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Summary of the UPICT Protocol for ^{18}F-FDG PET/CT Imaging in Oncology Clinical Trials

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Abstract

The Uniform Protocols for Imaging in Clinical Trials (UPICT) ^{18}F-FDG PET/CT protocol is intended to guide the performance of whole-body FDG PET/CT studies within the context of single- and multiple-center clinical trials of oncologic therapies by providing acceptable (minimum), target, and ideal standards for all phases of imaging. The aim is to minimize variability in intra- and intersubject, intra- and inter-platform, interexamination, and interinstitutional primary or derived data. The goal of this condensed version of the much larger document is to make readers aware of the general content and subject area. The document has several main subjects: context of the imaging protocol within the clinical trial; site selection, qualification, and training; subject scheduling; subject preparation; imaging-related substance preparation and administration; imaging procedure; image postprocessing; image analysis; image interpretation; archiving and distribution of data; quality control; and imaging-associated risks and risk management.

Keywords

fluorodeoxyglucose; PET CT; protocol; guideline

The Uniform Protocols for Imaging in Clinical Trials (UPICT) working group, supported by the Radiological Society of North America and the Clinical and Translational Science Awards from the National Institutes of Health, has developed a detailed template to specify

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No potential conflict of interest relevant to this article was reported.

the use of imaging in a clinical trial. This template was used in writing the FDG PET/CT Protocol document, which is intended to guide the performance of whole-body ^{18}F-FDG-PET/CT studies within the context of single- and multi-center clinical trials of oncologic therapies by providing acceptable (minimum), target, and ideal standards for all phases of the imaging (1). The aim is to minimize variability in intra- and intersubject, intra- and interplatform, interexamination, and interinstitutional primary or derived data.

FDG PET/CT studies performed in accordance with this protocol could have potential utility in the use of qualitative, semi-quantitative, or quantitative data for single-time-point assessments (e.g., diagnosis, staging, eligibility assessment, or investigation of predictive or prognostic biomarkers) or for multi–time-point comparative assessments (e.g., response assessment or investigation of predictive or prognostic biomarkers). More generally, such standardization of FDG PET/CT within the conduct of clinical trials should support internal decision making in drug, biologic, and device development, provide data to support registration and market-label indications, and allow the eventual qualification of one or more imaging biomarkers (perhaps as surrogates for clinical endpoints) by supporting metaanalyses of multiple clinical trials (possibly over different compounds or devices and as contributed by different companies).

This protocol is complementary to recently published guidelines by the Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine (2) that are focused primarily on the clinical and quantitative FDG PET/CT imaging procedure. There is some inevitable overlap in the two documents, but the emphases and goals are different. Although focused primarily on the use of FDG PET/CT in the conduct of oncologic clinical trials, the UPICT Protocol has significant utility in reducing the bias and variability of imaging studies in clinical practice. Similarly, the recently published society guidelines (2) contain information useful in conducting clinical trials, but the information is not as in-depth as that provided in the UPICT Protocol.

The protocol presented here represents the work of people from around the world and from the following organizations: Society of Nuclear Medicine and Molecular Imaging Clinical Trials Network, UPICT, and Quantitative Imaging Biomarkers Alliance, which are supported by the Radiologic Society of North America and the European Association of Nuclear Medicine. Many of the concepts were derived from earlier papers (3,4). The publication of this UPICT guideline coincides with the “Profile” technical specifications developed by the FDG PET/CT oncology group of the Quantitative Imaging Biomarkers Alliance (5). The FDG PET/CT Profile is a document that includes a claim on the measurement performance of FDG PET/CT imaging if certain conditions are met. These conditions include a subset of the UPICT components listed below, as well as requirements on equipment, software, and other components of the imaging chain. The imaging protocol components of the FDG PET/CT Profile were based on the UPICT Protocol. However, although the two documents have similar protocol components, they are not identical.

This document, which is a condensed version of the detailed UPICT Protocol, provides a comprehensive overview; readers contemplating using the protocol to assist in designing a

clinical trial should consult the original document, which is available online as a supplemental data file (supplemental materials are available at http://jnm.snmjournals.org).

The organization and major headings in this document match the organization of the UPICT template and of the full FDG PET/CT Protocol.

CONTEXT OF THE IMAGING PROTOCOL WITHIN THE CLINICAL TRIAL

Utilities and Endpoints of the Imaging Protocol

The protocol should explicitly state the purpose for which the FDG PET/CT study will be used in the clinical trial. The protocol should be clear as to the specific qualitative, semiquantitative, or quantitative metrics that will be used.

Timing of Imaging within the Clinical Trial Calendar

The protocol should specifically define an acceptable time interval between the FDG PET/CT image acquisition and the index intervention and therapeutic interventions (e.g., chemotherapy, radiotherapy, or prior treatment). The protocol should also define an acceptable timing variance for performance of FDG PET/CT studies.

Suggested parameters for the timing of FDG PET/CT within oncologic trials include the following: When the results of FDG PET/CT are a study entry criterion, the acceptable time interval for baseline scanning before initiation of the index intervention is 28 d, the target time is 21 d, and the ideal time is 14 d. For FDG–avid and evaluable tumors, the minimum interval between the last dose of chemotherapy or biologic therapy and FDG PET imaging ideally should be 10 d, with an acceptable interval of up to 14 d. If FDG PET/CT is being used during an ongoing treatment schedule (perhaps as an early predictor of response), the test should be performed at an interval determined by factors such as treatment type, specific cancer diagnosis, specific treatment target, and details of the treatment schedule. In trials that include radiation treatment, the minimum delay after the end of therapy is 8 wk for acceptable performance and at least 3 mo for target-level performance. When FDG PET/CT is used to assess the response of lymphoma, imaging should not be performed until at least 3 wk after the completion of chemotherapy for acceptable performance and 8–12 wk for target performance. For intratherapy evaluation, studies may be performed during therapy.

Protocol Requirements

The imaging protocol must contain documentation on how preenrollment imaging should be managed; specifically, will imaging obtained before enrollment be used as baseline imaging and, if so, under what specific conditions.

The clinical trial protocol should explicitly state the management of FDG PET/CT (and all other imaging tests) performed outside the specified time window of scheduled imaging. The clinical trial protocol should also describe in detail how FDG PET/CT studies that are not performed according to the clinical trial protocol specifications (and associated documents such as the imaging manual and site manual) should be managed.

The UPICT Protocol addresses the performance of FDG PET/CT only in the context of a clinical trial. However, since imaging studies other than FDG PET/CT might influence the conduct of the clinical trial, including the timing and performance of the FDG PET/CT studies, the clinical trial protocol should explicitly state how all imaging tests should be managed with regard to the conduct of the trial.

Subject Selection Criteria Related to Imaging

Relative Contraindications and Remediations—Inability to comply with or tolerate FDG PET/CT imaging may be a relative exclusion criterion. A plasma glucose level above the threshold stated below may necessitate rescheduling of the FDG PET/CT study. Performing FDG PET scanning on subjects who have recently (within 24 h) received steroids may affect glucose control and hence standardized uptake value (SUV) quantitation.

Absolute Contraindications and Alternatives—The protocol should specifically define a threshold blood glucose level that should represent an absolute exclusion criterion for participation in any clinical trial that depends on FDG PET/CT imaging for any primary or a quantitative secondary endpoint. The threshold of 200 mg/dL (~11.1 mmol/L) (6) is the most widely used. Another level, suggested by the European Association of Nuclear Medicine, is a blood glucose level of no more than 126 mg/dL (~7.0 mmol/L) (4). This level is rigorous and should be regarded as ideal. However, the level is so low that it may significantly impair subject accrual.

Additional suggested exclusion criteria include weight exceeding table limits and a history of life-threatening allergic reactions to contrast medium if used in the study.

Relative contraindications become absolute when they can no longer be remediated. When the FDG PET/CT imaging endpoint is a trial endpoint, the subject would be excluded from the trial.

Imaging-Specific Inclusion Criteria—When longitudinal FDG PET/CT measurements are to be used as a primary endpoint, a minimum baseline tumor FDG avidity based on SUV (e.g., the most FDG–avid tumor activity should be greater than 1.5 times the hepatic mean + 2 SDs) is necessary for a subject to be eligible for the study. A minimum lesion size or number may also be necessary.

SITE SELECTION, QUALIFICATION, AND TRAINING

Personnel Qualifications

Before trial activation and subject accrual, each site must have technical, physics, physician, and radiochemistry personnel trained in the use of FDG PET/CT in oncologic clinical trials.

Technical—Appropriate education, training, and certification of technologists are required before they can perform oncologic FDG PET/CT. Certification should be equivalent to the recommendations published by the Society of Nuclear Medicine and Molecular Imaging Technologist Section and the American Society of Radiologic Technologists (7).

Physics—Individuals serving as physicists in a clinical trial using FDG PET/CT should be certified in medical nuclear physics or radiologic physics by the American Board of Radiology or the American Board of Science in Nuclear Medicine, or they should hold equivalent certification in other countries. Otherwise, it is acceptable that they are able to demonstrate equivalent training and experience.

Physician—Imaging experts interpreting PET/CT scans should have appropriate, documented, training in both PET and CT (8).

Other (e.g., Radiochemistry, Radiobiologist, or Pharmacist)—For oncologic FDG PET/CT, the qualifications of the personnel involved in the preparation of the FDG should comply with the specifications of title 21 of *Code of Federal Regulations* part 212 or the international equivalent, as appropriate to the regulatory jurisdiction within which the FDG will be administered. In the United States after December 12, 2015, FDG obtained for use in clinical medicine (i.e., commercially marketed) must be obtained from a manufacturer that has obtained Food and Drug Administration (FDA) approval of the FDG (under either a new drug application or an abbreviated new drug application). After that date, all other uses of FDG that has been produced from a source not approved by the FDA must be in accordance with an FDA investigational new drug application or an approved Radioactive Drug Research Committee application.

Imaging Equipment

Use of a standardized phantom to qualify a scanner is the minimum acceptable requirement for clinical trials. If detectability, resolution, and contrast recovery are a critical component of the trial, use of a standardized multicompartmental phantom is required.

The attributes of the qualified PET/CT systems and ancillary systems should be specified in the imaging portion of the protocol and should include, at a minimum, detector scintillators other than NaI (bismuth germanate, gadolinium silicate, lutetium oxyorthosilicate, or lutetium–yttrium oxyorthosilicate); a full detector array for tomographic imaging; a multislice CT scanner, preferably with at least 4 detector rows; and a dose calibrator capable of measuring positron activity.

Infrastructure

All sites participating in an oncologic clinical trial using FDG PET/CT must have oversight by an Institutional Review Board or an equivalent group; a Radiation Safety Committee or an equivalent body; and an entity designated to oversee the privacy of personal health care information (e.g., Health Insurance Portability and Accountability Act Board or equivalent). Participating sites must also have the infrastructure to perform the specified acquisition, archiving, anonymization, and transfer of imaging data as required by the trial protocol, along with the ability to perform and report the quality control (QC) procedures specified within the trial protocol.

Protocol-Specific Training

For clinical trial personnel performing FDG PET/CT imaging, the protocol should enumerate any protocol-specific training not covered in the “Personnel Qualification” section above.

SUBJECT SCHEDULING

Before scheduling an FDG PET/CT study, diabetic subjects should test their ability to maintain reasonable fasting blood glucose (FBG) levels while avoiding insulin close to the time of FDG administration. For known diabetic subjects with anticipated FBG measurements of between 126 and 200 mg/dL (~7.0–11.1 mmol/L) on the day of the examination, the following scheduling recommendations apply.

Ideal, or Target

Subjects with type I or II diabetes should be scanned early in the morning, before breakfast, and insulin or hypoglycemic medication should be withheld if glucose levels remain in the acceptable range. Whether the morning medication will need to be withheld should be established from morning FBG levels before the study.

Less Desirable but Acceptable

Subjects with type I or II diabetes who cannot reliably attain acceptable glucose levels early in the morning should be scheduled for late-morning imaging, should eat a normal breakfast at 7 AM, should take their normal morning diabetic drugs, and then should fast for at least 4 h before the examination. This strategy is acceptable for nonquantitative PET/CT, for endpoints that are not for the primary aim, and for subjects whose baseline study was performed with an FBG of less than 200 mg/dL (~11.1 mmol/L) but who have become hyperglycemic secondary to treatment effect or disease progression.

SUBJECT PREPARATION

Before Arrival

The main purpose of subject preparation is to reduce physiologic FDG uptake in normal tissue while maintaining and optimizing tracer uptake in the target structures (tumor tissue).

Diet—Subjects should eat no food (either oral or parenteral) for an absolute minimum of 4 h before FDG injection to achieve acceptable performance (target performance is a minimum of 6 h). Subjects scheduled for morning PET/CT should not eat after midnight and should preferably have a light meal the evening before the PET/CT study. Subjects scheduled for afternoon PET/CT may have a light breakfast before 8 AM. Medication can be taken as prescribed. It may be prudent to follow a low-carbohydrate diet for 24 h before the study, with fasting for the final 6 h, but this recommendation is optional.

Fluid Intake—Subjects should be well hydrated (before and after FDG administration) both to ensure a low FDG concentration in the urine and to reduce radiation exposure, particularly to the kidneys and bladder. The protocol should be uniform for the trial.

Other Activities—Subjects should avoid strenuous exercise before the PET/CT examination for a minimum of at least 6 h (ideally 24 h).

Premedication for Iodinated Contrast Reactions—Performing FDG PET/CT in the context of recent (within 24 h) steroid administration may affect a subject's glucose control and hence SUV quantitation. Consequently, if the protocol requires CT with intravenous contrast enhancement in addition to the PET/CT examination, special consideration is needed for subjects with an iodinated contrast allergy, who will require steroid premedication.

On Arrival

On arrival of the subject, compliance with preprocedure instructions should be documented on case report forms, as well as the occurrence of any potentially confounding events.

Ancillary Testing—Subject height and body weight must be measured precisely at the time of the baseline study. For serial studies, weight should be measured directly before each PET/CT study.

Management of prescan FBG results is needed on the day of the FDG PET/CT study. For known diabetic subjects with an FBG of less than 200 mg/dL (~11.1 mmol/L), the baseline scan should be performed as scheduled, given the caveats described in the "Subject Scheduling" section above and the inclusion and exclusion criteria described in the "Subject Selection Criteria Related to Imaging" section above. Specifically, if a subject has an FBG of less than 200 mg/dL (~11.1 mmol/L), the cause should not relate to administration of regular or short-acting insulin within the 4 h preceding the PET/CT study. For known diabetic subjects (and subjects not previously known to be diabetic) with an FBG of more than 200 mg/dL (~11.1 mmol/L), the baseline or follow-up scan should be rescheduled only if the quantitative FDG PET/CT results are to be used as a primary endpoint. However, if the FDG PET/CT examination is contributing to secondary or exploratory endpoints or is being used as a qualitative measure, the subject does not need to be rescheduled. To achieve target performance, the baseline scan should be rescheduled and the referring physician should be contacted if a subject not known to be diabetic has an FBG of more than 150 mg/dL but less than 200 mg/dL (~8.3–11.1 mmol/L). Consideration should be given to handling the data differently for subjects who have a significant change in FBG between baseline and follow-up studies.

Preparation for Examination—To avoid altered biodistribution of the FDG, it is critical that subject preparation after arrival and before imaging be standardized among all sites and subjects throughout the trial. The waiting and preparation rooms should be relaxing and warm (>75°F [22°C]) during the entire uptake period. Blankets should be provided if necessary. The subject should remain recumbent or may be comfortably seated; activity and conversation should be minimized. The subject should void immediately (5–10 min) before the FDG PET/CT image acquisition phase of the examination.

IMAGING-RELATED SUBSTANCE PREPARATION AND ADMINISTRATION

FDG must be produced under current good manufacturing practices, as specified by the FDA (title 21 of *Code of Federal Regulations* part 212), European Union, European Pharmacopeia, or another appropriate national regulatory agency.

Substance Description and Purpose

A brief statement about FDG as the imaging agent should be included in the clinical trial protocol where appropriate; for example: “FDG is a glucose analog. Its use in oncology is based on the fact that most types of tumors use more glucose than most other types of normal tissue.”

Dose Calculation or Schedule

The method to determine the FDG dose should be included in the clinical trial documentation. The dose may be specified as fixed or as per kilogram of body weight with a range of acceptability, and the dose may be tied to 2-dimensional versus 3-dimensional scanning modes and acquisition time per bed position.

Timing, Subject Activity Level, and Factors in Initiation of Data Acquisition

It is extremely important that the time interval between FDG administration and the start of emission scanning be consistent and that when a scan is repeated on the same subject, the same interval be used. For the baseline study, the time between FDG administration and the start of emission scanning should be 60 min, with an acceptable window of 55–75 min. When a scan is repeated on the same subject, it is essential to apply the same time interval with an acceptable variance of ±15 min (with a target of ±10 min), provided that the scan does not begin before 55 min after injection of FDG.

Administration Route

FDG should be administered intravenously through a large-bore (≥21 gauge) indwelling catheter placed anatomically remote from any sites of suspected disease (e.g., in the extremity contralateral to the site of disease), preferably in an antecubital vein. Intravenous ports should be used only if no other venous access is available.

Administration Apparatus

Either manual or automated injection systems may be used to administer the FDG. When manual administration is used, a 3-way valve should be attached to the intravenous cannula to allow at least a 10-mL flush with normal saline after FDG injection. When an automated administration system is used, the manufacturer’s instructions should be followed.

IMAGING PROCEDURE

Required Characteristics of Resulting Data

Data Content—For most oncology indications, images should cover the skull base (external auditory meatus) to the mid thigh. If other ranges are used, such as the whole body, the clinical trial protocol should provide specific instructions with justification. The

scanning direction should be caudocephalad to minimize effects from increasing bladder activity during the scan. The scanning direction specified in the protocol should be duplicated at follow-up time points.

Either of two different scanning strategies can be used for FDG PET/CT acquisition.

Strategy 1 is applied for FDG PET/CT in which the CT portion is used for attenuation correction and localization only (no diagnostic CT intent). A CT scout scan (also called a topogram) is followed by a CT scan for anatomic localization and attenuation correction, which is followed by a PET emission scan.

Strategy 2 is applied for FDG PET/CT in which diagnostic CT is performed in conjunction with FDG PET. With no or minimal patient motion, the contrast-enhanced CT scan is acquired after the PET emission scan. There are other feasible approaches, but they are less desirable.

- Contrast Material. The presence of a positive contrast agent (intravenous or oral) can affect the CT attenuation map and result in variability of the quantitative SUV evaluation. Therefore, intravenous contrast material should not be administered before the PET scan. Dilute positive oral contrast material is acceptable, although if possible it should be avoided.
- Respiratory Motion Compensation. Respiratory motion causes SUV errors through motion blurring and attenuation correction mismatches between the CT transmission map and the emission data. The subjects should be asked to use similar shallow breathing during both the PET and the CT acquisitions; respiratory gating might be used if called for in a given protocol.
- CT Technique. The actual kVp and exposure (CT dose index, dose–length product) for each subject should be recorded at each FDG PET/CT imaging procedure. CT dose exposure should be appropriately reduced in smaller patients and children. The CT technique (mAs, pitch, collimation, kVp, and slice thickness) should result in an exposure that is as low as reasonably achievable yet meets the goal of the imaging study. The technique used for a particular subject should be repeated during all subsequent FDG PET/CT procedures on that subject while in the clinical trial.

Performance of a single diagnostic-quality CT study before or after the emission scan for all purposes (i.e., anatomic localization, attenuation correction, and diagnostic CT information) is considered unacceptable for clinical trial use.

Data Structure—The matrix size, slice thickness, and reconstruction zoom should yield a target reconstructed voxel size of 3–4 mm in all 3 dimensions (i.e., not achieved through postprocessing), although not necessarily isotropic. Ideally, the reconstructed voxel size should be as small as possible without introducing artifacts and should be consistent across all clinical trial sites.

Data Quality—Image quality and quantitative output should be such that when the same acquisition and reconstruction protocol as used in subject scanning is applied to the protocol-specified phantom, the output should meet QC standards as stated in the "QC Procedures" section below.

Imaging Data Acquisition

All serial scans on any individual subject should be performed on the same previously qualified scanner for each time point if quantitative results are to be used for primary or secondary trial endpoints.

The time per bed position should be related to injected dose, patient body habitus, and scanner sensitivity. Typically, the times range from 2 to 4 min for 3-dimensional systems. In general, increased scanning time per bed position will improve image quality and may be useful when quantitative metrics are used as a primary endpoint.

During PET/CT, subjects should be positioned preferably with their arms over their head, to minimize beam-hardening and field-of-view truncation artifacts. Alternatively, the arms can be positioned along the sides of the patient for head and neck imaging.

Imaging Data Reconstruction

PET emission data must be corrected for scanner geometry and detector efficiency (i.e., normalization), system dead time, random coincidences, scatter, and attenuation. Attenuation correction should be performed using CT images. Images should also be reconstructed without attenuation correction to allow for QC assessment by visual inspection of attenuation correction artifacts. The CT and PET images should be inspected to confirm adequate coregistration, and any misregistration should be documented because it may invalidate the data. PET scanners must be cross-calibrated with the specific dose calibrator that is used to measure patient doses. Ideally, PET scanners and dose calibrators should be calibrated using traceable standards, such as National Institute of Standards and Technology ^{68}Ge or the appropriate regional regulatory equivalent.

IMAGE POSTPROCESSING

Definitions of Input Data

Raw Data—*Raw data* is an ambiguous term, as it can refer to scanner raw data (i.e., sinograms or list-mode) or image raw data. This term should not be used.

Raw Projection Data—The term *raw projection data* refers to data as acquired by the scanner before reconstruction (i.e., sinograms or list-mode). When this term is used, the user should specify the exact type of raw projection data.

Reconstructed Image Data—The term *reconstructed image data* refers to image data exactly as produced by the reconstruction process on the PET/CT scanner; that is, a stack of Digital Imaging and Communications in Medicine (DICOM) slices constituting a PET image volume with no processing other than that occurring during image reconstruction.

Postprocessed Image Data—Postprocessed image data are from an image that has been transformed in some manner, including but not limited to, smoothing, sharpening, image zooming, rotation or translation, resampling, interpolation, slice averaging, and maximum-intensity projection. Postprocessed image data are typically a stack of DICOM slices.

Secondary Image—*Secondary image* is an ambiguous term, as it can refer to either postprocessed image data or a DICOM secondary capture image. This term should not be used.

Methods

After data collection and image reconstruction as detailed in the "Imaging Procedure" section above, reconstructed image data (PET images) are generated that meet the image characteristics defined by the trial. For both visualization/interpretation and quantification, no unintended additional image processing (interpolation, rebinning, reorientation, zooming) should be applied to the originally reconstructed PET data.

Postprocessed data may be used for visualization and to facilitate placement of the region of interest (ROI) or volume of interest (VOI). However, the underlying reconstructed image data should be used for all quantitative purposes.

If images are anonymized to remove protected health information, no information that affects quantitation should be removed.

IMAGE ANALYSIS

Input Data and Covariates for Analysis

Image quantitation is typically performed by determining the SUV of a tumor and, ideally, of a reference normal organ (liver or aorta). SUV can be calculated in several ways. The most common are SUVbw (with reference to body weight), SUVlbm (with reference to lean body mass), and SUVbsa (with reference to body surface area [rarely used]).

The SUV measure to be used should be specified for each protocol and should be applied consistently at all sites, across all subjects and all imaging time points, and for all lesion measurements. Each SUV statistic defined above may be measured in different ways: as SUV_{max} (single-voxel [hottest voxel in tumor ROI or VOI]), SUV_{mean} (mean SUV for ROI or VOI), or SUV_{peak} (subcategory of SUV_{mean} in which volume [3-dimensional] or area [2-dimensional] is defined specifically).

Methods

The ROI (or VOI) tool needs to be prescribed. The UPICT Protocol lists a catalog of potential strategies but does not stipulate any one as preferred. However, the trial design should specify the strategy to be used. Strategies can be manual, semiautomated, or automated. Manual requires the intervention of an expert interpreter to define ROI or VOIs. Semiautomated requires some user intervention to define tumor boundaries, usually threshold-based. Automated requires no user intervention. Values derived from automated

and semiautomated methods may vary between software platforms and even versions of the same software.

IMAGE INTERPRETATION

Methods

Image interpretation methods take the input data and then discriminate (qualify as a lesion and, if so, then target or nontarget); compare (to baseline); and derive (or use a combination of target/nontarget/presence of new disease/absence of new disease to describe, stratify, and potentially classify into discrete response assessment categories [response, stable disease, progressive disease] to obtain output data).

Minimum Metabolic Threshold—In this interpretation method, a minimum FDG avidity is required and should be specified in the clinical trial protocol. This minimum can be determined by either a subject-specific threshold, as proposed by PERCIST (9), or a general cutoff. For a general cutoff, an SUV_{max} of 4 is suggested for all target lesions, although in settings such as the lung or breast a lower minimum SUV_{max} may be acceptable.

Anatomic Lesion Size—This interpretation method takes into account the influence of anatomic measurability of lesion size, including the reportability of lesion anatomic size. Lesions selected as targets on the basis of meeting minimum metabolic activity thresholds as defined in PERCIST need not meet minimum size requirements, although if multiple lesions with similar FDG activity are present, the hottest anatomically measurable lesion is preferable to an FDG–avid lesion that is not anatomically measurable. Tumors should typically be more than 2 cm in diameter at baseline for target lesion inclusion.

Glucose Normalization—It is not clear yet if corrections for glucose level enhance the ability of PET to predict treatment response.

On-Study Evaluation—The workflow for analysis and interpretation of nonbaseline imaging examinations (i.e., on-study evaluations) is based on the response assessment paradigm that has been chosen for the specific clinical trial. Possible approaches include following the single lesion with the most avid FDG uptake that was identified at baseline, measuring the most FDG–avid single lesion but not necessarily the same lesion from time point to time point, summing and following the 5 most FDG–avid lesions as defined on the baseline examination, or summing the 5 most FDG–avid lesions as defined on each examination independently.

In addition, consideration should be given to determination of total lesion glycolysis, which is defined as the product of SUV_{mean} and volume. The use of total lesion glycolysis has not yet been validated across multiple tumor types in a multiinstitutional setting. Hence, this approach is regarded as exploratory at this time.

Summary Output Data (Response Assessment)

Objective Response—The description of response should preserve the intrinsically continuous and quantitative nature of PET SUV. Determination of whether a response has

occurred at all is critical (i.e., if the quantitative alteration is greater than expected due to intrinsic biologic variability and measurement error). It may also be convenient to further classify or categorize response (e.g., PMD, CMR, PMR, and SMD, as defined below). The categorization schema used for a particular clinical trial should be clearly outlined in the protocol before activation and data analysis.

An example categorization schema follows.

- PMD (progressive metabolic disease): defined as a significant increase in tumor uptake compared with baseline. For target lesion assessment, it is proposed that at least a 30% increase in FDG uptake, with at least a 1.0 increase in SUV, be used as the threshold for PMD. Additionally, unequivocal progression of FDG–avid nontarget lesions or new lesions is an indicator of PMD.
- CMR (complete metabolic response): defined as complete resolution of FDG uptake within measurable target lesions; that is, the uptake is less than or indistinguishable from blood-pool levels.
- PMR (partial metabolic response): defined as at least a 30% reduction in measurable FDG uptake in the target tumor as determined by SUV_{max}. The absolute drop in SUV must be at least 1.0 as well. There should also be no increase in uptake in nontarget lesions and no new lesions.
- SMD (stable metabolic disease): not CMR, PMR, or PMD.

Outcome Measures—One outcome measure is best subject response (e.g., CMR, PMR, SMD, and PMD), which is noted during the time from the start of treatment to the time of disease progression or recurrence or of termination of the subject from the clinical trial. Another measure is duration of best response in a given subject, which is measured from the date that the best-subject-response criteria are first met to the date that disease progression or recurrence is first noted or the date that the subject completes the trial follow-up period. A third measure is duration of overall response in a given subject, which is measured from the date that the CMR or PMR criteria are first met to the date that PMD is first noted or the date that the subject completes the trial follow-up period. A fourth measure is time to progression, which is measured from the date that treatment starts to the date that PMD is first noted on PET/CT; the PET/CT examination can be either protocol-specified or unscheduled. A fifth measure is duration of SMD, which, in subjects who do not achieve an observed CMR or PMR, is defined as the time from initiation of therapy to the time of PMD. The final outcome measure is progression-free survival, which is defined as the time from the initiation of therapy to the time of PMD or death; progression-free cancer-specific survival is measured from the time that therapy begins to the time that PMD or death due to cancer occurs.

ARCHIVING AND DISTRIBUTION OF DATA

Central Management of Imaging Data

Data should be stored and transmitted in compliance with the pertinent DICOM standards.

Anonymization Schema

Data anonymization should be performed on a third-party or PACS workstation in a manner that is compliant with the Health Insurance Portability and Accountability Act and with the directions of the clinical trial.

Archiving

The following types of data should be archived: primary source image data, reconstructed image data, postprocessed image data, analysis results, and interpretation results. If possible, the data should be stored indefinitely. Otherwise, the retention period should be in accordance with any applicable regulations.

Quality Control (QC)

QC for the Site

Procedures: The imaging QC section of the clinical trial protocol should specify how site compliance will be verified and documented. There should be specific site report forms and checklists to facilitate the verification and documentation of QC for the following: clock calibration and synchronization, scale and stadiometer calibration, glucometer calibration, dose calibrator performance, and performance of the CT component of PET/CT scanners. Daily CT QC performed before scanning should minimally include air calibration, measurement of water CT numbers and SD, and a check for the absence of artifacts. The PET component of the PET/CT scanner must be cross-calibrated with the same dose calibrator used to assay patient injections. Phantom calibration should be performed at least annually using acceptable standards. QC of PET/CT scanners should, minimally, be performed according to the vendor schedule and specifications.

Baseline Metrics Submitted Before Subject Accrual: Representative human subject images consistent with the specifics of the clinical trial should be carefully examined to finalize site qualification.

Metrics Performed or Submitted Periodically During the Trial: The results of the QC performed per the “Procedures” section above should be provided at least annually and should be available for any site audit.

QC for Imaging-Related Substance Preparation and Administration—FDG must be obtained from a source that is approved by the geographically appropriate regulatory mechanism (e.g., in the United States, an FDA-issued new drug application, abbreviated new drug application, or investigational new drug application).

Other Types of QC—QC procedures must also be in place for injection and imaging of individual subjects, image reconstruction, image postprocessing, image analysis, and image interpretation.

IMAGING-ASSOCIATED RISKS AND RISK MANAGEMENT

Radiation Dose and Safety Considerations

The protocol and informed consent form should describe the estimated administered dose range and estimated whole-body radiation exposure (expressed as effective dose in mSv) for the FDG to be administered and the CT used in conjunction with the FDG PET. In addition, both documents should provide comparator (equivalency) radiation examples. The estimates of radiation dose will be protocol-specific and based on factors such as the number and frequency of studies.

Imaging Agent Dose and Safety Considerations

Recommended text for inclusion in clinical trial protocols is as follows: “There is a potential small risk of allergic reactions from CT contrast agents. No allergic reactions have been reported for FDG.”

Imaging Hardware-Specific Safety Considerations

Per the recommendations of the FDA, before beginning the first CT portion of the PET/CT scan the operator should determine whether implanted or externally worn electronic medical devices are present, and if so, should minimize the radiation exposure to the device.

Management and Reporting of Adverse Reactions to the Imaging Agent

Adverse reactions to FDG PET/CT during the trial should be recorded using an embedded general mechanism for tracking and reporting of such events. It is reasonable to limit the time frame for possible adverse event attribution to less than 24 h after administration.

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