the assessing diagnosis performance of CECT at 2 months after cTACE and the diagnosis of incomplete treatment response or incomplete necrosis of HCC 1 week after cTACE would allow additional treatment. The precarious conclusion regarding these results may let to raise the question whether CEUS is more sensitive than CECT or CEMRI in detecting earlier the small areas of HCC after TACE. Furthermore, the use of CEMRI with low molecular weight and water soluble contrast agents at 4 week after treatment is difficult to differentiate granulation tissues from residual HCC and peripheral viable HCC from inflammatory infiltration around tumors [39-41]. CECT has been commonly used as the standard imaging modality to evaluate the treatment response of HCC after TACE. However, several studies have reported a weak diagnostic performance of CECT for assessing diagnosis of residual tumor after cTACE. Study compared CEUS at 1 month after TACE with CECT at 1 month using digital angiography as a reference standard. In order to detect viable tumors, the result of this study show that CEUS detected all cases of incomplete response, while CECT had sensitivity of 86.9%, specificity of 100%, positive predicted value of 100%, and negative predictive value of 83.3% [33]. Similarly, another study about the diagnosis performance of CEUS with CECT performed 0.5 to 2 months after TACE to assessing diagnosis of viable HCC using histology as reference standard reported that the sensitivity, specificity and accuracy of CEUS be 95.9%, 100% and 96.2 %, respectively, while CECT be 76%, 100% and 77.7%, respectively [23]. The diagnosis performance of CECT after drug-eluting beads TACE (DEB-TACE) may change the diagnostic result due to less susceptible of DEB-TACE to artifacts compared to lipiodol TACE. Furthermore, CECT was reported as comparable result to CEMRI after liipiodol free treatment group of patients [3, 33]. In DEB-TACE, the half-life of doxorubicin is normally long time that is why a very assessment of treatment response after treatment could be appropriate and the degree of tumor necrosis could be underestimated. There is no any studies comparing CEUS with CECT after DEB-TACE, hence it let to raise the question whether CEUS is more accurate then CECT in detecting the viable HCC after DEB-TACE. In comparison to CEMRI or CECT at 1 month, CEUS performed 1 to 2 weeks after DEB-TACE was reported the result of 100% sensitivity, specificity, positive predicted value, negative predictive value, and accuracy. Therefore, by using cTACE or DEB-TACE, CEUS may still detect the viable or non-viable tumor that is important to require retreatment or additional treatment (radiofrequency or microwave ablation) earlier than the typical 4 weeks imaging of CECT or CEMRI [42, 43]. The result of CEUS 1 week after TACE varies with the different type of reference standard that was used. By using histology as reference standard to differentiate viable and non-viable HCC, a study reported that CEUS has sensitivity of 100% and specificity of 81% [39]. Another study reported that a sensitivity of 100% and specificity of 100% when using CECT at 2 months after TACE as the reference standard [13]. The assessing diagnosis of CEUS 1 week after TACE to guide additional treatment such as radiofrequency or microwave ablation may transform the partial necrosis into complete necrosis of tumor and decrease the rate of tumor recurrence after treatment. TACE combined with radiofrequency ablation has been reported the better result compared to TACE alone [35, 44].

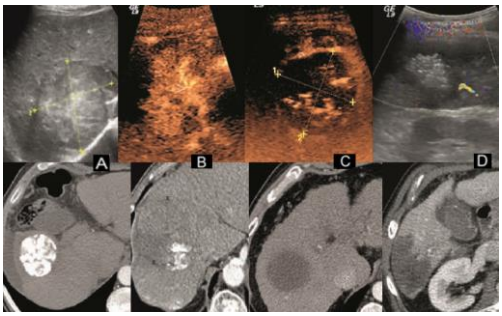

Figure1. Arterial phase imaging of HCC after TACE shows as non-treatment response (A), incomplete treatment response (B); complete treatment response (C) and infarction around HCC (D).

Table1. Combative Criteria between mRECIST and RECIST for the treatment evaluation of HCC

	RECIST	**mRECIST**
CR (Complete Response)	Disappearance of all target lesions	Disappearance of any intra-tumoral arterial enhancement in all target lesions
PR (Partial Response)	Decrease at least a 30% in the sum of diameters of all target lesions, taking as reference in the baseline sum of the diameters of target lesions	Decrease at least a 30% in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference in the baseline sum of the diameters of target lesions
SD (Stable Disease)	Neither partial response nor progressive disease	Neither partial response nor progressive disease
PD (Progressive Disease)	Increase in 20% in the sum of diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	Increase in 20% in the sum of diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started

The Advantages and Limitations of CEUS for Assessing Diagnosis of HCC after TACE

The most important advantages of CEUS are the higher accuracy in detecting residual or viable HCC at 1 week after TACE and the lack of radiation in situations when repeated imaging is required after TACE. The use of CEUS avoids the use of iodinated contrast agents in case of acute renal failure as the result of cirrhotic liver of HCC patients. CEUS with the second generation of contrast agent can detect the small areas of viable HCC which may be overlooked by CECT or even CEMRI and can be performed repeatedly at bedside. Other advantages of CEUS is that it is less expensive than CECT or CEMRI and can be used instead of CECT in case of lipiodol artifacts and instead of CEMRI in case of TACE related enhancing signal at unenhanced T1. CEUS may decrease the number of CECT examination after TACE and the combination of CEUS and CECT/ CEMRI could achieve better results in suspicious cases [30, 31].

There some limitations of CEUS based on the results of numerous studies. First of all, multiple tumors have to be studied separately with CEUS in order to detect changes in its hyper arterial enhancement. With our experience three lesions can also be evaluated if at least two lesions are located close to each other and another lesion can be evaluated with another injection of the second generation of contrast agent up to 1 ml. Study have reported that CEUS is efficient in assessing diagnosis around 62% of HCC patients with multiple tumors (2 to 3 lesions). Second, hypo-vascular tumors presented as hypo/ isoenhancement before TACE and may be difficult to be assessed after TACE with CEUS. This limitation is detected in CEUS, CECT and CEMRI. It is possible to use TIC in CEUS software which could quantify enhancement of tumors better than visual assessment and use mRECIST for tumors assessment in CECT or CEMRI in order to get an appropriate diagnosis and overcome this limitation [32]. Third, an increased echogenicity may impair CEUS assessment. This limitation is due to gas bubbles trapped in the embolic material or post necrotic gas formation presented some day after TACE (post TACE hyper echogenicity) and it will disappear 1 week after TACE. This post TACE hyper echogenicity may lead to non-diagnosis CEUS of pre and post TACE in all HCCs (29.3%), one lesions (14.8%), and multiple lesions (41.7%) [32, 36]. Last, the limitations are an operator dependent CEUS performance and greater intra- and inter- reader variability compared to CECT/CEMRI. By using CEUS, the detection challenges are HCC located deep into the liver (impaired detection when tumors at a distance of 8 to 10 cm from the skin and when using first generation contrast agent, Levovist), tumors covered by the lung or diaphragm, and in patients with cirrhosis obesity or meteorism. Therefore, the use of CEUS with second generation contrast agent (SonoVue) may overcome some of these detection challenges [43, 45].

New Technical Imaging to Evaluate the Treatment Response of HCC after TACE

To overcome the above limitation, new imaging techniques and software used with CEUS have been developed to the assessing diagnosis and management of HCC. However, they all stand as promising new imaging modalities; the limited experience and insufficient evidence for their use in clinical practice are challenges. There are several new imaging techniques used with CEUS including dynamic CEUS with quantification, Fusion techniques (CEUS-CT or CEUS-MRI) and three-dimensional CEUS technique (3D CEUS). First of all, dynamic CEUS with quantification is a promising imaging modality. A new functional technique is used as quantitative analysis of tumor perfusion by perfusion software and time intensity curves (TIC). This new technical CEUS is essential for early assessment of treatment response; especially to assess vascularization of HCC treated with vascular targeting agents since it would enable an optimization of individualized treatment. Study, which used dynamic CEUS to assess the grade of hyper vascularization of HCC before and after DEB-TACE with post-interventional angiography and post-procedural CT as the gold standard, have reported and concluded that quantification of the

reduction of micro vascularization of HCC using perfusion software with TIC analysis might be a valuable peri-interventional device during DEB-TACE [46]. Secondly, Fusion technical imaging by using CEUS with CECT or CEMRI, a new technical imaging modalities which enable a precise mapping of tumor, were used in post-interventional follow-up of HCC after TACE. Study showed that image fusion with volume navigation of post-interventional CEUS performed immediately after treatment with pre-interventional CECT or CEMRI provides an exact mapping of microcirculation and an accurate localization of residual tumor foci of HCC after TACE. A high correlation between early fusion imaging of CEUS with CECT or CEMRI and CECT achieved at 6 weeks after TACE allowed an early assessment of therapeutic success [47]. Finally, 3DCEUS is a new technical imaging which one study reported that improved visualization of tumor vascularity in three orthogonal planes and was used to assess the treatment response of HCC. However, the result of this study shows similar diagnostic performance between 2D and 3DCEUS (performed 1 month after treatment) by using CEMRI or CECT as standard reference. This study provides preliminary results and in order to show the theoretical superiority of 3DCEUS, new data and multicenter studies are compulsory needed [48].

Conclusion

Over the past decades, the different treatment options such as loco-regional and systemic therapies are suitable alternative to surgery of HCC patients and an accurate assessing diagnostic of viable HCC is important to the treatment response. Of all available imaging modalities including CECT and CEMRI, CEUS is a valuable imaging modality to assess the treatment response of HCC after TACE, especially lipiodol TACE and may provide comparable sensitivity and other benefits to CECT. In the standard timing of HCC assessment after TACE (1 to 2 months), the diagnostic performance of CEUS seems to be better than that of CECT and at least similar to that of MRI. CEUS performed 5 to 7 days after TACE could decide whether there is a need for retreatment or others additional treatments. As the result of the assessment, the rate of tumor necrosis significantly increases patient survival and residual/ viable HCC determines additional treatment. As the result of new techniques and software, contrast-enhanced imaging may have their advantages in assessing diagnosis of HCC treatment response. For example, dynamic CEUS with quantification, a technical development based on real-time fusion of CEUS with CECT or CEMRI, and 3D CEUS been reported to improve the study of tumor vascular perfusion and the response assessment of HCC. The perspectives of contrast-enhanced imaging in clinical practice are promising and the development of new contrast agents, as well as new software for analyzing images will gradually evolve. This will create new prospects for characterizing hepatic lesions and assessing treatment response of HCC after TACE.

References

[1] Kim DY, Han K-H. Epidemiology and surveillance of hepatocellular carcinoma. Liver Cancer. 2012;1(1):2-14.

[2] Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(9):1485-91.

[3] Kloeckner R, Otto G, Biesterfeld S, Oberholzer K, Dueber C, Pitton MB. MDCT versus MRI assessment of tumor response after transarterial chemoembolization for the treatment of hepatocellular carcinoma. Cardiovascular and interventional radiology. 2010;33(3):532-40.

[4] Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet (London, England). 2003;362(9399):1907-17.

[5] Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology (Baltimore, Md). 2003;37(2):429-42.

[6] Yim HJ, Suh SJ, Um SH. Current management of hepatocellular carcinoma: an Eastern perspective. World journal of gastroenterology. 2015;21(13):3826-42.

[7] Imai N, Ishigami M, Ishizu Y, Kuzuya T, Honda T, Hayashi K, et al. Transarterial chemoembolization for hepatocellular carcinoma: A review of techniques. World J Hepatol. 2014;6(12):844-50.

[8] Arora A, Kumar A. Treatment Response Evaluation and Follow-up in Hepatocellular Carcinoma. J Clin Exp Hepatol. 2014;4(Suppl 3):S126-S9.

[9] Sieghart W, Pinter M, Reisegger M, Müller C, Ba-Ssalamah A, Lammer J, et al. Conventional transarterial chemoembolisation in combination with sorafenib for patients with hepatocellular carcinoma: a pilot study. European radiology. 2012;22(6):1214-23.

[10] Huppert P. Current concepts in transarterial chemoembolization of hepatocellular carcinoma. Abdominal imaging. 2011;36(6):677-83.

[11] Bouvier A, Ozenne V, Aubé C, Boursier J, Vullierme MP, Thouveny F, et al. Transarterial chemoembolisation: effect of selectivity on tolerance, tumour response and survival. European radiology. 2011;21(8):1719-26.

[12] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Seminars in liver disease. 2010;30(1):52-60.

[13] Takayama T, Makuuchi M, Hirohashi S, Sakamoto M, Okazaki N, Takayasu K, et al. Malignant transformation of adenomatous hyperplasia to hepatocellular carcinoma. Lancet (London, England). 1990;336(8724):1150-3.

[14] Minami Y, Kudo M, Kawasaki T, Kitano M, Chung H, Maekawa K, et al. Transcatheter Arterial Chemoembolization of Hepatocellular Carcinoma: Usefulness of Coded Phase-Inversion Harmonic Sonography. American Journal of Roentgenology. 2003;180(3):703-8.

[15] Minami Y, Kudo M. Therapeutic response assessment of transcatheter arterial chemoembolization for hepatocellular carcinoma: ultrasonography, CT and MR imaging. Oncology. 2013;84 Suppl 1:58-63.

[16] Kudo M, Matsui O, Izumi N, Kadoya M, Okusaka T, Miyayama S, et al. Transarterial chemoembolization failure/refractoriness: JSH-LCSGJ criteria 2014 update. Oncology. 2014;87 Suppl 1:22-31.

[17] Bargellini I, Bozzi E, Campani D, Carrai P, De Simone P, Pollina L, et al. Modified RECIST to assess tumor response after transarterial chemoembolization of hepatocellular carcinoma: CT-pathologic correlation in 178 liver explants. European journal of radiology. 2013;82(5):e212-8.

[18] Shim JH, Han S, Shin YM, Yu E, Park W, Kim KM, et al. Optimal measurement modality and method for evaluation of responses to transarterial chemoembolization of hepatocellular carcinoma based on enhancement criteria. J Vasc Interv Radiol. 2013;24(3):316-25.

[19] Sun-young K, Rhim H, Lim H, Park C, Lee W, Do Y, et al. Completeness of Treatment in Hepatocellular Carcinomas Treated With Image-guided Tumor Therapies: Evaluation of Positive Predictive Value of Contrast-enhanced CT with Histopathologic Correlation in the Explanted Liver Specimen. Journal of computer assisted tomography. 2006;30:578-82.

[20] Liu M, Lin MX, Lu MD, Xu ZF, Zheng KG, Wang W, et al. Comparison of contrast-enhanced ultrasound and contrast-enhanced computed tomography in evaluating the treatment response to transcatheter arterial chemoembolization of hepatocellular carcinoma using modified RECIST. European radiology. 2015;25(8):2502-11.

[21] Cristea CG, Gheonea IA, Săndulescu LD, Gheonea DI, Ciurea T, Purcarea MR. Considerations regarding current diagnosis and prognosis of hepatocellular carcinoma. J Med Life. 2015;8(2):120-8.

[22] Zheng SG, Xu HX, Liu LN. Management of hepatocellular carcinoma: The role of contrast-enhanced ultrasound. World journal of radiology. 2014;6(1):7-14.

[23] Bruix J, Sherman M, American Association for the Study of Liver D. Management of hepatocellular carcinoma: an update. Hepatology (Baltimore, Md). 2011;53(3):1020-2.

[24] Lencioni R, Cioni D, Crocetti L, Franchini C, Pina CD, Lera J, et al. Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. Radiology. 2005;234(3):961-7.

[25] Nicolau C, Vilana R, Bianchi L, Brú C. Early-stage hepatocellular carcinoma: the high accuracy of real-time contrast-enhanced ultrasonography in the assessment of response to percutaneous treatment. European radiology. 2007;17 Suppl 6:F80-8.

[26] Solbiati L, Ierace T, Tonolini M, Cova L. Guidance and monitoring of radiofrequency liver tumor ablation with contrast-enhanced ultrasound. European journal of radiology. 2004;51 Suppl:S19-23.

[27] EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. Journal of hepatology. 2018;69(1):182-236.

[28] European Association for the Study of the L, European Organisation for R, Treatment of C. EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. Journal of hepatology. 2012;56(4):908-43.

[29] Marcus CD, Ladam-Marcus V, Cucu C, Bouché O, Lucas L, Hoeffel C. Imaging techniques to evaluate the response to treatment in oncology: current standards and perspectives. Critical reviews in oncology/hematology. 2009;72(3):217-38.

[30] Moschouris H, Malagari K, Papadaki MG, Kornezos I, Stamatiou K, Anagnostopoulos A, et al. mRECIST criteria and contrast-enhanced US for the assessment of the response of hepatocellular carcinoma to transarterial chemoembolization. Diagn Interv Radiol. 2014;20(2):136-42.

[31] Minami Y, Kudo M. Imaging Modalities for Assessment of Treatment Response to Nonsurgical Hepatocellular Carcinoma Therapy: Contrast-Enhanced US, CT, and MRI. Liver Cancer. 2015;4(2):106-14.

[32] Moschouris H, Malagari K, Papadaki MG, Kornezos I, Gkoutzios P, Tepelenis N, et al. Short-term evaluation of liver tumors after transarterial chemoembolization: limitations and feasibility of contrast-enhanced ultrasonography. Abdominal imaging. 2011;36(6):718-28.

[33] Salvaggio G, Campisi A, Lo Greco V, Cannella I, Meloni MF, Caruso G. Evaluation of posttreatment response of hepatocellular carcinoma: comparison of ultrasonography with second-generation ultrasound contrast agent and multidetector CT. Abdominal imaging. 2010;35(4):447-53.

[34] Kono Y, Lucidarme O, Choi SH, Rose SC, Hassanein TI, Alpert E, et al. Contrast-enhanced ultrasound as a predictor of treatment efficacy within 2 weeks after transarterial chemoembolization of hepatocellular carcinoma. J Vasc Interv Radiol. 2007;18(1 Pt 1):57-65.

[35] Xia Y, Kudo M, Minami Y, Hatanaka K, Ueshima K, Chung H, et al. Response evaluation of transcatheter arterial chemoembolization in hepatocellular carcinomas: the usefulness of sonazoid-enhanced harmonic sonography. Oncology. 2008;75 Suppl 1:99-105.

[36] Moschouris H, Malagari K, Papadaki MG, Kornezos I, Matsaidonis D. Contrast-Enhanced Ultrasonography of Hepatocellular Carcinoma After Chemoembolisation Using Drug-Eluting Beads: A Pilot Study Focused on Sustained Tumor Necrosis. Cardiovascular and interventional radiology. 2010;33(5):1022-7.

[37] Schacherer D, Girlich C, Zorger N, Wiest R, Schoelmerich J, Feuerbach S, et al. Sono-hepatic-arteriography (Sono-HA) in the assessment of hepatocellular carcinoma in patients undergoing transcatheter arterial chemoembolization (TACE). Ultraschall in der Medizin (Stuttgart, Germany : 1980). 2010;31(3):270-5.

[38] Wiggermann P, Wohlgemuth WA, Heibl M, Vasilj A, Loss M, Schreyer AG, et al. Dynamic evaluation and quantification of microvascularization during degradable starch microspheres transarterial Chemoembolisation (DSM-TACE) of HCC lesions using contrast enhanced ultrasound (CEUS): a feasibility study. Clinical hemorheology and microcirculation. 2013;53(4):337-48.

[39] Morimoto M, Shirato K, Sugimori K, Kokawa A, Tomita N, Saito T, et al. Contrast-enhanced harmonic gray-scale sonographic-histologic correlation of the therapeutic effects of transcatheter arterial chemoembolization in patients with hepatocellular carcinoma. AJR American journal of roentgenology. 2003;181(1):65-9.

[40] Cho YZ, Park SY, Choi EH, Baik SK, Kwon SO, Kim YJ, et al. The usefulness of contrast-enhanced ultrasonography in the early detection of hepatocellular carcinoma viability after transarterial chemoembolization: pilot study. Clin Mol Hepatol. 2015;21(2):165-74.

[41] Yan F-H, Zhou K-R, Cheng J-M, Wang J-H, Yan Z-P, Da R-R, et al. Role and limitation of FMPSPGR dynamic contrast scanning in the follow-up of patients with hepatocellular carcinoma treated by TACE. World journal of gastroenterology. 2002;8(4):658-62.

[42] Moschouris H, Malagari K, Kornezos I, Papadaki MG, Gkoutzios P, Matsaidonis D. Unenhanced and contrast-enhanced ultrasonography during hepatic transarterial embolization and chemoembolization with drug-eluting beads. Cardiovascular and interventional radiology. 2010;33(6):1215-22.

[43] Shaw CM, Eisenbrey JR, Lyshchik A, O'Kane PL, Merton DA, Machado P, et al. Contrast-enhanced ultrasound evaluation of residual blood flow to hepatocellular carcinoma after treatment with transarterial chemoembolization using drug-eluting beads: a prospective study. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 2015;34(5):859-67.

[44] Zhao M, Wang JP, Li W, Huang ZL, Zhang FJ, Fan WJ, et al. [Comparison of safety and efficacy for transcatheter arterial chemoembolization alone and plus radiofrequency ablation in the treatment of single branch portal vein tumor thrombus of hepatocellular carcinoma and their prognosis factors]. Zhonghua yi xue za zhi. 2011;91(17):1167-72.

[45] Youk JH, Lee JM, Kim CS. Therapeutic response evaluation of malignant hepatic masses treated by interventional procedures with contrast-enhanced agent detection imaging. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 2003;22(9):911-20.

[46] Uller W, Wiggermann P, Gössmann H, Klebl F, Salzberger B, Stroszczynski C, et al. Evaluation of the microcirculation of hepatocellular carcinomas using contrast-enhanced ultrasound with intraarterial and intravenous contrast application during transarterial chemoembolization with drug-eluting beads (DEB-TACE): preliminary data. Clinical hemorheology and microcirculation. 2011;49(1-4):55-66.

[47] Ross CJ, Rennert J, Schacherer D, Girlich C, Hoffstetter P, Heiss P, et al. Image fusion with volume navigation of contrast enhanced ultrasound (CEUS) with computed tomography (CT) or magnetic resonance imaging (MRI) for post-interventional follow-up after transcatheter arterial chemoembolization (TACE) of hepatocellular

carcinomas (HCC): Preliminary results. Clinical hemorheology and microcirculation. 2010;46(2-3):101-15.

[48] Bartolotta TV, Taibbi A, Matranga D, Midiri M, Lagalla R. 3D versus 2D contrast-enhanced sonography in the evaluation of therapeutic response of hepatocellular carcinoma after locoregional therapies: preliminary findings. La Radiologia medica. 2015;120(8):695-704.