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Clinical Trials Network and the [^{18}F]FLT Demonstration Project

Continuing Education for Nuclear Pharmacists
And
Nuclear Medicine Professionals

By

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COURSE OUTLINE

CLINICAL TRIALS NETWORK AND THE [^{18}F]FLT DEMONSTRATION PROJECT

STATEMENT OF LEARNING OBJECTIVES:

Describe the clinical trials network and the roles pharmacists can have in it.

1. Understand the rationale for the establishment of SNM's Clinical Trials Network
2. Understand the purpose and mechanisms underlying the Biomarker Use Pathway
3. Understand the pharmacology and potential utility of the Biomarker Use Pathway's pilot agent, [^{18}F]FLT

CLINICAL TRIALS NETWORK AND THE [^{18}F]FLT DEMONSTRATION PROJECT

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INTRODUCTION

Society of Nuclear Medicine (SNM) Clinical Trials Network (CTN)

In October, 2007, the Society of Nuclear Medicine (SNM) met with the Food and Drug Administration (FDA), the National Cancer Institute (NCI) and representatives of pharmaceutical industry about the possibility of a multi-center investigational new drug (IND) application for [^{18}F]fluorothymidine (FLT = 3'-deoxy-3'-[^{18}F]fluorothymidine). The SNM formally established the Clinical Trials Network (CTN) in September, 2008 followed by the announcement by the FDA of the approval of the first multi-center IND for FLT on October 1, 2008. Information on the CTN can be found on the SNM website at www.snm.org/clinicaltrials.

The rationale for the establishment of the CTN can be synopsized in the preamble to the webpage home page.

> *A major barrier to the development of new and effective drugs has been the time, complexity and cost of the regulatory process. In recent years, the potential for imaging biomarkers to reduce this burden on the drug development process has become widely accepted as a means to speed the time to clinical use. (http://interactive.snm.org/index.cfm?PageID=8813)*

In other words, the purpose of the CTN is to facilitate the effective use of molecular imaging biomarkers (e.g., radiopharmaceuticals, contrast agents, bioluminescence agents) in multi-center clinical (i.e., therapeutic) trials. Inherently, the "effective use" will require that these imaging biomarkers be validated for their intended purpose (e.g., assess response to treatment, categorize or stratify patients for inclusion in trials) and available for use in a reliable and reproducible fashion whereby the information gathered from this use can be successfully applied in the approval process for therapeutic drugs. To this end, the CTN created the Biomarker Use Pathway designed to coordinate the planning and data collection of the multi-center clinical trials (i.e., CRO-type functions) utilizing the imaging biomarkers; the framework to generate centralized multi-center IND applications (e.g., FLT) and registries for both manufacturing and imaging sites, capable of producing the biomarkers and generating the imaging data,

respectively. Therefore, the CTN, with the cooperation of the FDA, assists in coordinating the three-way cooperation between imaging centers, local manufacturing sites (currently, radiopharmaceutical) and pharmaceutical industry users (Figure 1) all with the expressed purpose to bring new drugs to market in the most expeditious manner.

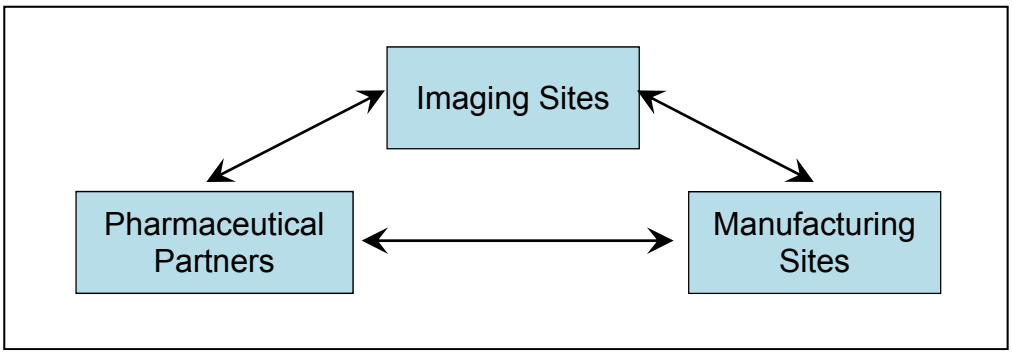


Figure 1. Components of the CTN designed to facilitate the effective use of molecular imaging biomarkers in multi-center clinical trials.

The governance of the CTN consists of a Strategic Planning Committee, whose membership is drawn from the leadership, membership and staff of the SNM, and a series of Operations Committees. The Operations Committees are:

- Scanner Validation Committee
- Database Committee
- Manufacturers Registry Committee
- Trial Design Committee
- Site Qualification Committee
- Site Orientation and Education Committee

Each of these committees is responsible for a given component of the CTN's mission.

Registries

The CTN supports two types of registries, one for imaging centers and one for manufacturing sites. The Imaging Site Registry is designed to ensure that the site has the capabilities necessary to generate quality imaging-based data. Each site must demonstrate that it has state-of-the-art imaging technology, appropriately trained staff and the ability to adhere to standardized methods. Demonstration of this methodological adherence is through participation in the PET Phantom

Program (see Figure 2). Imaging Site registration is required for the participation in therapeutic clinical trials under the auspices of the CTN. No fee is charged for this registration. Currently, more than 200 imaging sites worldwide are registered. Specific information on the Imaging Site Registry is available at http://interactive.snm.org/index.cfm?PageID=8816.

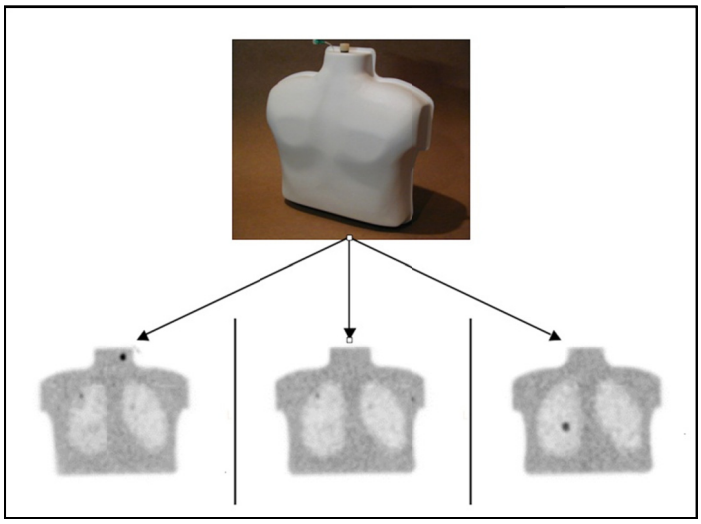


Figure 2.PET Phantom Program. Example of the oncology torso phantom used in the Imaging Site certification and representative PET images illustrating simulated lesions. (Images are courtesy of Dr. Paul Christian and Dr. Michael Graham.)

The purpose of the Manufacturers Registry is the identification and qualification of manufacturing sites capable of the effective execution of the chemistry and manufacturing controls (CMC) of biomarker INDs. Qualification involves the assessment of the site's capabilities with respect to equipment, staffing and management resources. In addition, the Manufacturers Registry is designed to connect pharmaceutical partners interested in using a biomarker with qualified manufacturers within specific geographic areas. Currently, there are more than 200 registered Manufacturing Sites. There is no fee for participation in this registry. Specific information on the Manufacturers Registry is at http://interactive.snm.org/index.cfm?PageID=8818.

Multi-center INDs

The concept of the multi-center IND evolved from the joint efforts of the SNM, FDA and NCI. The original multi-center IND for FLT, a promising but under-utilized biomarker for cell proliferation, was made possible by a letter of cross-reference to a master FLT IND held by the Cancer Imaging Program at the NCI and combined features of the single-site INDs from the Mayo Clinic, University of Iowa, the University of Pennsylvania, the University of Utah, and the University of Washington. Each site had unique end-product specifications and different processes and equipment for manufacturing. The FDA acknowledged that a single manufacturing process and end-point specification was not feasible for all potential users of FLT. Therefore, the FDA has agreed to review both the FLT manufacturing processes on an individual

production site basis and the multiple final products (formulations) for acceptable endpoint specifications. Each manufacturing site must provide their unique CMC information for FDA review. SNM's multi-center INDs will provide the information necessary for cross-reference in the pharmaceutical clinical trials including standardized and harmonized imaging protocols.

Future Biomarker Use Pathway candidates for multi-center INDs will embody the following features. Specifically, have

- Established pharmacology and toxicology.
- Established chemistry and manufacturing (CMC) information from multiple manufacturing sites.
- Established multiple methods for production on different synthesis equipment.
- A minimum of one site with an on-going human study that demonstrates both safety and efficacy of the proposed agent.
- A minimum of one well-defined, clinical (human) imaging protocol.

The Biomarker Use Pathway is not limited to PET agents only but contrast agents for MRI, fMRI, CT, ultrasound (US) and optical imaging agents are all potential candidates for multi-center INDs. The fundamental goal is to provide a means by which imaging information can be widely and consistently applied to address critical questions in therapeutic clinical trials, resulting in reliable data acceptable to the FDA for making drug approval or labeling decisions.

SURROGATE MARKERS IN CANCER TREATMENT

There are significant needs for surrogate markers to assess response to treatment in many diseases, but especially in cancer treatment, whether in treatment trials or to personalize medical care. Cancer is frequently a life-threatening disease, but survival, although the ultimate assessment of the success or failure of a particular therapeutic option, is not a timely or, in some cases, an ethical marker. As molecular medicine evolves, validated markers of critical cellular processes are needed to assess intermediate response measures. In order for the goal of personalized medicine to be recognized, methods need to be developed to determine whether a particular therapeutic course is working or not and at a point of time where viable alternatives remain available. Having a reliable method to predict early in the course of therapy the eventual

patient's outcome will provide for the optimization of treatment. Specifically, a less toxic initial approach, potentially decreasing adverse effects, could be employed if biomarkers, such as imaging changes, could signal the need to intensify treatment or institute an alternative therapy, possibly based on a molecular mechanism refined by information gathered from the biomarker. In addition, the knowledge of probable or impending treatment failure could result in the discontinuation, thereby avoiding the side effects of ineffective treatments, and/or the institution of alternative therapies, such as surgery, in a timely manner. Future directions may be aimed at the molecular characterization of disease (e.g., tumors) so that the *a priori* choice of treatment is made on a rational basis.

Treatment response in oncologic treatment trials is frequently based on the World Health Organization's (WHO) RECIST (**R**esponse **E**valuation **C**riteria **i**n **S**olid **T**umors) measures. RECIST measures are based on changes in tumor size as determined by CT imaging. Recently, an alternative called PERCIST (**PE**T **R**esponse **E**valuation **C**riteria **i**n **S**olid **T**umors), a measure that is based on changes in FDG-based tumor standardized uptake values (SUVs) has been proposed[1, 2]. The merits of RECIST versus PERCIST in the personalization of cancer therapy have recently been reviewed in a special supplemental issue of the Journal of Nuclear Medicine (volume 50, supplement 1, May, 2009).

Part of the factors that influence SUVs in general are presented in Figure 3. The factors in unbolded text are technical in nature and independent of the tracer being imaged. The bolded text are factors that are tracer and/or patient-dependent factors, some of which represent the process of interest (e.g., glucose metabolism) and some of which are nuisance factors that may adversely affect the information content of the images. The effect of blood glucose on FDG SUV is one of these nuisance factors. Figure 4 represents the theorized pharmacokinetic model for the biodistribution of FDG. Cellular uptake and retention of FDG utilizes transport into the cells via the glucose transporters (GLUT) and phosphorylation to FDG-6-P via hexokinase. Both processes operate in competition with endogenous glucose. Furthermore, the action of the various GLUTs are, in some cases, insulin-independent and in others, insulin-dependent. Therefore, the blood glucose level influences the uptake of FDG by competing for transporter and hexokinase action as well as stimulating insulin and the insulin-dependent uptake into tissues

such skeletal muscle and brown fat. Consistency in these types of factors at each imaging time is needed to accurately assess response to treatment with monitoring FDG SUVs.

Although FDG is an incredibly useful radiopharmaceutical for the diagnosis, staging, assessment of response to therapy and evaluation of recurrence, it is not a perfect tracer for malignant disease. FDG uptake maps glucose metabolism, a metabolic process that is not specific to tumor tissues. This results in poor signal-to-noise properties in tissues with naturally high glucose metabolic rates (e.g., brain) and interference from factors that increase glucose metabolism (e.g., inflammation, brown fat). Therefore, there is a need for alternative radiopharmaceuticals for monitoring the response to treatment in malignancy.

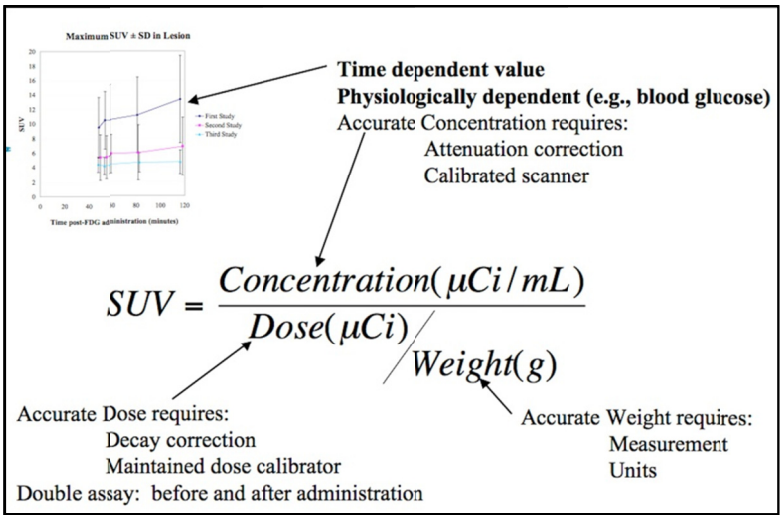


Figure 3. Factors affecting the standardized uptake value (SUV) for [^{18}F]fluorodeoxyglucose (FDG). Note the factors in bold are tracer and/or patient-dependent whereas the other factors are influenced by the technical rigor of the PET Imaging Center.

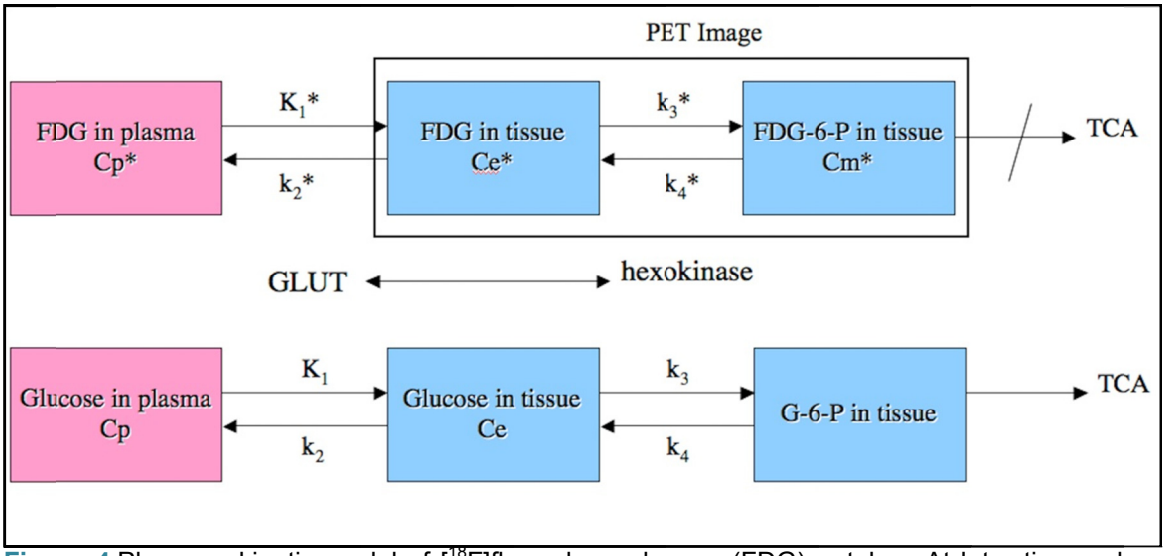


Figure 4. Pharmacokinetic model of [^{18}F]fluorodeoxyglucose (FDG) uptake. At later times when the FDG plasma concentrations are low, the PET image incorporates signal from both FDG in tissue as well as FDG-6-phosphate (FDG-6-P). FDG will compete with endogenous glucose for transport into the cells by the glucose transporters (GLUT) and phosphorylation by hexokinase.

FLT DEMONSTRATION PROJECT

3'-Deoxy-3'-[^{18}F]Fluorothymidine (FLT) is a thymidine analogue utilized as a marker of DNA synthesis and therefore, an index of cellular proliferation. FLT uptake can potentially provide information regarding tumor proliferation, therefore, a means to detect and evaluate the status of tumors and metastases. A synopsis of the chemistry, pharmacology (animals and humans) and dosimetry of FLT can be found in the Molecular Imaging and Contrast Agent Database (MICAD) at http://www.ncbi.nlm.nih.gov/books/NBK23373/.

Comparison of FDG and FLT

Figure 5 compares FDG and FLT imaging and illustrates the similarities and differences between the uptake and distribution of the two radiopharmaceuticals. Both tracers are taken up by tumors, typically, more intensely with FDG than FLT. Both tracers are excreted in the urine, therefore, the urinary tract system, especially the bladder, is "hot", potentially interfering with the detection of lesions in the pelvic area. The liver exhibits moderate uptake with both agents, but there is significantly more uptake in the spleen and heart with FDG than with FLT. Bone marrow exhibits variable uptake, generally at a low to moderate level (unless the marrow is stimulated for example by a colony simulating factor or rebound stimulation in response to prior chemotherapy) with FDG; whereas, bone marrow exhibits intense uptake with FLT. The brain exhibits intense uptake with FDG (because the brain is dependent on glucose metabolism as its primary energy source), whereas, there is essentially no uptake of FLT into the brain because FLT does not cross the intact blood-brain barrier. Contrast-enhanced brain lesions will display FLT uptake (see "brain" entries in Table 1 below for more information).

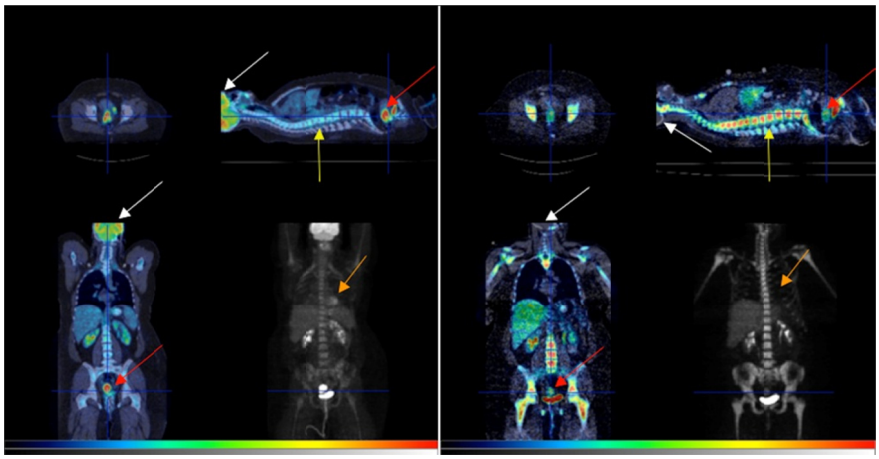


Figure 5. FDG versus FLT imaging. FDG (left panel) and FLT (right panel) of the same patient with cervical cancer. Differences between the two types of images are demonstrated in the uptake in the tumor (red arrows), brain (white arrows), heart (orange arrows) and bone marrow (yellow arrows).

FLT Pharmacology and Pharmacokinetic Model

The pharmacokinetic model generally applied for FLT analysis is presented in Figure 6. This model is a similar configuration (i.e., plasma plus two tissue compartments) as to what is utilized for FDG, however, there are significant differences between the two models. Specifically, 1) intracellular transport uses the nucleoside transporters rather than GLUT; 2) phosphorylation is catalyzed by thymidine kinase rather than hexokinase; 3) available plasma FLT is reduced by metabolism to the glucuronide; and 4) FLT competes with blood thymidine levels rather than blood glucose. Blood glucose level constitutes a significant competition for FDG uptake whereas, the relatively low endogenous thymidine levels in humans do not represent a significant influence on FLT uptake. On the other hand, high endogenous thymidine levels in some strains of mice and rats adversely affects the utility of FLT imaging in pre-clinical work.

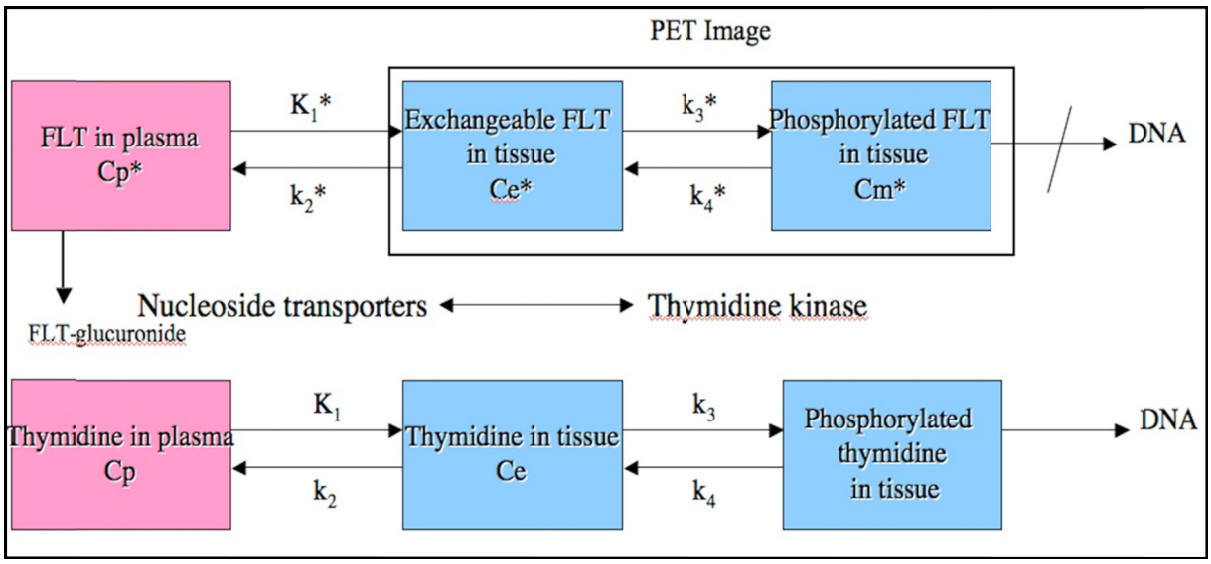


Figure 6. Pharmacokinetic model of [^{18}F]fluorothymidine (FLT) uptake. At later times when the FLT plasma concentrations are low, the PET image incorporates signal from both FLT in tissue as well as phosphorylated FLT. FLT will compete with endogenous thymidine for transport into the cells by the nucleoside transporters and phosphorylation by thymidine kinase (TK1). However, endogenous thymidine levels are relatively low in humans.

As illustrated in Figure 7, the factors that influence FLT SUVs have similar technical components to the determinants for FDG SUVs (gray font –factors, part of which are considered as part of the certification for the Imaging Registry) but the time and physiologically-dependent features are unique to FLT. Diagnostic and monitoring utility of FLT requires that the only factors that induce a change in the SUV are the processes of interest, not nuisance factors such as changes in tracer delivery or sequestration in other organs, and that the relationship between FLT uptake and the pathological process (in this case, proliferation) is consistent between patients.

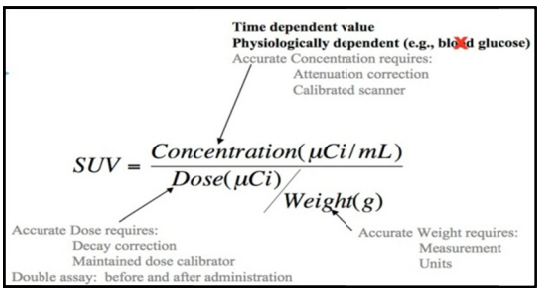


Figure 7. Factors affecting the standardized uptake value (SUV) for [^{18}F]fluorothymidine (FLT). Note the factors in bold are patient-dependent whereas the other factors (gray) are influenced by the technical rigor of the PET Imaging Center and are consistent

FLT Plasma Concentrations and Metabolism

Figures 8 and 9 examine the FLT plasma concentration versus time and the fraction of unchanged FLT versus time for a sample of subjects pre- and mid-therapy. From this information, it appears that when normalized for dose, there is minimal inter- or intrasubject variability in the amount of FLT available for uptake into the tumor/metastases and that this availability is not altered by a cycle of chemoradiation treatment. Consistent availability of tracer to the tissues bodes well for the observed changes with therapy to be reflective of changes in the process of interest, in this case, proliferation. An exception to this pattern could theoretically occur in the case of organ failure that alters the metabolism and/or excretion of the tracer. In the case of liver failure, more unchanged FLT may be available for uptake into the cells, disrupting the usual relationship between SUV and proliferation. In renal failure, reduced clearance of the FLT-glucuronide may increase the FLT plasma levels and reduce the fraction unchanged. For example, in a response monitoring series in head and neck cancer, one of the subjects developed acute renal failure between the pre- and mid-therapy images. The renal failure was likely secondary to high-dose cisplatinum with his serum creatinine precipitously increasing from 0.8 mg/dL to 4.0 mg/dL. Post-therapy, his serum creatinine level returned to 1.4 mg/dL. His pre-therapy FLT plasma levels and metabolism were consistent with those of the

other subjects both pre- and mid-therapy. However, his mid-therapy, unchanged FLT plasma values increased approximately 50% and the fraction of unchanged FLT at 60 minutes decreased by 35% (from 76% to 49%), indicative of the reduced urinary excretion of FLT (Ponto, unpublished). Therefore, if organ function remains stable (even if impaired) across the treatment regimens, FLT delivery to the tumor (and metastases) should remain relatively stable with changes in uptake likely to reflect legitimate changes in proliferation.

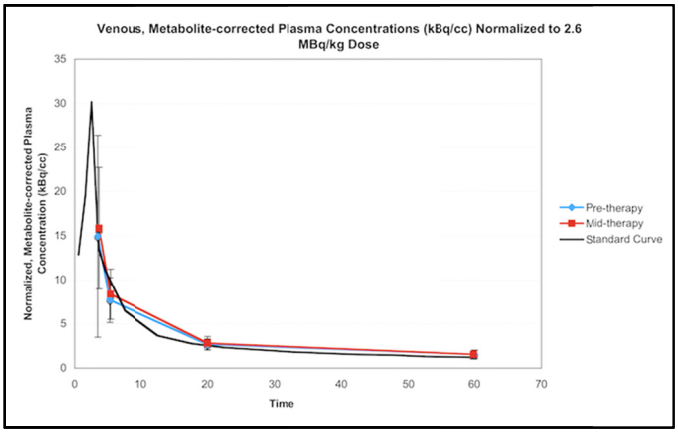


Figure 8. FLT Plasma Concentrations. Plot depicts standard curve for FLT plasma concentration in kBq/cc normalized to a dose of 2.6 MBq/kg derived from arterial blood sampling (Menda, et al., 2009[3]) and venous blood samples pre-therapy (blue diamonds) and mid-therapy (red squares) (derived and updated from Ponto, et al., 2010[4]). Note the small intersubject variability and the lack of change with therapy.

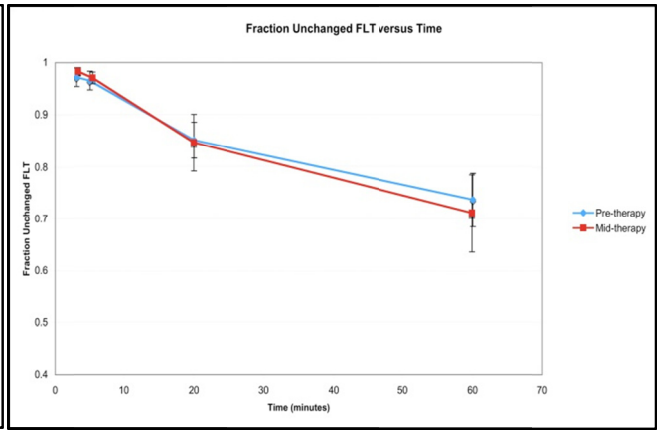
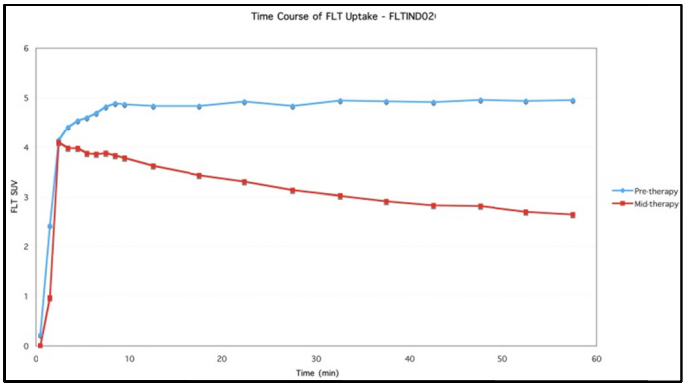


Figure 9. FLT Metabolism. Plot depicts the fraction of unchanged FLT versus time pre-therapy (blue diamonds) and mid-therapy (red squares). Note the small intersubject variability and the lack of change with therapy.

Image Timing

The utility of static imaging for the characterization of a physiological process ideally, especially if the agent will have clinical potential, needs to reach a plateau level within a reasonable period of time, that accurately reflects the pharmacokinetics of the tracer. Or, in other words, for FLT, a parameter such as SUV determined at a time such as 60 – 120 minutes post-injection (a time when count-statistics are adequate with tracer doses that do not impose too large a dosimetry burden) accurately reflects proliferation in a reproducible manner. Figure 10 illustrates the time course of tumor uptake of FLT pre- and midtherapy in two different subjects. Note the rapid increase and plateauing of FLT uptake pre-therapy in both subjects with a more gradual obtainment of a plateau in the mid-therapy imaging. The change in the pattern of the FLT time

course with therapy is driven by changes, primarily, in k_3 (thymidine kinase phosphorylation) with essentially no change in K_1 and k_2 (that is why the initial phases of the time course do not differ significantly). For clinical utility, there needs to be a robust time window for optimal imaging. Figure 11 demonstrates the consistency between the FLT SUV determined from 55 to 60 minutes and a broader time window ranging from 65 to 100 minutes post-injection. Note the high correlation between the two measures indicative of little change within this window. Figure 12 shows the significant change in FLT SUV (maximum and mean), determined at 60 minutes and during a whole-body imaging acquisition for primary head and neck tumors, cervical spinal marrow and metastases. Figure 13 compares the change in FLT SUV to the change in the influx rate constant, K-Patlak (determined from a Patlak analysis (requiring dynamic imaging and information on plasma FLT concentrations versus time)). The large correlation ($r > 0.9$) between the SUV and K-Patlak indicates that similar information on proliferation changes may be garnered from the technically much less difficult and clinically feasible semi-quantitative SUV approach to data analysis as that determined from the more technically demanding Patlak analysis. Therefore, FLT imaging needs to be initiated after a minimum of 45 minutes to accurately reflect changes in proliferation[3]; that, although consistent imaging times should always be used for all studies, the optimal imaging time window is flexible enough to accommodate a clinical scenario; and that the simpler SUV parameter is adequate to characterize the change in proliferation.



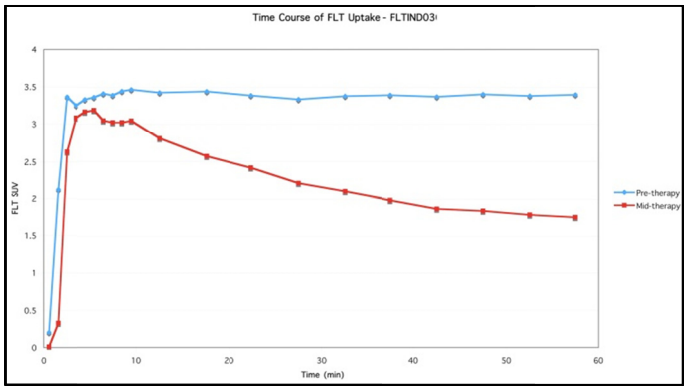


Figure 10. Examples of FLT uptake in head and neck tumors versus time pre-therapy (blue diamonds) and mid-therapy (red squares). Note the similarities in the initial influx of tracer (indicative of comparable K_1 and k_2 parameters) and the lower and later plateau values (indicative of changes in primarily k_3). See Figure 6 for definitions of pharmacokinetic parameters.

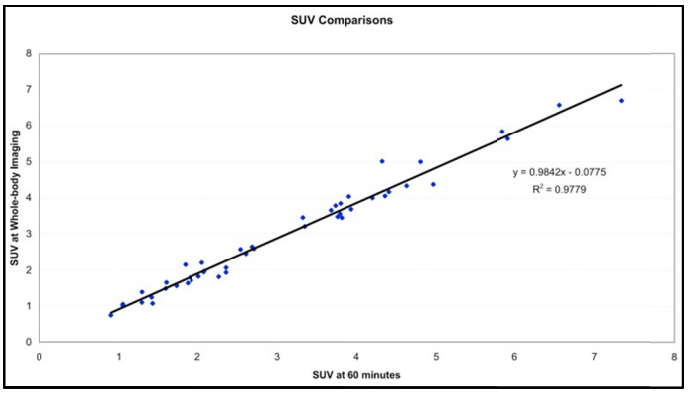


Figure 11. Relationship between the mean standardized uptake value (SUV) during the whole-body acquisition (average = 75.0 ± 6.0 minutes, range = 65 – 100 minutes) versus the SUV at the end of the dynamic acquisition (55 – 60 minutes post-injection). Derived and updated from Menda, et al. 2009[3] and Ponto, et al., 2010[5].

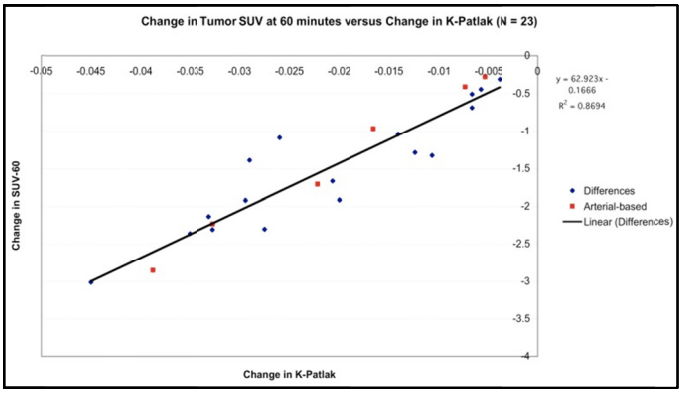
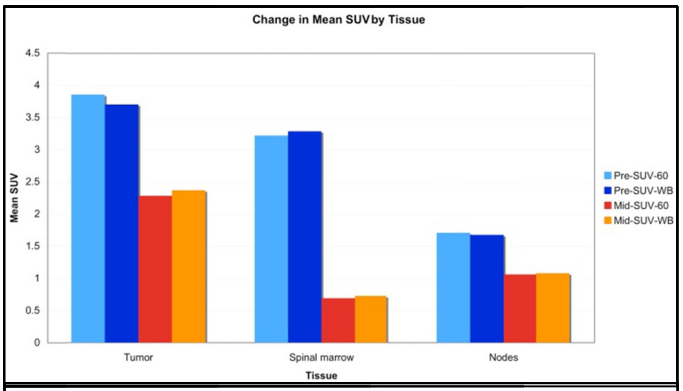


Figure 13. Change in mean tumor SUV at the end of dynamic imaging versus the change in the non-compartmental parameter, K-Patlak, determined over the dynamic imaging period. The red squares are data determined from arterial sampling and the blue diamonds are data determined from the standard curve calibrated from the individual's venous samples. Derived and updated from Menda, et al., 2009[3].



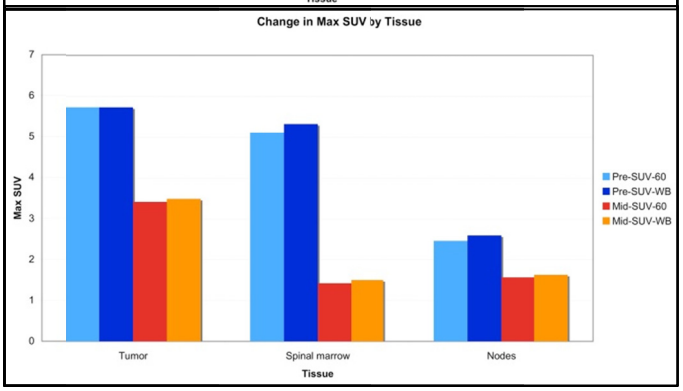


Figure 12. Change in SUV mean (acquired at 55 – 60 minutes, SUV60 and during whole-body imaging, SUV-WB) and maximum for the primary head and neck tumor, cervical spinal marrow and FLT-avid nodes within the dynamic field-of-view. Derived and updated from Menda, et al., 2009[3], Menda, et al., 2010[6] and Ponto, et al., 2010[5].

Utility of FLT Imaging

Table 1 lists the tissue and/or type of pathology for which FLT imaging utility has been evaluated as well as references for information on FLT pharmacokinetics, dosimetry and general review articles. Specific information on the utility of FLT in each of the types of cancer listed is beyond the scope of this lesson, however, the references presented will provide the reader with an informed starting point for the evaluation of potential FLT uses.

Table 1

FLT References by tissue/pathology type, general information (e.g., dosimetry, pharmacokinetics) and review articles

Tissue/Pathology	Reference
Bone marrow disorders	6-9
Breast cancer	10-17
Colorectal cancer	18-23
Esophageal cancer	17, 24-26
Gastric cancer	27, 28
Germ cell tumors	29
Gliomas	30-45
Head and neck cancer	3, 5, 46-53
Hepatocellular carcinoma	54
Leukemia	55
Lung cancer	48, 56-71
Lymphoma	72-76
Melanoma	77, 78
Neurosarcoidosis	79
Pancreatic cancer	80
Renal carcinoma	81
Sarcomas	50, 82-84
Dosimetry and toxicology	33, 45, 85-87
Pharmacokinetics	19, 30-32, 47, 48, 85, 88-92
Tumor volume measurements	17
Reviews	93-100

Two examples of the use of FLT treatment and toxicity response assessments are presented below.

Head and neck cancer

Evaluation of the response to a single cycle of platinum-based chemotherapy and 10 Gy of a 70 Gy radiation therapy regimen in head and neck cancer has been studied by Menda, et al.[3, 6] . An example of pre-therapy and mid-therapy images for one of the subjects in the series is presented in Figure 14. Note the large tumor in the jaw area, visible on both scans, and the profound reduction in FLT uptake in the cervical spinal and clavicular marrow with therapy. The change in cervical spinal marrow, an area exposed to both chemo- and radiation therapy, versus the lumbar marrow metabolism, an area only exposed to the chemotherapy, provides insight into the relative influences of each type of cancer therapy on bone marrow suppression and the associated cytopenias. Kinetic-based analyses have indicated that the combined chemoradiation therapy reduced cervical spinal marrow metabolism by approximately 75% whereas chemotherapy reduced the lumbar marrow metabolism by approximately 12%[6]. Further analyses found that the mid-therapy marrow metabolism (red line) was inversely related to the calculated radiation dose (black line) administered to the cervical spinal marrow[101]. See Figure 15.

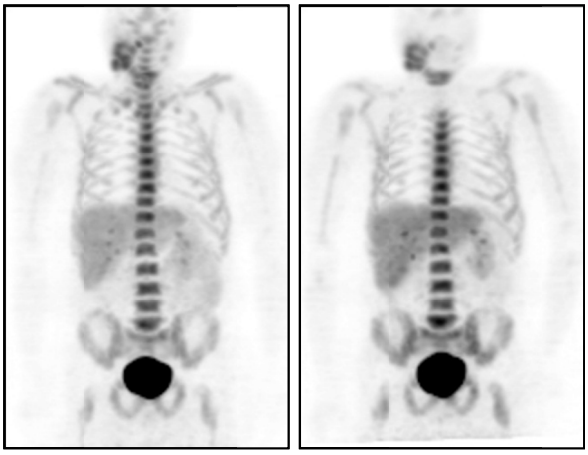


Figure 14. Maximum-intensity projection images of head and neck cancer patient pre-therapy and mid-therapy (10 Gy and 1 cycle of cisplatin plus paclitaxel). Note the large tumor in the jaw, visible on both scans, and the profound reduction in FLT uptake in the cervical spinal and clavicular marrow with therapy.

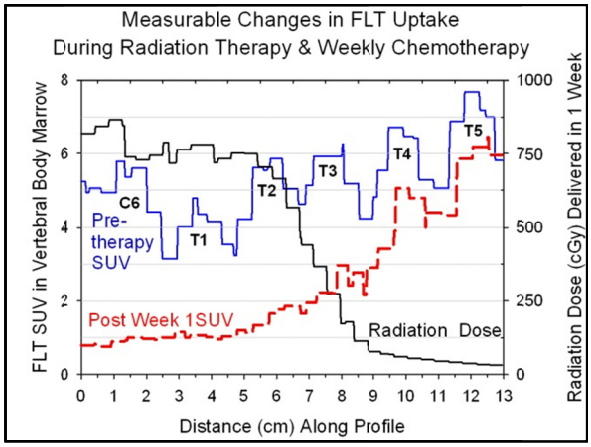


Figure 15. Relationship of spinal marrow SUV and radiation dose (cGy) by distance along profile (i.e., vertebrae; C6 to T5). The black line is the radiation dose in cGy delivered in the one week time interval. The blue line is the pre-therapy SUV in the vertebral body marrow. The red line is the mid-therapy (i.e. Post Week 1) SUV over the same profile. Note the inverse relationship between the mid-therapy SUV and the radiation dose (cGy). Derived from McGuire, et al., 2011[101].

Cervical cancer

Cervical cancer is treated with a combination of chemo- and radiation therapy. The pelvis (sacrum, coxae and femoral head and neck) contains approximately 37% of the total volume of red marrow[102]. It has been hypothesized that the radiation therapy dose-based suppression of the marrow contained within the pelvis, irradiated during the treatment of cervical cancer, hinders the ability of patients to receive their complete course of chemotherapy in the prescribed time frame. However, exclusion of the entire bony pelvis in targeted radiation therapy planning is not possible, but exclusion of the most metabolically-active marrow is theoretically possible. FLT imaging provides a method for the identification and stratification of marrow function for radiation therapy treatment planning and the sensitivity of the relationship between radiation dose and marrow function provides a means by which this toxic sequelae could be monitored. Figure 16 illustrates the effects of chemoradiation therapy on a cervical tumor and the pelvic bone marrow.

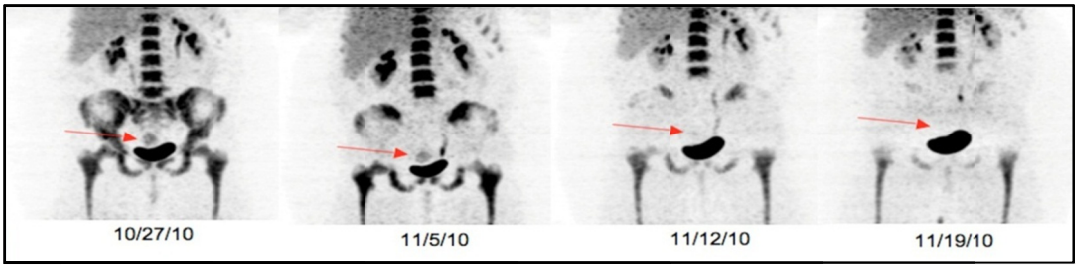


Figure 16. FLT images of response to treatment (9 Gy/week plus 40 mg/m2/week cisplatin) of cervical cancer with pre-therapy FLT pelvic marrow uptake as a factor in the radiation treatment planning. Red arrow identifies the tumor. Images are scaled to 10 kBq/cc.

CONCLUSIONS

The Clinical Trials Network is designed to establish a framework for the effective implementation of imaging biomarkers for the assessment of response in therapeutic clinical trials, thereby facilitating the expeditious approval of new drugs. To this end, imaging site and manufacturers site registries and the multicenter IND mechanism have been established. The first entry in the Biomarker Use Pathway, [^{18}F]fluorothymidine (FLT), is now available for monitoring the response to therapy in oncologic drug trials. The potential role for nuclear pharmacists in this endeavor runs the gamut from facilitating their associated imaging sites and their nuclear pharmacies in successfully meeting the requirements for registration and enrollment in clinical trials to envisioning new agents for inclusion in the multicenter IND process.

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ASSESSMENT QUESTIONS

1. The purpose of the SNM's Clinical Trials Network (CTN) is to facilitate the effective use of imaging biomarkers in multicenter therapeutic trials by

    a. Linking sponsors of trials with qualified radiopharmaceutical manufacturing sites.
    b. Linking sponsors of trials with qualified imaging sites.
    c. Providing multicenter INDs
    d. Facilitating the standardization and harmonization of imaging protocols.
    e. All of the above.

2. Imaging Site Registry requires all of the following except

    a. State-of-the-art imaging technology.
    b. Appropriately trained imaging staff.
    c. Fee for participation as a registered imaging site
    d. Ability to adhere to standardized methods as demonstrated by imaging of the PET Phantom.
    e. All of the above are required.

3. The Manufacturer Registry is designed to

    a. Identify manufacturing sites capable of effective execution of CMC defined in the particular IND.
    b. Qualify manufacturing sites capable of effective execution of CMC defined in the particular IND.
    c. Link sponsors of clinical trials to manufacturers within specific geographic areas.
    d. All of the above.

4. [^{18}F]Fluorothymidine (FLT) is the initial CTN Demonstration Project for the following reasons except

    a. FLT is a promising but under-utilized tracer for amyloid deposition, the hallmark pathology of Alzheimer's disease.
    b. A number of single site INDs were available for FLT made by a variety of processes resulting in multiple final products with acceptable endpoint specifications therefore, providing an ideal scenario for a multicenter IND.
    c. FLT is a promising but under-utilized biomarker for cell proliferation.
    d. Efficacious surrogate markers are needed for oncologic therapeutic trials and there is evidence of the potential of FLT in the monitoring of the response to therapy in a variety of tumor types.

5. Significant differences exist in the appearance of an FLT versus an FDG image in all of the areas but

    a. Brain
    b. Bladder
    c. Heart
    d. Bone marrow
    e. Tumor

6. Both FLT and FDG are generally modeled using a two tissue compartment model (i.e., plasma plus two states in tissues). Which of the following statements is true regarding the model.

    a. FLT is transported from the blood into the cells by the actions of nucleoside transporters.
    b. FLT is phosphorylated and then incorporated into DNA.
    c. FLT is phosphorylated by thymidine kinase.
    d. FLT must be metabolized to the glucuronide before cellular incorporation.
    e. All of the above are true.

7. Monitoring the response to treatment using an imaging biomarker requires that:

    a. Changes in uptake of the tracer reflect changes in the process of interest only.
    b. Pharmacokinetics of tracer delivery to the tissue of interest (e.g., tumor) is consistent between the imaging times.
    c. Full kinetic modeling must always be applied to the analysis of the imaging data because simplified methods like SUVs do not adequately reflect changes in the process of interest.
    d. All of the above are true.
    e. A & B above are true.

8. Reliability and comparability of SUVs from time 1 to time 2 depend on all of the following but:

    a. The adherence to strict technical methodologies.
    b. Identical levels of the physiologic process being mapped (e.g., glucose metabolism, proliferation).
    c. Similar delivery of the tracer on a dose administered (i.e., mCi/kg) basis to the tissue of interest.
    d. Lack of significant changes in organ function that mediates excretion and/or metabolism of the tracer.
    e. All of the above are required.

9. FLT imaging of bone marrow function is potentially useful for:

    a. Determining the degree and extent of bone marrow suppression secondary to treatments such as radiation therapy.
    b. Mapping marrow space for radiation therapy treatment planning.
    c. Determining the relative contribution of radiation therapy and chemotherapy to marrow suppression.
    d. Detecting compensatory increases in marrow function.
    e. All of the above are potentially useful.

10. Changes in FLT uptake in tumors with chemoradiation is driven primarily by changes in the activity of:

    a. Hexokinase
    b. GLUT
    c. Thymidine kinase (TK1)
    d. Nucleoside transporters
    e. BACE1

11. Non-pathological FLT uptake occurs in all of the following structures except:

    a. Liver
    b. Bone marrow
    c. Brain
    d. Heart
    e. Brain and heart

12. FLT update in bone marrow:

    a. Occurs only as a consequence of bone marrow neoplasms or metastases.
    b. Is more profoundly reduced by radiation therapy than by radiation therapy.
    c. Is increased with in the radiation treatment field.
    d. Is unaffected by chemoradiation treatments.

13. Early response of tumors to chemoradiation therapy can potentially be assessed by changes in all of the following FLT parameters, except:

    a. K_1
    b. K_{FLT}, influx rate constant determined from compartmental modeling.
    c. K_{Patlak}, rate constant determined from Patlak noncompartmental modeling.
    d. Maximum SUV
    e. Mean SUV

14. Accurate standardized uptake values (SUVs) require all of the following but:

    a. Accurate calibration of the scanner.
    b. Accurate measurement of the administered dose.
    c. Accurate measurement of the blood glucose level.
    d. Accurate measurement of the patient's weight.
    e. Accurate measurement of the time between administration of the dose and imaging.

15. The potential role(-s) for nuclear pharmacists in the Clinical Trials Network (CTN) is/are:

    a. To assist associated imaging facilities to meet the requirements for Imaging Site Registration.
    b. To facilitate meeting the requirements for Manufacturer Site Registration at their nuclear pharmacy.
    c. To assist in generating the CMC information at their site for inclusion in a multicenter IND.
    d. To provide ideas and feedback to the CTN for new agents to be included in the Biomarker Use Pathway.
    e. All of the above.

16. FLT is:

    a. Metabolized to FLT-monophosphate by nucleoside transporters.
    b. Metabolized by FLT-glucuronide by thymidine kinase.
    c. Metabolized to FLT-glucuronide and then excreted.
    d. Not metabolized.
    e. B and C above.

17. TK1:

    a. Phosphorylates thymidine and FLT so that both can be incorporated into DNA.
    b. Phosphorylates thymidine and FLT but only thymidine is incorporated into DNA.
    c. Phosphorylates thymidine but not FLT but both are incorporated into DNA.
    d. Transports thymidine and FLT from plasma into the cells.
    e. None of the above.

18. The use of FLT for monitoring the response to therapy requires:

    a. The comparison of SUVs determined at very early times since changes with therapy occur in the initial uptake of FLT not the phosphorylation.
    b. The comparison of SUVs determined at later times (> 45 minutes post-administration) since changes with therapy occur in the phosphorylation of FLT not in the initial uptake.
    c. Compartmental modeling of FLT kinetic parameters because SUV changes do not robustly characterize changes with therapy.

d. Non-compartmental modeling of FLT kinetic behavior because compartmental modeling and SUV parameters do not robustly characterize changes with therapy.
e. Comparative imaging with FDG because FLT imaging alone does not robustly characterize changes with therapy.

19. FDG is:

a. An ideal agent for monitoring tumor response to therapy because the uptake is only affected by treatment-related effects.
b. An ideal agent for monitoring tumor response to therapy because it captures changes in inflammatory responses as well as tumor metabolic changes.
c. An inappropriate agent for monitoring tumor response to therapy because glucose metabolism does not change with chemoradiation therapy.
d. An useful but not ideal agent for the monitoring of tumor response to therapy because factors like blood glucose and inflammation not just tumor metabolism may influence uptake.
e. Never used for monitoring the response of tumors to therapy.

20. Requirements for future candidates for the Biomarker Use Pathway multi-center INDs include all but the following:

a. The agent must have an established pharmacology and toxicology.
b. The agent must be a radiopharmaceutical for PET or SPECT use.
c. The agent must have an established chemistry and manufacturing (CMC) information from multiple manufacturing sites with multiple methods for production on different synthesis equipment.
d. The agent must have a minimum of one site with an on-going human study that demonstrates both safety and efficacy.
e. The agent must have a minimum of one well-defined, clinical (human) imaging protocol.