Assessment of Liver Tumor Response to Therapy: Role of Quantitative Imaging

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Quantitative imaging is the analysis of retrieved numeric data from images with the goal of reducing subjective assessment. It is an increasingly important radiologic tool to assess treatment response in oncology patients. Quantification of response to therapy depends on the tumor type and method of treatment. Anatomic imaging biomarkers that quantify liver tumor response to cytotoxic therapy are based on temporal change in the size of the tumors. Anatomic biomarkers have been incorporated into the World Health Organization criteria and the Response Evaluation Criteria in Solid Tumors (RECIST) versions 1.0 and 1.1. However, the development of novel therapies with different mechanisms of action, such as antiangiogenesis or radioembolization, has required new methods for measuring response to therapy. This need has led to development of tumor- or therapy-specific guidelines such as the Modified CT Response Evaluation (Choi) Criteria for gastrointestinal stromal tumors, the European Association for Study of the Liver (EASL) criteria, and modified RECIST for hepatocellular carcinoma, among many others. The authors review the current quantification criteria used in the evaluation of treatment response in liver tumors, summarizing their indications, advantages, and disadvantages, and discuss future directions with newer methods that have the potential for assessment of treatment response. Knowledge of these quantitative methods is important to facilitate pivotal communication between oncologists and radiologists about cancer treatment, with benefit ultimately accruing to the patient.

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Abbreviations: ADC = apparent diffusion coefficient, EASL = European Association for Study of the Liver, FDG = fluorine 18 fluorodeoxyglucose, PERCIST = Positron Emission Tomography Response Criteria in Solid Tumors, PET = positron emission tomography, RECICL = Response Evaluation Criteria in Cancer of the Liver, RECIST = Response Evaluation Criteria in Solid Tumors, ROI = region of interest, SUL = standardized uptake value corrected for lean body mass, SUV = standardized uptake value, TACE = transcatheter arterial chemoembolization, TARE = transcatheter arterial radioembolization, WHO = World Health Organization

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Introduction

Treatment options for hepatic malignancies include surgery, systemic chemotherapy, external beam radiation therapy, and interventional techniques. The therapy chosen depends on the tumor type, its stage, and many confounding clinical variables. When feasible and indicated, surgery is the preferred therapeutic method.

There has been substantial recent progress in nonsurgical therapeutic options for malignant primary and metastatic liver tumors. Systemic chemotherapy plays an important role in treatment of metastatic liver disease, but its role remains limited in the management of hepatocellular carcinoma (1). Molecular-directed chemotherapies for hepatic metastatic disease and advanced hepatocellular carcinoma target specific biologic pathways, such as angiogenesis, tumor metabolism, and tumor proliferation (2). On the other hand, locoregional therapies have the advantage of treating malignant liver tumors without the risk of potential side effects from systemic chemotherapies.

All these therapies, as stand alone or in combination, have created a new challenge for radiologists, who must assess the response of liver tumors to therapy. Whereas the goal of locoregional therapy is inducing necrosis, molecular-directed therapies interfere with tumor growth (3). Therefore, tumor shrinkage may not be apparent or may be absent with either method (3,4). In addition, hepatic malignancies may appear hyperenhanced or hypoenhanced relative to the normal parenchyma. Specific instructions regarding the best contrast material–enhanced phase to measure tumors are required to avoid variability in results. For example, hypervascular lesions such as hepatocellular carcinoma and hepatic metastases of neuroendocrine tumor should be measured in the arterial phase, whereas hepatic metastases of colorectal cancer must be measured in the portal venous phase.

During the costly and time-consuming steps of clinical trials to obtain regulatory approval of drugs and for the efficacy evaluation of locoregional therapies for hepatic malignancies, imaging biomarkers can provide reliable quantitative assessment of tumor treatment response by acting as surrogate endpoints to the traditional survival-based endpoints. Accurate evaluation of the efficacy of new therapies at earlier stages is crucial to avoid potential toxic reactions, unnecessary interventions, and costly failure (5).

The widely used anatomic imaging biomarkers are based on the cytotoxic effects of the chemotherapeutic agents and demonstrate a change in tumor size as a measure of tumor response.

However, for molecular-targeted and locoregional therapies, hepatic tumor physiologic factors such as angiogenesis, hypoxia, and cellular proliferation are more relevant for demonstrating tumor response and thus require the development of new functional imaging biomarkers.

This article reviews the quantification methods used for evaluating the treatment response of liver tumors, summarizing their applications as well as the advantages and disadvantages of each method. New imaging biomarkers currently in development are also discussed. These quantification methods are categorized based on the mechanism of therapy and tumor type (Fig 1).

Current Size-based Criteria

Objective assessment of tumor size is commonly used in clinical practice to determine the response of tumors to therapy. In clinical trials, objective response based on a change in tumor size may be translated to an earlier clinical endpoint, in substitution for overall survival (6). These imaging criteria are best suited for assessing tumor response to cytotoxic chemotherapies (7) and include the World Health Organization (WHO) criteria, Response Evaluation Criteria in Solid Tumors (RECIST) 1.0, and RECIST 1.1.

WHO Criteria

Created in 1979, the WHO criteria established an objective standard for identifying the response of a tumor to treatment that was based on clinical, radiologic, biochemical, or surgical-pathologic staging. The radiologic criteria are based on a bidimensional measurement that corresponds to the surface area approximation, which is calculated by multiplying the maximum diameter by its longest perpendicular diameter (Fig 2). When a patient has multiple lesions, the sum of the areas of all measured lesions must be calculated. The WHO criteria established four different categories for evaluating overall tumor response: complete response, partial response, stable disease, and progressive disease (which are classified by the percentage of change in the overall tumor burden) (8) (Table 1).
Figure 1. Current and evolving oncologic imaging biomarkers as they apply to assessment of treatment response. The anatomic criteria are based on tumor size reduction and are best applied for cytotoxic therapies. The functional criteria are based on specific tumors and therapy. Molecular criteria such as PERCIST are tumor dependent and apply to fluorodeoxyglucose (FDG)-avid cancers. Many evolving imaging biomarkers are being evaluated for specific tumors and treatment options and remain to be validated. DWI = diffusion-weighted imaging, EASL = European Association for Study of the Liver, irRC = Immune-related Response Criteria, MRE = magnetic resonance (MR) elastography, mRECIST = modified RECIST, MRS = MR spectroscopy, PERCIST = Positron Emission Tomography Response Criteria in Solid Tumors, RECICL = Response Evaluation Criteria in Cancer of the Liver, RECIST = Response Evaluation Criteria in Solid Tumors, WHO = World Health Organization.

Figure 2. High-grade sarcoma in a 63-year-old woman with a liver metastasis. Axial contrast-enhanced computed tomographic (CT) images show the difference between the WHO criteria (a) and RECIST (b). The WHO criteria are based on the sum of the areas (white cross) of all measured lesions; RECIST emphasizes the sum of the longest diameters (white line) of a limited number of target measurable lesions.
The WHO criteria gained wide acceptance among oncologists and were adopted as the standard method for evaluating tumor response in many oncologic trials (10). However, limitations of the criteria were recognized, and modifications to improve the reproducibility of measurements or to accommodate new technologies were required. Some of these limitations included (a) unspecified or unclear imaging methodology, (b) lack of a minimum size definition for measurable lesions, (c) unspecified maximum number of lesions to be measured in patients with multiple lesions, and (d) possibility of mathematical errors with multiplication and summation of lesion sizes for each patient (11,12).

Response Evaluation Criteria in Solid Tumors 1.0
In 2000, the WHO criteria were revised and RECIST version 1.0 was published (Table 1). To address the limitations of the WHO criteria, RECIST 1.0 specified the minimum size of target lesions to be greater than or equal to 1 cm, a criterion that thus minimizes “partial volume” effects seen on CT scans. A maximum of five target lesions per organ and 10 target lesions in each patient are measured (11). RECIST 1.0 uses the sum of the longest diameters of target measurable lesions based on a one-dimensional measurement (Fig 2). As is the case with tumors in other organs, the largest hepatic tumor may not always be the best target lesion because it may have poorly defined margins, which hamper the measurement and may affect accuracy and reproducibility of quantification (Fig 3). With the RECIST standard, the enhancing rim of a target lesion is included in the measurement.

Although RECIST 1.0 brought many advances and facilitated comparison of the results among clinical trials, some shortcomings persisted, including (a) the limit of 10 target lesions was set without scientific evidence or theoretical justification, (b) no parameters were defined for measuring response to cytostatic chemotherapies or locoregional therapy, and (c) guidelines for measuring lymph nodes were not defined (2,12–14).

Table 1
Evaluation of Overall Tumor Response According to the WHO, RECIST 1.0 and 1.1, Choi, and Immune-related Response Criteria

<table>
<thead>
<tr>
<th>Response Category</th>
<th>WHO Criteria*</th>
<th>RECIST 1.0 and 1.1</th>
<th>Choi Criteria</th>
<th>Immune-related Response Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>Disappearance of all lesions</td>
<td>Disappearance of all lesions. RECIST 1.1 added disappearance of pathologic lymph nodes</td>
<td>Disappearance of all lesions</td>
<td>Disappearance of all lesions</td>
</tr>
<tr>
<td>Partial response</td>
<td>≥50% decrease in sum of cross-product of target lesion(s)</td>
<td>≥30% decrease in sum of maximum diameter of target lesion(s)</td>
<td>Decrease in longest diameter ≥10% or in attenuation (HU) ≥15%. No new lesions and no obvious progression of immeasurable disease</td>
<td>≥50% decrease in tumor burden relative to baseline</td>
</tr>
<tr>
<td>Stable disease</td>
<td>Neither partial response nor progressive disease</td>
<td>Neither partial response nor progressive disease</td>
<td>Neither partial response nor progressive disease</td>
<td>Neither partial response nor progressive disease</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>&gt;25% increase in sum of cross-product of target lesion(s)</td>
<td>&gt;20% increase in sum of diameters. RECIST 1.1 added: must have at least 5-mm absolute increase in sum</td>
<td>Increase in longest diameter ≥10% without meeting tumor attenuation criteria for partial response. New lesions, new intratumoral nodules, or increase in size of existing intratumoral nodules</td>
<td>≥25% increase in tumor burden relative to nadir</td>
</tr>
</tbody>
</table>

Source.—Adapted, with permission, from reference 9.
Note.—For all categories except stable disease, confirmation studies are performed at least 4 weeks apart.
*Cross-product = longest diameter multiplied by longest perpendicular diameter.
Response Evaluation Criteria in Solid Tumors 1.1

In 2009, RECIST was revised to version 1.1 (14). The four categories of tumor response in RECIST 1.1 are summarized in Table 1. There are four major differences between RECIST versions 1.0 and 1.1 as they relate to liver tumors (14–16), summarized as follows.

1. The maximum number of target lesions per patient and per organ has been reduced to five and two, respectively (Fig 4).

2. Besides the 20% increase in the sum of the target lesions, classification of progressive disease now requires a 5-mm absolute increase in the sum of the longest diameters of the target lesions. This increase may prevent substantial errors in cases with small tumors.

3. A lymph node is now considered a measurable and possible target lesion if it measures more than 15 mm in the short axis. This expansion in the definition of a target lesion may be important in patients with hepatic malignancies who have periportal lymphadenopathy.

4. RECIST 1.1 includes molecular imaging by integrating the use of fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) in the assessment of new lesions. If a patient underwent a baseline FDG PET study with negative results and then new lesions appear in the most recent study, these lesions are classified as progressive disease. However, if a lesion is detected at FDG PET and the patient has no baseline study results, comparison with CT scans should be performed to determine the presence of progressive disease.

Figure 4. Multiple hepatic metastases from colorectal carcinoma in a 55-year-old man. Axial contrast-enhanced CT images illustrate the difference between tumor measurements with RECIST 1.0 (a) and RECIST 1.1 (b). In the RECIST 1.0 system (a), a maximum of 10 target lesions per patient are measured, with a maximum of five per organ. In the RECIST 1.1 system (b), a maximum of five target lesions per patient are measured, with a maximum of two per organ.
Locoregional therapies such as radiofrequency ablation, transcatheter arterial chemoembolization (TACE), and transcatheter arterial radioembolization (TARE) with yttrium 90 induce cell death or necrosis. Locoregional therapies may lead to stability of tumor size or even an increase in hepatic tumor size after therapy, a feature that limits the role of size-based criteria for assessing tumor response in this setting (4,18). Similarly, molecular-targeted therapies may not change hepatic tumor size because of alteration of cell growth signaling or may alter the morphology of the tumor by affecting tumor angiogenesis. For example, hepatic metastases of colorectal cancer that respond to bevacizumab, an antiangiogenic monoclonal antibody, will demonstrate homogeneous hypodensity with well-defined margins, but they may not decrease in size (19) (Fig 5).

**Figure 5.** Hepatic metastasis from colorectal cancer in a 62-year-old man. (a, b) Coronal contrast-enhanced CT images obtained before (a) and after (b) bevacizumab therapy demonstrate a slight decrease in lesion size and a morphologic change from a heterogeneous lesion with irregular borders to a homogeneous hypodensity mass with sharp margins. (c) Posttreatment coronal FDG PET/CT fused image illustrates the lack of metabolic activity in the hepatic metastasis.

RECIST 1.1 has some limitations. (a) It assumes, similar to WHO and RECIST 1.0, that all lesions are spherical and that they decrease or increase in size uniformly; however, it has been shown that liver tumors may not be spherical (17). (b) Necrotic tumors are considered immeasurable on the basis of RECIST 1.0 and 1.1. However, as described in the next section, with many new locoregional or systemic therapies, necrosis may indicate favorable tumor response. (c) As with its predecessors, RECIST 1.1 does not define the standard phase of contrast material enhancement for measuring specific tumors. This criterion may be important if the lesion is best seen during either the arterial or venous phase of enhancement (10,15,16).
To address these complexities in assessing the response of hepatic malignancies to therapy, quantitative functional criteria that are specific to tumor type and therapy have been developed. Examples include the Modified CT Response Evaluation Criteria for Gastrointestinal Stromal Tumors (Choi criteria), the European Association for Study of the Liver (EASL) guidelines, modified RECIST, and Response Evaluation Criteria in Cancer of the Liver (RECICL). Unlike anatomic imaging biomarkers, many functional imaging biomarkers demonstrate hepatic tumor response on the basis of tumor viability, which is assessed by measuring the residual enhancing tissue.

**Modified CT Response Evaluation Criteria (Choi Criteria)**

Advanced cases of gastrointestinal stromal tumor (GIST) had limited therapeutic options until the introduction of imatinib, a tyrosine kinase inhibitor, which affects tumor cell growth signaling and has improved the prognosis of patients with this tumor (20). Studies have shown that use of tumor size alone to assess tumor response in patients with advanced GIST who undergo imatinib therapy results in a significant underestimation, especially in the early stage of treatment (21,22).

In 2007, Choi et al (22) proposed new GIST-specific criteria that include evaluation of changes in CT attenuation in these lesions after imatinib therapy. They demonstrated good correlation between attenuation change seen at CT and tumor response seen at FDG PET. They also showed that some GIST lesions could even increase in size, despite clinical and FDG PET results, a finding that emphasizes the limitation of size-based criteria.

In applying the Choi criteria, the CT attenuation coefficient of the GIST lesion should be measured in a circular region of interest (ROI) during the portal venous phase of enhancement. Partial response is defined as a decrease in tumor attenuation greater than or equal to 15% or a decrease in the longest diameter of the tumor greater than or equal to 10%, compared with baseline measurements (Fig 6). The Choi criteria are summarized in Table 1.

Change in lesion attenuation similar to that described in the Choi criteria has been extrapolated to the assessment of tumor response in other cancers, such as colorectal cancer liver metastases treated with bevacizumab or TARE (19,23). A recent study of patients with colorectal cancer liver metastases treated with TARE correlated the decrease in attenuation in the metastases with their appearances at FDG PET and demonstrated that changes in CT attenuation at 1 month after therapy may predict tumor response, as shown with FDG PET (24).
A downside of evaluating tumor attenuation change is its dependence on manual placement of a ROI, which is subject to selection bias. A recent study, designed in response to that limitation, demonstrated that evaluation of the attenuation of the entire volume of a liver lesion (three-dimensional measurement) has less variability and better reproducibility than the two-dimensional ROI measurement (25).

**EASL Criteria**
Locoregional therapies for hepatocellular carcinoma have a role in palliative treatment for patients who are not candidates for resection, for stabilizing tumors in patients on the hepatic transplantation waiting list, and for downstaging tumors initially considered outside criteria for transplantation (26,27). Because locoregional therapies may increase tumor dimensions due to necrosis or hemorrhage, the role of tumor size quantification in assessing tumor response in this setting is limited (28). For example, a 5-mm safety zone in radiofrequency ablation will result in a larger treated lesion, compared with its size measured in the baseline study (29,30).

The EASL criteria were developed in 2000 to address these shortcomings in the follow-up of hepatocellular carcinoma response to locoregional therapies. Residual viable tumor tissue, defined as the arterially enhancing tissue within the treated hepatocellular carcinoma, is measured to assess treatment response. The EASL criteria use bidimensional measurements and categorize response similarly to the WHO guidelines (28) (Table 2) (Fig 7).

Forner et al (32) evaluated 55 patients with hepatocellular carcinoma treated with locoregional therapies and demonstrated that, when compared with EASL criteria, the RECIST system was not a valuable method for accurate assessment of tumor response. More recently, Memon et al (33) compared WHO and EASL criteria in the evaluation of response to locoregional therapies (TACE and TARE) in patients with hepatocellular carcinoma, and they concluded that survival could be predicted more consistently with EASL criteria than with WHO guidelines.

**Modified RECIST**
In 2010, a modified RECIST system was proposed (7). These new criteria incorporate assessment of residual viable tumor on the basis of the EASL criteria into the RECIST system, thus bringing quantification of tumor viability in synchrony with the RECIST method of measurement. Modified RECIST quantifies the longest diameter of the enhancing part of hepatocellular carcinoma, which is assessed in the arterial phase of CT or magnetic resonance (MR) imaging and measured to avoid any major areas of intervening necrosis (7) (Fig 7). Modified RECIST follows the same response categories as RECIST 1.1 (Table 2).
Two recent studies of patients with hepatocellular carcinoma treated with TACE have shown that use of modified RECIST and EASL criteria results in better intercriterion agreement and better prediction of long-term survival, compared with WHO guidelines and RECIST (34,35). Prajapati et al (36) compared EASL criteria and modified RECIST in a study of patients with unresectable hepatocellular carcinoma treated with TACE with drug-eluting beads and showed that use of modified RECIST had the most significant correlation with patient survival.

Modified RECIST has also shown good correlation with prognosis in patients with hepatocellular carcinoma treated with sorafenib (37). Edeline et al (38) compared RECIST and modified RECIST to evaluate response of hepatocellular carcinoma to sorafenib and found a significant difference in the distribution of responses, as assessed by RECIST and modified RECIST: 26.2% of the patients who were classified as having stable disease according to RECIST were reclassified as responding to treatment, according to the modified RECIST. To date, the role of modified RECIST for evaluating response of hepatic metastasis to therapy has not been well established.

A substantial limitation of all current criteria for quantifying liver tumor response to locoregional therapies is the lack of provision for the fact that different liver tumors in the same patient may be treated at different points. That is, the same patient may have both treated and untreated tumors.
Response Evaluation Criteria in Cancer of the Liver

RECICL, proposed by the Liver Cancer Study Group of Japan, addresses specific points pertinent to locoregional therapies and molecular-targeted therapies for hepatocellular carcinoma (31). RECICL quantifies tumor necrosis to determine the effects of treatment. However, unlike modified RECIST, RECICL also incorporates ablation margin into its categorization of treatment effects. Also, unlike other response criteria, RECICL provides specific recommendations about the timing of follow-up imaging on the basis of the type of therapy. For example, response is evaluated at 1 month after TACE but at 6 months after TARE. RECICL quantifies necrosis by using the cross-sectional area, and a dense accumulation of lipiodol is judged to be necrosis (39). In addition to imaging findings, RECICL includes tumor marker levels to predict prognosis (Table 2).

RECICL has yet to be validated as a surrogate endpoint in large randomized clinical trials.

Immune-related Response Criteria

In 2009, Immune-related Response Criteria were created to assess the response of metastatic melanoma to ipilimumab, but the system has been applied to other cancer immunotherapy trials (9). Ipilimumab is a monoclonal antibody that blocks cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), resulting in T-cell activation, proliferation, and lymphocyte infiltration into organ tissues and tumors, which eventually leads to tumor cell death. With immunotherapy, the size of the lesions may not change, despite positive therapeutic effects. Apparent initial increase in tumor burden may be present, a finding that is likely related to transient immune-cell infiltrate, edema, or continued growth of the tumor before sufficient immune response occurs. The sum of products of the largest perpendicular diameters is calculated, similar to the method used in the WHO guidelines. Up to five index lesions per organ and up to 10 index visceral lesions can be measured at baseline. At follow-up, new index lesions can be added to the overall tumor burden, limited to five new lesions per organ and up to 10 new visceral lesions. The minimum measurable size of each lesion is defined as $5 \times 5$ mm (Table 1). Confirmation by repeated imaging after 4 weeks is necessary when disease is not stable (Fig 8). More important, the presence of new lesions does not constitute progression.

Current Molecular Imaging Criteria

FDG PET is an imaging technique that allows evaluation of tumor metabolism in vivo (2). FDG uptake is objectively measured as standardized uptake value (SUV) in PET/CT and may correlate with tumor histologic characteristics, surgical stage, and prognosis (40). There is growing evidence regarding the importance of FDG PET in the evaluation of hepatic malignancies and their responses to different therapies (22,41,42) (Fig 9).
Figure 9. GIST in a 46-year-old man with multiple hepatic metastases treated with imatinib. (a, b) Pretreatment axial CT image (a) demonstrates multiple hepatic metastases that appear hypermetabolic in the FDG PET/CT image (b). (c, d) Axial CT image obtained at 8-month follow-up (c) shows a decrease in the number and size of the liver lesions, findings consistent with partial response. However, the correlative FDG PET/CT image (d) shows resolution of hypermetabolic liver lesions, indicative of complete response.

Positron Emission Tomography Response Criteria in Solid Tumors

PET Response Criteria in Solid Tumors (PERCIST) is a relatively new initiative that may serve as a useful tool for assessing treatment response in FDG-avid malignancies, particularly those treated with cytostatic therapies (43). PERCIST is based on the change of SUV measurement within the tumor and the assumption that it provides a reproducible and reliable quantification of tumor metabolism (43). To understand PERCIST, some preliminary concepts must be explained: (a) SUV should be measured within a 1-cm³ spherical ROI and be corrected for lean body mass (SUL); (b) there is limited detection of lesions smaller than 1.0 cm; (c) a minimum waiting time of 10 days is recommended after completion of the chemotherapy cycle, before imaging with FDG PET; (d) the patient’s serum glucose level should be measured before PET and must be less than 200 mg/dL; (e) the baseline PET scan should be obtained at 50–70 minutes after FDG injection, and the follow-up scan should be obtained within 15 minutes of the same time frame; and (f) tumor size should be 2 cm or greater in diameter for accurate measurement, although smaller lesions of sufficient FDG uptake can be assessed (43).

PERCIST adapts the RECIST 1.1 principles and measures the SUL peak in up to five index lesions (up to two per organ) with the highest FDG uptake. Response to therapy is expressed as a percentage change in SUL peak (or sum of the lesions’ SULs) between the pretreatment and posttreatment scans (43).
Although PERCIST can be used for the assessment of therapeutic response in FDG-avid hepatic metastasis, its role remains to be validated in prospective trials.

**Evolving Imaging Biomarkers**

Newer methods to assess tumor response based on volumetry, tumor vascularity, tumor cellularity, and tumor metabolism are evolving. However, they have not been validated by large clinical trials, and they lack standard quantitative criteria to

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**Figure 10.** Hepatocellular carcinoma in a 65-year-old man who underwent TARE, followed by TACE. (a, b) Axial CT images show a hepatic lesion with heterogeneous distribution of necrosis (*), ethiodized oil (arrow) and residual tumor (arrowhead) in the arterial phase (a), which demonstrates washout in the equilibrium phase (b). (c) Colorized map shows the distribution of viable tumor (pink), necrosis (orange), and ethiodized oil (blue). (d) Volumetric image illustrates the complex nonspherical shape of the whole lesion and its different components.

PERCIST classifies objective response in four categories: complete metabolic response, partial metabolic response, stable metabolic disease, and progressive metabolic disease. In summary, complete resolution of all FDG-avid lesions is required to classify the case as a complete metabolic response, a minimum reduction of 30% in the target measurable tumor FDG SUL peak represents partial metabolic response, and an increase greater than 30% represents progressive metabolic disease. Progressive metabolic disease can also be suggested by new FDG-avid lesions. Stable metabolic disease is used for lesions that do not satisfy criteria for partial metabolic response or progressive metabolic disease (43).
define progression of disease. Some examples of these newer methods include volumetric quantification of the whole tumor and necrotic component, diffusion-weighted imaging, tumor perfusion, MR spectroscopy, ultrasound (US) and MR elastography, and lesion growth kinetics.

Volumetric Quantification
All response criteria that measure the tumor uni- or bidimensionally presume that lesion diameter directly correlates with its volume. This assumption is based on the belief that tumors grow and shrink in a spherical manner, which is not accurate (44). Quantification by volumetry can be a more accurate reflection of the actual tumor size than uni- or bidimensional measurements (44) (Fig 10). Linear tumor measurement has also demonstrated more interobserver variation than volumetry in patients with hepatocellular carcinoma (45).

Advances in CT technology allow isotropic data acquisition with highly accurate and reproducible tumor volumetry (46). Semiautomated segmentation techniques use software algorithms to measure tumor volume after the user outlines the ROI. Use of volumetry, rather than uni- or bidimensional measurements, can modify classification of tumor response in up to one-third of patients (46,47). A recent study has shown the feasibility of volumetric tumor measurement as well as semiautomatic quantification of tumor enhancement (viable tissue) for hepatocellular carcinoma lesions after TACE (48). Volumetric quantification of hepatocellular carcinoma necrosis has been shown to be more reproducible than the EASL criteria (49) (Fig 11).

Figure 11. Hepatocellular carcinoma in a 51-year-old man who underwent 90Y radioembolization. (a) Pretreatment axial CT image in the late arterial phase shows an avidly enhanced hepatic lesion, with only small foci of nonenhancement. (b) On an axial CT image 1 month after treatment, the lesion area is heterogeneously enhanced, with large areas of necrosis (arrow) with intervening viable tumor tissue (arrowheads). There is no change in tumor size. (c, d) Axial images show significant change in the volume of necrosis (red area). The pretreatment necrosis volume was 0.49 mL (0.7% of the whole lesion) (c), but 1 month after treatment the necrosis volume increased to 18.3 mL (24.8% of the entire lesion) (d).
Figure 12. Hepatocellular carcinoma treated with $^{90}$Y radioembolization in a 73-year-old woman with a cirrhotic liver. (a, b) Axial MR image (a) and diffusion-weighted image (b) obtained before treatment demonstrate a hypervascular lesion (arrow) with a small amount of necrosis in segment VIII and no significant diffusion restriction evident with the diffusion-weighted sequence (b), with an ADC value of $1.0 \times 10^{-3}$ mm$^2$/sec. (c, d) Axial MR image (c) and diffusion-weighted image (d) obtained in the arterial phase 45 days after treatment demonstrate a decrease in lesion size (arrow) and new foci of necrosis. Increase in the ADC value to $1.6 \times 10^{-3}$ mm$^2$/sec suggests good tumor response (d).

Limitations of tumor volumetry include (a) lack of consensus regarding the criteria for assessing response on the basis of tumor volume; (b) it is still a time-consuming method, and (c) it requires specific software for accurate estimation of tumor volume (17,46,47).

**Diffusion-weighted Imaging of Liver Lesions**

Diffusion-weighted functional MR imaging, a technique that is based on a sensitivity to the water content in tissue and random Brownian motion of water molecules, has been helpful in liver tumor detection, tumor characterization, and monitoring response to treatment (2,50).

The apparent diffusion coefficient (ADC) value, a diffusion-weighted imaging parameter, has been correlated with the tumor proliferation index and tumor grade before therapy, as well as with the presence of necrosis and tumor cell apoptosis after successful treatment (51,52). Studies have shown a potential to characterize malignant lesions and to differentiate viable tissue from necrosis on the basis of ADC cut-off values, because necrosis has higher ADC values (53,54). For patients with hepatocellular carci-
noma treated with sorafenib, a transient decrease in tumor ADC value approximately 1 month after treatment has been reported to suggest hemorrhagic necrosis; however, a sustained decrease in ADC at 3-month follow-up may indicate viable tumor or tumor progression (55).

ADC values in patients with hepatocellular carcinoma treated with TARE have been shown to increase, a finding suggestive of cellular necrosis, and increased ADC values in such cases may be an early marker of treatment response before changes in tumor size are observed (56) (Fig 12). More recently, use of volumetric ADC measurements to assess response to locoregional therapies in patients with hepatic metastases of neuroendocrine tumor and cholangiocarcinoma has shown good correlation with prognosis (57).

Despite the increasing use of ADC values in clinical practice, reproducibility of volumetric quantification with diffusion-weighted imaging is not well established. ADC values can be affected by different sequence acquisition parameters, types of MR imaging systems, and the location and size of the tumor. Also, ADC values change nonlinearly over time, which may result in substantially different measurements when they are not obtained at the same time points among different patients (57,58).

Liver Tumor Perfusion
Because antiangiogenic drugs inhibit the proliferation of tumor vessels, evaluation of physiopathologic modifications in vascularity may provide a more appropriate method for monitoring effects of treatment (52). Assessment of perfusion parameters at CT and MR imaging provides information about tumor vascularity when dynamic contrast-enhanced techniques are used to analyze temporal changes in tissue enhancement (59).

A recent study of CT perfusion parameters in hepatic metastases of colorectal cancer treated with conventional chemotheraphy and antiangiogenic bevacizumab demonstrated direct correlation between higher capillary permeability and future treatment response (52). This effect could be related to a widely developed vascular network within responding lesions, which allows better distribution of drug molecules.

In patients with hepatocellular carcinoma successfully treated with TACE, CT perfusion imaging demonstrated substantial reductions in hepatic arterial fraction, hepatic arterial perfusion, and hepatic blood volume, findings that may predict treatment response (60). In MR imaging perfusion studies, hepatocellular carcinoma nodules treated with the multikinase inhibitor sorafenib showed a higher decrease in \( K_{trans} \), which represents the volume transfer constant between blood plasma and the extravascular extracellular space. This finding reflects a decrease in tumor permeability and correlates with longer progression-free survival and overall survival (61).

MR imaging perfusion parameters were also studied in 20 patients with hepatic metastases of neuroendocrine tumor treated with \(^{90}Y\)-labeled octreotide (62). Responsive hepatic metastases demonstrated lower baseline distribution volume and higher baseline arterial flow fraction, as well as significant increase in the liver distribution volume after therapy.

In a recent study, Messiou et al (63) compared CT and MR imaging perfusion parameters in the assessment of advanced solid tumors treated with antiangiogenic therapy. They found better reproducibility of dynamic contrast-enhanced MR imaging and showed that a reduction in perfusion parameters related to tumor response was evident as early as 7 days after treatment.

Widespread incorporation of perfusion as a biomarker has been hampered by inconsistencies in quantification results from different software and acquisition methods, as well as the time-intensive analysis of data (64,65). High radiation dose remains a potential limitation of using CT perfusion studies.

MR Spectroscopy
MR spectroscopy is a technique in which different metabolites and their relative concentration in tissue can be determined on the basis of chemical shift phenomenon. The spectrum is obtained within a voxel of the organ or ROI. The different metabolites are identified by their particular frequency or spectral position, which is expressed as a shift in the frequency relative to a standard. In hydrogen 1 MR spectroscopy, choline is a metabolite of particular interest because it is a measure of increased cellular turnover and is increased in tumors and inflammatory processes (66). Other metabolite peaks that may be assessed in \(^1\)H MR spectroscopy are those for creatinine and citrate.

In phosphorus 31 MR spectroscopy, important resonances include phosphomonoesters and phosphodiester. These represent a heterogeneous mixture of compounds that share a similar chemical
signature (ie, a phosphomono- or di-ester bond) but otherwise have diverse chemical structures and functions. In general, phosphomonoesters are associated with cell membrane synthesis and are increased in voxels that contain actively growing tumor, whereas phosphodiesters are associated with cell membrane breakdown and are increased during tumor necrosis (Fig 13). The ability of MR spectroscopy to measure and differentiate compounds related to cell turnover may allow detection of tumor response before a macroscopic change such as volume or size alteration can be seen (66).

In a study conducted with 3.0-T proton MR spectroscopy, Wu et al (67) demonstrated that hepatocellular carcinoma tended to have higher choline levels compared with those in uninvolved liver parenchyma. However, the choline-to-lipid ratio in tumors compared with that in the uninvolved liver did not reach statistically significant differences for clinical application. Use of proton MR spectroscopy to assess response of hepatocellular carcinoma after TACE has also been evaluated, and responsive tumors showed a decrease in the choline peak; thus, this biomarker may have potential prognostic value as an indicator of treatment efficacy. The absence of a constant internal reference for choline level remains a limitation, since the use of a relative ratio is necessary (67,68). Continued improved hardware and increased magnetic field strengths with optimization of sequences to reduce or eliminate motion and field heterogeneities are essential before MR spectroscopy can be incorporated in the routine quantitative imaging of liver tumors.
**Figure 14.** Dysplastic nodule in segment V of the liver in a 61-year-old man with cirrhosis. (a–c) T2-weighted MR image (a) demonstrates a slightly hypointense T2 signal within the dysplastic nodule (arrow), compared with a hyperintense signal on the T1-weighted image obtained before contrast material injection (b) and no arterial enhancement on the postcontrast image (c). (d) Axial image from MR elastography demonstrates that the dysplastic nodule has lower stiffness (green), compared with the adjacent cirrhotic liver parenchyma (red).

**US and MR Elastography**

In elastography, low-frequency mechanical waves are propagated, and the resulting tissue displacements are measured and used to evaluate shear or mechanical properties (69,70). This assessment provides additional information about the mechanical properties of hepatic masses that may help to differentiate malignant from benign hepatic lesions (71) (Fig 14). In a preliminary study that used MR elastography, malignant liver tumors demonstrated significantly higher stiffness than did benign tumors (72). US elastography in animal liver models demonstrated that ablated liver lesions are usually stiffer and that the stiffness of the lesions increases steadily with the duration of heating (72).

The ability of US and MR elastography to demonstrate response of liver tumors to treatment has not been assessed. Potential limitations include evaluation of a relatively “stiff” lesion such as
hepatocellular carcinoma in the setting of a “stiff” (cirrhotic) liver and lack of studies that demonstrate reproducibility of US and MR elastographic results in assessing tumor response to therapy.

Growth Kinetics
Quantification of tumor growth has been correlated with different tumor histologic characteristics, patient survival, and therapeutic effectiveness (73,74). Different formulas to assess growth kinetics are used: growth rate, percentage growth rate, specific growth rate, doubling time, and reciprocal doubling time. For all these formulas, two different tumor measurements and an interval time are required. Growth kinetics have been evaluated in lung, renal, and pancreatic tumors (73,75,76), among others. However, to our knowledge, there have been no comparable studies of these techniques for evaluating response of liver tumors.

Conclusions
Quantitative imaging allows robust evaluation of hepatic tumor response. In addition to size changes, various biologic and functional parameters can be quantified by using new imaging technologies. Measurement of these parameters is especially important for the evaluation of tumor response to novel targeted therapies, in which change in functional status sometimes precedes anatomic modification. Familiarization with these different biomarkers is important to facilitate pivotal communication between oncologists and radiologists with regard to patient cancer treatment.

References


Assessment of Liver Tumor Response to Therapy: Role of Quantitative Imaging

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The widely used anatomic imaging biomarkers are based on the cytotoxic effects of the chemotherapeutic agents and demonstrate a change in tumor size as a measure of tumor response.

Page 1782
However, for molecular-targeted and locoregional therapies, hepatic tumor physiologic factors such as angiogenesis, hypoxia, and cellular proliferation are more relevant for demonstrating tumor response and thus require the development of new functional imaging biomarkers.

Page 1785
The maximum number of target lesions per patient and per organ has been reduced to five and two, respectively.

Page 1786
Locoregional therapies may lead to stability of tumor size or even an increase in hepatic tumor size after therapy, a feature that limits the role of size-based criteria for assessing tumor response in this setting. Similarly, molecular-targeted therapies may not change hepatic tumor size because of alteration of cell growth signaling or may alter the morphology of the tumor by affecting tumor angiogenesis.

Page 1788
Modified RECIST quantifies the longest diameter of the enhancing part of hepatocellular carcinoma, which is assessed in the arterial phase of CT or MR imaging and measured to avoid any major areas of intervening necrosis.