CITY OF HOPE NATIONAL MEDICAL CENTER
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DEPARTMENT OF MEDICAL ONCOLOGY AND THERAPEUTICS RESEARCH

TITLE: F18 NaF PET/CT and Whole Body and axial MRI for the Detection of Metastases in Patients with Biochemical Recurrence of Prostate Cancer

CITY OF HOPE PROTOCOL NUMBER: 13365 **VERSION: 04**

DATE(S) OF AMENDMENT AND REVISION:

COH Initial Submission	Protocol dated 08/29/13	Version 00
COH Amendment 01	Title Page dated 09/30/14	Version 01
COH Amendment 02	Protocol dated 12/16/14	Version 02
COH Amendment 03	Protocol dated 04/08/16	Version 03
COH Amendment 04	Title Page dated 10/27/17	Version 04

DISEASE SITE: PROSTATE CANCER

STAGE (if applicable): IV, (M0 – biochemically recurrent prostate cancer)

MODALITY: Imaging: F18 NaF PET/CT and Whole Body/axial (WB/axial) MRI

PHASE/TYPE: Phase II Imaging /non-therapeutic

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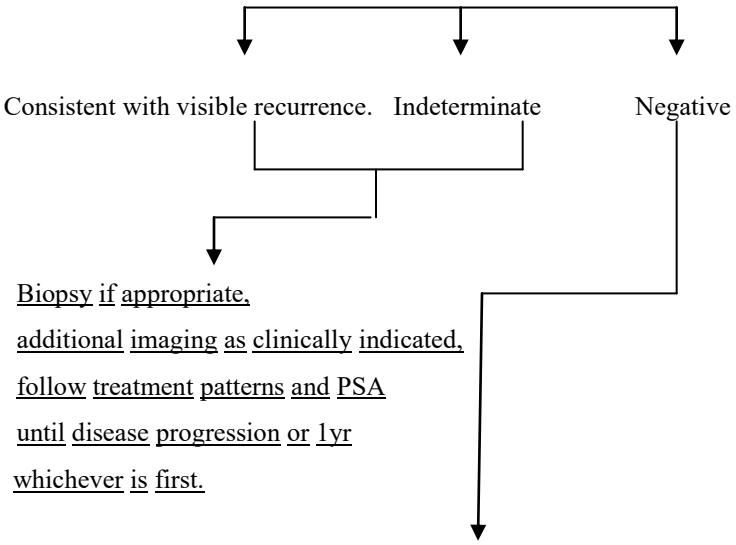
City of Hope, South Pasadena, CA

Experimental Design Schema

Consent/Registration

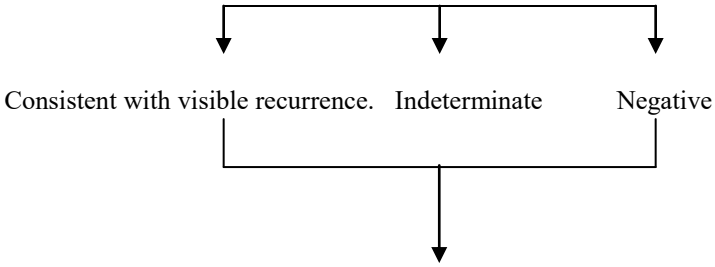
CT chest, abdomen, pelvis, BS (TXR as needed)

Possible outcomes



WB/axial MRI F-18 NaF PET/CT

Possible outcomes



Biopsy, when feasible recommended in all patients with MRI or NaF PET/CT consistent with recurrence or indeterminate
Record PSA response to Salvage Therapy (if given), perform 4-6 month follow up scans if clinically indicated and follow for 1yr or until progression

Protocol Synopsis

Protocol Title:
F18 NaF PET/CT and WB/axial MRI for the Detection of Metastases in Patients with Biochemical Recurrence of Prostate Cancer (PC)
Brief Protocol Title for the Lay Public (if applicable):
Using newer scan techniques to screen for recurrence in prostate cancer patients who have rising PSA after prostatectomy
Study Phase:
Phase II
Participating Sites:
City of Hope Cancer Center
Rationale for this Study:
Current imaging modalities have low sensitivity to detect recurrence in patients who have rising PSA after prostatectomy as evidenced by a high percentage of patients who fail to respond to salvage local therapy. While not routinely used, MRI is part of the NCCN guidelines for evaluating disease in this patient population, and F-18 NaF PET/CT is FDA approved for the detection of bone metastasis, the most common site of distant recurrence. As a result, we will implement the routine use of these new imaging modalities in addition to the historically used imaging tests in a prospective cohort to document the added benefit. We hypothesize that combination of WB/axial MRI and F-18 NaF PET/CT will localize the site of recurrence in significant proportion of these patients.
Objectives:
Primary Objective : To determine the proportion of patients with biochemically-recurrent PC in whom imaging with WB/axial MRI and F-18 NaF PET/CT results in detection of metastatic disease not visualized on CT scan and bone scan. **Secondary Objectives:** To estimate the percent of eligible patients with negative, indeterminate and positive CT scan/bone scan and targeted X-rays if done. To determine the proportion of patients with biochemically recurrent PC in whom recurrence in the prostate bed can be visualized using WB/axial MRI in the absence of detection using CT scan. To correlate the presence of metastatic disease detected using WB/axial MRI and/or F-18 NaF PET/CT with the predicted 6-year probability of progression-free survival based on the Memorial Sloan Kettering Cancer Center salvage RT PC nomogram, and with PSA levels at baseline. To compare the role of axial MRI of the spine to WB/axial MRI with respect to their ability to identify sites of disease. Similarly, to evaluate the relative contribution of F-18 NaF PET and MRI.

Patients with two PSA values ≥0.2 ng/mL at least 4 weeks after prostatectomy will undergo imaging studies including CT of the chest, abdomen and pelvis and bone scan. Targeted X Rays will be obtained in case of equivocal findings if suggested by the radiologist. The results of the scans will be classified as: 1) consistent with visible recurrence, 2) indeterminate 3) negative. Patients who were classified as having negative bone scan and CT scan (estimated ≥90% of patients) will undergo MRI (axial MRI and WB MRI) and F-18 NaF PET/CT. The outcome of these studies will be reported as 1) consistent with visible recurrence, 2) indeterminate 3) negative. In cases of findings consistent with visible recurrence or indeterminate a biopsy of the lesion of interest will be recommended if feasible. Any enrolled patient without a positive biopsy will be followed and their treatment (at discretion of treating physician), PSA values and outcome will be recorded to evaluate the scan result specificity and sensitivity in relation to additional information provided with follow-up (e.g. if patients undergo Salvage Radiation Therapy, PSA response will be recorded which will have significant implication in the interpretation of radiologic findings (see 10).Subsequently all patients without biopsy proven metastasis will undergo follow up imaging studies (the type of imaging to be recommended by radiologist)) within 4-6 months to reassess any abnormalities in the context of time, ongoing therapy or no therapy.
Sample Size:
Total Sample size is 56. Anticipated accrual is 2-3 patients a month.
Estimated Duration of the Study
24 months
Summary of Subject Eligibility Criteria:
Patients with 2 PSA values ≥0.2 ng/mL at least 4 weeks after surgery will be evaluated. Patients who were started on androgen deprivation therapy will not be allowed on this protocol Patients who have started radiographic evaluation and underwent CT scan and/ or BS prior to registration to the study will be able to participate under a late registration provision, provided that WB/axial MRI and F-18 NaF PET/CT can be completed within 4 weeks of the CT scan and BS.
Investigational Product Dosage and Administration:
Not Applicable.
Clinical Observations and Tests to be Performed:
CT of the chest, abdomen and pelvis and bone scan. Targeted X Rays if suggested by the radiologist. If negative, WB/axial MRI and F-18 Sodium Fluoride PET /CT. Biopsy of suspected lesions will be performed if feasible, and repeat scans will be performed for patients with suspicious lesions.
Statistical Considerations:
Sponsor/Licensee:
City of Hope
Case Report Forms

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Abbreviations

Abbreviation	Meaning
AE	Adverse Event
CFR	Code of Federal Regulations
COH	City of Hope
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data Safety Monitoring Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
IRB	Institutional Review Board
NCI	National Cancer Institute
PD	Progressive Disease
PI	Principal Investigator
PMT	Protocol Monitoring Team
SAE	Serious Adverse Event

1.0 Objectives

Primary Objective:
To determine the proportion of patients with biochemically-recurrent PC in whom imaging with WB/axial MRI and F-18 NaF PET/CT results in detection of metastatic disease not visualized on CT scan and bone scan.

Secondary Objectives:

1. To estimate the percent of eligible patients with negative, indeterminate and positive CT scan/bone scan and targeted X-rays if done.
2. To determine the proportion of patients with biochemically recurrent PC in whom recurrence in the prostate bed can be visualized using MRI in the absence of detection using CT scan.

3. To correlate the presence of metastatic disease detected using WB/axial MRI and/or F-18 NaF PET/CT with the predicted 6-year probability of progression-free survival based on the Memorial Sloan Kettering Cancer Center salvage RT PC nomogram, and with PSA level at baseline.
4. To compare the role of axial MRI of the spine to WB/axial MRI with respect to their ability to identify sites of disease. Similarly, to evaluate the relative contribution of F-18 NaF PET and WB/axial MRI.

2.0 Background

2.1 Introduction/Rationale for Development

Background

Each year, approximately 32,000 men in the United States will have a recurrence of prostate cancer (PC) after radical prostatectomy.[1] For most of these patients the only manifestation of recurrent disease is an increasing level of serum prostate specific antigen (PSA) in the blood detected through routine monitoring after surgery. A PSA level of ≥0.2 ng/mL is considered the threshold for biochemical recurrence.[2] For those patients who have a recurrence, some will have disease that is initially confined to the prostate bed and pelvis. Patients who have not previously received adjuvant radiation therapy (RT) can potentially be cured by local salvage RT. However, this treatment approach is complicated by the inability to distinguish between those patients with an isolated local recurrence and those patients with occult distant metastases who will not benefit from salvage RT.[3, 4] Therefore accurate localization of recurrent disease has significant therapeutic implications.

Currently, there is no consensus regarding the use of specific imaging techniques in patients with biochemically recurrent prostate cancer. National Comprehensive Cancer Center (NCCCN) guidelines suggest obtaining "+/- CT scan, +/- bone scan, +/- Ultrasound, +/- MRI" indicating lack of any meaningful guidelines. In addition, in 2011, the FDA approved F-18 NaF PET/CT for the detection of bone metastases for Medicare beneficiaries through the Coverage with Evidence Development/National oncologic PET Registry program (NOPR) adding to the available options with limited guidelines. Currently at City of Hope, patients who present with a PSA level of ≥0.2 ng/mL after radical prostatectomy typically undergo computed tomography scan (CT) of the abdomen and pelvis, bone scan (BS), targeted X-rays (TXR), and occasionally Prostascint scanning, with the primary goal of excluding the presence of metastatic disease. However, these imaging modalities often fail to detect metastatic disease, especially early in the course of PC recurrence when the cancer burden is low.[5] The value of abdominal and pelvic CT in the detection of metastases in patients with biochemically-recurrent PC is low, especially when PSA levels are <10 ng/mL.[6]The detection of metastatic bone cancer with BS is low because it detects bone deposits from osteoblasts, not directly from cancer cells;[7] BS is positive in <1% of patients who present with biochemically-recurrent PC and a PSA level of <10 ng/mL.[5] Prostascint scanning has significant limitations because it only recognizes the intracellular domain of prostate specific membrane antigen (PSMA) and, likely due to the low detection rate, Prostascint scans do not correlate with the efficacy of salvage RT in PC.[8] As a result, the reported long-term success rate of salvage RT (in patients with negative CT scan and bone scan) ranges from 10-50%. This suggests that the majority of patients (50-90%) with biochemically-recurrent PC have occult metastases that are not visualized by standard imaging approaches,[9, 10,11]. It is therefore clinically very important to improve the accuracy of radiologic assessment of patients with biochemically recurrent PC. This may have significant importance in the appropriate selection of patients for local salvage therapy or systemic treatments. Our

strategy involves the application of the two more recent imaging techniques (each either part of the NCCN guidelines or FDA approved) that have demonstrated the potential to better detect distant metastatic disease in patients with high risk prostate cancer. As the previous studies did not restrict the population to biochemically recurrent prostate cancer only, additional studies in this specific and more uniform patient population are needed to help refine and provide more meaningful imaging guidelines, motivating this prospective imaging study. Specifically, these imaging tests are often not routinely covered by insurance in this setting despite the NCCN and FDA guidelines/approval, and we hope that this study will help convince the community that these newer tests are justified in this specific patient population.

MRI

MRI can detect bone metastases in cancer patients. It's superiority over bone scan has been repeatedly demonstrated [12, 13, 14, 15]. As a result, some have called MRI a "gold standard" for detection and confirmation of bone metastases [(14, 15, 16)], although due to availability, inconvenience and cost, many centers have not adopted its routine use.

Classically, the terms sensitivity and specificity are used in evaluating diagnostic tests. However, it is infeasible to know if microscopic metastatic disease was missed when the scans are negative, and as a result the human studies comparing MRI to bone scan and targeted X-rays use a measure of "sensitivity" (based on "best valuable comparator (BVC)") that only conveys that the MRI is superior to bone scan and targeted X-rays. In a study by Lecouvet et al. [(17)] 66 patients with high-risk prostate cancer were evaluated with standard bone scan and X-rays and MRI of the axial skeleton. BVC was a panel of reference consisting of the CT correlation of equivocal MRI findings, prospective systematic follow-up bone scan and MRI studies at 6 months, and clinical and biologic follow-up obtained during 6 months of follow-up. MRI did not incorrectly declare any patient to have metastatic disease out of the 25 without evidence of metastasis at initial staging based on final BVC attribution.l. In addition, of the 41 patients determined to have metastatic disease by BVC, all 41were positive on MRI, suggesting that MRI did not miss any lesions identified by other scans. More importantly, 7 of the 23 (30%) of patients who would have been considered negative with bone scan and targeted X-rays were determined to have metastatic disease on MRI, and considered positive by BVC. Combined, this demonstrates that MRI has high specificity (no false positive calls), did not miss any positive findings on bone scan and X-ray, and was able to visualize evidence of metastatic disease in 30% of the patients deemed negative on bone scan and X-ray. As a result, there is a general consensus about the superiority of MRI techniques over bone scan in the detection of bone metastases, although the high sensitivity quoted in the literature is known to not relate to the more classic definition of sensitivity (e.g. sensitivity to detect a known lesion of a certain size) and the quoted specificities also need further evaluation

Whole-body MRI (WB MRI) has a number of distinct advantages over other imaging techniques, including the ability to simultaneously assess bone and soft tissue, high soft tissue contrast, no ionizing RT, and a versatile ability to measure both anatomic and functional tissue properties based on different tissue contrast modes. WB MRI has been shown to be feasible for detecting metastasis in cancer patients.[18, 19] WB MRI has also demonstrated superiority in detecting bone metastases in high-risk PC patients compared with standard imaging techniques.[17] Diffusion Weighted Imaging MRI (DWI-MRI) is another specialized MRI imaging technique that has been applied as a WB scan to detect abnormal tissue cellularity in cancer patients.[20] WB DWI-MRI outperformed BS in detecting bone metastases in a study of 100 patients with high-risk PC (56 of these patients had biochemical recurrence following local therapy). Specifically, WB DWI-MRI detected bone metastases in 5 of 44 (11%) of patients in whom BS was negative.[21] By conducting both axial MRI and WB MRI the performance of the MRI imaging should be better than one alone, and the differences between these two MRI imaging approaches can also be explored.

<u>F-18 sodium fluoride imaging with positron emission tomography CT (F-18 NaF PET/CT)</u>

F-18 NaF PET/CT is a molecular imaging technique FDA approved for detection of bone metastasis in PC patients. Fluoride tracer uptake is a biomarker for bone metabolism. PET/CT has higher resolution, contrast, and sensitivity than traditional bone single-photon emission computed tomography (SPECT) imaging and greater specificity than BS.[22] CT alone may be unable to identify small metastatic lesions <3mm. The functional contrast provided by the PET tracer may be able to partially overcome this shortcoming.

In the series of 44 high-risk prostate cancer patients Even-Sapir et al. [23] reported that 21patients were negative on the F-18 NaF PET/CT, and all of these patients had no clinical or imaging evidence of metastatic spread for at least the 6-month follow-up period. In addition, 23 patients were determined to have metastatic disease based on definitive PET/CT, biopsy, imaging and follow-up. 20 of the 23 were determined to be positive based on PET/CT and 3 were equivocal. By comparison, BS was negative in 10, and BS plus SPECT were negative in 5. In another study positive detection rate by F-18 NaF of bone metastases not seen on CT and bone scan was 16.2%.[24]

The complementary strengths of MRI and PET/CT imaging suggest an advantage to combining these scans for staging patients. Previous research has explored the suitability of combining WB/axial MRI with PET/CT in cancer patients,[25] and the advantage of a multiparametric approach towards detecting metastatic spread in PC patients has been suggested.[26]

However, no group has evaluated F-18 NaF PET/CT plus WB/axial MRI in patients with biochemically recurrent prostate cancer (or prostate cancer in general), nor have they evaluated it in the context of patients with negative CT scan, BS and targeted X-rays. In view of the poor performance of currently utilized imaging techniques coupled with data supporting both F-18 PET/CT and MRI, along with NCCN guidelines for the use of MRI and FDA approval of F-18 NaF PET/CT for evaluating bone lesions, we propose a novel diagnostic approach: adding WB/axial MRI and F-18 NaF PET/CT to standard imaging (CT scan and BS) for patients negative on CT scan and BS to better detect and characterize metastatic and recurrent disease in biochemically-recurrent PC patients. If successful, our study has the potential to change the paradigm of disease management for patients with biochemically recurrent PC by: 1) identifying a clinically significant proportion of patients with distant metastasis and excluding them from salvage RT, thus sparing them the morbidity and cost of an unnecessary treatment; and 2) enriching for patients who have the highest likelihood of benefitting from salvage RT, thus better justifying RT-associated morbidity and the substantial cost of treatment.

Hypothesis

We hypothesize that combination of WB/axial MRI and F-18 NaF PET/CT will detect metastatic disease in a significant proportion of patients (>5%) with biochemically recurrent prostate cancer who have a negative bone scan, CT scan and targeted X-rays.

2.2 Overview of Proposed Study

After informed consent is obtained, patients will be screened for eligibility. Eligible patients will be registered for a study. The 6-year probability of progression-free survival based on the Memorial Sloan Kettering Cancer Center salvage RT PC nomogram will be recorded. Patients will then undergo imaging studies including CT of the chest, abdomen and pelvis. Targeted X-rays (TXR) will be obtained in case of equivocal findings if suggested by the radiologist. Patients who have CT scan and or bone scan that are interpreted as positive or indeterminate will be managed in a standard way at the discretion of the treating physician. That will frequently include additional imaging modalities and therapy as appropriate , Patients with CT scan and bone scan that are interpreted as negative (estimated ≥ 90 %) will undergo WB/axial

MRI scan and 18-F NaF PET/CT scan. All imaging studies should be ideally completed within a 4-week period, although up to 8 weeks will be allowed.

One of the possible outcomes will be assigned to WB/axial MRI scan, and F18 NaF PET/CT scan: 1) consistent with visible recurrence 2) indeterminate 3) negative. In cases when the combination of WB/axial MRI and 18-F NaF PET/CT scan are interpreted as consistent with recurrence or indeterminate biopsy of the lesion of interest will be recommended if feasible (The presence of histologically proven metastasis will be considered the "gold standard" for the confirmation of metastasis, while recognizing that such confirmation will be rarely achieved.).Fifty six patients will be evaluated over 24 months.

3.0 Patient Eligibility

Prior to the initiation of screening procedures, the purpose and procedures of the study will be explained to each subject, and each subject will then sign an Institutional Review Board (IRB) approved consent form. The subject will subsequently undergo screening assessments to determine if he meets the eligibility criteria for the study.

3.1 Inclusion Criteria

3.1.1 History of prior radical prostatectomy for prostate cancer

3.1.2 Two PSA values ≥0.2 ng/mL at least 4 weeks after prostatectomy.

3.1.3 Patients who have started radiographic evaluation and underwent CT scan and/ or bone scan prior to registration to the study will be able to participate under a late registration provision, provided that the more modern scans (WB/axial MRI and F-18 NaF PET/CT) can be completed within 8 weeks after CT scan and bone scan.

3.1.4 Patients must be ≥ 18 years old.

3.2 Exclusion Criteria

3.2.1 Patients with known metastatic disease

3.2.2 PSA recurrence not verified by elevated PSA as discussed in the eligibility section.

3.2.3 Patients who initiated androgen deprivation therapy or other systemic therapy (chemotherapy, immunotherapy, targeted therapy) for PSA recurrence. Nutritional supplements used for treatment of PSA recurrence will be allowed

3.3 Inclusion of Women and Minorities

Prostate cancer is exclusively disease of men. The study is open anyone regardless of race and ethnicity. Efforts will be made to extend the accrual to a representative population, but in a trial which will accrue approximately 55 subjects, a balance must be struck between subject safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to racial or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

4.0 Screening and Registration Procedures

4.1 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Studies or procedures that were for clinical indications (not exclusively to determine study eligibility) may be used for baseline values, even if the studies were done before informed consent was obtained. Reference is made to Section 9.0 – Study Calendar.

4.2 Informed Consent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the subject and a signed informed consent will be obtained. Documentation of informed consent for screening will be maintained in the subject's research chart and medical record.

4.3 Registration Requirements/Process

Once the signed informed consent has been obtained, all pretreatment evaluations have been performed, and patient's eligibility has been confirmed by the study coordinator a patient will be entered on study.

To register a patient, the research nurse or data manager must complete the eligibility/registration form and fax a copy of the completed eligibility checklist, required pre-study tests (laboratory and pathology report), signed Informed Consent, signed Patients' Bill of Rights and HIPAA authorization form. (FAX Number: 626-256-8654).

The nurse or data manager must log into the Electronic Data Capture (EDC) system and enter the eligibility/registration data for their reserved patient. To complete the registration process, the study coordinator will:

- Verify eligibility
- Register the patient on study
- Assign a patient accession number
- Confirm the patient study number in the EDC system
- Call the research nurse or data manager and verbally confirm that the patient information is available to view in the EDC system.

5.0 Intervention

After informed consent is obtained, patients will be screened for eligibility. Eligible patients will be registered for a study. The 6-year probability of progression-free survival based on the Memorial Sloan Kettering Cancer Center salvage RT PC nomogram[11] will be recorded. Patients will then undergo including CT of the chest, abdomen and pelvis and BS. TXR will be obtained in case of equivocal findings if suggested by the radiologist. Patients who had positive or indeterminate bone scan or CT scan will be taken off the study. Patients with negative bone scan and CT scan will undergo WB/axial MRI scan, and 18-F NaF PET/CT scan. All imaging studies will be completed within an 8 -week period. If the patients underwent standard CT scan and bone scan prior to enrollment to the study, they will be able to participate under a late registration provision, provided that the more modern scans (WB/axial MRI and F-18 NaF PET/CT) can be completed within 8 weeks of CT scan and bone scan.

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5.1 Methods

CT scan

A protocol routinely used at City of Hope for a CT scan of the chest/ abdomen/ pelvis will be used for this study. A non-contrast scan will be initially acquired over the liver and the kidneys. 125 mL Isovue 370 iodinated contrast agent (Bracco, Princeton, NJ) adjusted for weight will be injected intravenously. After a 40-second delay, a chest scan will be acquired. Following a cumulative 75-second delay, an abdominal scan will be acquired from the diaphragm to the pelvic crest. 180 seconds will be allowed to elapse to permit contrast to reach the bladder before a final pelvic scan is acquired. Each scan will be acquired in a single breath hold with the following parameters: 120 kV, pitch = 1.375, mA selected based on patient weight, and reconstruction using filtered back projection (FBP) with matrix size = 512 x 512 with two different resolutions 2.5mm x 2 mm and 5 mm x 5 mm, and slice overlap of 0.5 mm and 0 mm, respectively.

Bone Scan (BS)

A protocol routinely used at City of Hope for a BS will be used in this study based on a dual-head GE Infinia Imaging System (GE Medical Systems, Waukesha, WI). 18 m Ci Tc-99 m methylene diphosphonate (MDP) will be injected intravenously. The patient will be asked to void all fluids prior to image acquisition. 2.5 hours post-injection, the patient will be scanned in the anterior to posterior direction with a single WB pass. Spot images will be taken of the lateral skull, anterior/ posterior chest and pelvis, and any other areas requested by the referring physician. Total imaging time will be 40-60 minutes. Data will be acquired for a total of 1000 k counts for the torso and 500 k for the extremities and will be reconstructed on a 256 x 256 matrix.

WB/axial MRI

All MR images will be acquired on a 3T MRI System (Magnetom Verio Model, Siemens Healthcare, Erlangan, Germany). The MR exam will consist of three types of images; T2-weighted, T1-weighted, and DWI. The sequence parameters for each of these scans are shown below (Table 2). DWI-MRI will consist of an echo planar imaging sequence with diffusion-sensitizing gradients in x, y, and z planes that will be applied before and after 180° pulses. Diffusion will be measured in orthogonal planes and averaged in order to avoid directional bias since it is expected that tumors will show anisotropic movement of water. Images will be acquired for two b-values (50, 800) reflecting a range of sensitivity for the pulse sequence to changes in diffusion.

Table 2: Sequence parameters for anatomic MRI acquisitions

	T2 Whole Body Coronal – breath hold		**T1 Whole Body Coronal –breath hold**		**DWI Whole Body Axial**	
	Head	**Thorax**	**Head**	**Thorax**	**Head**	**Thorax**
Sequence	STIR	Same	SE	TSE	EP 2D Diff	Same
TR (ms)	5000	3000	500	750	9000	Same
TE (ms)	105	93	8.7	8.7	70	Same
TI (ms)	200	Same	-	-	-	-
FOV (mm)	480 x 480	450x450	480x480	same	400 x 400	Same

Slice (mm)	5.0	Same	5.0	same	5.0	Same
Matrix Size	384 x 384	Same	384 x 384	same	160 x 160	Same

F-18 Na-F PET/CT

F-18 Na-F PET/CT scan will be performed using a standard clinical protocol commonly used at City of Hope. All images will be acquired on a helical 16 Slice Discovery ST (GE Medical Systems, Waukesha, WI). Approximately 10 mCi in 1-1.5 mL of NaF will be injected intravenously based on patient weight. A period of 45 minutes will be allowed to permit tracer circulation, uptake, and clearance prior to the scan. Image acquisition will consist of as many bed positions as required to cover the entire patient from head-to-toe for approximately 2 minutes per bed position. PET data will be reconstructed using an iterative algorithm with matrix size = 128 x 128, FOV = 70 cm, slice thickness of 5.5 mm, attenuation, random, scatter, decay, and dead time corrections. The CT part of the scan will be acquired without contrast and 120kV and mA adjusted based on the patient, pitch=1. CT images will be reconstructed using FBP with matrix size=512 x 512, 0.25 mm slice overlap, 0.98 mm isotropic in plane resolution, and 3.27 mm slice-thickness.

5.2 Planned Duration of the Study

5.2.1 The initial imaging studies will be performed within 8 weeks of registration o the protocol, Subsequent follow up imaging will be performed within 4-6 months after registration to the study.

5.3 Subject Follow-Up

Patients will be followed clinically and will undergo periodic laboratory and radiographic tests until week 52 or until disease progression requiring therapy (see Study calendar 9.0).

6.0 Delays / Modifications to Imaging Studies Schedule

In case the patient is not able to complete all the required imaging procedures within 8 weeks, patient will be replaced. However patients who completed all the standard imaging studies (CT scan and bone scan) and at least one newer imaging study (WB/axial MRI, F-18 NaF PET/CT) will be considered for analysis. Patients who decline recommended biopsy will not be excluded from analysis.

7.0 Data and Safety Monitoring

7.1 Definition of Risk Level

This is a Risk Level 2 study, as defined in the "City of Hope Data and Safety Monitoring Plan", http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx because it involves imaging studies and biopsies where the risk of harm is low.

7.2 Monitoring and Personnel Responsible for Monitoring

The PI is responsible for monitoring protocol conduct. The PI will report to the COH DSMC any deviations, adverse events and/or serious adverse events related to study procedures and report unanticipated problems to the DSMC and IRB.

7.3 Definitions

Adverse Event - An adverse event (AE) is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Serious Adverse Event (SAE) ***[21 CFR 312.32] is defined as*** **any expected or unexpected adverse event** ***that results in any of the following outcomes:***

- Death
- Life-threatening experience (places the subject at immediate risk of death from the event as it occurred);
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect
- Secondary Malignancy, or
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasisas of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) – Any incident, experience or outcome that **meets all three** of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

7.4 Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems: Unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting electronically in iRIS (http://iris.coh.org).

Serious Adverse Events - ***All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx and Table 1 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org/).***

Adverse Events - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the protocol continuation reports (see Table 1 below).

Table 1: City of Hope Adverse Event and Unanticipated Problem Reporting Timelines for the DSMC and IRB

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required*
Unlikely, Unrelated	No reporting required*	No reporting required*
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	5 calendar days
Unlikely, Unrelated	5 calendar days	5 calendar days
	Grade 1 and 2 AND resulting in hospitalization#	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days

*Such events are not required to be reported to the DSMC. These events should be included with the SAE/AE summary provided in the IRB Annual Continuation reports.

Hospitalization = Unplanned admission equal to or greater than 24 hours

Required Reporting Timeframe to IRB of Record		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual

8.0 Risks

8.1 CT scan

There is a slight risk of developing an allergic reaction to the iodine contrast material. This reaction can be mild (itching, rash) or severe (difficulty breathing or sudden shock). Death resulting from an allergic reaction is rare. Most reactions can be controlled by the use of additional drugs to prevent the allergic type reaction. Participants should inform their doctor if they have allergies of any kind (such as hay fever, iodine allergy, eczema, hives, or food allergies). The contrast material used during a CT scan can also cause water loss or damage to the kidneys that may lead to kidney failure. This is of particular concern if there is underlying poor kidney function, dehydration, or diabetes. Participants will be exposed to a limited and medically acceptable dose of radiation during the procedure. There is always a slight risk from being exposed to any radiation, including low levels of X-rays used for a CT scan. Participants may also experience discomfort related to lying still in an enclosed space for a prolonged period of time.

8.2 Bone scan

There is a slight risk of developing an allergic reaction to the contrast material.. This reaction can be mild (itching, rash) or severe (difficulty breathing or sudden shock). Death resulting from an allergic reaction is rare. Most reactions can be controlled by the use of additional drugs to prevent the allergic type reaction. Participants should inform their doctor if they have allergies of any kind (such as hay fever, iodine allergy, eczema, hives, or food allergies). There is always a slight risk from being exposed to any radiation, including low levels used for a bone scan. Participants may also experience discomfort related to lying still in an enclosed space for a prolonged period of time.

8.3 PET/CT

The tracer used in the PET/CT scan is radioactive but short lived and poses little to no risk. Participants may experience claustrophobia from being inside the PET/CT scan or experience mild discomfort from lying on the PET scanner table. A sedative such as Diazepam or lorazepam may be prescribed if participant is unable to relax, lie still, or for those who experience claustrophobia. There can be side effects from diazepam or lorazepam. The more common side effects are:

- Drowsiness which is temporary and may require additional medication
- Dizziness which is temporary and may require additional medication
- Dry mouth which is temporary and may require additional medication
- Diarrhea which is temporary and may require additional medication
- Upset stomach which is temporary and may require additional medication
- Blurred vision which is temporary and may require additional medication

Participants may experience pain and tenderness, bruising or a skin reaction at the injection site when given the study drug injection that will be administered through an intravenous (IV) catheter. As with any IV placement, there is a risk of infection at the site but the careful and clean procedure used for placing the IV almost completely removes this risk.

8.4 MRI

Risks include possible anxiety and claustrophobia related to being placed in the large body scanner; temporary discomfort related to having to lie still during the procedure; and possible pain, infection and bleeding related to venipuncture if contrast dye is used. Because MRI works through a powerful magnetic field, it cannot be done if participants have a pacemaker, intracranial aneurysm clips or other metal implants (for example, types of implants used in eye surgery or orthopedic [bone] surgery), artificial limbs and other medical devices that contain iron. Also, there is a risk that metal objects coming near the magnet may become dangerous as they are pulled toward the magnet. The magnetic field will stop a watch that is within several yards of the magnet. Severe injury or death can occur when subjects with implanted neurological stimulators undergo MRI scans. Participants should discuss any metal devices in their body with the study staff. In addition, when having an MRI scan, iron pigments in tattooed eyeliner or in eye makeup can potentially cause temporary skin irritation and/or swelling around the eye. For subjects that need an MRI scan and have reduced kidney function there is a chance of developing "nephrogenic systemic fibrosis," a condition characterized by thickening and itchiness of the skin, stiffening of the joints and possible reduction in the ability to move around. This condition is associated with the MRI contrast agent gadolinium and occurs mostly in subjects with severe kidney disease. The risk to subjects with mild kidney problems is anticipated to be small. Participants will be questioned and examined, if necessary, to confirm that they may undergo MRI scanning without additional risk. An x-ray may be performed to rule out the presence of a suspected foreign body before the MRI.

8.5 Biopsy

Biopsy will be recommended in selected patients (Table1)

Risks of biopsy will depend on the site of biopsy and patient's underlying medical conditions like potential coagulopathy. Risks include: Pain and discomfort, bleeding at the biopsy site, tenderness at the biopsy site, scarring at the biopsy site, rarely, an infection at the biopsy site.

9.0 Study Calendar

Table 1 Schedule of Events (time scale in weeks)

	Week						
	Pre-Study *	1-8	1-8	1-12	16-24	28-36	40-52
Informed consent	X						
Demographics	X						
Medical history	X						
Physical exam	X				X	X	X
Performance Status	X				X	X	X
CBC w/diff, plts	X				X	X	X
Serum chemistry [a]	X				X	X	X
PSA	X				X	X	X
Testosterone	X				X	X	X
Radiologic evaluation (bone scan, CT chest abd / pelvis [b]		X			X[f]		
Targeted (Xrays) [c]		X			X[f]		
WB/axial MRI, F-18 NaF PET/CT [d]			X		X[f]		
Biopsy of suspected abnormality [e]				X			

* Prestudy tests should be performed within 8 weeks of registration.

a) Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.

b) If bone scan and/or CT scan and/or targeted X-rays were already performed before study registration they can be utilized for the study purposes under late registration provision, provided that patients can be registered and complete WB/axial MRI and F-18 NaF PET/CT within 8 weeks of the oldest standard study.

c) If recommended by radiologist due to inconclusive findings on bone scan and CT scans.

d) WB/axial MRI F-18 NaF PET/CT will be performed AFTER bone scan, CT scan and (if needed) targeted X-rays have been completed. All the imaging studies should be completed within 8 weeks of registration (except under late registration provision – see b).

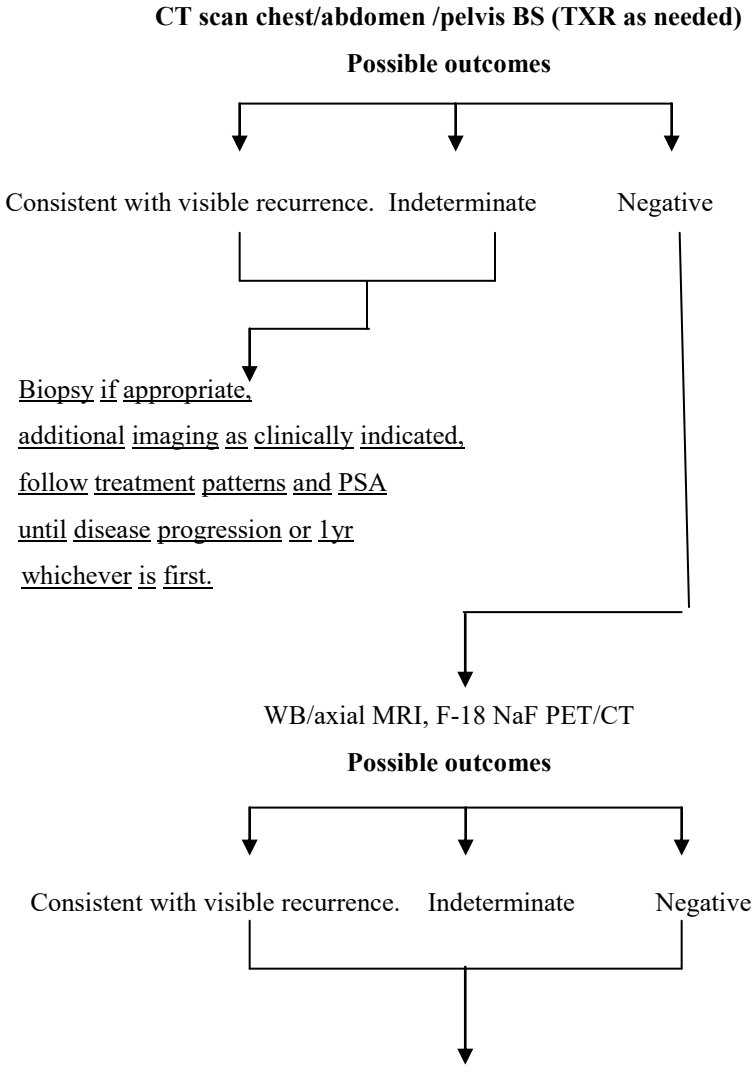
e) In patients in whom the results of WB/axial MRI and /or F-18 NaF PET/CT are consistent with recurrence or indeterminate.

f) In patients in whom the results of all the imaging studies and biopsy (if performed) were not conclusive for metastasis. The specifics of which imaging study (or studies) to be performed at week 16- 24 will be determined based on the recommendation of radiologist.

10. Endpoint Evaluation Criteria/Measurement of Effect

All scans will be interpreted by two board-certified radiologists with CT, MRI and nuclear medicine expertise who will be dedicated members of the research team. In cases of differences in interpretation between the two radiologists, the final reading will be determined by consensus conference involving a third radiologist, also a dedicated member of the research team. One of the three possible outcomes will be assigned to the combination of CT scan and BS (and TXR) if obtained: 1) consistent with visible recurrence 2) indeterminate or 3) negative.

Figure 1.



Biopsy, when feasible recommended in all patients with MRI or NaF PET/CT consistent with recurrence or indeterminate
Record PSA response to Salvage Therapy (if given), perform 4-6 month follow up scans if clinically indicated and follow for 1yr or until progression

Patients who have CT scan and /or bone scan that are consistent with or indeterminate for metastases will be managed in a standard fashion at the discretion of treated physician. It may include additional imaging studies, biopsies and subsequent therapy. Patients with CT scan and bone scan interpreted as negative (estimated ≥ 90%) will undergo additional imaging. including WB/axial MRI and F-18 NaF PET/CT. Possible outcomes :1) consistent with recurrence 2) indeterminate 3) negative will be assigned to WB/axial MRI and F-18 NaF PET/CT. In cases of WB/axial MRI interpreted as consistent with visible recurrence or indeterminate a biopsy of the lesion of interest will be recommended if feasible.

10.1 Verification of Scan Results

10.1.1 Biopsy of Suspected Metastases

Biopsy of metastatic sites of prostate cancer patients is feasible.[27] Bone biopsies of patients with known, advanced metastatic prostate cancer are performed with increasing frequency with yield exceeding 50 % (personal communications, Dr. Maha Hussein , University of Michigan) We estimate that in our population of patients biopsies will be accomplished in approximately 25% of cases of suspicious lesions because of their likely small size or difficult location and targeting . Based on our personal experience and personal communications we anticipate extremely high willingness of patients to undergo biopsy of suspected lesions.

The presence of histologically proven metastasis will be considered the “gold standard” for the confirmation of metastasis. However since majority of patients will not be able to undergo biopsies we will utilize two additional strategies to confirm the interpretation of imaging studies.

10.2.PSA Response To Salvage Radiation Therapy

The majority of our population of patients (unless biopsy proven metastases are discovered) will be offered salvage radiation therapy to the prostate bed. The concept of this therapy is that all the recurrent cancer cells may be located in the radiation field around prostate bed. Therefore the expected result of salvage RT is PSA level becoming undetectable (<0.04 ng/dL) within 6-8 weeks following completion of therapy.

Possible scenarios:

a) The undetectable PSA level following salvage RT would be a very strong indicator that any visible abnormalities outside of the radiation field are false positives. If those lesions were “real” metastases (even extremely small) they would be expected to produce detectable amounts of PSA.

b) If PSA does not become undetectable (< 0.04 ng/dL) in patients with completely normal scans that would be considered false negative.

c) In patients who have abnormalities visible on the scans and inwhom salvage RT to prostate bed does not result in undetectable PSA level, then it is highly likely that the visible lesions are indeed true positives (likely sources of persistent PSA elevation). This scenario is the most difficult to interpret, because it is possible (but in my opinion much less likely) that the source of PSA is related to invisible metastases and identified lesions are benign.

10.2 Follow-up scans

Evolution of lesions over the period of time provides invaluable help in the verification of original interpretation of the scans even in the absence of biopsy. Therefore all the patients will undergo follow up scans (the type advised by radiologist) 4-6 months after registration to the protocol. These scans will be interpreted in the context of ongoing therapy (i.e. hormonal therapy) or observation. Several possible scenarios will allow us to interpret and verify the findings on the original scans.

a) The persistence, growth, increase in numbers and intensity of enhancement of lesions in patients on observation would strongly favor the interpretation of a true positive finding.

b) Complete stability over time or resolution of lesions without ongoing therapy would strongly favor false positive interpretation.

c) Evolution of lesions (regression, radiologic signs of healing in the context of ongoing hormonal therapy (and lack of any history of trauma) would strongly support the interpretation of true positive scans

d) Complete stability of lesions despite ongoing hormonal therapy would favor false positive interpretation

By combining these three elements of verification of original interpretation of WB/axial MRI and F-18 NaF PET/CT we will be able to provide the most robust assessment of sensitivity and specificity of these imaging modalities in the literature that may prove to be quite useful in the management of patients with biochemically recurrent prostate cancer.

Table 1

Interpretation of Imaging with WB/axial MRI and F-18 NaF PET/CT based on subsequent biopsy, therapy and follow up imaging (not all patients will be classified as below depending on additional systemic therapy given)

Original MRI/PET Interpretation	**Biopsy**	**PSA response to salvage RT**	**Follow up scans**	**FINAL Interpretation of Baseline MRI/PET**
Mets	+	NA	Regardless	TP
	– or NA	<0.04	Mets	Indeterminate
			Indeterminate	FP
			No mets	FP
		≥0.04	Mets	TP
			Indeterminate	TP
			No mets	Indeterminate
		NA	Mets	TP
			Indeterminate	TP
			No mets	FP
Indeterminate	+	NA	Regardless	TP
	- or NA	<0.04	Mets	Indeterminate
			Indeterminate	FP
			No mets	FP
		≥0.04	Mets	TP
			Indeterminate	TP
			No mets	Indeterminate
		NA	Mets	TP
			Indeterminate	Indeterminate
			No mets	FP
Negative	N/A	<0.04	Mets	Indeterminate
			Indeterminate	TN
			No mets	TN
		≥0.04	Mets	FN
			Indeterminate	FN
			No mets	Indeterminate
		NA	Mets	Indeterminate
			Indeterminate	TN
			No mets	TN

TN – True negative FN – False negative

TP – True positive FP – False positive

11.0 Data Reporting/Protocol Deviations

11.1 Confidentiality and Storage of Records

The original data collection forms will be stored at the originating institution in a secure location. Study data will be entered into an electronic case report form (eCRF) using an encrypted, password protected, secure electronic data capture (EDC) application that meets all HIPAA requirements. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed. Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. They will be made available for review, as required by the FDA, HHS, or other authorized users such as the NCI, under the guidelines established by the Federal Privacy Act and rules for the protection of human subjects.

11.2 Subject Consent Form

The original signed and dated Informed Consent form, HIPAA research authorization form, and the California Experimental Subject's Bill of Rights will be stored in the research record. At the time of registration, a copy of the original signed and dated consent documents will be available to the patient and another copy will be stored in the medical record. All Institutional, NCI, Federal, and State of California requirements will be fulfilled.

11.3 Data Collection Forms and Submission Schedule

All data will be collected using Medidata EDC electronic case report forms. Data will be sent to the City of Hope Department of Biostatistics and stored in a secure location.

11.3.1 Eligibility Checklist

The Eligibility Checklist must be completed by a protocol nurse or clinical research associate and signed by an authorized investigator prior to registering the subject. See Section 4.3 for the registration procedure.

11.3.2 Prior Therapy Forms and On-Study Forms

Within two weeks of registration, the clinical research associate will submit Prior Therapy Forms and On-Study Forms.

11.4 Protocol Deviations

11.4.1 Deviation Policy

This protocol will be conducted in accordance with COH's "Clinical Research Protocol Deviation Policy" located at http://www.coh.org/dsmc/Documents/Institutional%20Deviation%20Policy.pdf.

Deviations from the written protocol that could increase patient risk or alter protocol integrity require prior IRB approval of a single subject exception (SSE) request. In addition, if contractually obligated, the sponsor must also approve the deviation. IRB pre-approved SSE protocol modifications are considered an amendment to the protocol and not a deviation. The submission of a deviation report is not required.

Brief interruptions and delays may occasionally be required due to travel delays, airport closure, inclement weather, family responsibilities, security alerts, government holidays, etc. This can also extend to complications of disease or unrelated medical illnesses not related to disease progression. The PI has the discretion to deviate from the protocol when necessary so long as such deviation does not threaten patient safety or protocol scientific integrity. Examples include, but are not limited to: a) dose adjustments based on excessive patient weight; b) alteration in

treatment schedule due to non-availability of the research participant for treatment; c) laboratory test results which are slightly outside the protocol requirements but at levels that do not affect participant safety. These instances are considered to be deviations from the protocol. A deviation report will be submitted to the DSMC/IRB within five days.

11.4.2 Reporting of Deviations

All deviations will be reported to the COH DSMC within five days. The DSMC will forward to report to the IRB following review.

11.4.3 Resolving Disputes

The COH Investigational Drug Service (IDS) cannot release a research agent that would cause a protocol deviation without approval by the PI. Whenever the protocol is ambiguous on a key point, the IDS should rely on the PI to clarify the issue.

In situations where there is misperception or dispute regarding a protocol deviation among the persons involved in implementing the protocol, it is the responsibility of the PI to resolve the dispute and the PI may consult with the DSMC chair (or designee) to arrive at resolution.

12.0 Statistical Considerations

We expect more than 90% of the patients enrolling in this study will be negative for metastatic disease based on CT, bone scan and targeted X-rays if ordered.

Primary Endpoint/Sample size justification:

With 56 patients enrolled, we expect more than 45 patients or more to be negative for metastatic disease based on CT, bone scan and X-rays. Historically, more than half of these patients are expected to have undocumented metastatic disease. The use of WB/axial MRI and 18-F NaF PET will be considered worthwhile if more than 8% of these patients (8% rate) are determined to be positive for metastatic disease based on the newer scan technologies. Assuming 45 patients, this requires at least 4 patients to be determined to have metastatic disease on the newer scans that were considered to be without metastatic disease on the standard scans. With 45 patients, and requiring at least 4 patients, there is less than a 5% chance of declaring a discouraging 3% rate to be promising (type I error), and greater than 86% power for declaring a true 15% rate to be a success. The actual power should be higher as it is expected number of patients negative on standard scans is approximately 49 patients. The percent of patients with negative standard scans and positive on the newer scans can be estimated with a 95% CI half-width of less than 15%. Final determination of success will include an evaluation of the follow-up scans and treatment results (when applicable) to fully evaluate the role of the newer scans.

Accrual:

56patients will be accrued over 24 months for an accrual rate between 2-3 patients a month.

Secondary Endpoints:

The secondary endpoints in the context of this study are exploratory:

1. To estimate the percent of eligible patients with negative, indeterminate and positive CT scan/bone scan and targeted X-rays if done. With 56 patients, the percent positive for metastatic disease can be estimated with a 95% CI half-width of less than 13%.

2. To determine the proportion of patients with biochemically recurrent PC in whom recurrence in the prostate bed can be visualized using MRI in the absence of detection using CT scan. This is exploratory, since detection in the prostate bed on CT does not preclude patients from RT salvage therapy, the denominator for this rate will not be known or estimated a priori.

3. To correlate the presence of metastatic disease detected using WB/axial MRI and/or F-18 NaF PET/CT with the predicted 6-year probability of progression-free survival based on the Memorial Sloan Kettering Cancer Center salvage RT PC nomogram, and with PSA level at baseline.

4. To compare the role of axial MRI of the spine to WB MRI with respect to their ability to identify sites of disease. Similarly, to evalue the relative contribution of F-18 NaF PET and MRI. This is an exploratory aim as the number of patients with sites of disease visualized on the MRI technology will not be known a priori.

13.0 Human Subject Issues

13.1 Institutional Review Board

In accordance with City of Hope policies, an Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol and the informed consent form prior to initiation of the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

13.2 Recruitment of Subjects

Patients for the study with will be recruited from patients undergoing therapy for metastatic castration resistant prostate cancer at the City of Hope Cancer Center

13.3 Advertisements

Advertisements to include print, media (radio, television, billboards), telephone scripts, lay summary to be posted on City of Hope's public Clinical Trials On-Line^{SM} website, etc., will be reviewed and approved by the IRB prior to their use to recruit potential study subjects.

13.4 Study location and Performance Sites

This study will be performed at City of Hope

13.5 Confidentiality

This research will be conducted in compliance with federal and state of California requirements relating to protected health information (PHI). The study will record individual results of imaging studies and this will be linked to the subject's identity using a coded study number. The principal investigator, co-investigators, and radiology technicians will have access to this information, but all information will be treated confidentially. No identifiers will be used in any subsequent publication of these results.

13.6 Financial Obligations and Compensation

Therapy on the protocol utilizes standard of care and newer imaging. The standard of care scans (CT scan, bone scan and if needed targeted X-Rays) and if needed biopsy of suspected lesions will be the responsibility of the research participant and/or the insurance carrier. The research participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The research participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the research participant were not in a research study. Newer imaging studies (WB/axial MRI, F-18 NaF PET/CT) will be covered by a study budget. Neither the research participant nor the insurance carrier will be responsible for these procedures related to this study.

In the event of physical injury to a research participant, resulting from the newer scan procedures, appropriate medical treatment will be available at the City of Hope to the injured research participant, however, financial compensation will not be available. The research participant will not be paid for taking part in this study.

13.7 Informed Consent Processes

The Principal Investigator or IRB approved named designate will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Research subjects will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope. Research subjects will be afforded sufficient time to consider whether or not to participate in the research.

Should sufficient doubt be raised regarding the adequacy of comprehension, further clarifications will be made and the questionnaire repeated until a satisfactory result is obtained. Prospective research subjects who cannot adequately comprehend the fundamental aspects of the research study with a reasonable amount of discussion, education and proctoring will be ineligible for enrollment. For those subjects who do comprehend the fundamental aspects of the study, consent will be obtained and documented, followed by eligibility testing. The research team will review the results of eligibility testing and determine if the subject is a candidate for study enrollment.

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