



Beyond RECIST

Volumetric and Functional Tumor Analysis in Oncology Clinical Trials

Presented by Median Technologies, The Imaging Phenomics Company™

Contents

- 01 Introduction
- 02 Routine Versus Advanced Endpoints
- 04 Volume-Based Endpoints
- 10 Making Volumetric Tumor Measurements: The Nuts and Bolts
- 11 Adding Value to Clinical Trials: Are Volumetric Assessments a True Reflection of Drug Response?
- 12 Summary

The Median Technologies Team



Fredrik Brag

CEO, Chairman and Co-founder
fredrik.brag@mediantechnologies.com



Jeanne Hecht

Chief Operating Officer
jeanne.hecht@mediantechnologies.com



Nicholas Campbell

Chief Commercial Officer
nicholas.campbell@mediantechnologies.com

Medical imaging is an integral part of oncology clinical trial design due to its non-invasive nature and ability to detect biological and physiological phenomena. Traditionally, anatomical quantitative image analysis relied on linear measurements of tumor size. However, these unidimensional size measurements often fail to completely capture morphological and other physiological and metabolic changes that occur in response to treatment, particularly for today's new targeted cancer therapies. Volume-based measurements and functional imaging, which encompass the whole tumor and reflect physiological changes, can be used to make both morphological and functional measurements, and in certain instances, may allow clinicians to more accurately assess response. In this white paper, we describe several volume-based criteria and functional imaging, including dynamic contrast-enhanced MRI/CT and diffusion-weighted MRI.

Routine Versus Advanced Endpoints

Overall survival remains the gold standard for evaluating efficacy of cancer therapies in the clinical trial setting. However, in many cases, this is not practical for reasons of timing and cost. Imaging-based endpoints often serve as surrogates and are used to assess progression of disease or response to treatment through anatomical measurements of tumor size using standard CT or MRI. Tumor size measurements are linked to clinical outcomes using response criteria, which govern how and when measurements are made, the number of measurements to make, and the magnitude of change needed to conclude that disease progression or treatment response has occurred.

Today, most clinical trials involving solid tumors rely on Response Evaluation Criteria in Solid Tumors (RECIST), a set of response criteria that were originally introduced in 2000 and later revised in 2009 (RECIST 1.1) for the standardization of the evaluation and measurement of the impact of a drug therapy on a tumor. RECIST 1.1 is currently considered the gold standard for oncology trials that have tumor progression or objective response as endpoints. RECIST uses unidimensional measurements of longest diameter (except for lymph nodes, where the smallest axis is taken into account) in a defined number of lesions to classify patients as having a complete response, partial response, stable disease, or progressive disease. [Eisenhauer 2009] (See RECIST 1.1 at a Glance, Table 1) The technology and training required to make these simple linear measurements are widely available at clinical sites around the world. RECIST is well known to regulatory agencies and is required for phase 3 approval. [Goldmacher 2012; Mozley 2010]

RECIST Isn't Perfect

Although RECIST 1.1 endpoints are the most widely used criteria for evaluating tumor response, it also comes with significant challenges. The first is tumor shape. Not all tumors are spheres, and linear measurements may be particularly complicated for irregularly shaped or morphologically complex tumors. Once treatment begins, tumors may not expand or shrink uniformly; tumors often grow asymmetrically, with different areas changing at different rates. In such cases, overall volume may shrink, while longest diameter remains unchanged.

The RECIST criteria were traditionally used to evaluate efficacy of chemotherapies; however, in today's era of molecularly targeted therapies, an effective treatment may not shrink tumor size at all, but rather may trigger a cytostatic response or alter physiological properties such as angiogenesis, metabolism, or cell proliferation. With immunotherapies, treatment may result in tumor shrinkage that is preceded with an initial tumor enlargement, a state that would be classified as progressive disease using RECIST. The RECIST definition of stable disease is incredibly broad and may not be sensitive enough to detect small changes in tumor mass. A tumor size increase of up to 20% or a decrease of up to 30% can still be categorized as stable disease. [Goldmacher 2012]

RECIST1.1 at a glance

Lesion Measurement	Unidimensional
Baseline Lesion Size	= >10 mm
Baseline Lesion Number	5 lesions total, 2 per organ
Appearance of New Lesions	Always represents PD
Response	CR = complete disappearance of all lesions PR = >30% decrease in SoD SD = when neither PR nor PD can be established PD = >20% increase in SoD (minimum 5 mm)

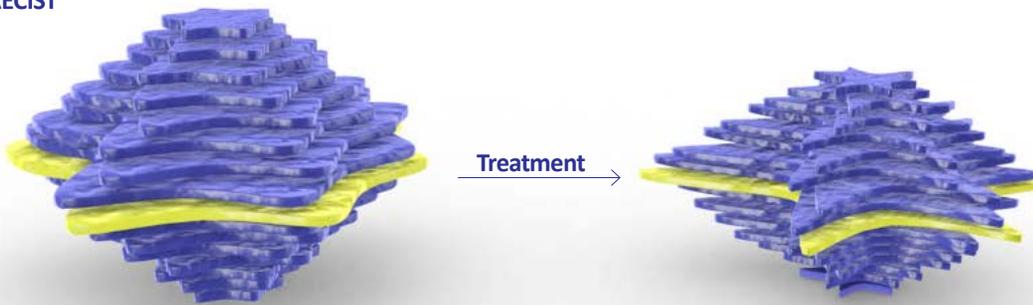
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; SoD = sum of diameters for all target lesions

Advanced Imaging and Experimental Endpoints

Advanced functional imaging methods have been developed to address the inherent limitations of RECIST and to provide additional measures of efficacy for modern drug classes. Functional changes often occur much earlier than morphological changes and thus can be used to detect early response to treatment. Many advanced imaging techniques, such as dynamic contrast-enhanced MRI, perfusion CT, and diffusion-weighted MRI, are considered to be experimental endpoints, as they have not completed the rigorous validation process needed to qualify as true surrogate endpoints. They have shown the potential to assess tumor response, but additional validation and standardization are necessary before they will be widely adopted. [Hayes 2016] As such, advanced imaging techniques often appear in early-phase trials or are performed as secondary measurements in conjunction with routine endpoints. Studies are currently underway to further examine the relationship between experimental endpoints and more traditional imaging measurements, and how experimental endpoints relate to clinical outcomes.

Herein we describe the method and use of 3-dimensional volume-based endpoints, such as volumetric CT, dynamic contrast-enhanced MRI, perfusion CT, and diffusion-weighted MRI. Volumetric endpoints offer increased sensitivity for linear anatomical measurements and provide physiological information necessary to interpret response to highly selective, targeted therapies, particularly in cases where RECIST falls short.

RECIST



Traditional measurements

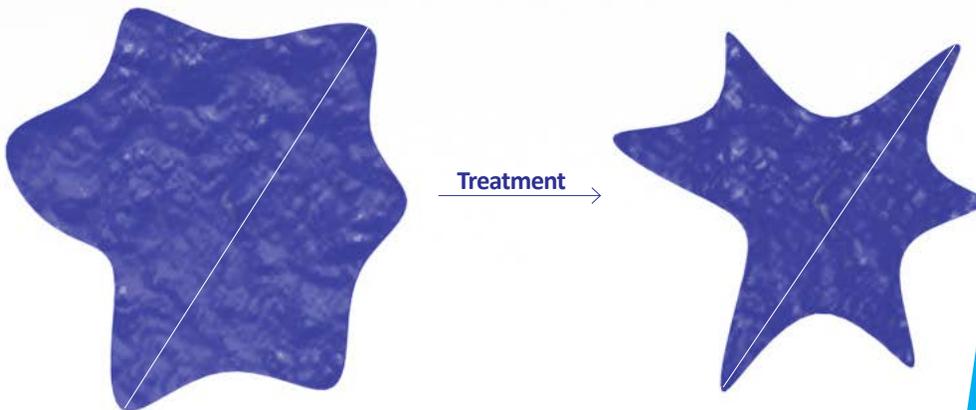


Figure 1. Volume versus longest diameter: overall volume shrinks, while longest diameter remains unchanged.

Volume-Based Endpoints

One of the primary benefits of volume-based endpoints is their ability to detect treatment response at an early time point—often much sooner than when simpler morphological changes can be detected. In oncology trials, this ability to “preview” response gives clinicians the ability to select or stratify patients, define a dose or develop a dosing schedule, modify a personalized treatment plan, or quickly remove a patient from a trial, if necessary. [Tunariu 2012]

Computerized Tomography (CT)

Whole tumor volume can be assessed during routine CT imaging using a computerized or semi-automated segmentation algorithm (see Segmentation section below) that calculates volume from each CT slice. The 3-dimensional, anatomical measurements generated with this method can overcome some of the challenges associated with unidimensional RECIST measurements. The major advantage is the increased sensitivity of volume measurements, which provides greater power to detect change. For example, given a sphere-shaped tumor, a 20% increase in tumor diameter (RECIST definition of progressive disease) correlates to a 72.8% change in volume, and a 30% decrease in diameter (RECIST definition of partial response) correlates to a 65.7% decrease in volume. [Goldmacher 2012] Making volume measurements instead of linear measurements also removes inter-reader variability in placement of the unidimensional diameter, because the entire tumor is measured in one study. Mozley et al. assessed measurement variability in a clinical trial setting by performing a head-to-head comparison of inter-reader variability for linear versus volumetric measurements using a subset of data derived from a multinational, phase 1 clinical trial. The study found that inter-team agreement was greater among volume measurements than for linear measurements, and volumetric measurements were associated with lower variability in determining nadir. [Mozley 2012] Previous studies have also shown that volumetric measurements were able to predict progressive disease sooner than unidimensional RECIST measurements in patients with either thyroid or lung cancer. [Force 2011] To date, volumetric analysis is most often performed in the setting of lung cancer, particularly for the irregularly shaped lesions found in patients with non-small cell lung cancer (NSCLC).

In oncology trials, volume-based measurements on CT scans can be used to:

- Monitor response to treatment and predict clinical outcomes in lung cancer patients
- Screen patients for lung cancer. [Horeweg 2013]
- Make anatomical size measurements in cases where unidimensional RECIST measurements fall short. [Mozley 2010]

Efforts to Qualify CT Volumetric Measures as Endpoints for Lung Cancer

The Quantitative Imaging Biomarker Alliance (QIBA) recently released a QIBA Profile: CT Tumor Volumetric Change that outlines best practices for reproducible and reliable image acquisition and data reconstruction. The creation of the QIBA Profile is part of a larger effort, conducted in conjunction with the wider medical imaging community, to establish a process map for qualifying volumetric measures on CT as a biomarker for treatment response. This process includes determining whether the measurement is accurate, technically feasible, and more highly sensitive than RECIST, and whether changes in volume are medically meaningful. [Mozley 2010] Volumetric response criteria will also be needed to define categories of response and to set thresholds for determining change.

“The creation of the QIBA Profile is part of a larger effort, conducted in conjunction with the wider medical imaging community, to establish a process map for qualifying volumetric measures on CT as a biomarker for treatment response.”

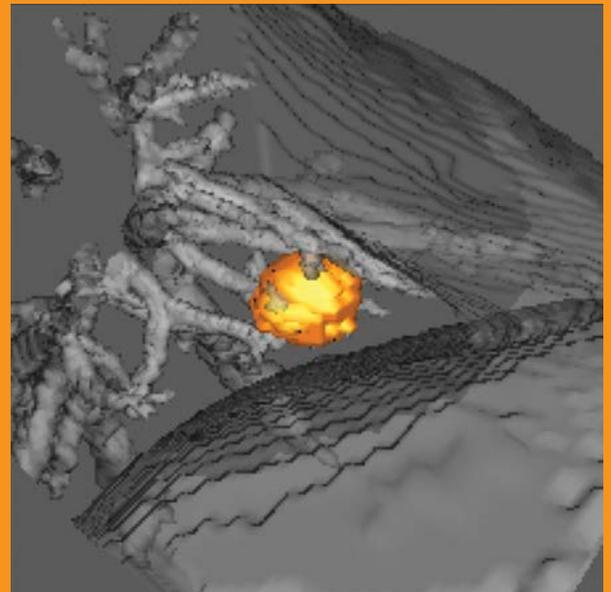
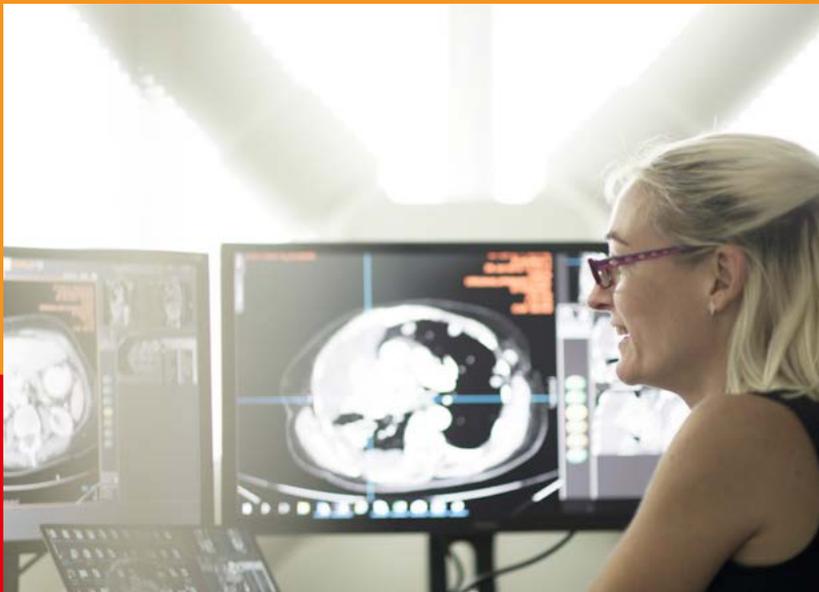


Figure 2. Volume Measurements in Action: Lung CT Volumetric CT scan of a lesion in a patient with NSCLC using Median Technologies' Lesion Management Solution software.

Dynamic Contrast-Enhanced MRI and CT

Dynamic contrast-enhanced MRI (DCE-MRI; also performed with CT, known as DCE-CT or perfusion CT), measures time-dependent enhancement of tumors after injection of intravenous contrast agent prior to MRI/CT imaging. Quantitative measurements can be made based on the kinetic properties of the contrast agent. This allows for the tracking and monitoring of vascular properties for tumors and surrounding normal tissue, including blood volume, regional blood flow, volume of the extravascular space, and the presence of hypoxia. [Cao 2011; Prezzi 2015] For DCE-MRI, the primary output is the rate constant for the transfer of gadolinium contrast agent between the blood plasma and the extravascular space, K_{trans} . [Tunariu 2012] For perfusion CT, the primary readouts are relative blood volume (rBV) and relative blood flow (rBF). [Tunariu 2012] Although perfusion CT displays greater resolution than DCE-MRI and is associated with FDA-cleared analysis software, the required dose of ionizing radiation limits its ability to be used in trials with repeated scanning.

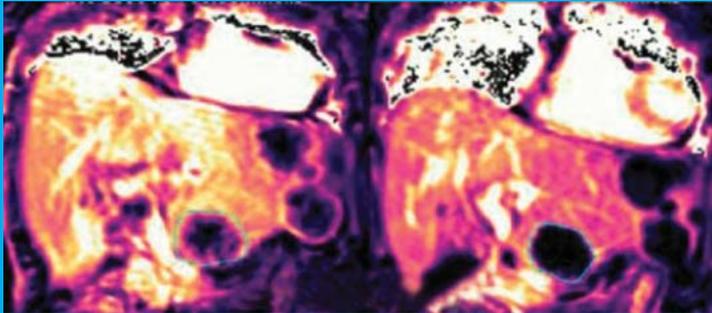
DCE-MRI/CT provides information on vascular density, vascular permeability, and nutrient/oxygen delivery to the tumor. [Prezzi 2015] It is well established that tumors upregulate angiogenic factors that create a disorganized, highly permeable, immature, and tortuous tumor vasculature; identifying this vasculature signature could help identify new areas of metastasis, predict response to treatment, or be an indicator of tumor aggressiveness. [Cao 2011]

Although DCE-MRI/CT still requires additional technical standardization and clinical validation in order to qualify as a surrogate endpoint, the National Cancer Institute's (NCI) Cancer Imaging Program has developed [DCE-MRI imaging guidelines](#) for clinical trials that include recommendations on technical parameters needed to address issues of accuracy and reproducibility.

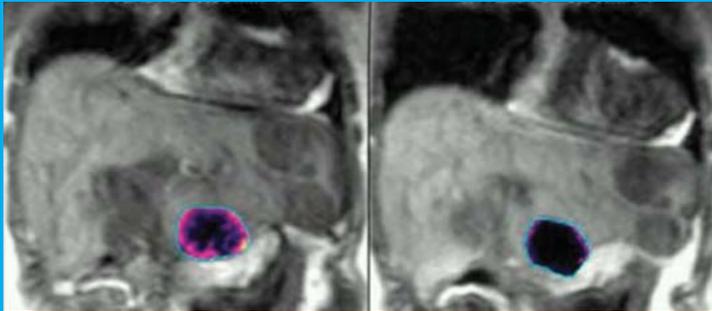
In oncology trials, DCE-MRI/CT can be used to:

- Measure early treatment response for therapeutic agents that affect tumor vascularity and angiogenesis (angiogenesis inhibitors, vascular disrupting agents, immunotherapies), but may not alter tumor size until much later (or at all).
- Monitor for hypoxia, as studies have shown that hypoxic tumors are resistant to chemotherapy and radiation treatment. [Serkova 2011; Cao 2011] This allows clinicians to predict response and alter treatment accordingly.
- Monitor normal tissue for radiation-induced injury, which allows clinicians to determine a patient's therapeutic index during high-dose radiation treatment. [Cao 2011]
- Perform in vivo staging based on tumor characteristics





IAUGC₅₀ (mMGd.min)

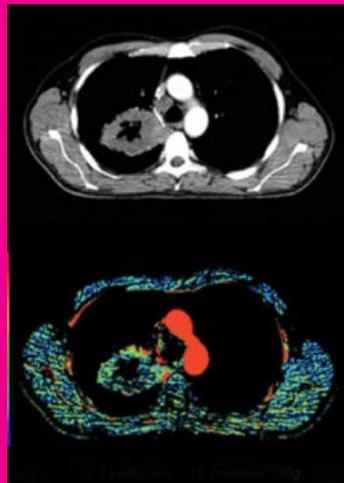


k^{trans} (min⁻¹)

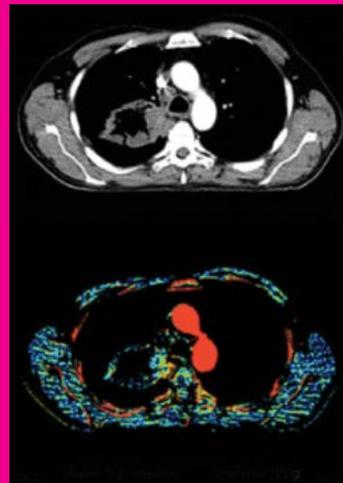
Figure 3. DCE-MRI in Action DCE-MRI scans before (left) and 28 days after (right) treatment with an angiogenesis (VEGF) inhibitor in a patient with metastatic colorectal carcinoma. Tumor size remains stable while tumor vascularity is reduced. DCE-MRI has been used in over 40 phase 1 clinical trials to demonstrate efficacy of VEGF inhibitors. [Tunariu 2012; open access]



Baseline perfusion = 95.2ml/min/100g



Week 3 = 18.2ml/min/100g



Week 6 = 7.0ml/min/100g

Figure 4. Perfusion CT in Action Perfusion CT scans before (A), 3 weeks after (B), and 6 weeks after (C) treatment with an angiogenesis inhibitor (sorafenib) and an EGFR inhibitor (erlotinib) in a patient with metastatic NSCLC. The longest diameter of the lung lesion remains stable, but the perfusion decreased significantly starting at week 3. [Lind 2010; open access]

Diffusion-Weighted MRI

Diffusion-weighted MRI (DW-MRI) measures differences in the random diffusion of water molecules (Brownian movement) across cell membranes, and thus becomes a method for assessing cell membrane integrity and cell density. [Pradhani 2009] DW-MRI measurements produce an apparent diffusion coefficient (ADC) that is specific for each tissue type. The rate of diffusion (and thus, the ADC) across cell membranes differs depending on the state of the tissue: necrotic cells (with increased porosity) have a much higher ADC than healthy cells, while rapidly proliferating tumor cells (with increased density) have a lower ADC than healthy cells. Quantitative measurement of ADC can serve as a biomarker for treatment response: a cytotoxic treatment that causes necrosis can be detected as a rise in ADC, while tumor progression (growth, invasion, or metastasis) can be detected as a lowering in ADC. [Faas 2008; Serkova 2011]

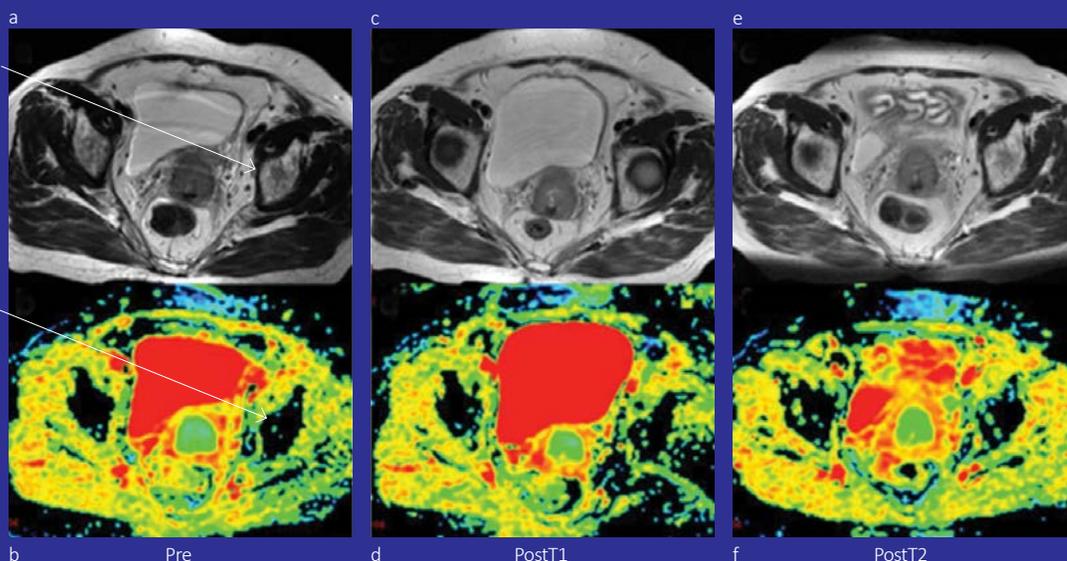
DW-MRI holds great promise for oncology trials, as the procedure does not require contrast agent, does not involve ionizing radiation, and can be easily incorporated into current patient evaluations. [Pradhani 2009] In 2009, an [NCI-sponsored committee released consensus guidelines and recommendations on the use of DW-MRI as a cancer biomarker](#).

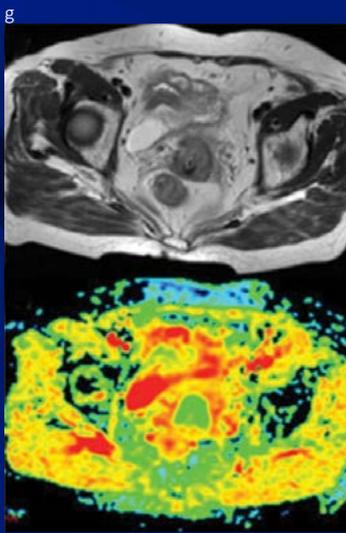
In oncology trials, DW-MRI can be used to:

- Detect primary tumors and metastases: tumor tissue has a lower ADC value than surrounding healthy tissue.
- Tumor characterization, as an indication of aggressiveness: malignant tumors have a lower ADC value than benign lesions. [Koh 2007]
- Monitor treatment response: treatments that result in tumor necrosis, loss of cell membrane integrity, or increased extracellular space will have a higher ADC than pretreatment values. [Thoeny 2010]
- Predict response to cytotoxic treatment:
 - Before treatment: tumors with a low pretreatment ADC values respond better to chemotherapy and radiation than tumors with high pretreatment ADC values. [Thoeny 2010]
 - After treatment, an early increase in ADC value corresponds to better clinical outcome. [Thoeny 2010]

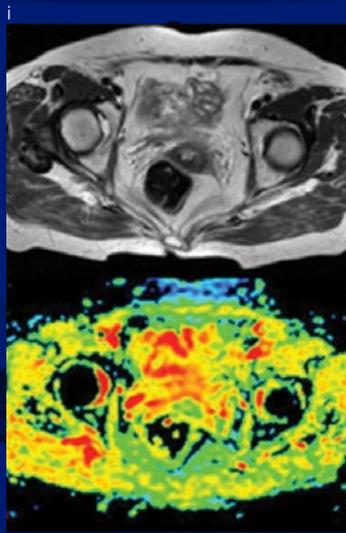
Figure 5. DW-MRI in Action

DW-MRI may be used to detect and monitor early therapeutic response to cytotoxic agents. For example, in patients with uterine cervical cancer who were undergoing concurrent chemoradiation treatment, investigators found that there was a positive correlation between percent change in ADC value at 3, 7, 14, and 21 days after therapy and the percent tumor size reduction (as measured by conventional MRI) at 2 months after treatment. [Liu 2015] The top panels are conventional MRI scans, and the bottom panels are ADC maps generated using DW-MRI. The ability to determine treatment response at an early time point is important for treatment planning and diagnosis; if a treatment failure is determined early, there is an opportunity to transition a patient to a 2nd or 3rd-line treatment strategy or remove the patient from the trial, minimizing cost and the potential for adverse events to the patient.

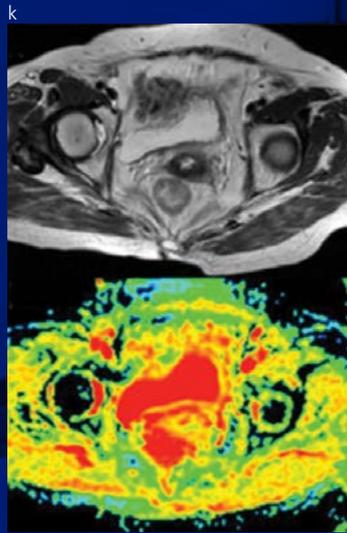




h PostT3



j PostT4



l PostT5

Making Volumetric Tumor Measurements: The Nuts and Bolts

Segmentation

Volume is most accurately obtained using a segmentation process, which can be performed in a manual, computerized, or semi-automated method. Manual segmentation requires the image reader to manually draw a line around the tumor in each slice and define the adjacent areas of nonmalignant tissue. Tumor volume is calculated for each slice, and total tumor volume is the result of summing tumor volumes from all slices. Manual segmentation is both highly accurate, yet very time consuming. *[Goldmacher 2012]*

Computerized segmentation uses algorithms to define tumor edges and calculate volume. Although this method is fast, powerful, and saves time by not requiring human input, it is prone to errors. Semi-automated segmentation combines the accuracy of manual measurement with the power and speed of computer algorithms. After the user manually draws a region of interest around a tumor, the volume is calculated using automated methods. *[Goldmacher 2012]* A number of commercial and publicly available segmentation software programs, like Median Technologies' Lesion Management Solutions (LMS), are available.

Technical Factors that Influence Precision

In order for volumetric analysis to truly reflect disease state, the measurements must be made with precision, meaning they must exhibit low variance and be reproducible with repeat measurements. A variety of technical parameters can influence precision, although the exact parameters necessary to make precise measurements are dependent on tumor type and the imaging modality.

[Goldmacher 2012; Mozley 2010]

- Lesion Size: larger lesions are more accurately measured than smaller lesions.
- Lesion Shape: spherically shaped lesions are more accurately measured than irregularly shaped lesions.
- Slice Thickness: smaller slice thickness is more accurately measured than larger slice thickness, as reduced pixel size increases resolution.
- Image Contrast: improved image contrast (either through the use of properly timed intravenous contrast agent for DCE-CT or greater magnetic strength for DW-MRI) increases image resolution and allows for more accurate measurements, as tumor boundaries are better defined.

RECIST 1.1 is Still Required for FDA Approval

Volumetric and functional measurements can certainly add value to a clinical trial. However, it is important to note that they cannot substitute for RECIST in phase 3 approval studies in solid tumors. RECIST1.1 remains the gold standard for phase 3 evaluation of treatment response, as it has undergone the thorough validation and standardization process needed for consideration as a true surrogate for clinical outcome by the FDA. As advanced imaging endpoints continue to evolve and their standardization continues to be developed, it is possible that one day they may acquire the surrogate endpoint designation as well.

Adding Value to Clinical Trials: Are Volumetric Assessments a True Reflection of Drug Response?

As volumetric imaging methods continue to be studied, questions arise about whether volume measurements can truly improve trial quality or just add to overall costs and complexity.

Do Volumetric Measurements Benefit a Clinical Trial?

Volumetric imaging offers greater measurement sensitivity and potential earlier detection of response, which is important for both ethical and practical reasons. [Mozley 2010] Determining patient response early allows a patient to stop an ineffective treatment sooner (and potentially transition to an alternate, more effective treatment) and prevents premature termination of an effective treatment. Although volumetric imaging may be more complex and therefore more costly to perform, the greater sensitivity associated with volumetric measurements can increase the statistical power per subject. This means fewer subjects are necessary per trial, and each subject may be enrolled for a shorter period, decreasing overall trial time and cost. This also potentially enables more new therapeutics to travel through the drug pipeline and at a faster rate. [Mozley 2010] [Mozley 2012, Goldmacher 2012, QIBA Profile vCT]

Are Volumetric Measurements Medically Meaningful?

In order for volumetric imaging to add value to a clinical trial, the data generated must be able to impact clinical decision-making and be associated with clinical outcomes. Although the issue of value is still being determined, several studies suggest that volumetric assessment does indeed add value. For example, a retrospective analysis of 42 lung cancer patients participating in an open-label phase 2 study found that volumetric measurements on first follow-up (4 weeks after starting treatment) were better able to predict overall survival than RECIST measurements. [Hayes 2016] The study used a semi-automated segmentation algorithm to assess tumor volume from CT images and applied RECIST-based, ellipsoid volumetric criteria to categorize patients as having complete response, partial response, stable disease, or disease progression. Patients who were classified as partial responders had a 1-year overall survival rate of 70%, while those classified as non-responders had a 1-year survival rate of 46%. There was no difference in survival rates among partial responders and non-responders according to RECIST. [Hayes 2016] This study suggests that a positive response to treatment, as measured through changes in tumor volume, may correlate with clinical benefit.

Why It's Important to Add Volume Data to a Clinical Study

Capturing tumor volume data during a clinical trial can add significant value to a study. Three-dimensional measurements can be easily incorporated into existing clinical trial workflows using cloud-based automated image acquisition and management software like Median Technologies' Lesion Management Solutions (LMS) software. The simultaneous detection of unidimensional and 3-dimensional measurements allows for the efficient analysis of both routine and advanced endpoints, providing robust evaluation and quantification of disease status. In early phase trials, the increased sensitivity of volume-based measurements provides an earlier indication of response, allowing for fast and informed "go or no go" decisions to be made. In later phase trials, advanced imaging endpoints can be correlated to standard RECIST1.1 to assess therapeutic efficacy. The automated image and management software like Median's LMS software that captures volume data also improves clinical trial efficiency and workflows, standardizing image acquisition and interpretation to reduce variability among readers and clinical trial sites.

Summary

Three-dimensional, volume-based measurements address some of the inherent limitations of unidimensional RECIST measurements, provide additional measures of efficacy for modern drug classes, and allow for earlier detection of therapeutic response. Although not yet accepted as true surrogate endpoints, studies are underway to further examine the relationship between these experimental endpoints and more traditional imaging measurements, and how volume-based measurements relate to clinical outcomes. Early studies indicate that volume-based measurements are both medically meaningful and add value to a clinical trial. Volume measurements can be easily incorporated into existing clinical trial workflows using segmentation software that also improves trial efficiency and reproducibility. As advanced imaging endpoints continue through the validation and standardization process, it is our hope that they eventually achieve surrogate endpoint status, ultimately adding to the arsenal of therapeutic response tools available to clinicians in the clinical trial setting.

Median's Technologies' image interpretation system, Lesion Management Solution (LMS), offers 3D measurements that are easily incorporated into existing clinical trial work flows. This allows for the efficient analysis of both routine and advanced endpoints, providing robust evaluation and quantification of disease status. By automatically capturing volume data we improve clinical trial efficiency and work flows, standardizing image acquisition and interpretation to reduce variability among readers and clinical trial sites.

Visit our website www.mediantechologies.com to learn how Median Technologies can easily add volume data and improve your clinical trial.



median

The Imaging Phenomics™
Company

About Median Technologies

Median Technologies provides innovative imaging solutions and services to advance healthcare for everyone. We leverage the power of Imaging Phenomics™ to provide insights into novel therapies and treatment strategies. Our unique solutions, LMS for lesion management and iBiopsy™ for imaging phenotyping, together with our global team of experts, are advancing the development of new drugs and diagnostic tools to monitor disease and assess response to therapy.

Median Technologies supports biopharmaceutical sponsors and healthcare professionals around the world to quickly and precisely bring new treatments to patients in need, with an eye on reducing overall care costs. This is how we are helping to create a healthier world.

ALMDT

LISTED

ALTERNEXT

Median Technologies

inforequest@mediantechnologies.com

mediantechnologies.com