Review

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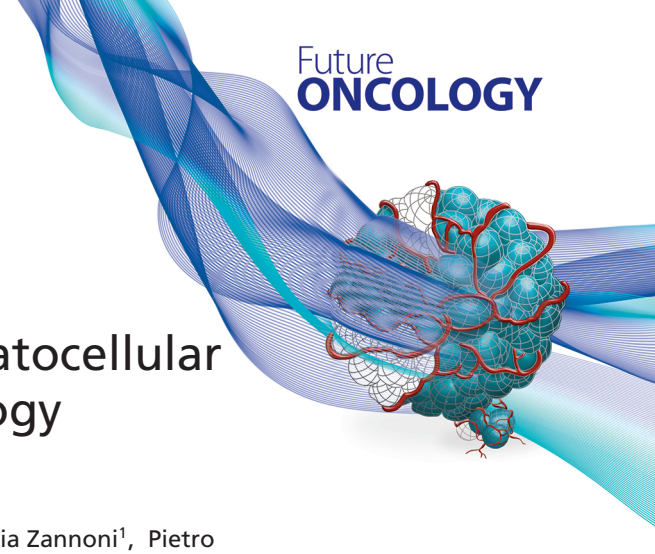

Assessment of the response of hepatocellular carcinoma to interventional radiology treatments

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According to Barcelona Clinic Liver Cancer (BCLC) guidelines, interventional radiology procedures are valuable treatment options for many hepatocellular carcinomas (HCCs) that are not amenable to resection or transplantation. Accurate assessment of the efficacy of therapies at earlier stages enables completion of treatment, optimal follow-up and to prevent potentially unnecessary treatments, side effects and costly failure. The goal of this review is to summarize and describe the radiological strategies that have been proposed to predict survival and to stratify HCC responses after interventional radiology therapies. New techniques currently in development are also described.

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The limitations of conventional imaging criteria

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death [1,2]. According to Barcelona Clinic Liver Cancer (BCLC) guidelines, interventional radiology procedures are valuable treatment options for many HCCs that are not amenable to resection or transplantation [3]. In particular, BCLC-A patients are eligible both for thermal ablation, while BCLC-B patients are suitable for transarterial chemoembolization (TACE). Moreover, evidence suggests the potential employment of (transarterial radioembolization) TARE in the management of certain BCLC-C [4,5].

Accurate assessment of the efficacy of therapies at earlier stages enables completion of treatment prior to unfavorable geometries or bulk, and is essential to optimal timing of follow-up treatment and to prevent potentially unnecessary treatments, side effects and costly failure [6]. In trials as well as in clinical practice, imaging has been widely used to provide early end points that may predict response or even be a surrogate for overall survival [7]. The standard conventional method to define radiological responses of solid tumors consists of tumor size changes over time, based on the assumption that imaged and measured shrinkage is associated with a better response to therapy versus tumor increase in size (morphometry or morphology) [8,9]. The promise of quantitative imaging approaches is that such a measurement may provide an objective, reproducible and reliable end point for the assessment of overall response. The first proposed quantitative methodology was WHO bidimensional criteria [10], published in 1979, which was then followed by unidimensional measurements, Response Evaluation Criteria in Solid Tumors (RECIST), created in 2000 and updated in 2009 [11,12]. In both cases, the imaging response biomarker is the size of the tumor, which is estimated on the basis of the longest diameter (RECIST) or the two longest diameters (WHO) on single slice 2D images, usually axial [10–12]. Nevertheless, these simple anatomic criteria are hampered by some limitations. First, they assume that neoplastic nodules have a spherical shape and thus, they exhibit homogeneous size changes; however, malignant nodules are known to have irregular burden and morphology, whose maximum dimensions may not respect predominantly axial growth and whose margins

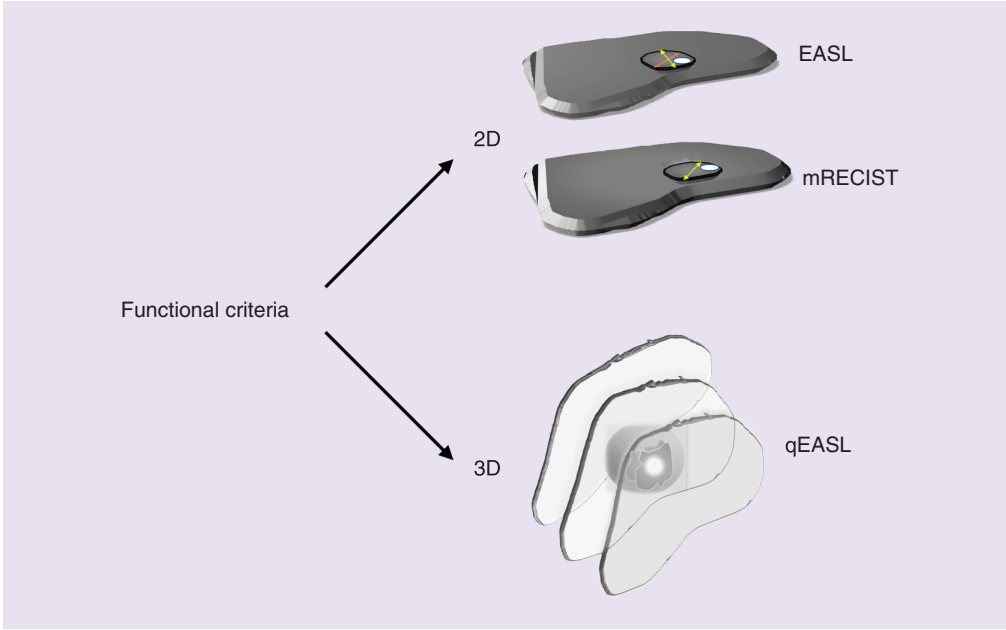

Figure 1. Diagram showing principal functional approaches.
EASL: European Association for Study of the Liver; mRECIST: Modified Response Evaluation Criteria in Solid Tumor; qEASL: Quantitative European Association for Study of the Liver.

may be challenging to define [8,13]; furthermore, these simple dimension-based criteria lack of sensitivity when applied to newer treatment paradigms whose mechanisms differ from traditional cytotoxic agents, and may not result in an immediate decrease of tumor size, despite efficacy on a molecular or cellular scale. This efficacy may not be translated into immediate lesions shrinkage, such as may be seen with immune infiltrate during a late response to pharmacologic immunotherapy [8,14–16]. This is also the case of infrared (IR) therapies that induce necrosis inside target lesions, without necessarily leading to any change of overall lesion size. Indeed, evidence shows that responding tumors may be dimensionally stable or even initially increase due to a combination of necrosis, hemorrhage, fibrosis or immunocyte infiltrate [17,18]. Therefore, this lack of correlation between size and tumor response after IR local and regional therapies has challenged radiologists to find new criteria to assess such responses after IR treatments or novel pharmacologic approaches. The goal of this review is to summarize and describe the different strategies seeking to provide reliable imaging biomarkers in order to better predict survival and to stratify HCC responses after IR therapies. New techniques currently in development are also described.

Different approaches are illustrated in Figure 1.

Functional criteria: from size to function

2D criteria

European Association for Study of the Liver criteria: a new concept: quantifying viable tissue

Developed in 2000, the European Association for Study of the Liver (EASL) criteria represent the first effort to establish the response of HCC to locoregional treatments on the basis of a functional approach [19]. Indeed, the EASL committee emphasized that a consistent assessment of the response requires distinguishing viable tumor tissue from adjacent necrosis caused by the procedure [19]. EASL determines response according to changes induced in the residual viable tissue rather than the dimensional modifications of the entire treated lesion, which often includes fully treated and untreated residual sectors [19].

Considering the hypervascular profile of HCC, the EASL criteria defined viable tumor tissue as the arterially enhancing tissue within the treated nodule. The viable EASL response is evaluated by bidimensional measurements (i.e., two perpendicular diameters) of the viable tissue, with subsequent categorization of those changes that is similar to the WHO categorization (Figure 1) [19].

According to the EASL criteria, local response to treatment is determined as follows (Table 1): complete response (CR): complete disappearance of enhancing tissue in target lesion(s); partial response (PR): ≥50% decrease in sum

Table 1. Response in target lesion: modified Response Evaluation Criteria in Solid Tumors versus European Association for Study of the Liver versus quantitative European Association for Study of the Liver.

Response category	mRECIST	EASL	qEASL
CR	Disappearance of any intratumoral arterial enhancement in all target lesions	Disappearance of all known disease and no new lesions determined by two observations not less than 4 weeks apart	Total disappearance of all known target lesions
PR	At least a 30% decrease in the sum of unidimensional diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions	At least 50% reduction in total tumor load of all measurable lesions determined by two observations not less than 4 weeks apart	At least 65% reduction in enhanced tumor volume after treatment
SD	Any cases that do not qualify for either PR or PD	Any cases that do not qualify for either PR or PD	Any cases that do not qualify for either PR or PD
PD	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started	At least 25% increase in size of one or more measurable lesions or the appearance of new lesions	At least 73% increase in enhanced tumor volume after treatment

CR: Complete response; EASL: European Association for Study of the Liver; mRECIST: Modified response evaluation criteria in solid tumor; PD: Progressive disease; PR: Partial response; qEASL: Quantitative European Association for Study of the Liver; SD: Stable disease.

of arterial enhancing area; stable disease (ST): does not qualify for CR/PR or progressive disease (PD); PD: ≥25% increase in sum of arterial enhancing area or appearance of new lesion(s) [8].

The role of EASL criteria in HCC response assessment was explored by a number of studies. Forner *et al.* [15] compared the accuracy of RECIST and EASL in 55 patients with HCC treated with locoregional therapies; this study showed that RECIST criteria (compared with EASL) underestimate CR's and PR's because therapeutic tumor necrosis may be measured as active tumor with RECIST.

EASL response criteria has a rational foundation, and as one might expect, EASL more consistently predicts survival following locoregional therapy of hepatocellular carcinoma using multivariate analysis [20].

Consideration of enhancement patterns and volumes may be the most predictive imaging criteria for response evaluation after chemoembolization in a study of 332 patients with intermediate stage HCC and Child–Pugh A cirrhosis HCC [21].

Despite these promising results, applying EASL criteria can have some practical limitations. The most important is the lack of guidelines regarding the choice of the target lesions (number and size of measurable lesions), which can be source of low inter-reader agreement or even bias, if readers subconsciously try to fit criteria to specific preselected lesions. Moreover, like WHO guidelines, EASL criteria are based on the multiplication and summation of diameters that can affect the reproducibility as well [22,23].

Modified RECIST: combining EASL with RECIST 1.1

In 2010, a panel of experts convened by American Association for the Study of Liver Diseases presented mRECIST criteria, incorporating the assessment of residual viable tumor on the basis of EASL criteria in a more updated RECIST framework. The rationale of this method was to simplify and unify the response assessment, providing a common and reproducible outcomes metric for the design of clinical trials in HCC [18].

In this scenario, the mRECIST guidelines define methods for image acquisition, target lesion selection and target lesion response to therapy [24]. Whether the patient is studied with contrast-enhanced computed tomography (CT) or with contrast-enhanced MRI, at the minimum a dual vascular phase study of the liver is required [18] with thin, contiguous slices specifically for multidetector CT.

Selection of target lesions is based on the same scheme of RECIST 1.1 guidelines, as detailed in Table 2. An intrahepatic target lesion should show arterial phase hyperenhancement with contrast-enhanced multiphasic CT or MRI, measure at least 1 cm in the arterial phase in at least one dimension, have well-defined margins and be suitable for repeated measurements [18]. It is important to measure the viable tumor on CT or MRI arterial phase to maximize the contrast definition between viable enhancing tumor tissue and avascular necrotic tissue. In addition, mRECIST recommends measurement of only the single largest diameter of the viable tumor component, avoiding any major intervention-related areas of necrosis (Figures 2 & 3) [18].

Table 2. Modified response evaluation criteria in solid tumor criteria.

Target lesion	Nontarget lesion	New lesions
• Nodular (clear boundaries, noninfiltrating) • Measurement of the arterial enhancing compartment on CT or MRI • Longest arterial enhancing diameter at least 1 cm • Extrahepatic or nonarterial enhancing lesions follow RECIST 1.1 • Two per organ, five in total	• All other tumor related lesions, enhancing or not • Portal vein neoplastic thrombosis • Porta hepatis lymph nodes with short axis ≥2 cm	• New arterial enhancing hepatic lesion ≥1 cm • New extrahepatic lesion ≥1 cm or new not porta hepatis lymph node ≥1.5 cm or new porta hepatis lymph node with short axis ≥2 cm • New or progredient pleural effusion or ascites (only if confirmed by cytological examination)

A new lesion <1 cm is followed-up. Once it reaches the diameter of 1 cm, a new lesion triggering progressive disease can be diagnosed. Time point of progressive disease is the point of first appearance of equivocal new lesion.
CT: Computed tomography; RECIST: Response Evaluation Criteria in Solid Tumor.

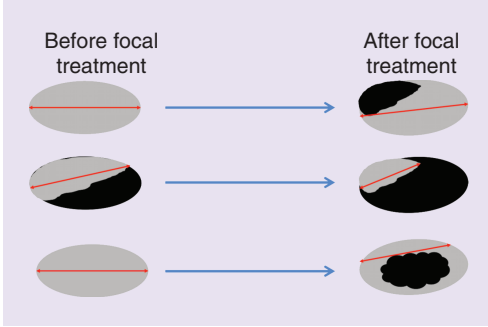

Figure 2. Visual example of measurements according to modified Response Evaluation Criteria in Solid Tumor. In black the treated necrotic area; in light gray the viable arterial enhancing tissue.

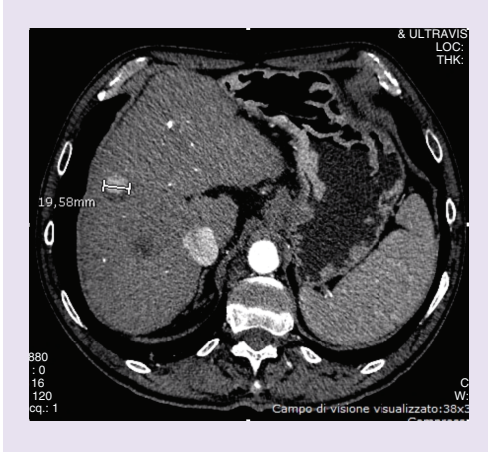

Figure 3. Computed tomography showing a viable tissue adjacent to a nonenhancing embolized lesion. Example of measurement according to modified Response Evaluation Criteria in Solid Tumor.

All extrahepatic lesions should be measured according to RECIST 1.1 criteria, beside portal hepatic lymph nodes that need a short axis diameter larger than 20 mm to meet target lesion criteria. Additionally, it is defined that atypical, nonenhancing HCCs should be measured by conventional RECIST 1.1. criteria [18].

As in RECIST 1.1 criteria, the maximum permitted number of target lesions is five in total and two for each organ. All other lesions are classified as nontarget (Table 2). mRECIST system also confirms that 'border-line' lesions, as poorly marginated, infiltrative HCC or malignant portal vein thrombosis should be labeled as nontarget due to the difficulty in performing reproducible measurements. Furthermore, it strongly suggests cytological confirmation of the neoplastic nature of any effusion that appears or worsens during treatment since its presence can change the response. Hydrodissection or sympathetic effusions are not specifically addressed. At last, in contrast with RECIST 1.1 guidelines, perihilar lymph nodes are considered malignant if the short axis is at least 20 mm, not 15 mm as before since benign lymphadenopathy is a relatively common finding in patients with cirrhosis even without HCC [18].

In the mRECIST system, CR is achieved when any intratumoral arterial enhancement in all target lesions disappears. The PR is at least a 30% decrease in the sum of diameters of viable target lesions, taking as reference the baseline sum of the diameters of target lesions. The PD is 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 target lesions recorded since the treatment started. The SD includes any cases that do not qualify for either partial response or PD (Table 1).

Since their introduction, mRECIST criteria have become the gold standard in the evaluation of HCC response [25]. Indeed, despite originally conceived to measure response in localized treatments (TACE and local ablation) [25], mRECIST are used to measure response in systemic therapy as well [25]. Several studies have demonstrated supremacy of functional criteria compared with previous size-based systems. A total of 332 consecutive patients with intermediate stage HCC who underwent TACE were analyzed, and intermodel agreement among different guidelines (WHO, RECIST, EASL, mRECIST) was examined [21]. The k-values of comparisons among WHO, RECIST and mRECIST guidelines were less than 0.20, whereas the k-value for the comparison of EASL and mRECIST guidelines was 0.94 [21]. Both EASL and mRECIST had the best correlation with survival prediction [21]. Functional criteria were independent predictors of overall survival and could be helpful in predicting long-term survival in HCC patients treated with TACE, which is reflected in multiple studies [26–28]. Notably, Prajapati *et al.* evaluated a cohort of 120 patients with HCC treated with DEB-TACE and concluded that mRECIST system has the best survival correlation [29].

Although practical, mRECIST has several limitations in assessing HCC response to therapy: first of all, subjectivity or potential for bias in the target lesion choice and also the lack of provision for the fact that in the same patient may have both treated and untreated tumors.

Second, it is logical that using the smallest sum of diameters recorded on imaging might introduce bias in favor of studies that sample (image) less frequently since the 'nadir' in shrinkage may be missed. Thus, the baseline comparison may be less accurate or rigid.

Moreover, mRECIST criteria, as well as EASL, base the viability assessment only on the arterial enhancement, which may underestimate the residual disease burden when considering nonenhancing HCCs, or the HCC that is more defined on nonarterial phases. It should be also considered that the arterial enhancement depends a lot of contrast injection parameters (concentration, volume, injection rate, injection location), scanner settings (kV, mAs) and patient cardiac output. Finally, no guidelines to face equivocal cases (such as the distinction between post-treatment inflammation and viable tissue) are provided [30,31].

LI-RADS: standardizing the response assessment

First introduced by the American College of Radiology in 2011, the Liver Imaging Reporting and Data Systems (LI-RADS) [32] is an extensive approach to categorize and assess residual or recurrent malignancy, including after locoregional therapies. Specifying response criteria with definitions, examples and a precise algorithm, LI-RADS guidelines are designed to standardize the response assessment and improve communication within HCC multidisciplinary teams, both for clinical practice and clinical trials [32].

According to LI-RADS algorithm, interpreting radiologists should first assess whether a treatment-related observation is evaluable or not. If evaluation is not possible due to image degradation or lack of multiphasic imaging, the radiologist should categorize it as LR-TR nonevaluable [32].

If the treated observation is evaluable, the radiologist should assign one of three available treatment response categories:

- LI-RADS treatment response (LR-TR) nonviable, when treated lesion shows complete lack of enhancement or expected treatment-specific enhancement patterns, such as a thin rim of hyperenhancement around the treated nonviable tumor which is occasionally seen after embolization or ablation.
- LR-TR viable, when the treated lesion shows features of viability as a nodular, masslike or thick irregular tissue in or along lesion margins, with any of the following features: arterial phase hyperenhancement or washout appearance or enhancement similar to pretreatment (Figure 4);
- LR-TR equivocal, when the radiologist is unsure about the assessment of tumor viability after treatment, and the observation do not clearly belong to LR-TR viable or LR-TR nonviable category. An example is the early post-treatment setting after transarterial radioembolization, in which the tumor may show residual enhancement and the differentiation between viable and nonviable tumor is not possible [33].

For categories LR-TR viable and LR-TR equivocal, the radiologist's report should include the size of the treated observation, measuring the longest diameter of the enhancing area without crossing intervening areas of nonenhancing tumor, consistent with mRECIST [34].

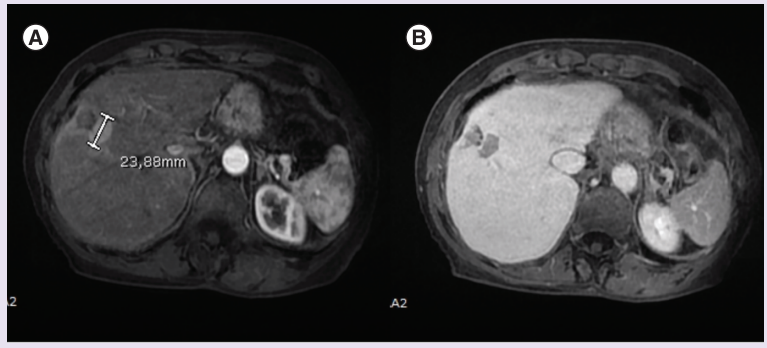

Figure 4. Example of Liver Imaging Reporting and Data Systems treatment response assessment. MRI showing a tissue adjacent to a thermal ablated lesion featured by arterial phase iperenhencement **(A)** and delayed phase wash-out appareance **(B)**, meeting the criteria for Liver Imaging Reporting and Data Systems treatment response viable.

Whenever available, pretreatment LI-RADS category or biopsy result should be included in radiologist report in order to estimate the percent response [32].

Measures of residual viable tumor influence transplant eligibility both in the case of locoregional therapy used as a bridge to transplant and in the setting of downstaging to achieve candidacy. However, LI-RADS specifies that radiologic viability is not necessarily coherent with pathologic viability, as imaging is not sensitive to microscopic or small foci of residual tumor [32].

Therefore, the combination of the assigned LI-RADS category and clinical assessment findings (such as aFP changes) is recommended to define optimal management of patient. It is suggested to repeat imaging with the same modality every 3 months for treated observations assigned to category LR-TR nonevaluable, LR-TR nonviable or LR-TR equivocal, whereas the decision to retreat or to perform alternative treatments in case of LR-TR viable category should be made on the basis of a tumor board or multidisciplinary discussion [32].

Moving from mRECIST, LI-RADS criteria reflect atypical HCC enhancement patterns, increasing the sensitivity for the detection of residual disease. Moreover, it assigns guidelines for follow-up in equivocal cases to ensure the optimum management of the patient.

Nevertheless, it should be noted that LI-RADS provides guidelines only to identify the viable tissue and not to classify its changes over time. An integration of LI-RADS with mRECIST could be thus necessary for the best response evaluation over time.

RECICL: the Japanese strategy

The aforementioned criteria represent the standard for the evaluation of the response of HCC in western countries. However, other methods have been suggested in other part of the world. Published for the first time in 1994 by The Liver Cancer Study Group of Japan, The Response Evaluation Criteria in Cancer of the Liver (RECICL), with their latest 2015 revision, are the reference methods for the HCC response assessment in Japan [35,36].

As described in the 2004 edition, RECICL are meant to be: simple and sufficiently applicable in daily clinical practice; internationally acceptable; primarily for locoregional treatments also applicable in radiation therapy and systemic chemotherapy as additional treatment methods; useful for the separable assessment of target lesions and overall response; and compliant with the sixth edition of the General Rules for the Clinical and Pathological Study of Primary Liver Cancer. Liver Cancer Study Group of Japan [37].

According to the latest edition of RECICL criteria, the evaluation of the response should consider the history of the liver cancer and previous treatments. Concerning the evaluation of HCC at the time of treatment initiation, the sixth edition of the General Rules for the Clinical and Pathological Study of Primary Liver Cancer (edited by Liver Cancer Study Group of Japan) recommend that the following information are detailed: tumor location; tumor size, number and presence of vascular invasion; macroscopic classification; tumor stage, according to the TNM classification, also if based on imaging only histological classification or differentiation [38]. Present treatment details and aFP levels should be also be considered.

Table 3. Treatment response of target lesions, 2015 Response Evaluation Criteria in Cancer of the Liver Edition.

Treatment effect categories	Criteria
TE4	Tumor necrosis of 100 or 100% reduction in tumor size
TE4a	Necrotized area larger than an original tumor (enough ablative margin)
TE4b	Necrotized area similar in size to an original tumor (insufficient ablative margin)
TE3	Tumor necrosis of 50–100% or 50–100% reduction in tumor size
TE2	Effect other than TE3 or TE1
TE1	Tumor enlargement of >50%

TE: Treatment effect.
Adapted with permission from [36] (2006).

Table 4. Overall response, 2015 Response Evaluation Criteria in Cancer of the Liver Edition.

Target lesions	Nontarget lesions	New lesions	Overall response
TE4	TE4	No	CR
TE4	TE3, TE2	No	PR
TE3	Non-TE1	No	PR
TE2	Non-TE1	No	SD
TE1	Any	Yes or no	PD
Any	TE1	Yes or no	PD
Any	Any	Yes	PD

CR: Complete response; PD: Progressive disease; PR: Partial response; SD: Stable disease; TE: Treatment effect.
Adapted with permission from [36] (2016).

The radiological assessment of the response should include the evaluation of every targeted nodule and an overall evaluation of the response odds ratio (OR) [36].

The evaluation of the treatment effect (TE) must be performed on every target nodule according to the criteria detailed in Table 3. RECICL criteria, as well as mRECIST, are functional criteria and therefore imply the differentiation between the residual tumor and the necrosis induced by the treatment. Alike EASL and mRECIST, this distinction is based on the arterial enhancement which distinguishes the vascularized tumor from the nonenhancing necrosis. Notably, the unstained region and the region of Lipiodol accumulation without wash-out are both regarded as necrotized regions. Both the necrotic and viable tissue should be measured to assess the ratio between these components [36]. The measurement evaluation is carried out in a bidirectional way, assessing the cross-sectional area of the tumor by multiplying the major axis of the maximum cross-section and the maximum diameter crossing the major axis at a right angle.

Both intra- and extrahepatic lesions are evaluated: two lesions per organ and a maximum of five lesions in total are designated as target lesions. If three or more intrahepatic lesions present, a maximum of three lesions should be counted as target lesions [36].

Regarding timing of evaluation, the optimal choice is 1–3 months after completion of ablation therapy and/or TACE. In chemotherapy regimens (including hepatic arterial infusion), treatment response should be assessed 1–3 months after the first administration of the anticancer agent and should be repeated every 1–3 months. Concerning radiation therapy, the evaluation is based on the best response that can be observed during the subsequent 6 months after treatment's start [36].

In 2015 version, OR evaluation has been amended to fit also the systemic therapy and radiotherapy using the criteria summarized in Table 4. The OR evaluation should be carried out at the optimal time point, considering TE of both intrahepatic and extrahepatic disease and the duration of TE, based on the four-grade system: CR, PD, PR and SD. The presence of new nodules should also be estimated. A new nodule should be defined by a typical enhancement pattern according to dynamic CT, dynamic MRI and contrast-enhanced US. Both intra- and extrahepatic new lesions should measure at least 10 mm and a lymph node with a minor axis of 15 mm is considered as metastatic [36].

However, considering that HCC is often a multicentric tumor, where different lesions represent independent nodules, the RECICL committee specifies that new nodules arising after IR focal treatments may not always

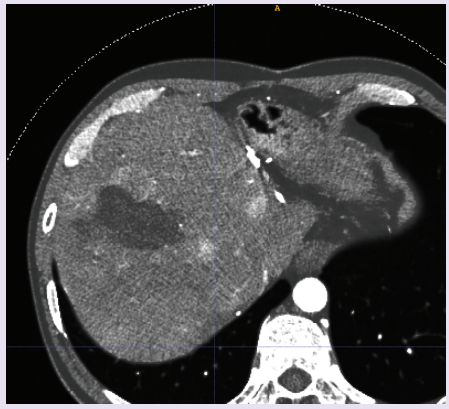

Figure 5. Viable tissue surrounding an ablated lesion in patient with multifocal hepatocellular carcinoma. Note the poor defined margins and the heterogeneous/patchy enhancement.

signify PD, and thus failure of the therapy. Therefore, RECICL criteria require to specify whether the new lesions is localized inside or outside a treated area since only unequivocally new lesions in the untreated area trigger progress [36].

The peculiarity of RECICL is that, conversely to western criteria, it benefits from the integration with clinical information such as biochemical biomarkers levels. Bidimensional measurements suffer from a lack of reproducibility, as previously stated for EASL, regardless of the rules for the choice of the diameters.

3D criteria

qEASL: from surface to volume

Introducing the concept of viable tissue, functional 2D criteria improved upon limitations of simple anatomic size-based criteria. Functional 2D criteria provide a more reproducible prediction of the response in HCC, when compared with RECIST or WHO [18,21,26].

Nevertheless, this bidimensional approach also has some drawbacks. First of all, the viable tissue is measured on a single axial slice, which is assumed to be representative of the entire tumor. This approximation implies the assumption that IR treatments induce homogeneous changes inside the target lesions, but this is not always true, especially when considering embolotherapies. Indeed, intra-arterial treatments lead to inhomogeneous necrosis as the result of an unequal distribution and embolization of the feeding vessels inside the HCC nodules. There is also an assumption that these changes will be best visualized on axial images instead of MPR [39].

Thus, in this scenario, the choice of the most representative slice turns to be a subjective process, which is hampered by a high inter- and intraobserver variability [40–42]. Moreover, the visual assessment of the viable tissue can be impossible when the tumor heterogeneity is represented by fragmentary contrast enhancement, which is irreducible to a single measurement (Figure 5) [43].

Proposed for the first time in 2012 [39], the quantitative EASL (qEASL) are 3D functional criteria that employ a volumetric quantification of the enhancing viable tissue to assess the response in HCC patients (Figure 1).

Namely, the viable tissue is computed tracing volumes of interest (VOIs) around the target lesions and identifying the voxels that enhance more than normal parenchyma in the arterial phase [39,43,44]: the sum of these enhancing voxels defines the viable tissue and can be expressed both as a volume (cm^3) or a percentage (%) of the total tumor volume.

To simplify and unify the response evaluation metrics, qEASL% criteria derive their cut-off values by converting the 20 and 30% diameter thresholds currently employed with RECIST and mRECIST into volume%'s (this is possible adopting the formula $V = 4/3pr^3$, where V is the volume, r is the radius and p is the mathematical constant signifying the ratio of the circumference to its diameter) [45]. Therefore, CR is defined as total disappearance of all known target lesions; PR as at least 65% reduction in enhanced tumor volume after treatment; PD as at least 73% increase in enhanced tumor volume after treatment and SD as any cases that do not qualify for either PR or PD (Table 1).

Although initially conceived only for MR imaging [39,43], qEASL has been shown to be a feasible method when applied to multiphasic CT as well [44].

Quantification of enhancing voxels is automated with postprocessing software. Thus, qEASL might theoretically enable a more accurate and earlier detection of residual disease, when this is too heterogeneous or too small to be visually identified, but this has not been validated [43].

Furthermore, the use of VOIs allows extension of the analysis to the entire tumor, avoiding sampling errors and reflecting the real distribution of the neoplasia, as confirmed by radiopathologic studies [46].

These benefits of qEASL might theoretically increase accuracy and reproducibility when compared with EASL and mRECIST, providing an earlier and more reliable radiologic biomarker to better stratify the responses in HCC patients [43,44]. Notably, 3D segmentation criteria can be successfully used also to predict the response after cTACE with CT scans, using subtraction techniques to differentiate between Lipiodol and enhancing tissue [44]. Thus, qEASL may find an application also in the assessment of the response after DEB-TACE with LUMI beads.

However, qEASL has some major limitations. First, qEASL requires a process of segmentation which can be time consuming, preventing practical clinical use. Semiautomatic segmentation software might improve workflow, efficiency and reproducibility [43,44]. The practical application of qEASL in the evaluation of the response of advanced or infiltrative HCC remains uncertain. Widespread tumor infiltration in advanced HCCs may preclude segmentation or volumetric analysis [47]. In addition, undifferentiated HCCs do not necessarily exhibit an arterial phase hyperenhancement, which can result in the underestimation of the progression, using qEASL criteria [48].

Future perspective

Texture analysis: beyond the ability of the eyes

In recent years interest in quantitative imaging is growing, particularly for the evaluation of tumors and cancer response to therapy. This reflects the necessity of having a personalized therapy always more customized to the specific tumor and patient, as well as a desire to derive models and automated rules from 'big data' via deep learning, machine learning, artificial intelligence and computer-assisted diagnosis.

Tissues are heterogeneous on the gross and cellular levels, but this heterogeneity is difficult to recognize with traditional imaging tools and often with the naked eye. Computed-tomography texture analysis (CTTA) may be a potentially useful tool that allows assessment and quantification of tumor spatial heterogeneity, and has shown a potential benefit in a variety of solid tumor [49].

Texture analysis, through statistical-, model- and transformation-based methods, analyzes the distribution and relationship of pixel or voxel gray levels in the image in terms of heterogeneity, mean gray level intensity, average, standard deviation, skewness and entropy, thus providing an objective, quantitative assessment of tumor characteristics. To perform CTTA postprocessing software or coded approach is needed [49].

To date, CTTA is mostly used in oncology imaging, for a variety of purposes: differentiate benign from malignant lesions, evaluate the lesion texture heterogeneity with the goal to personalize the treatment choice depending on the tumor behavior; for instance, Li *et al.* [50] in a study of 130 large HCCs (>5 cm), CT textural features showed positive and negative correlations with survival after liver resection and TACE, respectively. Texture analysis demonstrated the feasibility of using HCC patient stratification for determining the suitability of a specific choice of treatment.

A growing field in CTTA application is the evaluation of the association between the changes in texture parameters and therapy response after local or systemic cancer treatment. A modification in tumor heterogeneity (either increased or decreased) may be correlated with treatment response and prognosis/outcome in some scenarios [49]. Regarding HCC, a few studies have investigated the particular application of CTTA as an adjunct to conventional imaging interpretation.

Kloth *et al.* in 2017 [51] enrolled 28 patients with 56 typical HCCs who underwent DEB-TACE within 48 h after contrast-enhanced CT. The CTTA was subsequently performed and the results were compared with mRECIST and perfusion CT, which were used as a standard of reference. Certain CTTA-derived parameters were used both for prediction of response of HCC to DEB-TACE and for therapy monitoring. In particular, uniformity of skewness in the arterial phase and uniformity of heterogeneity in the portal-venous phase proved to be good predictors for CR.

Fu *et al.* in 2017 [52] explored the potential of texture analysis for appropriate patient selection and prognosis in 261 advanced HCCs with indication to TACE and sorafenib combination treatment. The study was conducted in two steps: first, texture analysis was tested as a prognostic coefficient in HCC patients treated with TACE; second, specific textural parameters were correlated with survival after combination therapy, as a prelude to selection of patients suitable for combination therapy. Their conclusion is that texture analysis is a promising tool in

appropriately selecting patients for TACE and sorafenib combination treatment; in particular patients with specific quantitative characteristics (Gabor-1-90 [filter 0] ≤3.8190 or wavelet-2-D [filter 1.5] ≤6.7515) appear to be most likely to obtain survival benefit from the combination therapy.

In conclusion, CTTA has shown promise in lesion characterization, pretreatment tumor assessment and response evaluation in HCC, but more studies are needed to confirm these findings and to establish a specific and useful protocol of application. The main benefit of CTTA is to overcome the visual assessment limitations by providing information from the acquired data that would be otherwise inaccessible without a mathematical method [49]. This extracted information enables a deeper characterization of the tissue, that hopefully better approaches pathology accuracy.

Moreover, the concept of heterogeneity is suitable to describe all sort of tumors, potentially surmounting the restriction imposed by the assessment of the contrast enhancement requirement, which is often absent in undifferentiated HCC [48].

Machine learning: the future

Machine learning is a term to describe a subfield of AI that allows computers to learn or build models with minimum interventions or input by a human [53]. Among the different techniques that fall under the machine learning umbrella, deep learning has emerged as one of the most promising applications for medical image analysis [54,55], such as in differentiation of chest diseases [56,57], detection in mammography [58,59], diagnosis of brain and psychiatric disease [60,61], identification of genetic markers in glioblastoma [62] and prediction of survival in women with cervical cancer [63] and in patients with amyotrophic lateral sclerosis [64].

This exciting approach incorporates computational models and algorithms that use convolutional neural networks (CNNs) to decode imaging raw data, ideally without the need for manual detection of specific features [54,65–67]. In deep learning, neural networks are composed of several convolutional layers, in which images are processed with several types of filter, that are known to be effective for pattern recognition of images [68]. Whereas conventional deep learning algorithms usually require input and manual labeling and extraction of features from images, in advance of 'learning', application of unsupervised CNNs allows the image itself to be used during the learning process [69]. Deep learning with CNNs achieved reliable performance in the pattern recognition of images [70,71], and it has the potential to evaluate the imaging biomarkers to stratify HCC responses after IR therapies without depending on the experience of the radiologist.

As we discussed above, the volumetric measurements are potentially a more accurate method for HCC monitoring, compared with the 2D measurements methods [11].

However, true volumetric measurements require manual delineation, which is time consuming and user dependent [72]. In the last decade, deep learning has been used for liver tumor segmentation in CT examination, but in the first studies manual crafting of the classification feature was required. Freiman *et al.* [73] describe a support vector machine classifier that automatically generates seeds for graph-based segmentation, whereas Zhou *et al.* [74] presented a semiautomatic method to extract the tumor contour on an initial CT slice that uses an support vector machine (SVM) classifier from randomly selected samples in a user-defined region of interest.

In 2015, Li *et al.* [75] described a stand-alone liver tumor segmentation method that uses a seven-layer CNNs. The CNNs have recently become a method of choice for AI in medical image processing [72].

Several recent studies show a tumor segmentation tool or task that could replace the time-consuming and nonreproducible manual segmentation [76,77]. The main assumption of these studies is that the baseline scan with the tumor delineation can be used as a patient-specific model to facilitate tumor segmentation in the follow-up examination [72]. The accuracy and robustness of the different measures of the tumor's volume considerably improve when the patient-specific baseline tumor segmentation was used.

One of the current limitations of these deep learning methods is that they require vast quantities of high-quality, labeled, ground-truth datasets of medical images to build models and learn how to detect abnormalities, and these datasets may be challenging, costly and time consuming to anonymize, sort, classify and label them [16–19].

Very recently, Abajian *et al.* [78] used MRI and clinical patient data as an input data to create an CNNs for the prediction of therapeutic outcomes of TACE treatment in 36 patients with HCC. This study predicted TACE's response with an overall accuracy of 78% (sensitivity 62.5%, specificity 82.1%, positive predictive value 50.0%, negative predictive value 88.5%), demonstrating that TACE outcomes in patients with HCC may be predicted preprocedurally by combining clinical patient data and baseline MRI with the use of deep learning methods.

Conclusion

Functional 2D criteria, especially mRECIST, represent the gold standard for the assessment of HCC response after IR therapies, given their simplicity and their reproducibility. Nevertheless, these criteria have multiple limits that hamper their implementation and practicality for complex cases. More advanced strategies, such as qEASL and texture analysis, can surmount these limitations with the help of postprocessing software that enable the extraction of data that are not visually assessable. Deep learning may evolve as a useful tool to overcome human interpreter limitations and provide surrogate imaging biomarkers for histology, susceptibility to specific therapies or outcomes. These exciting new methods await further development, refinement and validation with large cohort studies. Imaging is certainly a noninvasive window into the disease process, but we have only just begun to appreciate the potential utility and derived applications for the myriad of big data information obtained on a routine basis with modern imaging. As we move toward more efficient functional 3D interpretations and automated labeling and model building based on AI, we collectively search for deeper understanding of ways to better interpret this vast imaging data.

Summary points

- Interventional radiology procedures are valuable treatment options for many hepatocellular carcinomas that are not amenable to resection or transplantation.
- Accurate assessment of the efficacy of therapies at earlier stages enables completion of treatment, optimal follow-up and to prevent potentially unnecessary treatments, side effects and costly failure.
- Simple dimension-based criteria lack of sensitivity when applied to newer treatment paradigms (such as infrared therapies) that, differently from traditional cytotoxic agents, may not result in an immediate decrease of tumor size, despite efficacy on a molecular or cellular scale.
- Functional 2D criteria represent the current standard for the assessment of the response of hepatocellular carcinomas to IR therapies. Despite the differences, all functional 2D criteria (European Association for Study of the Liver, Modified Response Evaluation Criteria in Solid Tumor, Liver Imaging Reporting and Data Systems and Response Evaluation Criteria in Cancer of the Liver) are centered on the identification 'viable tissue' on the basis of a specific arterial enhancing pattern and the measurement of its size on 2D images.
- Functional 3D criteria employ a volumetric quantification of the arterial enhancing viable tissue to assess the response in hepatocellular carcinoma patients. Quantitative EASL potentially provide more reproducible than 2D criteria overcoming the sampling error by segmenting the entire lesion volumes and identifying the enhancing tissue voxels on segmented volumes of interests using postprocessing software.
- Texture analysis and machine learning are promising techniques that use advanced software to characterize voxel properties, otherwise precluded to human eye. They may allow an accurate identification and quantification of residual tissue also in equivocal, atypical and difficult cases.

Authors' contributions

BJ Wood and F Patella contributed in conception and design. BJ Wood helped in administrative support. All authors contributed in provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript.

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