Published in final edited form as:
Expert Rev Anticancer Ther. 2015 February ; 15(2): 199–205. doi:10.1586/14737140.2015.978861.

Assessing tumor response after loco-regional liver cancer therapies: the role of 3D MRI

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Abstract

Assessing the tumor response of liver cancer lesions after intraarterial therapies is of major clinical interest. Over the last two decades, tumor response criteria have come a long way from purely size-based, anatomic methods such as the Response Evaluation Criteria in Solid Tumors towards more functional, enhancement- and diffusion-based parameters with a strong emphasis on MRI as the ultimate imaging modality. However, the relatively low reproducibility of those one- and 2D techniques (modified Response Evaluation Criteria in Solid Tumors and the European Association for the Study of the Liver criteria) provided the rationale for the development of new, 3D quantitative assessment techniques. This review will summarize and compare the existing methodologies used for 3D quantitative tumor analysis and provide an overview of the published clinical evidence for the benefits of 3D quantitative tumor response assessment techniques.

Keywords

3D; ADC; intraarterial therapy; liver cancer; MRI; qEASL; quantitative imaging; RECIST; tumor response

Liver cancer represents a growing public health problem worldwide. With more than 800,000 newly diagnosed cases per year, hepatocellular carcinoma (HCC) is the most commonly diagnosed primary liver cancer, with rising incidences in Europe and the US [1]. Alongside HCC, liver metastases can be seen as one of the most challenging oncologic conditions and ultimately become the determining factor for quality of life and overall survival in patients with colorectal, neuroendocrine and breast cancer as well as other primary neoplasms [2,3]. Over the last two decades, catheter-based, intra-arterial therapies,

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Financial & competing interests disclosure

JF Geschwind is a consultant for Biocompatibles/BTG, Bayer HealthCare, Guerbet, Nordion/BTG, Philips Healthcare and Jennerex. He has received Grant Support from Biocompatibles/BTG, Bayer HealthCare, Philips Medical, Nordion/BTG, Threshold, Guerbet, DOD, NCI-ECOG and NIH-R01. He is also the founder and CEO of PreScience Labs, LLC. M Lin is an employee of Phillips Research North America. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

such as transarterial chemoembolization (TACE), have become the mainstay of palliative or salvage therapy in most of these patients [4]. Those therapies are meanwhile incorporated into the most commonly used staging systems for liver cancer and are furthermore officially included into treatment guidelines [4,5].

The role of MR imaging for diagnosis and post-procedural evaluation of treatment response cannot be overestimated [6]. As such, imaging-based reporting of tumor response can fulfill a dual role. On the one hand, response rates can be used as an indicator of therapeutic efficacy in prospective clinical trials as well as retrospective analyses, thus identifying potential benefits of one or the other technique. On the other hand, tumor response can also be seen as a surrogate marker for therapeutic efficacy in individual patients, which can then be translated into clinical treatment recommendations for non-responders [7]. Over the last decade, several assessment techniques were developed in order to achieve the goal of comparable, reproducible and clinically meaningful tumor response evaluation. Most intra-arterial therapies involve the element of embolization of tumor-feeding arteries, thus causing tissue necrosis without immediate effects on the overall lesion size. This mechanism limits the value of anatomic, nonfunctional measurements such as the Response Evaluation Criteria in Solid Tumors (RECIST). Additionally, there are considerable limitations of all 1D and 2D assessment techniques (e.g., modified (m) RECIST and European Association for the Study of the Liver [EASL]) including their limited reproducibility as well as their inability to evaluate the entire lesion. From a pathological standpoint, these surrogate markers of tumor response are inevitably inaccurate in predicting the true extent of the mostly heterogeneously distributed, necrotic tumor tissue [8–10]. The recent advent of novel segmentation algorithms has brought about a new generation of 3D quantitative image analysis techniques, capable of finally providing a volumetric assessment of tumor response. These new approaches were designed under the premise of finally achieving a reproducible, biologically accurate and clinically practicable whole tumor analysis, which would then replace the most commonly used, subjective response assessment methods.

In this review, we will summarize and compare the existing methodologies used for 3D quantitative tumor analysis. We will discuss the principles of tumor segmentation and provide the rationale for image registration prior to discussing the role of MR sequences that are being used for the functional analysis of tumor characteristics. Finally, we will provide an overview of the published clinical evidence for the benefits of 3D quantitative tumor response assessment techniques.

Tumor segmentation

The ability to volumetrically segment a liver lesion in a workflow-efficient and pathologically accurate manner is of critical importance for clinically successful implementation of 3D quantitative tumor assessment techniques. In the past, manual segmentation techniques have been frequently used for study purposes; however, the time-consuming process of a slice-by-slice segmentation is clinically impracticable. The advent and expansion of powerful Digital Imaging and Communications in Medicine data analysis software has allowed for the introduction of workflow-efficient, semi- and fully-automated tumor segmentation algorithms. Currently, several competing concepts with different

degrees of user–software interaction are being proposed. The automated systems require only minimal user–system interaction and define tumor borders using a 'random walker' algorithm [11,12]. This image segmentation technique is based on the manual placement of a small number of seed points along tumor margins that can then be used for the fully-automated extraction of tumor edges for the entire lesion. Other techniques are based on seed-growing algorithms and require the user to select a region of defined signal intensity by placing the seed point in the center of the lesion. This step is followed by a fully-automated identification of neighboring voxels with comparable signal intensity. The final extent of the segmentation can then be manually corrected by the user [13]. An alternative approach in software-assisted tumor segmentation uses non-Euclidean geometry and theory of radial basis functions for a semiautomated segmentation of objects with straight edges and corners [14]. This fully interactive process allows the user to define an initial control point and to expand the volume in 3D by dragging it to the boundary of the tumor. This system permits user input and corrections at all steps of the process. The main benefit of the fully or largely automated approaches is their workflow efficiency. However, these systems may be anatomically less accurate compared to the semi-automated systems that offer full user control over the segmentation process. An additional benefit of the semiautomated techniques is their universal applicability across different MRI sequences as well as other cross-sectional modalities [15,16]. Importantly, these systems have been pathologically validated and were shown to offer a high inter-observer agreement [17]. However, until today, neither one of the systems was recommended as gold standard. Figure 1 provides, in step-wise fashion, the semiautomated workflow of 3D tumor segmentation.

Image registration

A 3D quantification of most functional tumor parameters, such as the extent of tissue diffusion or contrast enhancement, requires multiple MRI sequences for an accurate computation of the respective value (e.g., upon image subtraction) [18]. As such, an anatomically accurate co-registration of different MRI sequences (e.g., native and contrast-enhanced T1 sequence) represents a technical precondition that must be fulfilled prior to quantifying the signal in a voxel-by-voxel fashion. Currently, there are two fundamentally different approaches, the non-deformable or rigid and the deformable or non-rigid algorithm [10,19]. The rigid approach uses anatomic landmarks/structures such as bones, blood vessels or internal organs as markers in order to align two Digital Imaging and Communications in Medicine matrices by translation and rotation and without deforming individual voxel shape or size [20]. The benefit of this technique lies in the anatomic accuracy with regard to the measured tissue volumes. However, the respiration cycle dependence as well as the high deformability of the liver makes this organ highly susceptible to potential changes in its shape both between different sequences of a single study and even more so between two different studies. The non-rigid approach addresses this concern through deformation/warping of the 3D image matrix in order to achieve an anatomically fitting overlay between two different datasets, which may potentially cause volumetric inaccuracy [19]. Similar to the segmentation techniques, both automated and semi-automated image registration algorithms exist, and further research is warranted that would compare the accuracy of the different registration instruments with the goal of defining potential recommendations.

MR sequence selection

The bulk of available clinical data on regional characterization of liver tumors with 3D quantitative MRI focuses on contrast-enhanced T1 or diffusion-weighted MR sequences [11,14]. The rationale for the use of multi-phasic contrast-enhanced MRI in HCC is based on the diagnostic recommendations for these typically hyper-vascular lesions, which show conspicuity on the arterial-phase and washout on the delayed-phase T1 images [21,22]. Accordingly, the use of lesion enhancement as a marker for tumor response after intra-arterial therapy has been established for mRE-CIST and EASL guidelines [22,23]. In addition, there is clear evidence for the good radiological–pathological correlation between the presumably viable tumor described as contrast enhancement on 3D quantitative MRI and the pathologically estimated necrosis in tumor explants [8,15]. As for secondary liver cancers, both contrast-enhanced and diffusion-based 3D quantitative imaging were demonstrated as feasible in the analysis of tumor response after intra-arterial therapy [24,25]. Specifically, apparent diffusion coefficient (ADC) maps have been used for the assessment of regional changes in tumor tissue in a variety of non-HCC liver cancers such as neuroendocrine tumors, cholangiocarcinoma and islet cell tumors [25–27]. While offering significant benefits in patients with contraindications for intravenous MR contrast application, there are some disadvantages to the use of ADC maps, resulting in its low clinical adoption. These limitations include that the diffusion-based quantification techniques cannot be translated or directly compared with other cross-sectional modalities, such as contrast-enhanced computed tomography or intra-procedural cone-beam computed tomography. When compared to T1 sequences, ADC maps show a lower signal-to-noise ratio and have a lower spatial resolution [28]. These characteristics can become a significant limitation when outlining tumor contours during segmentation and are even more problematic in smaller tumors where volumetric changes of the viable volume after intra-arterial therapies is subtle [29]. In addition, ADC values measured in focal liver lesions are known to be highly dependent on the liver lobe localization and the selected b-values [30]. In fact, most existing works on 3D quantitative assessment of tumor response with ADC maps used a deformable inter-study registration algorithm that may technically lead to volumetric miscalculation. Ultimately, clinical decisions on the choice of the sequence or their combinations should remain in the hands of the radiological reader. Therefore, the ideal 3D quantification device should allow for the reader to choose both contrast-enhanced and diffusion-weighted MR imaging for analysis.

Clinical evidence

Hepatocellular carcinoma

One of the first attempts to use software-assisted 3D quantitative evaluation of MRI signal in HCC tumors after TACE was carried out in a population of 48 patients with a total of 71 lesions, which were treated within a single institution. A fully-automated image registration algorithm was used to co-register T1-weighted, T2-weighted and diffusion-weighted sequences for each pre- and post-treatment study. The authors used the first post-procedural MRI, acquired within 1 month after TACE, in order to segment the lesions using the ‘random walker’ technique. After the segmentation, the datasets were used for a voxel-wise

calculation of the relative volumetric changes in ADC values as well as venous enhancement after TACE. The resulting values were then correlated with tumor response according to RECIST and mRECIST, which was calculated using the late follow-up imaging, acquired 6 months after treatment. As a result, the authors identified a strong correlation between early 3D quantification of tumor response with RECIST and mRECIST response. The authors concluded that 3D quantitative assessment of functional parameters (diffusion and enhancement) may represent an early predictor of tumor response [11]. Although most diagnostic techniques utilize the arterial phase of the contrast-enhanced MRI in order to assess HCC tumor necrosis, the authors did not explain their decision to use the portal-venous phase for 3D assessment. This study was followed up by a publication from another group that presented a different approach in 3D quantitative tumor analysis of HCC lesions after TACE. A total of 20 prospectively recruited patients with HCC underwent drug-eluting beads-TACE and were included into the study collective. For all analyzed patients, both baseline and the follow-up MR images were used for an individual intra-study analysis without inter-study registration. The authors used a semi-automated segmentation technique on arterial-phase contrast-enhanced MRI. Upon segmentation, an image subtraction step was performed to remove the background enhancement (native T1) from the arterial-phase MRI. Subsequently, the authors used a region-of-interest, placed in extra-tumoral liver tissue, in order to define the threshold for true contrast enhancement within the tumor. The volumetric quantification of the enhancing tumor volume was then used for the assessment of tumor response and referred to as quantitative (q) EASL. Importantly, this study was the first to establish the workflow efficiency of 3D quantitative tumor analysis and estimated the median 3D segmentation time to be as short as 65 seconds per patient [14]. An additional validation step for the qEASL technique has been recently made available through a radiological–pathological correlation study. In this study, a total of 17 patients with HCC, who were treated with conventional or drug-eluting beads-TACE prior to surgical tumor removal (resection or liver transplantation), were analyzed using the qEASL algorithm. As a result, the correlation between pathological tumor necrosis and the 3D quantitative estimate on the last preoperative MRI was very strong and even surpassed the manual assessment done by radiologists [15]. A true breakthrough for the clinical role of 3D quantitative assessment of tumor response was achieved by a recently published two-part validation study. In the first part of this study, a large single-institution analysis included a total of 143 patients, who were randomly divided into a training and validation dataset. Volumetric tumor changes after TACE were assessed using both ADC maps and contrast-enhanced MRI by applying an automated segmentation and quantification algorithm. The ideal cutoff values for the definition of tumor response were identified using a split-group cross-validation approach. As a result, patients with a 65% decrease in volumetric enhancement and those with a 23% increase of the ADC value were classified as responders [31]. In the second part of this study, the authors used the identical dataset for a comparison of the volumetric techniques with the current, clinically used RECIST, mRECIST and EASL techniques to stratify between responders and non-responders. Importantly, Kaplan–Meier analysis of overall survival for responders and non-responders identified both volumetric techniques as superior to the concurrent imaging response criteria [32]. This result is encouraging and must be seen in context with other studies on the role of 3D quantitative

response assessment, which can be now considered as technically fully validated in patients with HCC.

Cholangiocarcinoma & liver metastases

The growing role of intra-arterial therapies in unresectable cholangiocarcinoma and metastatic liver disease as well as the inability of conventional techniques such as mRECIST and EASL to correctly assess tumor response provided the rationale for the use of 3D quantitative techniques. In a retrospective analysis in 29 patients with unresectable cholangiocarcinoma, the authors used ADC maps in order to calculate the volumetric functional mean changes after TACE. Again, an automated segmentation technique was used upon inter-study registration prior to performing a voxel-wise analysis of the tumor tissue. The authors were able to assess all tumors using the whole-tumor 3D technique; however, they noted that conventional analysis using mRECIST and EASL was impossible in one-third of the collective due to inhomogeneous enhancement pattern. As a result, patients with a volumetric increase of the ADC signal above 45% were shown to have a favorable response and a longer overall survival after TACE [26]. This study exemplified the benefits of volumetric whole-tumor analysis in non-HCC lesions and has demonstrated superiority over non-3D techniques. As for secondary liver tumors, several studies that explore the role of 3D tumor response quantification have been made available. For instance, a study on neuroendocrine liver metastases was conducted in a total of 71 patients who were treated with conventional TACE (n = 41), Yttrium 90 radioembolization (n = 11) or drug-eluting beads-TACE (n = 19). The authors used automated index lesion segmentation in order to analyze the changes in functional tumor parameters on the follow-up MRI 1 month after intra-arterial therapy. As a result, the authors identified that diffusion-weighted and contrast-enhanced MRI, both in the arterial and in the portal-venous phase, were feasible for 3D quantitative characterization of tumor response. However, the authors deviated from previously published volumetric thresholds for the prediction of survival benefits in patients who responded to intra-arterial therapy [25]. The use of the qEASL technique for the assessment of metastatic liver disease was recently presented for melanoma lesions. This single-institution study included a total of 15 patients into the analysis and performed the analysis using arterial-phase contrast-enhanced MRI. The authors emphasized the particular benefit of the qEASL algorithm that included the subtraction of the native T1 sequence from the contrast-enhanced MRI. This step isolated the true extent of the contrast uptake in the frequently hyperintense native T1 background due to melanin accumulation and provided an accurate, volumetric quantification of the signal before and after TACE. The authors extrapolated the volumetric threshold of 65% signal reduction from the RECIST guideline by using the formula for the volume of a sphere in order to define patients as responders. As a result, patients who were classified as responders demonstrated a significantly higher median overall survival according to qEASL, while no stratification was achieved when using mRE-CIST or EASL [24]. Figure 2 illustrates the use of 1D, 2D and the recently introduced 3D assessment techniques. In addition to the present results, many other studies are underway to establish and further validate the new criteria in patients with metastatic liver cancer.

Expert commentary

In conclusion, there is growing evidence in support of the clinical use of 3D quantitative tumor assessment for diagnostic and follow-up purposes in liver cancer patients treated with loco-regional therapies. The main benefit of the 3D analysis over existing techniques lies in its ability to provide a whole, complete tumor assessment which, without a doubt, is pathologically more accurate and representative. The introduction of reliable and workflow-efficient tumor segmentation algorithms has facilitated the dissemination of these novel assessment approaches; however, the need for dedicated software remains to be the most significant obstacle to a more ubiquitous use of those systems. The available clinical data strongly support the advantages of 3D quantitative tumor analysis over non-3D techniques for the assessment of tumor response. 3D systems are capable of identifying and isolating true responders from those patients who would profit from additional loco-regional tumor therapy. However, the bulk of the data has been generated using retrospective databases. While statistically convincing, no clinical validation within a prospective, randomized trial has been presented until today. A major drawback continues to be the necessity of dedicated software that would allow for a dissemination of these techniques beyond academic institutions. However, it can be expected that the overwhelming evidence in support of 3D tools will ultimately foster the dissemination beyond tertiary care centers.

Five-year-view

The next generation of 3D quantification tools will have to master several challenges. These systems should be designed as fully translatable across cross-sectional imaging modalities, especially in light of the growing role of 3D quantitative intra-procedural imaging and its potential as a predictor of short-term response [33]. There is a clear need for a consensus on volumetric thresholds that will be used to define tumor response in individual patients. As for the validation of these systems, it can be expected that only radio-pathologically validated systems will be fully accepted for everyday clinical use, and more studies in this regard can be anticipated. The final verdict on the choice of MR sequence as well as the extent of system–reader interaction is yet to be delivered and will mostly be defined by both individual preferences, clinical evidence and clinical availability of the required software. However, it is likely that more 3D systems will be used in the future and it will be up to the community of diagnostic and interventional radiologists to define and renew the recommendations for 3D imaging in order to achieve reliable and comparable data.

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•• of considerable interest

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Key issues

- 3D quantitative MR image analysis plays an important role in the assessment of tumor response after loco-regional, intra-arterial therapies of liver cancer.
- 3D tumor assessment techniques are more reproducible and accurate as compared to conventional methods such as Response Evaluation Criteria in Solid Tumors, modified Response Evaluation Criteria in Solid Tumors and European Association for the study of the liver.
- Modern tumor segmentation tools allow for improved clinical workflow efficiency.
- Fully-automated segmentation algorithms require minimal user input, yet may be less accurate compared to semi-automated systems.
- Image registration is a key element for intra- and inter-study tumor analysis.
- The use of contrast-enhanced T1 sequences may facilitate a more reproducible and accurate 3D tumor analysis compared to the apparent diffusion coefficient maps.
- Full technical, clinical and radiological–pathological validation exists in support of 3D tumor analysis after intra-arterial therapies of hepatocellular carcinoma.
- Several clinical studies provided relevant evidence in support of 3D quantitative imaging after intra-arterial therapies of metastatic liver cancer.
- Future studies should define volumetric thresholds for tumor response.

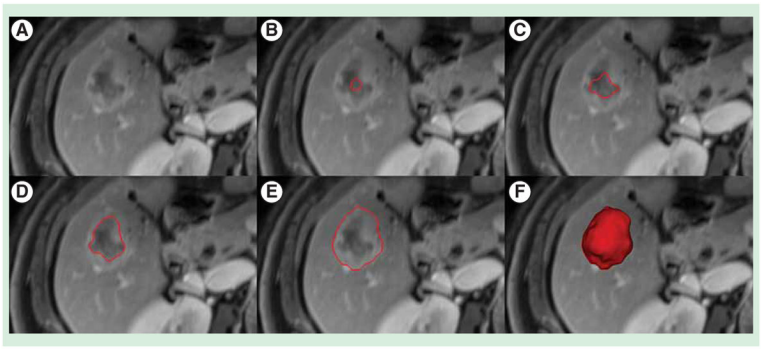

Figure 1. Segmentation

The figure illustrates a step-wise segmentation of a liver tumor. The baseline image **(A)** is a contrast-enhanced portal-venous phase T1 MRI. The lesion demonstrates central necrosis and rim enhancement. The semi-automated segmentation process starts from a central seed point **(B)**, which is being expanded **(C–E)** to include the entire lesion **(E)**. The segmentation results in a 3D mask which encompasses the entire tumor volume **(F)**.

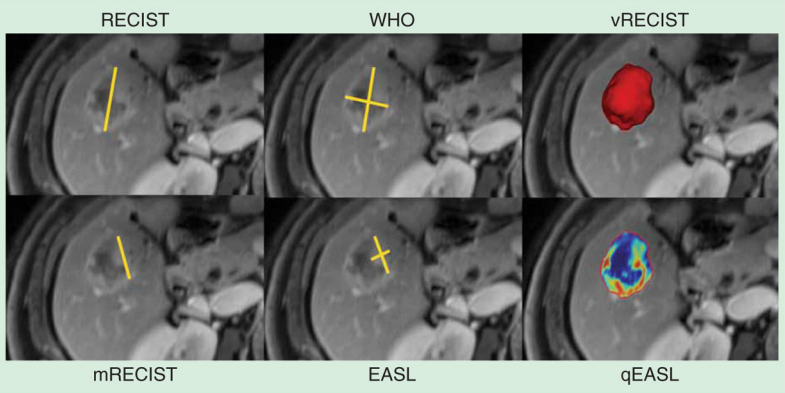

Figure 2. Comparison of tumor assessment techniques

This figure illustrates different techniques of tumor assessment. The upper row shows measurements of the overall tumor size (1D: Response Evaluation Criteria in Solid Tumors [RECIST], 2D: World Health Organization [WHO], 3D: volumetric Response Evaluation Criteria in Solid Tumors [vRECIST]). The lower row illustrates enhancement-based techniques (1D: modified Response Evaluation Criteria in Solid Tumors [mRECIST], 2D: European Association for the Study of the Liver [EASL], 3D: quantitative European Association for the Study of the Liver [qEASL]).