# $^{11}$C-METHIONINE, 2-[$^{18}$F]-FLUORO-2-DEOXY-D-GLUCOSE, AND [$^{18}$F] DIHYDROTESTOSTERONE (FDHT) PET IMAGING IN PATIENTS WITH PROGRESSIVE PROSTATE CANCER



STUDY COORDINATORS:

| | |
|---|---|
| Steven M. Larson, M.D. | (212) 639-7373 |
| Michael J. Morris, M.D. (*) | (212) 639-5132 |
| Mentor: Howard I. Scher, MD(*) | (212) 639-2364 |

DEPARTMENT OF DIAGNOSTIC RADIOLOGY:

| | |
|---|---|
| Nuclear Medicine/Cylotron : | Tim Akhurst, MD, Henry Yeung, MD, Ronald D. Finn, PhD, Heiko Schoder, MD |
| Medical Imaging: | Larry Schwartz, MD. |

DEPARTMENT OF MEDICAL PHYSICS:

John Humm, PhD, Yusef Erdi, PhD

GENITOURINARY ONCOLOGY SERVICE, DEPARTMENT OF MEDICINE:

Howard I. Scher, MD,* Susan Slovin, MD,PhD*; Christine Liebertz, RN; Tracy Curley, RN; Robert Motzer, MD; Dean Bajorin, MD; Lou Kampel, MD; Jason Koutcher, MD,PhD.

DIVISION OF HEMATOLOGIC ONCOLOGY:

David Golde, MD.

DEPARTMENT OF BIOSTATISTICS AND EPIDEMIOLOGY:

Glen Heller, Ph.D.

DEPARTMENT OF CLINICAL CHEMISTRY:

Morton Schwartz, PhD.

CLINICAL TRIALS OFFICE:

Karen Siedlecki

(*) designated to obtain informed consent

MEMORIAL SLOAN-KETTERING CANCER CENTER
1275 York Avenue
New York, NY 10021
(212) 639-2364

## 1.0 PROTOCOL SUMMARY:

The imaging modalities used to monitor prostate cancer in man are limited. The disease typically spreads to osseous sites, where changes are difficult to quantitate on a serial basis. The proposed trial is the first in a series of studies designed to evaluate the biology of prostate cancer *in vivo* using PET imaging. It is based on the ability of positron emitting radiopharmaceuticals to serve as tracers of biologic events. In this study, we will examine the metabolic properties of $^{11}$C-methionine and FDG in prostate cancer by PET imaging.

Initially, we will define the degree of correlation between FDG or C-11-methionine and standard imaging modalities such as CT/MRI and bone scans. We have observed discordance between uptake of [$^{11}$C]-methionine (CMET) and FDG in individual sites.(*1*) Pilot studies have given us a basis for estimates of variability and differences between FDG and CMET, and kinetic data has led to the design of acquisition protocols that make whole body PET imaging of CMET practical in patients. As such, we will continue to compare on a site by site basis the uptake of $^{11}$C-methionine and FDG by performing whole body PET imaging following each radiopharmaceutical administration. Comparisons will be made to bone scintigraphy using 99m-Tc scanning, computed tomography, and, when clinically indicated, magnetic resonance imaging to assess whether sites detected by PET imaging are identified using standard imaging techniques and *vice versa*. Also, where tumor sites are identified on PET scans, a semiquantitative index, the standardized uptake value (SUV), as well as related parameters of total lesion metabolism (TLM) will be calculated as an objective measurement. In selected patients, imaging will be performed with F-18 fluoro dihydrotestosterone (FDHT), obtained through a collaboration with Michael Welch, Ph.D. of Washington University, St. Louis.(*2*)

We will also define the utility of PET as an outcome measure following treatment by assessing the effects of treatment on SUV. Selected patients will be asked to undergo follow-up PET scanning along with follow-up bone scintigraphy, CT or MRI, where clinically appropriate.

All patients with histologically documented progressive prostate cancer are eligible, including those with localized disease, rising PSA, non-castrate metastatic, and castrate metastatic disease. Progression may be defined either by a rise in PSA of $\geq$ 50%, development of new bone lesions or an increase in pre-existing lesions, or an increase in measurable disease.

Patients will undergo PET scanning using either FDG either alone or with CMET or DHT (performed the day following the FDG scan). Serum will be drawn to define the pharmacokinetic properties of the tracer. Serial PET scans will be performed at baseline, four weeks, and twelve weeks and six months, in conjunction with bone scanning, CT/MRI, where clinically appropriate, unless the patient is on a clinical trial that dictates otherwise. These will be compared with baseline scans and available prior scans .

## 2.0 OBJECTIVES:

The primary objectives of this study are:

2.1 **Homogeneity of the metabolism of prostate cancer metastases:** To explore the FDG and CMET metabolism in tumors by PET in progressive prostate cancer, on a site by site basis.

2.1 **Diagnostic ability:** To explore the diagnostic ability of FDG and, in selected cases $^{11}$C-methionine, by comparing PET scanning to standard of care diagnostic studies, which include the 99m-Tc bone scan, computed tomography, and magnetic resonance imaging.

2.2. **Treatment effects:** To explore changes in the relative tumor uptake, as defined by such quantitative measures as the standardized uptake value (SUV) and the total lesion metabolism (TLM), for FDG and $^{11}$C-methionine after systemic therapy(ies). To determine which tracer, FDG or CMET, surrogates for glucose metabolism and amino acid synthesis respectively, is the superior predictor of treatment response.

2.3 FDHT Imaging: In selected patients who are progressing and have advanced androgen-independent prostate cancer, we will develop pilot data on the in vivo targeting and biokinetics of F-18 FDHT by PET imaging. When feasible, biopsy samples will be obtained from index lesions in order to correlate the level of FDHT uptake with androgen receptor expression, as determined by immunohistochemistry.

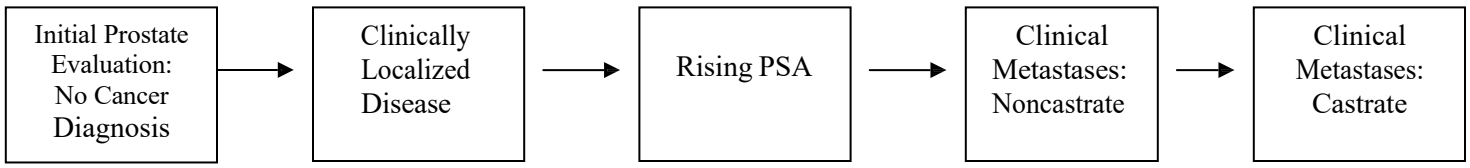
## 3.0 RATIONALE AND BACKGROUND

3.1 Disease Information

The patterns of spread of prostate cancers make it difficult to quantify tumor regression and progression in a reproducible way, because the standard phase II response criteria do not apply.(*3*) Bone, the most common site of spread, is particularly difficult because tumor growth in the marrow results in osteoblastic changes on plain radiographs which, in the end stage, results in complete replacement of the marrow space. While most physicians accept that sclerotic healing of a lytic lesion constitutes tumor regression, the sequential monitoring of lesions that are initially sclerotic is problematic as histologic reversion to a normal bone architecture rarely occurs. Even if all tumor cells are destroyed there may be no visible plain radiographic changes. In these cases, only a direct biopsy can determine if viable tumor cells are present.

To circumvent this problem, and before the availability of PSA measurements, many investigators restricted entry on clinical trials to selected patients with bi-dimensionally measurable tumor masses.(*4*) This excluded the majority of patients from trials. Others attempted to assess response by combining subjective parameters, such as changes in performance status or pain relief, with indirect objective measures such as changes in hemoglobin or weight.(*5*) Over the past five years, we have developed a clinical trial methodology to evaluate new therapeutic approaches based on serial PSA determinations.(*6*) Entry requires clear documentation of disease progression, controlling for the hormone sensitivity of the tumor,(*7*) controlling for steroid hormone withdrawal responses,(*8*) and reporting the outcomes of the trial on the basis of post-therapy changes in PSA, measurable disease, and radionuclide imaging independently.(*6*) The definition of progression includes serial elevations in PSA values, which have been shown to antedate clinical and radiographic evidence of progression for patients with both hormone-naive and hormonally relapsing disease.

More recently, we developed a clinical states model for progression that highlights easily recognized clinical milestones, and provides a background to determine when to recommend treatment, to select a particular approach, and to assess treatment effects.(*9*) In this trial, patients with progressive disease in all disease states will be studied.




3.2 Conventional Imaging Modalities

Radionuclide bone scanning: Standard bone scintigraphy is limited because it reflects the reaction of bone to surrounding cancer rather than providing a direct measure of cancer activity. In one series of patients with a total of 100 bone scan abnormalities, 57 were confirmed by plain radiographs, and 42 showed normal corresponding plain radiographs; and 1 patient had a radiographic abnormality not detected by scintigraphy.(*10*) The flare phenomenon, a paradoxical increase in intensity after successful therapy, further complicates the interpretation of scans on a serial basis.(*11*) To begin to address these questions, we have developed a novel bone scan index,(*12*) which quantifies the percentage of bone involved by tumor, but this too does not provide an index of the viability of tumor.

Cross sectional imaging: Cross-sectional imaging modalities used in the evaluation of prostate cancer include computed tomography (CT) and magnetic resonance imaging (MRI). The utility of each of these modalities varies according to stage of the disease. CT is well suited for the detection of soft tissue disease, but has limited utility in assessing early changes in bone. It is not sensitive in detecting microscopic nodal disease or for detecting tumor in non-enlarged lymph nodes. In our experience, CT is also limited in evaluating disease confined to the prostate and adjacent area. MRI imaging is considered the modality of choice for the most accurate assessment in the region of the prostate, neurovascular bundles and seminal vesicles.(*13*) MRI can also detect soft tissue disease and is most useful to corroborate bone scintigraphic findings, since the earliest involvement is thought to be present in the bone marrow. MRI exhibits the highest sensitivity in the axial skeleton and pelvis, and is less effective in the ribs, chest wall, and skull.

3.3 Positron Emission Tomography

Positron Emission Tomography (PET) has the potential to detect the altered metabolism of the malignant state. This may improve detection as well as permit the quantitative monitoring of metabolic changes in tumors that are under treatment. Of the many radiopharmaceuticals used for PET scanning, the glucose analogs have been highly successful for imaging of a variety of human tumors and for monitoring response to therapy.(*14*) However, in a trial using FDG and PET imaging in androgen independent prostate cancers at MSKCC, only 18% of the metastatic sites detected by conventional bone scintigraphy metabolized FDG sufficiently to be visualized on PET imaging(14). Our preliminary results for this study show that over 70% of the abnormalities visualized on radionuclide bone scan are visible using FDG. This shows the importance of

controlling for disease progression prior to imaging as is required in this trial.(*1*) Recently, Dr. David Agus and coworkers studied the uptake of FDG in the androgen-dependent human prostate cancer xenograft CWR-22. High uptake values were recorded, but of greater interest was the finding that FDG uptake decreased within 24 hours following castration. The decrease preceded declines in PSA, suggesting that PET imaging may be useful to monitor the response to treatment.(*15*) This suggests that for many patients, serial changes in FDG may be useful to monitor disease status. One limitation of the study, however, was that entry did not require a strict definition of disease progression prior to imaging.

One hypothesis under study in this trial is whether $^{11}$C- methionine is more effective in visualizing androgen independent prostate cancer by PET imaging. The essential amino acid, $^{11}$C- methionine is a tracer that has been used to image a variety of human tumors.(*16-18*) In a preliminary report from Nilsson and coworkers, 12 patients with androgen independent prostate cancer underwent PET imaging with $^{11}$C- methionine. Uptake of the radiotracer was discovered in all known sites of bone and soft tissue lesions of patients visualized by standard bone scintigraphy or cross sectional imaging.(*19*) Ten patients had repeat PET scans. Those who responded to treatment had a reduced uptake of the radiotracer with no changes in the images generated by standard techniques. Our ongoing results show that 93% of index lesions were visible using $^{11}$C-methionine and 83% visible using FDG.(*1*) These biodistribution and metabolic findings require additional verification in a larger series.

**$^{11}$C-methionine and $^{18}$FDG whole body imaging**

We have performed a preliminary comparative study of $^{11}$C-methionine and $^{18}$F-FDG in 10 patients with prostate cancer, who were referred for PET imaging with progressive prostate cancer, as defined by serially rising PSA values and one or more new ("index") lesions on bone scan. Among the 10 patients, there were 13 such index lesions on bone scans. $^{11}$C-methionine imaged 12/13 (93%), and $^{18}$F-FDG 11/13 (83%) index lesions. The one lesion not imaged by CMET was subsequently judged to be avascular necrosis, based on its pattern of resolution on subsequent bone scans. $^{11}$C-methionine is very rapidly cleared from the blood, with rapid equilibration (10 minutes) in the tumor. The tumor uptake of $^{11}$C-methionine is consistently high, with standard uptake values (SUVs) ranging from 4.9 to 11.6. We have therefore shown that high-quality whole body PET imaging is feasible with $^{11}$C-methionine, despite the short 20-min physical half-life of carbon-11.

As accrual to the study has been limited by the need to generate $^{11}$C-methionine immediately prior to administration, and based on our preliminary results showing that a higher percentage of tumors are visualized with FDG than previously anticipated, we plan to perform FDG scans in all patients, and $^{11}$C-methionine when it is available. In cases where uptake is visible with FDG, repeat studies will be conducted after therapeutic intervention.

A few fully informed and consenting patients will be selected for studies with tracer FDHT. We will choose subjects that have actively metabolizing tumors on FDG or CMET, and who are expected to have high expression of androgen receptor such as hormonally naïve patients. In the first 10 subjects, we will perform dynamic acquisitions to study the rate of uptake over index lesions for 1 hour. If possible, we will obtain a biopsy of this site for immunohistochemical staining of AR expression.

3.4 Correlations between PET and standard imaging modalities:

In a preliminary analysis of 157 lesions in 18 patients with progressive metastatic disease, we have shown a high (71%) degree of concordance between FDG avid lesions and osseous metastases visualized by bone scans. In selected cases, lesions appeared on FDG PET earlier in the disease course relative to the bone scans. The correlation between FDG avid lesions and radiographically evident soft tissue disease is limited in areas around the ureters and bladder, through which the tracer is excreted ((*20*) and Morris et al, unpublished). As well, preliminary data suggest that changes in SUV may be useful as an early outcome measure in patients with castrate metastatic disease undergoing chemotherapy.(*21*) These data require confirmation and validation using larger numbers of patients and lesions. In addition, such associations cannot be presumed to be applicable to other disease states. To date, we have focused on patients with progressive metastatic disease; this protocol will include patients from all disease states.

Additional studies are therefore required to: (1) assess FDG-PET in prostate cancer patients with progressive disease of all clinical states, (2) to confirm these findings where the metastatic sites are rigorously assessed with larger numbers of patients, (3) to compare PET findings with those of standard bone scintigraphy, CT, or MRI, and (4) to compare posttreatment changes in SUV with changes in standard outcome measures such as PSA.

3.4 Equipment Information (PET)

The ADVANCE (General Electric Medical Systems) whole body PET scanner consists of 336 BGO detector units arranged to form 18 rings (separated by 1 mm retractable tungsten septa) with 672 crystals each, giving 35 contiguous 2-D image planes through an axial field of view of 15.2 cm. The maximum transaxial FOV is 55 cm in diameter through a 58 cm diameter patient port. The average axial resolution (FWHM) is 4.2 mm at r=0 cm; 5.5 mm at r = 10 cm; and 6.6 mm at r = 20 cm. Total system sensitivity is 223 Kcps/*u*Ci/cc with septa in and 1200 Kcps/*u*Ci/cc with septa out. Reconstruction time is <2 seconds per 4.25 mm slice at 128x128 pixels.(*22,23*)

3.5 Standard Evaluation Schema

The initial evaluation of a patient with progressive disease be it locoregional or metastatic, androgen dependent or independent, is directed toward determining disease extent and pattern of spread. This usually consists of a history and physical examination, a hematology, chemical and PSA profile, and for patients with androgen independent disease, a serum testosterone level. Imaging studies typically include a chest radiograph, a CT of the abdomen and pelvis, and radionuclide bone scan. To assess the prostate and pelvic lymph nodes, magnetic resonance imaging is recommended, because CT scanning is too insensitive to accurately reflect the presence or absence of disease, and to determine local extent within the prostate itself. Our experience to date shows that frequently, magnetic resonance imaging of the pelvis is negative, and because some patients do not have pelvic disease, we will only advise this test when clinically indicated. Further, because the results of CT and/or MR imaging do not change in the two week interval following an intervention, we will no longer require that all studies be completed prior to the performance of the PET scan. The presence or absence of other medical co-morbidities, such as cardiac or pulmonary disease, frequently mandates additional testing in this patient population.

## 4.0 BACKGROUND DRUG INFORMATION

4.1 $^{11}$C- methionine: L-methyl-$^{11}$C- methionine has undergone general safety testing. The preparation is apyrogenic and sterile, and is prepared in a form suitable for injection. It is formulated by the radiochemistry/cyclotron facility using established procedures. The individual patient doses will be tested by appropriate quality control procedures to ensure expected potency, purity, and apyrogenicity. An IND is not required at this time, as this study will be submitted for authorization and approval under the MSKCC Committee on radiation (Title 21, Part 361.1 of the Federal Code of Regulations). The product is produced at high specific activity, has been used on multiple occasions in humans at other centers, and has no evidence of pharmacological effect.

4.2 [$^{18}$F]-fluoro-2-deoxy-D-glucose: FDG has undergone general safety testing, is approved by the FDA, and is on the hospital formulary for use as a diagnostic agent.

4.3 [$^{18}$F]-dihydrotestosterone (FDHT)*:* Dihydrotestosterone is the predominant testosterone that is present in the prostate gland itself in animals. Welch, Katzenellenbogen and their colleagues have developed a variety of tracers for study of the androgen receptor. Preclinical evaluation of a variety of fluorinated steroids was undertaken in baboons. 16β-[$^{18}$F]-fluoro-5αdihydrotestosterone (FDHT) appeared to be the preferred agent in mammals due to favorable biodistribution and demonstrable androgen receptor binding. The plasma protein sex-hormone binding globulin (SHBG) is found in high concentration in primates in contradistinction to rodents. Plasma SHBG may therefore explain the higher uptake of FDHT into baboon prostatic tissue in comparison to other fluorinated steroids possibly related to reduced metabolic breakdown. The activity of FDHT in the region of the prostate peaked at 30-90 minutes post injection. At 60 minutes there was a high ratio of prostatic activity to soft tissue, blood and bone (>6:1, >3.5:1 and >7:1 respectively).(*24,25*) It appears that the ligand FDHT exhibits sufficient specific binding to androgen receptors in vivo to allow imaging of androgen receptor-positive tissue. Accordingly, in the orchiectomized host, where androgen receptor occupancy would be expected to be low, it seems feasible to image androgen receptor-positive human cancers. A protocol for the usage of this tracer in humans has yet to be developed. Using dynamic imaging with venous blood sampling we will determine the feasibility of use of this tracer in humans.

Washington University has initiated a clinical trial, and has studied 6 patients with PET imaging. The study is done under the auspices of the Washington University Radioactive Drug Research Committee (B. Siegal, Chairman), and this has been the basis for the dosimetry reported in the Appendices. No toxicity has been observed.

## 5.0 PATIENT ELIGIBILITY

5.1 Entry requirements:

5.1.1 Patients with histologically confirmed prostate adenocarcinoma.

5.1.2 Disease progression as demonstrated by:

5.1.2.1 A ≥ 50% increase in PSA which is sustained for a minimum of 3 observations obtained at least 1 week apart;

OR

5.1.2.2 Development of new lesions or an increase in pre-existing lesions on bone scintigraphy, or in measurable disease by CT or MRI.

5.1.3 Karnofsky performance status > 60%.

5.1.4 Informed consent.

5.2 Exclusion Criteria:

5.2.1 Patients with an active infection not controlled by antibiotics.

5.2.2 Patients with clinically significant pulmonary or cardiac (NYHA Class III or IV) disease.

## 6.0 PRETREATMENT EVALUATION

6.1 History and physical examination

6.2 Laboratory studies: CBC, PSA (within 2 weeks of study entry); serum testosterone (within 4 weeks of study entry).

6.3 Urinalysis (if normal, no culture required) to exclude urinary tract infection (within 2 weeks).

6.4 Bone scintigraphy (within 6 weeks of study entry or up to 2 weeks after entry); using the MSKCC bone scan index (appendix D)

6.5 Computed tomography of abdomen and pelvis (within 6 weeks before entry or up to 2 weeks after entry) and/or Modified MRI of the pelvis to image the prostate (includes retroperitoneum) at MSKCC within 6 weeks before entry or up to 2 weeks after entry as clinically indicated.)

6.6 Chest radiograph (within 6 weeks before entry or up to 2 weeks after entry)

## 7.0 TREATMENT PLAN

7.1 Patients will be fasting for 6 hours prior to PET imaging, with the exception of liberal water intake which is encouraged.

7.2 A blood glucose level will be obtained prior to FDG administration. Elevated baseline serum glucose levels have been reported to cause false negative results with FDG-PET imaging.

7.3 An intravenous catheter (heplock) will be placed in the nuclear medicine department for radiopharmaceutical administration and blood sampling.

7.4 $^{11}$C-methionine: Each patient will receive 10 -15 mCi of $^{11}$C-methionine intravenously with PET imaging beginning 10 minutes after the injection, for approximately 60 minutes total using standard imaging procedures, as described (B).

FDG: Each patient will receive 10 mCi of FDG intravenously followed by PET imaging for a total imaging time of approximately 60 to 75 minutes using standard imaging procedures.

7.5 Patients will be imaged using the ADVANCE (General Electric Medical Systems) whole body PET scanner.

7.6 The radiopharmacy will keep a log of all doses administered.

7.7 The intravenous catheter will be removed at the conclusion of imaging.

7.8 Unless otherwise specified by a clinical trial, patients can undergo serial scans 4 weeks, 12 weeks, and 6 months following the baseline scan. If the patient is receiving treatment on a clinical trial, then PET scanning will be performed according to the schedule outlined in the treatment trial. No more than 7 repeat studies will be performed in a one-year period. This ensures that the total exposure is less than 15 rads to the organ receiving the highest radiation dose per year (the left ventricle) (See appendix ).

7.9 Baseline $^{18}$F-FDHT scans can be performed within two weeks of a baseline FDG scan, as long as there has been no change to the patient's treatment in the interim. Those patients selected for serial PET imaging with $^{18}$F-FDHT will have all additional $^{18}$F-FDHT scans performed the day after the FDG scan. An index lesion will be selected from the previous CMET or FDG scan. The patient will be positioned on the scanner, with the index lesion positioned at the center of the 14.25 cm field of view. A 5 minute transmission scan will be performed to verify the correct location of the patient on the scanner. A dynamic PET image acquisition will be initiated immediately post injection with 10 mCi (370 MBq) of $^{18}$F-FDHT, to evaluate the rate of $^{18}$F-FDHT uptake in the index lesion. Dynamic scans consisting of 10 one-minute, and 10 five-minute frames will be acquired (total duration = 60 minutes). Up to a maximum of 17 serial blood samples will be taken at the following collection times when possible: 0, 0.5, 1, 1.5, 2, 3, 4, 5, 7, 10, 15, 20, 30, 40, 50, 60, and 120 minutes post injection. Blood samples will be counted on a well scintillation counter (LKB Wallac), to determine the blood clearance kinetics of the radiotracer. After the dynamic scan, a whole body scan will be performed, either in immediate continuation or following a short rest, if required by the patient. The whole body scan will follow our department $^{18}$F-FDG guidelines of 6-minute emission and 4-minute transmission scans per field-of-view. In selected patients, additional views, partial or total body, will be acquired between 2-4 hours post injection when possible, to assess retention of the tracer in the tumor. All images will be reconstructed by filtered backprojection and iterative reconstruction, with attenuation correction. The kinetics of tumor uptake will be determined by region-of-interest (ROI) analysis of the dynamic image data set. This data will provide plots of the tumor relative specific activity (μCi/cc of the $^{18}$F-FDHT) versus time post administration. Region-of-interest analysis over tissues e.g. brain, heart, liver, spleen, kidney, bladder, muscle and tumor on the decay corrected whole body images will enable relative uptake ratios (tumor/normal tissues) of the $^{18}$F-FDHT to be determined at between 1-2 hours post $^{18}$F-FDHT injection. Changes in the absolute tumor uptake of $^{18}$F-FDHT per unit administered dose relative to normal organs should reflect changes in androgen level expression in the tumor.

7.9.1 Patients will have a testosterone, sex hormone binding globulin, and DHT level drawn within 2 weeks prior to any FDHT scan.

## 8.0 TOXICITY ASSESSMENT AND MANAGEMENT

8.1 No toxicity is anticipated with the described radiopharmaceutical preparations or PET scanning. The formulations and doses of radiotracers are below defined levels for radiation toxicity. (Title 21,361.1).

8.2 Dosimetry Assessment: The total rad dose is below the limits set by the FDA for investigational radioactive drug studies, and falls within the Radioactive Drug Research Committee guidelines as defined by 5 rad/single organ/dose and 5 rad/year to the whole body, hematopoietic organs, gonads and eyes.

## 9.1 SERIOUS ADVERSE EVENTS (SAE) REPORTING

Any SAE must be reported to the IRB as soon as possible but no later than 5 calendar days. The IRB requires a Clinical Research Database (CRDB) AE report to be delivered to the Institutional SAE Manager (307 East 63rd Street, 1st Floor) containing the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. The report will be forwarded to the FDA by the Institutional SAE Manager through the IND Office.

## 10.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from the study at their request or for failure to comply with protocol requirements.

## 11.0 DATA ANALYSIS

The study design is such that the PET scan will be compared to the gold standards for the determination of sites of tumor. Each imaging modality will be independently evaluated. The PET protocol data analysis form (appendix E) allows the selection and recording of involved sites. Following independent recording and submission of the imaging interpretation data to the protocol data manager (JM), sites of uptake on PET scan will be compared to the detected sites by other imaging modalities with concurrence by HS and SML.

CT: Lesions on computed tomography will be selected and recorded which are reproducibly bidimensionally measurable (greatest dimension X perpendicular to greatest dimension) including adenopathy in the pelvis or retroperitoneum and soft tissue masses.

MRI: T1 and T2 weighted sequences will be obtained for each modified MRI scan of the pelvis which includes the retroperitoneum. Reproducible bidimensionally measurable (greatest dimension X perpendicular to greatest dimension) lesions will be selected and recorded including adenopathy in the pelvis or retroperitoneum, soft tissue masses, and bone metastasis.

PET: PET images will be interpreted and the results recorded on a standardized form (appendix E). The transmission data will be displayed alongside the emission corrected scans to allow anatomic localization of activity. The images should be reviewed in all standard planes and a volumetric projection if available.

Visual analysis will require the identification of abnormal uptake as being greater than background activity on the attenuation corrected images. Features of the primary tumor, including the presence or absence of metastases, will be recorded on a 5 point scale. (5 = definitely abnormal, 4 = probably abnormal, 3 = indeterminate, 2 = probably normal, 1 = definitely normal). Estimates of size will be provided for each lesion.

Using the attenuation corrected images, semiquantitative analysis will require identifying regions of interest (ROI) in areas of abnormality and the standard uptake value will be calculated based on the following formula:

$$\text{SUV} = \frac{\text{decay corrected mean ROI activity (mCi/ml)}}{\text{injected dose (mCi)/body wt (g)}}$$

Lesions will be indicative of malignancy if the SUV is > 2.5 in soft tissue or > 2.0 in bone. Values below these levels will be considered benign. Lesion to background ratios will also be calculated for the transmission corrected scans.

This analysis will be used on all selected PET scans, including retrospectively analyzing PET scans received prior to patient registration.

## 12.0 BIOSTATISTICAL CONSIDERATIONS

To assess the diagnostic implications of PET scanning with $^{11}$C-methionine and FDG, the sensitivity and specificity will be estimated by comparing PET scan results to "standard of care" diagnostic measures that include the 99m-Tc bone scan, computed tomography, and magnetic resonance imaging. Each patient will receive these standard diagnostic measures and PET scanning with both $^{11}$C-methionine and FDG. The diagnostic

"standard of care" scan (bone scan, CT or MRI) will be recorded as positive or negative for each site: bone and bone marrow and/or soft tissue

The sensitivity of PET imaging with $^{11}$C-methionine or FDG is defined as the ability of PET scanning to identify those metastatic lesions diagnosed by standard diagnosis using bone scan, CT, or MRI as "gold standard" and is determined by the proportion of patients with positive lesions as diagnosed by standard method who were identified by the PET imaging. The sensitivity will be measured for both androgen-dependent and androgen-independent prostate cancer patients, and on a site by site basis (bone and bone marrow, and soft tissue).

Assuming at least one site in each patient is assessed positive by the gold standard, the sensitivity of FDG and $^{11}$C-methionine can be conservatively estimated to within +/- 0.16. The total sample size for this study is 265.

To explore changes in metabolism during treatment based on PET imaging, the average SUV value will be recorded at 4 weeks, 12 weeks, and 6 months following the baseline scan. Summary measures such as the slope of the SUV trajectory and the area under the SUV curve will be recorded separately for FDG and $^{11}$C-methionine.

## 13.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

### 13.2 Research Participant Registration (PPR)

The following person(s) can obtain informed consent:

Michael Morris, MD
Howard Scher, MD
Susan Slovin, MD, PhD

Confirm in the electronic medical record that the patient has received the Notice of Privacy Practice. This must be obtained before the eligibility confirmation and obtaining of the research informed consent.

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain written informed consent, by following procedures defined in section entitled Informed Consent Procedures.

All particpants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am - 5:30pm at (646) 735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the informed consent form, the completed signature page of the Research Authorization and a completed Eligibility Checklist must be faxed to PPR.

During the registration process registering individuals will be required to answer specific eligibility questions and provide the following information:

| | |
|---|---|
| Registering Individual | [Last, First Name] |
| Notice of Privacy Status | [Yes, No, N/A] |
| Research Authorization | [Date] |
| MSKCC IRB Protocol# | |
| Attending of Record (if applicable) | [Last, First Name] |
| Consenting Professional | [Last, First Name] |
| Informed Consent Date | |
| Participant's Full Name | [Last, First Name] |
| Participant MRN | |

## 14.1 PROTECTION OF HUMAN SUBJECTS

### 14.2 Privacy

It is the responsibility of the Research Staff to ensure that Memorial Sloan-Kettering Cancer Center has on file a written acknowledgment of receipt by the subject of the Center's Notice of Privacy Practices. If the subject has not already done so, he/she must sign such an acknowledgment before participating in this study.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

## 15.1 INFORMED CONSENT PROCEDURES

Patients will be required to sign a statement of informed consent (appendix F), which meets the requirements of the code of Federal Regulations (Federal Register Vol. 46, No. 17, Jan. 27, 1981, part 50) and the IRB of this center.

Documentation of informed consent: The informed consent will be signed by the patient and consenting physician in triplicate. A signed original consent form is given to the patient. The second original is placed in the patient's medical record and the third original is kept on file in the office of clinical research.

### 15.2 Research Authorization

Procedures for obtaining Research Authorization: Before any protocol-specific procedures are carried out, investigators and/or designated staff will fully explain the details of the protocol, study procedures, and the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must sign the Research Authorization component of the informed consent form. The Research Authorization requires a separate

signature from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents.

## 16. BIBLIOGRAPHY

(1) Macapinlac HA, Humm JL, Akhurst T, et al: Differential metabolism and pharmacokinetics of L-[1-$^{11}$C]-methionine and 2-[$^{18}$F] fluro-2-deoxy-D-glucose (FDG) in androgen independent prostate cancer. Clin Pos Imag 2:173-181, 1999

(2) Liu A, Dence CS, Welch MJ, et al: Fluorine labeled androgens: radiochemical synthesis and tissue distribution studies on six fluorine-substituted androgens, potential imaging agents for prostate cancer. J Nucl Med 33:724-734, 1992

(3) Yagoda A, Watson RC, Natale RB, et al: A critical analysis of response criteria in patients with prostatic cancer treated with cis-diamminedichloride platinum II. Cancer 44:1553-1562, 1979

(4) Scher HI, Yagoda A: Clinical trials in prostatic cancer: Methodology and controversies. *In* Adenocarcinoma of the Prostate (Bruce AW, Trachtenberg J, eds). New York: Springer-Verlag, 1987, pp 197-220

(5) Robinson MRG: Carcinoma of the prostate: objective criteria of response. Am.J.Clin.Oncol. Suppl.2:s48-s52, 1988

(6) Scher HI, Mazumdar M, Kelly WK: Clinical trials in relapsed prostate cancer: defining the target. J Natl Cancer Inst 88:1623-1634, 1996

(7) Scher HI, Steineck G, Kelly WK: Hormone-refractory ("D3") prostate cancer: refining the concept. Urology 46:142-148, 1995

(8) Scher HI, Kelly WK: The flutamide withdrawal syndrome: its impact on clinical trials in hormone-refractory prostatic cancer. J Clin.Oncol. 11:1566-1572, 1993

(9) Scher HI, Heller G: Clinical states in prostate cancer: towards a dynamic model of disease progression. Urology 55:323-327, 2000

(10) Jones SC, Alavi A, Christman D, et al: The radiation dosimetry of 2-[F-18] fluoro-D-glucose in man. J Nuc Med 23:613-617, 1982

(11) Larson SM, Schwartz LH: Advances in imaging. Semin.Oncol. 21:598-606, 1994

(12) Sabbatini P, Yeung H, Imbriaco M, et al: The correlation of serial bone scintigraphy and PSA determinations in patients (Pts) with androgen independent prostate cancer. Proc.Am.Soc.Clin.Oncol. 15:254, 1996

(13) Rifkin M: Comparison of magnetic resonance imaging and ultrasonography in staging early prostate cancer. Results of a multi-institutional cooperative trial. Invest.Radiol. 26:1024-1025, 1991

(14) Larson SM: Positron Emission Tomography in Oncology and Allied Diseases. *In* Cancer: Principles and Practice of Oncology. (DeVita VT, Hellman S, Rosenberg SA, eds). Philadelphia: J.B. Lippincott, 1989, pp 1-12

(15) Agus D, Golde DW, Sgouros G, et al: Change in deoxyglucose accumulation is a biologic surrogate for response to hormone manipulation in a human xenograft model for prostate cancer. Proc Amer Assoc Cancer Res 39:(Abstract 1613), 1998

(16) Lindholm P, Leskinen-Kallio S, Grenman R, et al: Evaluation of response to radiotherapy in head and neck cancer by positron emission tomography and [11C]-methionine. Int.J Radiat.Oncol.Biol.Phys. 32:787-794, 1956

(17) Kubota K, Matsuzawa T, Ito M, et al: Lung tumor imaging by positron emission tomography using C-11 L-methionine. J Nucl.Med. 26:37-42, 1985

(18) Mosskin M, Bergstrom M, Collins VP, et al: Postiron emission tomography with 11C-methionine of intracranial tumors compared with histology of multiple biopsies. Acta Radiol.[Oncol]. 369:157-160, 1986

(19) Nilsson S, Kalkner K-M, Ginman C, et al: C-11 methionine positron emission tomography in the management of prostatic carcinoma. Antibody, Immunoconjugates and Radiopharmaceuticals 8:23, 1995

(20) Osman I, Akhurst T, Macapinlac H, et al: C-11 methionine and F-18 PET imaging: use in the evaluation of progressive prostate cancer. Proc Am Soc Clin Oncol 18:abstract 1203, 1998

(21) Morris MJ, Akhurst T, Kelly K, et al: PET as an outcome measure for metastatic prostate cancer (PC) treated with chemotherapy. Proc Amer Assoc Clin Oncol , 2000 (submitted)

(22) Degrado TR, Turkington TG, Williams JJ: Performance characteristics of a new generation PET scanner. J Nucl.Med. 34(5):101P, 1993

(23) Dahlbom M, Hoffman EJ, Hoh CK: Whole body Positron Emission Tomography: Part I. Methods and Performance Characteristics. J Nucl.Med. 33:1191-1199, 1992

(24) Choe YS, Lidstrom PJ, Chi DY, et al: Synthesis of 11β-[$^{18}$F]Fluoro-5α–dihydrotestosterone and 11β-[$^{18}$F]Fluoro-19-nor-5α-dihydrotestosterone: Preparation via halofluorination-reduction, receptor binding, and tissue distribution. J. Med. Chem. 38:816-825, 1995

(25) Bonasera TA, O'Neil JP, Xu M, et al: Preclinical evaluation of Fluorine-18-labeled androgen receptor ligands in baboons. J Nucl Med 37:1009-1015, 1996