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Quantitative Imaging in Cancer Clinical Trials

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Abstract

As anti-cancer therapies designed to target specific molecular pathways have been developed, it has become critical to develop methods to assess the response induced by such agents. While traditional, anatomic CT and MRI exams are useful in many settings, there is increasing evidence that these methods cannot answer the fundamental biological and physiological questions essential for assessment and, eventually, prediction of treatment response in the clinical trial setting, especially in the critical period soon after treatment is initiated. To optimally apply advances in

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quantitative imaging methods to trials of targeted cancer therapy, new infrastructure improvements are needed that incorporate these emerging techniques into the settings where they are most likely to have impact. In this review, we first elucidate the needs for therapeutic response assessment in the era of molecularly targeted therapy and describe how quantitative imaging can most effectively provide scientifically and clinically relevant data. We then describe the tools and methods required to apply quantitative imaging and provide concrete examples of work making these advances practically available for routine application in clinical trials. We conclude by proposing strategies to surmount barriers to wider incorporation of these quantitative imaging methods into clinical trials and, eventually, clinical practice. Our goal is to encourage and guide the oncology community to deploy standardized quantitative imaging techniques in clinical trials to further personalize care for cancer patients, and to provide a more efficient path for the development of improved targeted therapies.

Introduction

Oncology has recently developed a variety of new therapeutic agents that target specific molecular pathways as opposed to more traditional non-targeted cytotoxic chemotherapies. Similarly, medical imaging has developed from simple uses of X-rays to a range of advanced imaging techniques that are capable of quantitatively interrogating cancer biology at the physiological, cellular, and molecular levels. However, the imaging technology routinely employed in the clinical standard-of-care and clinical trial settings remains primarily dependent upon anatomic, size-based evaluation. Standard imaging response measures may not correlate with therapeutic effect and may not provide adequate early information about response and outcomes for many classes of new agents, for example, cytostatic drugs, tyrosine kinase inhibitors, anti-angiogenic and immune-based therapies. In such settings, tumor size may change little or even initially increase with effective treatment and, in fact, long term stability of tumor size may be a sign of a good response and longer term successful outcome from therapy. In light of these considerations, it is imperative that the imaging and oncology communities partner to ensure that selection of image modality, image acquisition and analyses are rationally paired with the anticipated concurrent effects of specific targeted therapies. In this review, we summarize the current state-of-the-art of cancer therapy response evaluation and limitations, review current and emerging quantitative imaging methods, and describe a framework for advancing quantitative imaging into clinical trials and practice. Our goal is to encourage the cancer and imaging communities to work jointly to develop and deploy quantitative cancer imaging methods that will support and guide improved evaluations of cancer response to modern cancer therapeutics.

Current State-of-the-Art for Response Assessment in Clinical Trials

Evidence supporting gross reduction in tumor size as a surrogate for effective therapy has led to establishment of size-based criteria for response (1-3). The most commonly used method for characterizing changes in tumor size is the Response Evaluation Criteria in Solid Tumors (RECIST; 4). The salient features of RECIST 1.1 are as follows. In a baseline (i.e., pretreatment) CT or MRI scan, up to five target lesions are identified and the sum of their

longest single dimension is recorded. At follow up, the percent change in the sum of these diameters is calculated and the response is classified into complete response (disappearance of all target lesions), partial response (> 30% decrease in the sum of diameters of the target lesions), progressive disease (>20% increase in the sum of diameters of the target lesions or appearance of new lesions), or stable disease (none of the above). While RECIST is widely accepted in cancer clinical trials, the limitations of these criteria are increasingly apparent. Here we discuss representative examples from brain and lung cancer.

The challenges of a one-dimensional morphology-based measurement in glioma have been apparent for some time. Primary resection creates a cavity that makes cancer size difficult to measure and tumor margins are frequently unclear due to abnormal MRI signal intensity at resection margins caused by gliosis. Radiation related imaging changes creates confusion in response assessment because it may appear as an enhancing mass lesion and/or create enhancement months to years after initial treatment. Newer therapeutic approaches (e.g., radiation combined with temozolomide, TMZ) present a similar challenge, and more often leads to non-progression related enhancement acutely after therapy. Conventional imaging is not effective in distinguishing this “pseudo-progression” (a worsening anatomic appearance of lesions due to treatment, not due to tumor progression) versus radiation necrosis from true progression of glioma. To complicate this common scenario, patients who are thought to be progressing are often switched to anti-angiogenic agents such as bevacizumab that may produce “pseudoresponse”—a reduction in enhancement and mass effect despite continued tumor growth. The Response Assessment in Neuro-Oncology (RANO) working group was established to develop better treatment response guidelines for high grade glioma trials (5). The fundamental innovation in RANO is the incorporation of additional MRI scans into the assessment system, such as perfusion and diffusion MRI. The fundamental innovation in RANO is the incorporation of the FLAIR (fluid-attenuated inversion recovery) MRI sequence into the assessment, which can reflect non-enhancing components of tumor. The addition of functional imaging methods (e.g., diffusion and perfusion MRI, and PET using amino acid agents) that can distinguish tumor response from blood-brain barrier effects (i.e., pseudo-progression) may provide additional information on response in the future.

In lung cancer, the use of RECIST is often confounded by surrounding parenchymal structural abnormalities, before and especially after treatment, which may or may not contain tumor (6). Quantitative imaging with volumetric CT (2) or PET imaging (7) has the potential to provide early assessment of molecularly targeted therapies by assessing biological changes in tumors that are likely to be clinically relevant even in the absence of tumor shrinkage. For example, in non-small cell lung cancer patients treated with erlotinib, a small-molecule tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR) a partial metabolic response, as measured by 2-[(18)F]-fluoro-2-deoxy-D-glucose PET (FDG-PET), is associated with improved progression free and overall survival, even in the absence of RECIST response, either during or after therapy (8). Similarly, for lung cancer treated with gefitinib (another EGFR targeted agent) volumetric CT was able to identify changes in tumor size not detected by standard RECIST measurements (9); and in another study, 3'-[(18)F]fluoro-3'-deoxythymidine PET (FLT-PET) indicated a decline in proliferation after one week of gefitinib treatment that predicted subsequent response at six weeks as assessed by standard, size-based criteria (10).

Overview of Quantitative Imaging Methods

Quantitative imaging refers to the systematic, objective measurement of numerically based information from digital images that is relevant to the assessment of the visualized tissue of interest. This approach differs from traditional radiological interpretation that is comprised of qualitative (visually based) assessment of the cancer by a radiologist recorded in a text report (e.g., “mild worsening of disease”) preferably with reporting of lesion morphology measurements. For clarity, we briefly describe several emerging quantitative imaging methods; the reader is encouraged to refer to Table 1 during the following discussion.

Perfusion measurements

Perfusion imaging usually involves the serial acquisition of MR or CT images before, during, and after an intravenous injection of a contrast agent. As the contrast agent enters a tissue, the signal intensity changes. The resulting signal intensity time course from a region of interest can be related to the concentration of contrast agent, which can then be analyzed with an appropriate pharmacokinetic model to estimate, for example, blood flow, vessel permeability, and tissue volume fractions (11).

Cellularity measurements

The microscopic thermally-induced behavior of molecules moving in a random pattern is referred to as self-diffusion or Brownian motion. The rate of diffusion of water molecules in cellular tissues is described by means of an apparent diffusion coefficient (ADC), the value of which largely depends on the density of barriers that a diffusing water molecule encounters, such as cell or nuclear membranes. MRI methods have been developed to measure the ADC, and in well-controlled situations the variations in ADC have been shown to correlate inversely with tissue cellularity (12), which may be used for determination of tumor response.

Metabolic measurements

The most commonly used PET imaging radiopharmaceutical in clinical practice is 2-[(18)F]-fluoro-2-deoxy-D-glucose or, simply, FDG. FDG is a glucose analogue that accumulates in areas of increased glycolytic activity, which is a near universal feature of cancer. It is well known that the activity of cell surface glucose transporters GLUT-1 and GLUT-3 (which transport FDG into the cells) and the intracellular enzyme hexokinase (which phosphorylates and traps FDG) are up-regulated in malignant cancer cells. As changes in the rate of glucose metabolism can provide an early and highly predictive indicator of response to therapy, FDG-PET is increasingly employed in clinical studies (13). However, unlike anatomic imaging-based measures, there are no widely agreed upon criteria for response by FDG-PET. There are an array of methods in current use for quantifying FDG-PET data (see Table 1), that include the standard uptake value (SUV), and, for cases where dynamic imaging is obtained, kinetic modeling. The SUV is a semi-quantitative metric based upon static uptake measurements that reports a percent of injected dose activity in a gram of tissue under investigation normalized to patient mass. Commonly used extensions of SUV include SUV_{max} , SUV_{mean} , and metabolic tumor volume (MTV). Kinetic modeling is more

quantitative in nature and can return estimates of the rate constants for glucose transport and consumption for a particular lesion of interest. An emerging standard that is gaining traction is the PERCIST (PET Response Criteria in Solid Tumors) response criteria have been proposed to provide systematic assessments of cancer treatment response by FDG-PET (14). These criteria rely primarily on static uptake measures such as SUV or SUL (SUV corrected for lean body mass).

Other PET radiopharmaceuticals target additional deregulated processes in cancer cells and may augment the ability of FDG to measure therapeutic response. For example, ^{18}F -fluorothymidine (FLT) was developed as a surrogate marker of cellular proliferation (15). Once transported to the tumor intracellular space by equilibrative nucleoside transporter ENT transporters, FLT is phosphorylated by thymidine kinase-1 (TK1), which is known to have a large increase in activity during DNA synthase phase of the cell cycle (S-phase). Since FLT monophosphate is not incorporated into DNA and is impermeable to the cell membrane, it is trapped intracellularly. Thus, rapidly proliferating (tumor) cells can present an increased retention of phosphorylated FLT. However, there are subtleties to consider; FLT retention is dependent on the salvage pathway of thymidine synthesis, which is activated when a cell cannot carry out *de novo* synthesis of thymidine during DNA replication. Thus, the importance of determining the contribution of the thymidine salvage pathway when FLT-PET is used to image and monitor tumor proliferation has recently been emphasized. Further systematic study in a variety of tumors and treatments, as well as multi-center validation, is needed to support the use of FLT as a response marker in clinical trials. An example is the recent completion of ACRIN 6688, a multi-center trial of FLT PET to monitor early response to neoadjuvant chemotherapy in breast cancer (16).

Radiomic measurements

Tumors are phenotypically and genotypically heterogeneous and there is evidence that heterogeneity is synonymous with malignancy (17). In quantitative imaging, heterogeneity is reflected in voxel-by-voxel functional parameter maps, and is increasingly quantified with texture analysis, leading to the new field of “radiomics” (18). “Radiomics” is the process of extracting and analyzing mineable quantitative descriptors of heterogeneity from radiographic images. The overarching hypothesis of radiomics is that these high-level image features reflect the underlying tumor pathophysiology. A related approach uses these features to drive mechanism based predictive models (19). While clearly in the early days of development, such analyses may provide significant improvements in the power of image biomarkers for prediction, prognostication, or response monitoring.

Pairing of imaging and therapy

While quantitative imaging can offer much complimentary information in the care and treatment of the cancer patient, it is important to note that each imaging metric has its own set of applications for which it is optimally designed; and this is dictated by both the biological and technical considerations. For example, whole body PET/CT and diffusion MRI can readily assess metabolic and cellular responses of both primary tumor and metastatic disease to treatment, whereas current contrast enhanced MRI methods are unable

to assess tumor perfusion in a whole-body examination and therefore has limited application in the metastatic setting. Another fundamental caveat is that before applying a quantitative imaging biomarker as an “endpoint”, it must be carefully validated in both the pre-clinical and clinical settings. While “ground truth” phantoms have been developed to validate a number of technical aspects of the imaging measures (20-25), there are several imaging methods for which phantom development may be impractical or not offer the proper biological insight (validating measures as biologic surrogates; e.g., cellular viability). However, there is a well-developed literature on all the methods listed in Table 1 for evaluation of cancer therapy response using clinical and/or pathological endpoints.

Consortia Efforts for Standardized Methods and Imaging in Clinical Trials

The National Cancer Institute has long recognized the importance of advanced imaging in oncology, and one of their current efforts is the Quantitative Imaging Network (QIN). The QIN is designed to promote development and validation of quantitative imaging methods and tools for the measurement of tumor response to therapies in clinical trial settings (26), with the overall goal of facilitating clinical decision-making. Key components/objectives of this effort include: 1) optimized and standardized methods for image acquisition, sharing, and cross-calibration of imaging results obtained at different centers, 2) optimized and standardized methods for quantitative image analysis, 3) tools for designing trials that involve quantitative imaging, and 4) reference data sets for development and validation of new quantitative imaging methods. The QIN attempts to build these components through four trans-network Working Groups: Data Acquisition Working Group, Image Analysis and Performance Metrics Working Group, Bioinformatics/IT and Data Sharing Working Group, and Clinical Trial Design and Development Working Group.

The Quantitative Imaging Biomarkers Alliance (QIBA) was organized in 2007 by the Radiological Society of North America (RSNA) as an initiative to advance quantitative imaging and the use of imaging biomarkers in clinical trials and clinical practice by engaging researchers, healthcare professionals and industry. The mission of QIBA is to improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients and time. The main output of QIBA are ‘Profiles’, which are documents that record the collaborative work by QIBA participants to provide one or more ‘Claims’ (which tell a user what quantitative results can be achieved by following the Profile) and associated ‘Details’ (which tell a vendor what must be implemented in their product and tell a user what procedures are necessary). QIN and QIBA are reciprocally-informed by having a cadre of members active in both groups. In this manner, efforts to improve quantitative imaging are complementary.

The American College of Radiology Imaging Network (ACRIN) is a clinical trials organization originally sponsored by the NCI Cancer Imaging Program to conduct clinical trials of imaging technologies as they relate to cancer. ACRIN's clinical trials encompass the full range of medical imaging research, including surveillance in high-risk populations, imaging biomarkers in early phase trials, prevention approaches in screening trials, and methodologies in comparative-effectiveness research. ACRIN recently merged with the Eastern Cooperative Oncology Group (ECOG) to form the ECOG-ACRIN Cancer Research

Group with the broader mission to improve patient outcomes through earlier cancer detection and more successful therapeutic interventions. Other clinical trial networks that have active imaging committees include the Southwest Oncology Group (SWOG), the Children's Oncology Group (COG), and Alliance for Clinical Trials in Oncology.

Logistical Challenges and Approaches for Quantitative Imaging in Cancer Clinical Trials

As the workflow of imaging in a clinical trial can be quite complex, the details of how advanced imaging is actually (practically) incorporated into clinical trials vary dramatically between institutions. Specifically, there are multiple components to be considered in a trial that uses quantitative imaging endpoints: 1) selection of the appropriate imaging endpoint and modality, 2) qualification of the quantitative imaging capabilities of participating sites, 3) data collection and image analysis for imaging endpoint determination, and 4) auditing and quality control for quantitative imaging data. These are briefly summarized below, with a discussion of the infrastructure needed to support these components.

Selection of the appropriate imaging endpoint and modality

While cancer clinical trial imaging endpoints have traditionally been sized-based, and have typically used CT or anatomic MRI images to measure size, the imaging endpoint landscape has been made more complex by the specific needs of certain organ sites (e.g., brain tumors) and differing patterns of response for specific types of treatment (e.g., immunotherapy). In addition, more recently developed functional and molecular imaging methods (see Table 1) are emerging as preferred endpoints in a few instances (e.g., FDG-PET/CT for lymphoma) and may offer powerful, but not yet fully validated, response markers that are often quite predictive of key clinical endpoints such as survival. Quantitative imaging for cancer clinical trials therefore increasingly requires a panel of experts to help guide the choice of imaging modality and endpoint criteria, tailored to the disease site, patient population, and type of treatment. Many cancer centers have assembled such teams of imaging response experts, and so have most clinical trials organizations, which increasingly house imaging science committees. Some groups have also developed the infrastructure to carry studies of investigational imaging methods as exploratory endpoints to support later use as an integral marker in cancer therapy trials. Recent examples include a study of FLT-PET as an early indicator of breast cancer treatment response (ACRIN 6688), carried out across nearly 20 sites (16), which was designed to validate FLT PET/CT as an early indicator of response in a multi-center setting, and a study of hypoxia in brain tumors (ACRIN 6684), where ¹⁸F-FMISO PET and advanced MR imaging methods were tested as predictors of progression-free and overall survival patients newly diagnosed glioblastoma multiforme. The QIN was designed to serve as a scientific resource for the needs of quantitative cancer imaging for cancer centers, clinical trials groups, and other groups using quantitative cancer imaging endpoint (27).

Qualification of quantitative imaging capabilities of participating sites

To achieve valid and reproducible endpoints, all involved sites must carry out the proposed imaging specified in the clinical protocol with sufficient quality to provide valid, reproducible results. In addition to assuring the needed site investigator and staff expertise, the process of site qualification includes assurance that the imaging devices used are able to perform the type of imaging specified, that the device is performing up to specifications, that the device is operated according to the protocol specifications, that the image data is properly handled for research including proper de-identification, and that the data is transferred in a timely fashion to a central analysis site (28,29). Many trials have study-specific imaging requirements for participating sites that often include scanner qualification procedures such as scanning a specific phantom or providing patient image examples. The expansion of the number and scope of such imaging qualification procedures in clinical trials is a necessary and positive step, but it can be time consuming and costly. This consideration has spurred recent efforts to standardize and streamline the qualification process without giving up the rigor needed for meaningful qualification. The science of quantitative imaging standards and qualification is a key focus of the QIN.

Data collection and image analysis for imaging endpoint determination

Central collection of imaging data is an essential need for a therapeutic clinical trial using quantitative imaging endpoints. Once collected, it is important that the data are transferred in a timely fashion to a central collection and/or analysis site. De-identification of image sets for archiving and central analysis can be a challenge because advanced imaging methods often use private tags in the DICOM (Digital Imaging and Communications in Medicine; a widely-used standard for distributing and viewing medical images) header for image acquisition parameters that are too new to have passed through the DICOM standards process. Private tags were developed to allow vendors to store any information they wished. This allowed backward compatibility with older software, but means that Protected Health Information may sometimes be present. They also provide a place to put parameters for new imaging methods before standards 'catch up'. Therefore, it can be important to remove some private tags to protect confidentiality but also important to maintain them when they contain important acquisitions parameters. Another challenge is the need to receive and archive images from many different types of devices, a process that has been aided by increasing image format standardization (30-32).

Image analysis presents a similar problem, assuring that the imaging metrics obtain from each measurement are consistent and reproducible, and meet the needs of the specific response criteria being used. A recent innovation involves directing the patient towards a different therapy or arm of the trial based on the results of early time point imaging data; i.e., an integral biomarker (33). In addition to requiring consistent and reproducible assessment, there is a necessity of having a panel of experts connected by a virtual network can provide centralized reads within 48 hours of acquisition. Thus, an active area of investigation, and an important focus of the QIN, is the development of tools for increasingly automated and reproducible image endpoint assessment.

Auditing and quality control for quantitative imaging data

Given the importance of assuring adherence to the imaging protocol, it is critical that the central data collection and/analysis facility site receive the data quickly, and then validate both adherence to the technical parameters, and that the images are acceptable for analysis. If the data might be submitted for FDA-approval of a therapy, it is essential to have a well-documented pathway from acquisition to final results posting. Once the images are transferred for analysis the processing methods that may be required for the new imaging methods must be understood, supported, and validated for all imaging devices included in the study; thus, careful management of all devices at all sites is required and any changes to analysis software must be confirmed to have no impact on measurements. Advances in imaging annotation and mark-up (34,35) provide a record of reader interpretation and image analysis and will be valuable tool in this regard. A final point to note is that experimental imaging methods may pose additional challenges for auditing and regulatory oversight, such as the need to carry out the study under an “investigational new drug/device” for investigational imaging probes or devices (see, e.g., 16).

Final thoughts on supporting imaging in clinical trials

This short discussion illustrates the logistic, technologic, and scientific infrastructure needs for deploying quantitative imaging in cancer clinical trials. The complexity and breadth of these needs have led to consolidation of efforts at individual cancer centers (many of whom have image shared resources, or “cores” providing such support), in pharma (where imaging Clinical research organization are frequently used), and clinical trials organizations (which has developed a centralized National Clinical Trials Network (NCTN) imaging core lab). Through its support of quantitative imaging expertise and research, the QIN provides a resource that supports the science of quantitative imaging and tools for quality control, standardized image acquisition, image analysis, and trial management key to cancer therapeutic trials.

Conclusions

As therapeutic regimens continue to grow in complexity and precision, the current clinical methods of radiological assessment of response will inevitably become inadequate. Emerging quantitative imaging methods are available for wide-scale deployment currently, and will increase in the immediate future. We posit that the current dearth of quantitative imaging in clinical trials is maintained because of insufficient awareness of the value of well defined and validated imaging endpoints in clinical trials, as well as the lack of organized infrastructure to effectively implement these alternative imaging biomarkers. These barriers are not insurmountable and it is our hope that the specific steps (outlined in section 5) will encourage and guide the oncology and imaging communities to deploy quantitative imaging techniques in clinical trials to facilitate precision care for cancer patients.

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Table 1
Common imaging metrics that are appropriate for application in cancer clinical trials

Imaging Modality	Parameter	Interpretation	Biological Strengths/Weaknesses	Technical Strengths/Weaknesses	Acquisition Needs	Analysis Needs
Volumetric CT	tumor volume	volume of tumor in mm ³	Provides data to immediately assess tumor burden/non-specific	Only requires routinely acquired clinical data/time consuming	high spatial resolution	standard of care software packages; some user skill
DCE-CT	tumor enhancement	qualitative or semiquantitative assessment of perfusion/permeability	Insight into tumor vascular properties/qualitative in nature, additional radiation dose	Easy to perform in the clinical setting/does not allow for quantitative interpretation	high spatial resolution, modest temporal resolution	standard of care software packages
DCE-CT	vessel perfusion and permeability	blood flow in units of mL(blood)/min mL(tissue)/min and permeability surface area product in unit of mL/s	Knowledge of tumor vascular properties/mixed measures of two vascular characteristics, additional radiation dose	Increased level of rigor/requires local expertise and proper software to execute properly	high temporal resolution, arterial input function	specialized software; close interaction with imaging core
DCE-CT	volume fractions	fraction of voxel that is (e.g.) blood or extravascular extracellular space	Knowledge of intra-tumoral make-up/Unproven clinical value, additional radiation dose	Increased level of rigor/requires local expertise and proper software to execute properly	high temporal resolution, arterial input function	specialized software; close interaction with imaging core
DCE-MRI	tumor enhancement	qualitative or semiquantitative assessment of perfusion/permeability	Insight into tumor vascular properties/qualitative or semiquantitative in nature	Easy to perform in the clinical setting/does not allow for quantitative interpretation	does not require high temporal resolution, moderate to high spatial resolution	standard of care software packages
DCE-MRI	vessel perfusion and permeability	contrast agent transfer rate constant in units of min ⁻¹ containing both blood flow in units of mL(100 mL tissue) ⁻¹ min ⁻¹ and permeability surface area product in unit of min ⁻¹	quantitative measure of tumor vascular properties/accuracy and precision prone to variations in data acquisition and analysis	Increased level of rigor in quantitative analysis/requires local or central expertise and proper software to execute properly	determination of pre-contrast T ₁ and arterial input function, high temporal resolution	specialized software (in-house, commercial, or publicly available); close interaction with imaging scientists
DCE-MRI	volume fractions	fraction of voxel that is (e.g.) blood or extravascular	quantitative measure of intra-tumoral make-up/accuracy and precision prone to variations in data acquisition and analysis	Increased level of rigor in quantitative analysis/requires local or central expertise and proper software to execute properly	determination of pre-contrast T ₁ and arterial input function, high temporal resolution	specialized software (in-house, commercial, or publicly available); close interaction with imaging scientists

Imaging Modality	Parameter	Interpretation	Biological Strengths/Weaknesses	Technical Strengths/Weaknesses	Acquisition Needs	Analysis Needs
DW-MRI	apparent diffusion coefficient	extracellular space extracellular space quantitative assessment of cell density	Estimates of cellularity/non-specific	Straightforward to implement in clinical settings/ADC quantification can be dependent on selection of diffusion weightings	multiple image sets with different diffusion weightings	standard of care software packages or specialized software (in-house, commercial, or publicly available)
FDG-PET	accumulation of tracer	qualitative assessment of glucose utilization	Well understood interpretation in context of cancer/difficult to interpret for organs with high background	Easy to perform in clinical setting/quantification issues	brief scan 60 minutes post injection	standard of care software packages
FDG-PET	SUV	semi-quantitative assessment of glucose utilization	Provides rough estimate of glucose utilization/unclear clinical utility	Easy to perform/lacks rigor and meaning	brief scan 60 minutes post injection	standard of care software packages; some user skill
FDG-PET	kinetic analysis	quantitative assessment of delivery, retention, and utilization of glucose	Well-defined interpretation/unclear clinical utility	Increased level of rigor/requires local expertise and proper software to execute properly	dynamic acquisition over the uptake time (~60 min)	specialized software; close interaction with imaging core
FLT-PET	accumulation of tracer	qualitative assessment of cell proliferation	Provides rough estimate of proliferation/difficult to interpret for certain tumors	Easy to perform in clinical setting/quantification issues	brief scan 60 minutes post injection	standard of care software packages
FLT-PET	SUV	semi-quantitative assessment of cell proliferation	Provides rough estimate of thymidine kinase activity/unclear clinical utility	Easy to perform/lacks rigor and meaning	brief scan 60 minutes post injection	standard of care software packages; some user skill
FLT-PET	kinetic analysis	quantitative assessment of delivery, retention, and utilization of cell proliferation	Well-defined interpretation/unclear clinical utility	Increased level of rigor/requires local expertise and proper software to execute properly	dynamic acquisition over the uptake time (~60 min)	specialized software; close interaction with imaging core