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Metrics That Matter

A Guide to Imaging Measurements in Oncology Clinical Trials

Presented by Median Technologies, The Imaging Phenomics Company®

Contents

Medical imaging is an integral component of clinical trials in oncology. For each image type, quantifiable information (referred to as quantitative imaging biomarkers) can be extracted and analyzed to answer questions about tumor types and stage, and to measure response to treatment. The most common assessment of response to therapy is to measure anatomical changes to the tumor. These changes are determined by measuring tumor size in a set of medical images before patient treatment and then measuring this same lesion in a new set of medical images after treatment, thereby measuring how much the tumor has changed with therapy. However, other quantitative imaging measures derived from functional imaging methods provide equally important physiological information about a tumor, including tumor metabolism, vascularity, and cellularity. In this white paper, Median Technologies provides a guide to various measurements used in imaging in oncology trials, describing both size-based and functional metrics and the various criteria that use them.

Definition of an Imaging Biomarker

A biomarker is a biological characteristic that can be objectively and reproducibly measured. It serves as an indicator of normal or pathological processes or therapeutic response. Likewise, an imaging biomarker (IB) is a characteristic that can be detected from an image. In oncology, there is widespread use of IBs in both patient care and clinical trials. Imaging biomarkers are used at all stages of a clinical trial. For example, prognostic or predictive imaging biomarkers can be used to efficiently enroll or stratify patients to ensure the highest likelihood of treatment success, while monitoring and response imaging biomarkers can be used to assess therapeutic efficacy.

Imaging biomarkers can be qualitative, such as the presence of lung nodules indicating diffuse disease, or quantitative, like lung nodule size before and after treatment. Multiple IBs can be derived from the same image, for example, linear measurements of a tumor to assess the objective response with therapy [see next section] and the change in that same tumor's volume. *[O'Connor 2016]*

In order to be used in clinical trials, quantitative imaging biomarkers undergo a rigorous qualification and validation process to ensure precision, accuracy, reproducibility, and a demonstrated association between the biomarker measurement and the presence of target disease or therapeutic response. *[Prescott 2013]*

Definition of Treatment Response Imaging Criteria

Imaging criteria are used to measure response to therapy in oncology clinical trials. Imaging criteria are used to define the context of treatment response assessment, such as tumor type, imaging modality, and acquisition parameters necessary to make an accurate and reproducible measurement. These criteria are based on imaging biomarkers extracted from the medical images under study and may be quantitative or qualitative. For example, imaging response criteria may include objective measures like tumor size and a set of rules such as size thresholds above which tumors are considered target lesions. Imaging response criteria are used to define a "treatment response" status, used by the radiologist to evaluate whether the response to therapy is complete or partial or conversely, if the disease is not responding or even progressing.

Tumor size can be evaluated using several measurement methods. A common method is the measurement of the longest diameter of the tumor. Response to treatment is then evaluated based on these tumor measures and if they fit specific rules ("cut-offs") for response. Thus, after treatment, for the most used Response Criteria in Solid Tumors (RECIST 1.1), total disappearance of target lesions or decrease under a specific size is considered as a complete response. However, size is not the only imaging metric used in imaging criteria. Functional metrics, including tumor metabolism, tumor cellularity, tumor volume, tumor vasculature, tumor necrosis and blood flow rate, also provide valuable information in an oncology trial for assessing objective response to treatment. More recently, advanced imaging features such as textural parameters reflecting tumor heterogeneity have been extensively studied and may become potential quantitative biomarkers for the near future of clinical trials. *[Ludvik 2008]*

Some endpoints based on imaging response criteria such as PFS can also be helpful as surrogate to traditional clinical endpoints such as OS. Surrogate endpoints save time and money in a clinical trial because they can be measured earlier and more frequently, and they require fewer enrolled patients.

To date, there are only two FDA-approved imaging response criteria for use in phase III, registration-enabling oncology trials. They are RECIST1.1 and the World Health Organization (WHO) response criteria. *[Prescott 2013]*

The next section presents various imaging criteria that are available for clinical trials in oncology.

Different Types of Imaging Criteria

Criteria Based On Morphological Measures

Unidimensional Measurement

The most common way to assess tumor size is by defining a unidimensional measurement of the tumor's longest diameter, also referred to as a linear size measurement. In clinical trials, patients' CT or MR scans are analyzed by selecting lesions of appropriate size (also known as target lesions) and by measuring the longest diameter of each individual tumor. Unidimensional line measurement forms the basis of RECIST1.1 criteria, and therefore is the most used metric to assess efficacy in oncology clinical trials for solid tumors.

When using RECIST1.1, up to 5 target lesions can be selected at baseline, and the sum of their diameters (longest diameter for non-nodal lesions and short axis for nodal lesions) is calculated to reflect the tumor burden for the patient. After the patient undergoes treatment, the same target lesions are measured again, and the percentage of change in the sum of diameters, plus the qualitative assessment of non target lesions and potential presence of new lesions, are used to classify response into one of four following categories:

1. Complete Response (CR)
2. Partial Response (PR)
3. Stable Disease (SD)
4. Progressive Disease (PD)

Target lesions are selected by the radiologist and assisted by image analysis software, like Median Technologies' Lesion Management Solution (LMS), and can be used to objectively determine tumor size and accurately calculate the percentage of change among different timepoints.

Unidimensional Measurement, Avoiding Areas of Necrosis and Focusing on Viable Tumor Part, Using Contrast-Enhanced CT or MRI

Anatomic size measurements do not always appropriately capture a positive tumor response, particularly when the therapeutic agent under investigation stabilizes disease rather than causes tumor shrinkage, or when the study is performed in certain cancer types. Specifically, clinical researchers found a poor association between clinical benefit and traditional methods for assessing therapeutic response in patients with hepatocellular carcinoma (HCC) who were treated with sorafenib (brand name Nexavar™, Bayer and Onyx Pharmaceuticals). *[Lencioni 2010]* This discrepancy was largely due to treatment-induced areas of necrosis, which gave the appearance of tumor enlargement. To overcome this, a new HCC-specific metric was created that focused only on viable tumor tissue (mRECIST). Unidimensional measurements that avoid areas of necrosis and focus on viable tumor part have been shown to be more accurate indicators of treatment response in this specific patient population and is the size metric of choice for HCC using mRECIST criteria. *[Lencioni 2010]*

Bidimensional Measurements

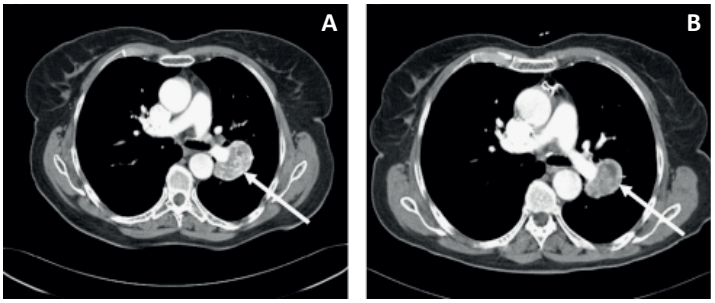
For bidimensional measurements using CT or MRI, two lines are placed across an individual tumor. The first line lies across the longest diameter and the second lies across the longest perpendicular diameter. The two values are then multiplied together. This measurement is also referred to as a cross-sectional measurement. Bidimensional measurements are a component of the original WHO criteria, but they have since been largely replaced with the unidimensional measurements of RECIST for most solid tumors, as single line measurements are easier to perform and therefore subject to less variability. *[James 1999]* However, bidimensional measurements are still the metric of choice in brain tumors (glioma, astrocytoma) and lymphoma, and remain an integral part of irRC, MacDonald, RANO, and Cheson criteria, which are described later in this white paper. *(See Table 3, Metrics by Cancer Type).*

Volumetric Measurements

Tumor size and shape can also be assessed by 3-dimensional, volumetric measurements, which can be performed during routine CT or MR imaging using a segmentation software that calculates the area of a region over several slices. Change in tumor volume can be an earlier and more sensitive indicator of tumor response than simple linear measurements, particularly for irregularly shaped or morphologically complex tumors. *[Goldmacher 2012]* Although no formal response criteria have yet been established for volume measurements on CT images, a QIBA (Quantitative Imaging Biomarkers Alliance) Profile has been created to address issues of accuracy and reproducibility of this metric. The QIBA Profile states that a true volume change (with 95% confidence) has occurred when the measured change is >24% in tumors with a longest diameter of 50-100 mm, >29% in tumors with a longest diameter of 35-49 mm, and >39% in tumors with a longest diameter of 10-34 mm. *[QIBA Profile, CT Tumor Volume Change for Advanced Disease]*

Attenuation Coefficient: CT

A tumor region of interest (ROI) is a manually or computer-assisted drawn line around the tumor mass on a CT image that separates tumor from the surrounding normal tissue. Within the ROI, the attenuation coefficient, which is based on CT-derived Hounsfield units (a quantity commonly used to express standardized CT numbers), can be calculated as a measure of necrosis. This measure can then be considered both morphological (density) and functional (reflection of necrosis). Measurement of the ROI/attenuation coefficient is included as part of the Choi criteria for patients with gastrointestinal stromal tumors (GIST) and as part of the Size and Attenuation CT (SACT) or Morphology, Attenuation, Size, and Structure (MASS) criteria for patients with renal cell carcinoma (RCC).



Longest tumor diameter and attenuation coefficient before (A) and after (B) sunitinib treatment in a patient with renal cell carcinoma. At baseline, the tumor measured 48 mm and the attenuation was 107 Hounsfield units (HUs); at first evaluation, tumor diameter decreased to 39 mm (-19%) and the attenuation decreased to 65 HUs (-39%). [Br J Cancer. 2010 Mar 2; 102(5):803-9. Open access]

Criteria Based On Functional Measurements

These functional measures are extracted from various imaging modalities such as PET, MRI or CT.

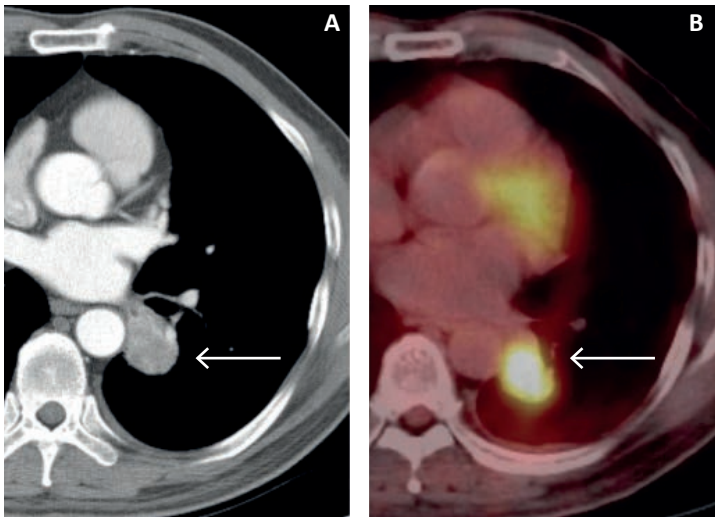
PET Imaging

Change in Standard Uptake Value (SUV)

Positron emission tomography (PET) is a form of functional imaging that measures the presence and accumulation of radiolabeled tracer throughout the body. Its accumulation into tumors produces a semi-quantifiable metric called the standard uptake value (SUV), which is calculated based on the percentage of injected radioactive tracer in the tissue of interest divided by the total body weight. The physiological significance of the tracer uptake depends on which tracer is used.

In oncology trials, most PET studies use the tracer 18F-fluoro-2-deoxy-glucose (FDG), a glucose analog used to assess the rates of tumor metabolism, which are higher in FDG avid tumor versus normal tissue. FDG SUV is a valuable metric because changes in SUV can be detected sooner than changes in tumor size, and it is often used as an early indicator of treatment response. Changes in FDG SUV can contribute to multiple imaging biomarkers. For example, it can be used to determine objective response by providing data for several response criteria (PERCIST, IWG-Cheson, Lugano, RECIL) or it can stand alone as a predictive/prognostic biomarker. FDG SUV can also be used as an early and robust response indicator in lymphoma trials to direct therapy selection *[Mankoff 2014]*, or baseline SUV can be used an indicator of overall prognosis in patients with non-small cell lung cancer. *[Na 2014]*

Examples of other PET tracers currently under development include 18F-fluorothymidine (FLT) and 18F-fluoro-estradiol (FES). FLT accumulation measures cell proliferation, and FLT SUV has been used as an early indicator of response to neoadjuvant chemotherapies in breast cancer patients (ACRIN 6688 trial). *[Mankoff 2014]* FES is taken up by cells expressing the estrogen receptor (ER), and FES SUV has been used as a predictive imaging biomarker to determine ER+ expression in breast cancer patients. *[Liao 2016]*

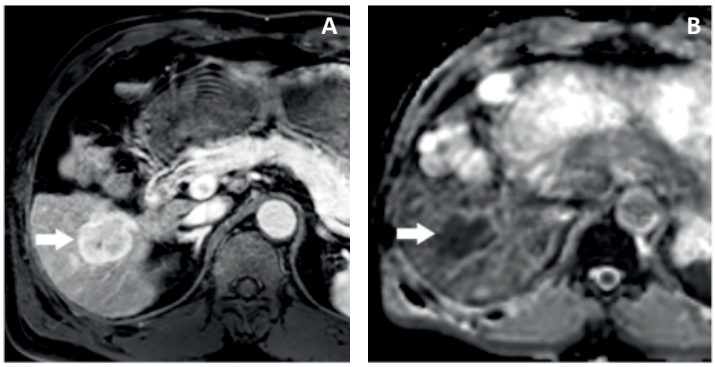


Contrast-enhanced CT (A) and FDG-PET/CT showing tumor hypermetabolism (B) in a patient with lung adenocarcinoma. [Korean J Radiol. 2013 Mar-Apr;14(2):375-83. Open access]

MRI

Change in Apparent Diffusion Coefficient (ADC): DWI-MRI

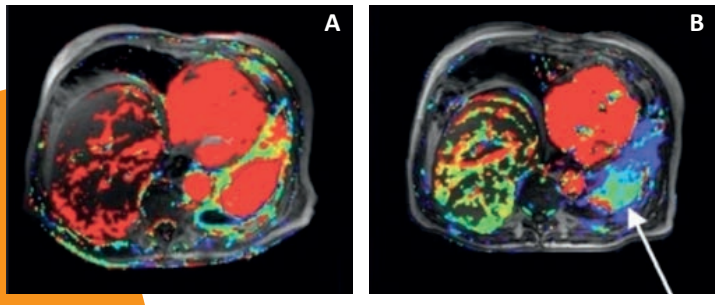
Diffusion-weighted MRI (DW-MRI) measures differences in the random diffusion of water molecules across cell membranes, and thus has become a method for assessing cell membrane integrity and cell density. The resultant metric is the change in apparent diffusion coefficient (ADC), which is a measure of cellularity (the relative proportion of tumor and normal cells in a sample). Tumor proliferation or progression (and thus increased cell number) results in a decrease in ADC, while treatment-induced necrosis causes an increase in ADC. Change in ADC is an effective early biomarker for treatment response, as vascular and cell death changes often precede changes in lesion size. *[Padhani 2009]* An increase in ADC is generally an indicator of successful treatment; however, large variations in ADC values among MR scanners and sites may complicate therapy assessment using this metric. *[Kwee TC, 2010]*



Contrast enhanced T1-weighted MRI showing enhanced tumor size (A) and apparent diffusion coefficient map showing relative tumor diffusion (B) in a patient with hepatocellular carcinoma. The hypointense signal on the ADC map (arrow, right) suggests restricted diffusion, which is highly suggestive of malignancy. [Korean J Radiol. 2015 May-Jun;16(3):449-64. Open access]

Change in the Transfer Constant (K^{trans}) or $IAUGC_{BN}$: DCE-MRI

Dynamic contrast-enhanced MRI (DCE-MRI) measures time-dependent enhancement of tumors after intravenous injection of gadolinium contrast agent. Quantitative measurements can be made based on the kinetic properties of gadolinium. 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. The primary metrics for DCE-MRI are the rate constant for the transfer of gadolinium contrast agent between the blood plasma and the extravascular space (K^{trans}) and the blood normalized initial area under the gadolinium concentration curve ($IAUGC_{BN}$). Both of these are used as pharmacodynamic biomarkers for anti-angiogenesis agents and other novel therapeutics that affect tumor blood supply. According to the DCE-MRI QIBA Profile, K^{trans} and $IAUGC_{BN}$ can be reliably measured from DCE-MRI data in lesions ≥ 2 cm. A 40% change in K^{trans} or $IAUGC_{BN}$ value is considered significant. *[QIBA Profile: DCE-MRI Quantification]*

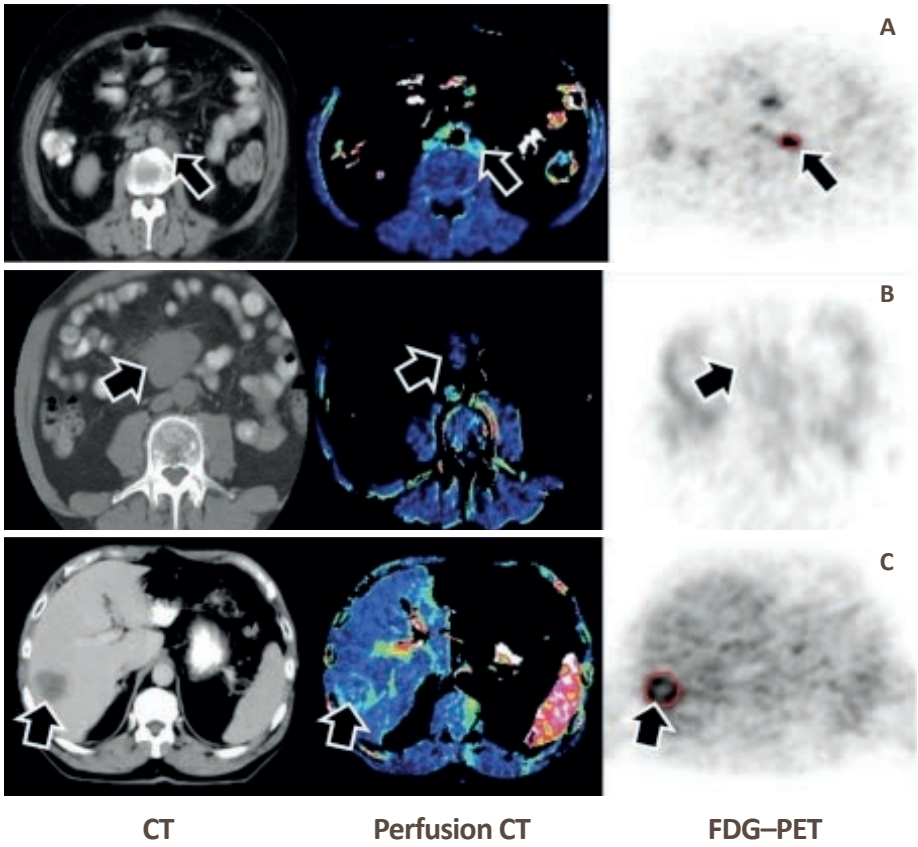


K^{trans} maps (a measure of tumor permeability) in a patient with squamous cell lung cancer before (A) and 6 weeks after (B) sorafenib treatment (an anti-angiogenic agent targeting VEGF and PDGF). Although there is little change in lesion size, the K^{trans} maps show reduced vascularity (arrow) indicating successful anti-angiogenic therapy. [J Clin Imaging Sci. 2011;1:38. Open access]

CT

Change in Blood Flow Rate (mL blood/mL tissue/min): Perfusion CT or DCE-CT

Perfusion CT measures the vascular properties of a tumor from a CT image, and like DCE-MRI, is based on quantitative assessment of the movement of contrast agent within a tumor region of interest. The primary metric derived from perfusion CT images is the change in blood flow rate (mL blood/mL tissue/min), which can be measured as a change in signal intensity as the contrast agent enters a tissue. 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.



Conventional CT (left), perfusion CT (middle), and FDG-PET (right) images of patients with (A) active lymphoma, (B) inactive lymphoma, and (C) colorectal liver metastases. Arrows indicate the tumor masses. There are high rates of blood flow and glucose uptake in the active lymphoma, while these rates are low in inactive lymphoma. Liver metastasis shows low blood flow and high glucose uptake. [Int J Mol Imaging. 2011;2011:679473. Open access]

(See Table 1 and Table 2 for various metrics used in criteria for imaging clinical trials.)

Measurements by Cancer/Treatment Type

A tumor's unidimensional diameter forms the basis of RECIST 1.1, and as such, it is the most commonly assessed metric for solid tumors during clinical trials. However, some cancer types, either because of their complex morphology or the way in which they respond to novel therapeutics, e.g., there is a change in metabolism rather than a change in size, or there is a pseudo-progression followed by a response during treatment, are most accurately assessed using alternative response criteria. As such, several other cancer-specific response criteria have been developed.

Immunotherapies are different from traditional chemotherapies because they enhance the patient's own immune system functions instead of directly killing cancer cells. This is the reason why immunotherapies demonstrate novel patterns of clinical response and why immune based criteria (i.e., irRC, irRECIST, iRECIST, iRANO) were developed. These immune response criteria take into account the pseudo-progression or the delayed response that can be encountered with immunotherapies and can be inaccurately interpreted with conventional criteria such as RECIST 1.1. *(See Table 3, Metrics by Cancer Type).*

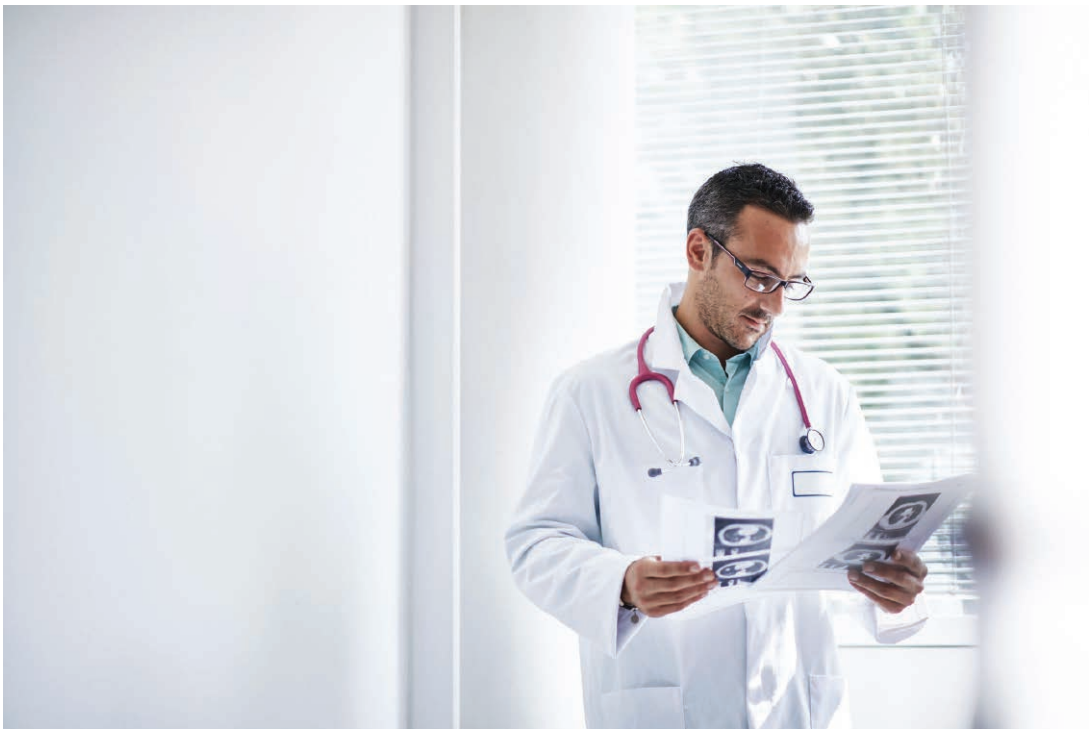
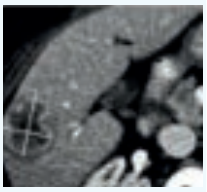
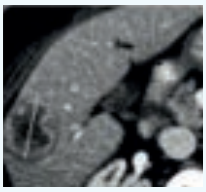
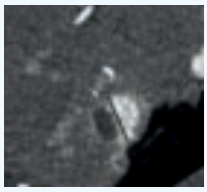
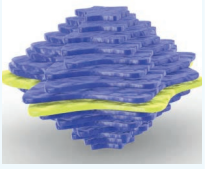
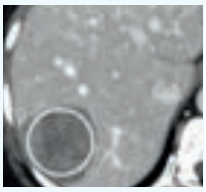


Table 1 and Table 2 present the various metrics used in criteria for imaging clinical trials.

Morphological

Table 1: Morphological information in criteria used in imaging clinical trials

Unidimensional	Bi-dimensional	Unidimensional, Avoiding Areas of Necrosis	Whole Tumor Volume	Attenuation Coefficient (Hounsfield units)
CT or MRI – Longest diameter Criteria: – RECIST – RECIST1.1 – irRECIST – RANO-BM – RECIST – RECIL	CT or MRI – Longest diameter X longest perpendicular diameter Criteria: – WHO – irRC – MacDonald – RANO, iRANO – Cheson – Lugano	CT or MRI – Longest diameter, viable tissue only Criteria: – mRECIST	CT or MRI	CT Criteria: – Choi – SACT – MASS
				

Functional

Table 2: Functional information in tumor response criteria used in imaging clinical trials

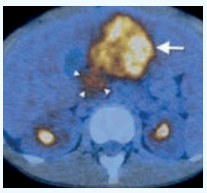
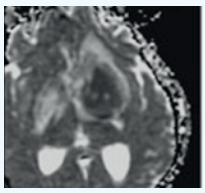
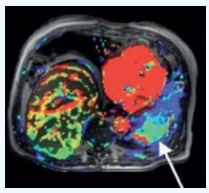
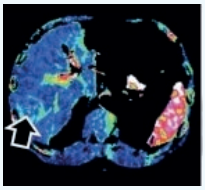
Standard Uptake Value	Apparent Diffusion Coefficient	K^{trans}	Blood Flow Rate
PET/CT Criteria: – PERCIST – IWG–Cheson	DW-MRI	DCE-MRI	Perfusion CT/ DCE-CT
			

Table 3 presents response criteria, metric and modality by cancer type.

Table 3: Cancer Type, Response Criteria and Metrics

Cancer Type	Response criteria	Metric	Modality
Solid tumors	RECIST 1.0	Unidimensional	CT or MRI
	RECIST 1.1	Unidimensional	CT or MRI
	WHO	Bidimensional	CT or MRI
	PERCIST	FDG SUV/SUL	FDG-PET
Brain tumors	MacDonald	Bidimensional	MRI
	RANO	Bidimensional	Contrast-enhanced MRI
	RANO-BM	Unidimensional	Contrast-enhanced MRI
Lymphoma	IWG-Cheson Lugano	Bidimensional, FDG uptake*	FDG-PET/CT and CT
	RECIL	Unbidimensional, FDG uptake*	FDG-PET/CT and CT
HCC	mRECIST	Unidimensional, avoiding areas of necrosis	Contrast-enhanced CT or MRI
GIST	Choi	Unidimensional, attenuation coefficient	Contrast-enhanced CT
RCC	SACT	Unidimensional, attenuation coefficient	Contrast-enhanced CT
	MASS	Unidimensional, attenuation coefficient	Contrast-enhanced CT
Immunotherapy-treated cancer	irRC iRANO	Bidimensional	CT or MRI
	LYRIC	Bidimensional, FDG uptake*	FDG-PET/CT and CT
	irRECIST, iRECIST	Unidimensional	CT or MRI

*FDG SUV semi-quantitative measurement is helpful but FDG uptake is primarily determined through visual qualitative assessment with 5point-scale Deauville criteria [Cheson 2014, RECIL, LYRIC]

irRECIST = immune-related RECIST; iRECIST = immune RECIST, irRC = immune-related response criteria; IWG = International Working Group; HCC = hepatocellular carcinoma; GIST = gastrointestinal stromal tumor; MASS = Morphology, Attenuation, Size, and Structure criteria; mRECIST = modified RECIST; PERCIST = PET response criteria in solid tumors; RANO = response assessment in neuro-oncology; RANO-BM = RANO brain metastases; RCC = renal cell carcinoma; SACT = size and attenuation contrast-enhanced CT criteria; WHO = World Health Organization

Conclusion

Imaging biomarkers are evaluated by various metrics, which serve as quantitative indicators of therapy efficacy. Size-based metrics and functional metrics can be measured by several methods. Response criteria, such as RECIST 1.1, use these size-based measurements to assess therapy response in patients. Whole tumor volume is another size-based metric whose use is increasing in clinical trials, and its incorporation into future response criteria is likely. Functional metrics, such as changes in SUV, ADC, K^{trans}, or blood flow rate can serve as early response indicators or predictive/prognostic biomarkers. Together, these size-based and functional metrics provide an accurate picture of tumor biology and physiology. Moreover, new imaging features such as texture analysis are under investigation as new quantitative biomarkers. Not every metric is applicable to all tumors. Although most solid tumors can be assessed with unidimensional size measurements like RECIST 1.1, some tumors, such as brain tumors, lymphomas, or tumors with complex behavior require cancer-specific measurements. In the era of novel immunotherapy drugs, new patterns of imaging response to therapy are observed and appropriate response criteria such as iRECIST are necessary to determine accurate objective response. Ultimately, the choice of measurement in a clinical trial will depend on the type of cancer, the therapeutic agent(s) under investigation, and the questions that investigators hope to answer.

Other Metrics That Matter: Quality and Performance Measurements

Imaging biomarker metrics are not the only measurements that matter in oncology imaging trials. Quality and performance metrics, although not the primary focus of this paper, are important and necessary for running a successful clinical trial.

Quality Measurements

Quality metrics are all metrics related to the quality of imaging data produced during a clinical trial. Clinical trial sites must comply with the imaging protocol in a high-quality manner so that it delivers valid and reproducible results. This means having an appropriately trained site investigator and staff, using imaging devices that are properly calibrated and performing up to specifications, following standardized methods for image acquisition (device parameters, slice thickness, patient positioning, appropriate anatomical coverage), performing high-quality image analysis (proper training of radiologists, patient de-identification, use of high-quality software to minimize variability), and strictly adhering to the protocol itself. *[Yankeelov 2016]*

Performance Measurements

Performance metrics are all metrics that are measured around the data, which indicate overall trial quality. These measurements include timely transfer of imaging data from the image acquisition site to a central reading site, timely reading of images by trial radiologists, establishing and following protocols for missing data, and de-identification of image sets. *[Yankeelov 2016]* There are two important performance metrics: the firsr is percent of site queries (percentage of images that are tagged by the reader as having an issue and must be referred back to the clinical site) and the second is percent of non-evaluable images (percentage of images that are not able to be evaluated by readers due to suboptimal data or incorrect data format). Both metrics can be an indicator of insufficient site training and are often easily rectified through additional education.

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Since 2002, Median has been doing one thing and one thing only - expanding the boundaries of the identification, interpretation, analysis and reporting of imaging data in the medical world. Median is at the heart of innovative imaging solutions to advance healthcare for everyone. As The Imaging Phenomics Company®, Median provides insights into novel therapies and treatment strategies. Our unique solutions for medical image analysis and 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 in bringing new and targeted treatments to patients in need with an eye on reducing overall costs. This is how we are helping to create a healthier world.

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