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Study Title: Novel Gallium 68 Citrate Imaging in Orthopedic Infections.

Principal Investigator: Nasrin Ghesani, MD

Study Site: Rutgers New Jersey Medical School

1. Purpose/Specific Aims:

The purpose of the current study is to demonstrate the feasibility and evaluate the accuracy of 68Gallium (^{68}Ga)-citrate positron emission tomography/computed tomography (PET/CT) in diagnosing prosthetic joint infection and compare it with ^{18}fluorine-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT). We expect that ^{68}Ga-citrate PET/CT will serve as a novel molecular-based sensitive functional imaging modality superior to FDG-PET/CT. We intend to translate the results of this preliminary study to fuel larger studies in the utility of ^{68}Ga-citrate PET/CT to evaluate prosthesis complications, where current available imaging techniques are challenging.

2. Background and Significance

Epidemiology:

A total of 4.5 and 6.7 million people in the United States are currently living with an artificial hip or knee. With aging of the population, and increased obesity and longevity, this number is likely to increase in the coming decades and will create significant challenges for management of long-term complications (1). The local complications of joint replacement include infection, instability and dislocation, aseptic loosening and periprosthetic fracture. Periprosthetic infection, the most devastating complication of joint replacement, is associated with significant morbidity and cost. The infection rates following primary implantation and revision surgery are approximately 1% and 3% for hip prostheses and 2% and 5% for knee prostheses, respectively (2, 3). The most common complication, on the other hand, is aseptic loosening which is most often caused by wear of the prosthetic components. For hip replacement, the risk of aseptic loosening leading to revision total hip arthroplasty is about 1 percent per year (4). It is crucial to differentiate prosthetic joint infection from aseptic loosening for appropriate patient management. The treatment for prosthesis infection generally involves both systemic antibiotics for an extended period and exchange arthroplasty in one or two stages, whereas aseptic loosening usually requires a single revision arthroplasty (5, 6).

Physical examination, laboratory tests, radiography and joint aspiration used to diagnose prosthesis infection are insensitive and/or nonspecific. Evaluation of prosthetic joint with morphologic imaging such as CT or MRI has been plagued by poor differentiation between infection and aseptic inflammation/loosening. These modalities are also hampered by artifacts produced by the prosthetic devices themselves (2). Functional modalities have the ability to detect infection when morphologic imaging is nonspecific (2, 7). Of these modalities, promising data exist

supporting combined leukocyte–marrow scintigraphy, 67Gallium (67Ga)-citrate imaging and 18fluorine-fluorodeoxyglucose-positron emission tomography (FDG-PET).

Current Diagnostic Techniques:

Combined leukocyte–marrow scintigraphy:
Combined 111Indium-labelled leucocyte-99mTechnetium-sulphur colloid marrow scintigraphy achieves a high diagnostic accuracy and is currently considered as the imaging modality of choice for diagnosing periprosthetic infection. However, combined leukocyte–marrow scintigraphy is time-consuming, labor-intensive, not widely available, and potentially hazardous because of direct handling of blood products (8).

^{18}F-FDG-PET:
FDG acts as a glucose analog and is taken up by metabolically active cells, namely leucocytes, neutrophilic granulocytes, and macrophages because of increased glucose metabolism and expression of glucose transporters in these cells. In the case of infection, it is also taken up by bacteria present in the infected tissue (9-12). This increased FDG uptake makes local detection of bacterial infections possible. Although FDG PET/CT has high diagnostic sensitivity to detect prosthetic joint infection, its specificity is low, that is, it fails to differentiate between prosthesis infection and aseptic loosening (7, 8, 10, 13-20). The presence of periprosthetic FDG uptake in a non-infected prosthesis can be explained by altered marrow distribution secondary to the placement of an orthopaedic prosthesis (15) and an immunological reaction to wear-induced polyethylene and metal particles released from the prosthesis inlay (7).

^{67}Ga-citrate Imaging:
Gallium-67 (67Ga) is a group IIIb transition metal, similar to the ferric ion in terms of its atomic radius, charge, and the inorganic complexes it forms. The uptake mechanisms of radiogallium are not fully understood (12, 21). The most generally accepted theory is that it may enter the cells by means of binding with circulating transferrin and use of transferrin receptors, and locally it may bind to lactoferrin produced by leucocytes and siderophores produced by infecting micro-organisms themselves (22-24). Another uptake mechanism may involve direct uptake of gallium by infective organisms, an occurrence that has been proven in vitro. Microorganisms grown in an iron-deficient environment produce siderophores that have an extraordinary binding affinity for gallium as well as iron. Because of little free iron present in most tissues, it is assumed that pathogenic microorganisms produce siderophores, and the siderophore–gallium complex is presumably then transported directly into the microorganism (25). Historically, 67Ga has been successfully implemented as an infection-detecting tracer in imaging of bone infections (21). However, the clinical application of 67Ga scintigraphy has been compromised due to several factors. The limited injectable activity (due to the long half-life of 78 hours) and the wide spectrum of gammas emitted by 67Ga-citrate reduce image quality and resolution. 67Ga-citrate is a cyclotron produced isotope and must be purchased commercially (21).

Novel ^{68}Ga-citrate PET/CT:
Gallium-68 (68Ga) is a positron-emitting cyclotron-independent radionuclide with a short half-life of 68 min. This radionuclide has been previously applied in labelling of oligonucleotides and peptides for PET imaging. 68Ga-citrate PET/CT scanning may overcome the shortcomings of 67Ga-citrate and FDG PET scanning. 68Ga-citrate has a similar mechanism of uptake and localization in the human body as 67Ga-citrate. However, as a different isotope of gallium, 68Ga-

citrate isotope presents many advantages over 67Ga-citrate in its use in the diagnostic work-up and management of patients with bone infection. First, 68Ga-citrate is a positron emitter, lending to higher resolution imaging over gamma emitters like 67Ga-citrate. Second, the half-life of 68Ga is much shorter than that of 67Ga (only 68 minutes), allowing patients to be given higher tracer doses and to be discharged almost free of the radioactivity. Third, the uptake phase is short, as is the whole-body image acquisition, allowing a shorter imaging time. Fourth, due to shorter half-life of 68Ga-citrate, there is significantly less radiation burden to patient compared to 67Ga-citrate. Recently, one of the commercial radiopharmacy in our area has housed Gallium generator and has promised us to deliver Gallium 68 Citrate. We recently received funding from Radiological Society of North America to assess utility of Gallium 68 Citrate in hepatocellular carcinoma patients. To our knowledge, we will be the only facility in United States pursuing such research.

Preliminary Studies:

Gallium labeled radiotracers are extensively researched in Europe, Asia and Africa. However, research in this area in United States is lagging behind due to lack of commercially available generator. In preliminary studies, 68Ga-citrate PET/CT has been successful to identify soft tissue cellulitis and abscess in humans and osteomyelitis in animal models (21). In animal models of Staphylococcus aureus infection, Kumar et al demonstrated avid uptake of 68Ga-citrate at infected lesions as early as 5 min following injection. Despite concomitant decrease in cardiac blood pool activity, the radiotracer uptake continued to increase for up to 6 h post injection (26). 68Ga-citrate PET/CT has been shown to be superior to FDG PET in differentiating early bone healing from osteomyelitis in rats (12). To the best of our knowledge, there is only a single human study from Italy aiming to evaluate the efficacy of 68Ga-citrate PET/CT in patients with acute osteomyelitis, chronic osteomyelitis, or diskitis (27). Although a small number of patients (4 of 31) were found to have false-positive scans, the authors reported a sensitivity of 100%, a specificity of 76%, and overall accuracy of 90% in identifying these patients' sites of infection. However, regarding periprosthetic infection, their study was limited due to availability of only 7 patients with bone implants (not necessarily prosthesis) and lack of comparison with FDG PET/CT. With this background, we aim to demonstrate the feasibility and evaluate the accuracy of 68Ga-citrate PET/CT in diagnosing prosthetic joint infection, and compare the results with those of FDG PET for the first time.

3. ***Research Design and Methods:***

In the proposed study, our aim is to evaluate the uptake of ^{68}Ga-citrate in patients with failed joint prosthesis and compare it with that of conventional ^{18}F-FDG PET/CT scan. To our knowledge, ours is the first such study attempting this assessment in human. We will perform PET/CT scan with ^{68}Galium citrate and ^{18}F-FDG in 17 subjects with failed hip or knee arthroplasty prosthesis. Both ^{68}Galium citrate and ^{18}F-FDG scans, done within 24-48 hours from each other, will be performed within 4 weeks before surgical evaluation/revision of the hardware.

Rationale for selecting 4-week interval before surgical evaluation is that in the case of periprosthetic infection, continued antibiotic therapy may affect the results of tissue histology/culture.

Sample Size: 17 subjects

Subjects: The study subjects will be a sample of patients more than 6 months after knee or hip replacement who present with joint pain to our orthopedic and/or infectious disease clinics. Seventeen consecutive subjects with radiographic findings concerning for prosthetic joint infection or aseptic loosening who will be going under surgical evaluation for a final tissue diagnosis within the next 4 weeks will be included in the study. If needed, we may also include patients with other forms of orthopedic hardware into the study.

University Hospital and Rutgers New Jersey Medical School (NJMS) serve as a high-volume regional care center for patients with complicated bone and joint infections. As a Level 1 Trauma Center for northern New Jersey, there is expertise in the management of post-traumatic neurosurgical and orthopedic infections, and in particular, chronic osteomyelitis and prosthetic device-related infections. Our facility cares for patients through a multidisciplinary approach with close collaborations across services including radiology and nuclear medicine, orthopedic and infectious diseases. The Division of Infectious Diseases has a designated Orthopedic Infectious Diseases Consult Service at University Hospital with two Faculty members specializing in the treatment of these infections. They provide in-hospital consultation and management with outpatient follow up, including management of patients in subacute care facilities and those receiving prolonged home antimicrobials. The service sees approximately 200 new patients annually. Therefore, it is expected that the 17 subjects needed for this protocol should be easily recruited within 12 months. As we already have resources set up to pursue Gallium 68 Citrate research, we believe that our center will be ideal location to pursue utility of this novel radiotracer in orthopedic infections.

Inclusion Criteria:

- Non-draining, swollen and painful joint prosthesis
- At least 6 months after joint replacement.
- Elevated ESR and CRP levels
- Pending surgical evaluation and tissue sampling within the next 4 week to differentiate between infection and aseptic loosening.

Exclusion Criteria:

- Pregnant or breast-feeding women.
- Inability to consent.
- Known or suspected hypersensitivity to metals or gallium.
- Drainage from the joint
- Active inflammatory/infectious process at any location other than prosthetic joint.
- History of HIV, lupus, rheumatoid arthritis and neutropenia

Population characteristics:

Record Selections: The following data will be obtained from the charts of the index cases:

1. Age
2. Gender
3. Race/ethnicity

4. Past Medical History
5. Past surgical history
6. Current medications
7. Prior medications
8. Weight, height and body mass index
9. History of alcohol abuse
10. History of intravenous drug use
11. Evidence of HIV infection (e.g. HIV RNA/DNA PCR, Western blot, viral load)
12. History of any other joint, connective tissue or systemic inflammatory diseases (e.g. systemic lupus erythematosus, sarcoidosis, amyloidosis)
13. Joint replacement postoperative course
14. White blood cell count
15. Erythrocyte sedimentation rate
16. C-reactive protein level
17. Histopathology for any biopsied joint/bone tissue
18. Pre and postoperative CT/MRI

Imaging Protocol:

The PI, Nasrin Ghesani, MD has obtained investigation new drug license from FDA for the investigational compound, 68Ga-citrate. IBA Molecular, a commercial radiopharmacy, will synthesize ^{18}F-FDG and ^{68}Ga-citrate according to the method described in the literature (28) and deliver to our facility in unit doses. Combined PET/CT imaging with both radiotracers will be performed using the Discovery LS scanner (GE Medical Systems, Waukesha, WI) within 4 weeks before surgical evaluation.

^{68}Gallium Citrate PET/CT scan: Approximately 5 mCi of 68Ga-citrate will be administered intravenously. Whole body PET/CT scan will be performed after 60 minutes of uptake phase. Positron emission data will be acquired for two sets, one starting from vertex to mid-thigh level and the second from pelvis to toes. Not being much higher in terms of radiation, we opted to image the entire body to include the area of interest, investigate the biodistribution of the radiotracer and look for other foci of infection, such as in case of multifocal osteomyelitis.

^{18}FDG PET/CT scan: Subjects will undergo FDG PET/CT scan using the same imaging parameters either on the same day or within the next 24-48 hours. The IBA Molecular radiopharmacy will synthesize ^{18}F-FDG and deliver to our facility in unit doses. The subjects will be requested to fast for a minimum of 4 h prior to PET acquisition. After confirmation of a blood glucose level ≤200 mg/dl, technologists will establish the intravenous access and the subject will receive approximately 10 mCi of ^{18}F-FDG intravenously. The subject will be placed in uptake room for 60 minutes to allow for optimal localization of the compound. The subjects will be requested to void prior to administration of 18FDG and again prior to image acquisition. Whole body PET/CT scan will be performed after 60 minutes of uptake phase using similar imaging parameters as described above.

Consent Procedures:

Written informed consent will be obtained from each subject after explaining the purpose of the study, description of experimental procedure (^{68}Ga Citrate PET/CT scan), and risk of radiation

exposure and other discomforts. The template of consent form is attached.

Recruitment Process:

We plan to recruit subjects exclusively from Orthopedic clinic or Orthopedic Infectious Diseases Consult Service at NJMS. NJMS orthopedic surgeons and infectious disease specialists will be notified to screen for the subjects. They will be provided with the subject screening log template containing eligibility criteria and consent forms. Subjects will be pre-screened during the office visits by orthopedic surgeons and orthopedic infectious disease specialists.

Upon identifying eligible subjects, the principal investigator will be notified. Subject will be screened either by PI or Co-PIs. If all screening data are available and the subject is eligible for the study, informed consent will be obtained and documented. The PI/Co-PIs will notify the staff at the Advanced Practice Imaging Center and schedule the subject. The technologists will contact the supplier of investigational radiopharmaceutical compound, IBA molecular, and order the compound. The PI/Co-PIs will contact the subject with date and time of test visit and directions to imaging center.

Test Visit:

Upon arrival to imaging center, the PI/Co-PIs will verify the subject's identity. The PI/Co-PIs will also verify that the consent form is signed.

Pre-imaging evaluation:

Following information will be obtained and documented:

- Current symptoms:
- Vital Signs:
- Weight (kg)
- Height (cm)
- Blood Pressure
- Heart rate
- Respiratory rate
- Short physical examination
- Brief review of symptoms
- Pregnancy test (In women of child bearing age)

Image Acquisition Parameters:

Gallium PET/CT: ^{68}Ga-citrate will be synthesized according to the method described in the literature (28). IBA Molecular, a commercial radiopharmacy, will obtain a ^{68}Ge/^{68}Ga generator that is produced by ITG Isotope Products. The IBA Molecular radiopharmacy will synthesize ^{68}Ga-citrate and deliver to our facility in unit doses. Technologists will establish the intravenous access and the subject will receive 5 mCi of ^{68}Ga-citrate intravenously. The subject will be placed in uptake room for 60 minutes to allow for optimal localization of investigational compound. Whole body PET/CT scan will be performed after 60 minutes of uptake phase.

Combined PET/CT imaging will be performed using the Discovery LS scanner (GE Medical Systems, Waukesha, WI). The CT scanner portion of the Discovery LS consists of a multi-detector helical CT (GE Lightspeed Plus, Waukesha, WI).

- Low dose CT scan will be performed followed by positron emission scan.
- CT imaging parameters will be as follows for a 6 to 7 bed position acquisition: 140 kVp, 80 mA, 0.8 s per CT rotation, pitch of 6, 22.5 mm/s table speed. CT thickness will be 5 mm.
- Positron emission data will be acquired for two sets of 6 positions, one starting from vertex to mid-thigh level and the second from pelvis to toes. Emission data will be acquired for 5 minutes for each bed position.
- PET images will be reconstructed using CT for attenuation correction with the ordered subset expectation maximization (OSEM) algorithm.

FDG PET/CT: Subjects will undergo FDG PET/CT scan using the same imaging parameters either on the same day or within the next 24-48 hours. The IBA Molecular radiopharmacy will synthesize ^{18}F-FDG and deliver to our facility in unit doses. The subjects will be requested to fast for a minimum of 4 h prior to PET acquisition. After confirmation of a blood glucose level ≤200 mg/dl, technologists will establish the intravenous access and the subject will receive approximately 10 mCi of ^{18}F-FDG intravenously. The subject will be placed in uptake room for 60 minutes to allow for optimal localization of the compound. subjects will be requested to void prior to administration of 18FDG and again prior to image acquisition. Whole body PET/CT scan will be performed after 60 minutes of uptake phase using similar imaging parameters as described above.

Post imaging evaluation:

Upon completion of test procedure, PI/Co-PIs will evaluate the subject and obtain following data:

- Brief review of symptoms including signs of allergic reactions:
  - Rash
  - Itching
  - Difficulty in breathing
  - Swelling of tongue
- Blood Pressure
- Heart rate
- Respiratory rate
- Short physical examination, including assessment of injection site for swelling, redness, discharge and tenderness

Follow-up:

PI/Co-PIs will make a phone call to subject on following day of each scan and on 7th day after completion of test procedure and gather following information:

- Interval development of rash, itching, difficulty in breathing, swelling of tongue, fever, chills or any unusual symptoms
- Injection site for swelling, redness, discharge and tenderness

If subject experienced any of the above described signs or symptoms, PI/Co-PIs will schedule a follow-up visit with referring physicians (NJMS orthopedic surgeons).

Data analysis:

For each subject, we will record the presence and location of abnormal uptake on both Ga and FDG PET/CTs. We will then generate a region-of-interest around each area of morphologic abnormality to calculate a mean standardized uptake value (SUV), a maximum SUV, and a target-to-background ratio. These values will be compared with those of contralateral normal joint. Radiotracer uptake pattern on each modality will be classified according to known methods (29). Using the macroscopic intraoperative and later tissue histology and culture as the gold standard, sensitivity, specificity, and positive and negative predictive values of Ga and FDG PET will be calculated and compared with each other.

Chart Review Process:

Electronic databases: PACS, EPIC, Logician (Electronic Medical Database of university hospital, affiliate of Rutgers New Jersey Medical School)

Data Manager: Nasrin Ghesani, MD
Data management service: RedCap

Protected Health Information will be only stored in RedCap. We do not plan to store PHI on personal or mobile devices such as laptops and memory sticks.

Coded Identifier List: DOB, MRN, name, dates of services

The file with the link between personal identifiers and the data will be kept for 6 years.

Data Collection Form: **Attached**

Risks of Harm:

This research study involves exposure to radiation emitted by the injected radioactive metal (^{68}Gallium citrate), injected radioactive glucose (^{18}fluorine-fluorodeoxyglucose) and the X-rays delivered by the CT scan.

The Human-use subcommittee and full Radiation Safety Committee of Rutgers New Jersey Medical School reviewed the dosimetry calculations of ^{68}Ga Citrate and ^{18}F FDG based on ICRP Report # 53 (30) and utilized updated tissue weighting factors published in ICRP Report # 103 (31) to arrive at effective doses (See attached PDF document titled: Dosimetry). Accordingly, from 5 mCi of 68Ga Citrate injection, female effective dose was calculated at 3.95 mSv and male effective dose was 3.89 mSv and from 10 mCi inection of ^{18}F FDG, female effective dose was calculated at 5.82 mSV and male effective dose was 5.71 mSv. The study total per annum equivalent doses and effective doses per research subject were found to be within FDA diagnostic limits as attached. Accordingly, the effective dose is a measure of radiation exposure that is used for calculation of risk. The unit of the effective dose is the millisievert (mSv). The average person in the United States of America receives an effective dose of about 3 mSv per year from naturally occurring radioactive materials

and cosmic radiation from outer space. These natural background radiation doses vary throughout the country. In New Jersey, radon gas is the largest source of natural background radiation. Americans also receive radiation exposures from man-made sources such as medical procedures and consumer products. The USA average exposure from all sources is about 6.2 mSv per year.

From the participation in the study while undergoing (no. of scans = 2) scans and radionuclide injections (no. of injections = 2):

- Total effective dose is calculated at 15.1 mSv for women and 14.9 mSv for men.
- Total dose to the critical organ, small intestine from injection of ^{68}Ga-citrate is calculated at 21.6 mSv.
- Total dose to the critical organ, urinary bladder wall, from injection of ^{18}F FDG, is calculated at 29.9 mSv.

As a result of each Gallium PET/CT scan:

- Effective dose to the women is calculated at 6.61 mSv; that is 3.95 mSv from radiation emitted by the radiogallium injected for the PET scan and 2.66 mSv from X-rays used in the CT scan.
- Effective dose to the men is calculated at 6.55 mSv; that is 3.89 mSv from radiation emitted by the radiogallium injected for the PET scan and 2.66 mSv from X-rays used in the CT scan.

As a result of F18-FDG PET/CT scan:

- Effective dose to the women is calculated at 8.48 mSv; that is 5.82 mSv from radiation emitted by the FDG injected for the PET scan and 2.66 mSv from X-rays used in the CT scan.
- Effective dose to the men is calculated at 8.37 mSv; that is 5.71 mSv from radiation emitted by the FDG injected for the PET scan and 2.66 mSv from X-rays used in the CT scan.

The risk associated with this level of radiation exposure is too small to be measured and is small when compared with other everyday risks. It is well below the limit of 50 mSv per study that is allowed by the US Food and Drug Administration for experimental studies in humans. It is also well below the limit of 50 mSv per year that can be received by US radiation workers.

Theoretically, radiation exposure can damage sperm and eggs. About 2000 mSv is required to cause temporary sterility in humans. The dose to the testes and ovaries from participation in this study is calculated at approximately 11.8 mSv and 13.3 mSv respectively, about 500 times lower that the dose that can cause permanent sterility. The scientists who studied the survivors of the atomic bomb in Japan did not demonstrate any increased genetic or reproductive effects in the next generation. However, experimentally we know that the ova ovulated in the first few cycles after an exposure to radiation have a higher risk of a genetic effect. The recommendations of the Health Physics Society (http://www.hps.org) for the women who have received radiation therapy are to wait for three cycles before they attempt to get pregnant. While participating in the study, the subjects will undergo PET/CT scan of the whole body and will have exposure far less then someone who is receiving radiation therapy to the abdomen and are not anticipated to be at higher risk of radiation exposure to the egg or sperm that could result in birth defects.

After undergoing PET scan, the subjects will be instructed to drink plenty of water and void frequently for the remainder of the day. They will be also instructed to not to have a close contact with pregnant women, babies and young children for at least 6 hours after their scan.

It is possible, but unlikely, that the ^{68}Gallium citrate/^{18}F-FDG injection will miss the vein. Though there is no subjective data available for such an event, there is a theoretical likelihood of developing skin cancer at the injection site from local radiation.

Unlikely non-radiation related risks from PET/CT scans include:

- Discomfort from lying still on the enclosed scanning table
- Bruising or bleeding at the site of injection of radiotracer
- Infection at the site of injection
- An allergic type or other adverse reaction to the ^{68}Gallium citrate or ^{18}F-FDG

Potential for Benefit

Our study proposing the ^{68}Ga-citrate PET/CT imaging will aid in management of prosthetic infections in many different ways. Currently, ^{68}Ga-citrate is not approved by Food and Drug Administration (FDA). Data obtained from this pilot study will aid in obtaining extramural funding to conduct a large-scale human study that may pave a road for obtaining FDA approval to use ^{68}Ga-citrate for clinical purpose. Routine clinical use of ^{68}Ga-citrate PET/CT imaging will aid in differentiating periprosthetic infection from aseptic loosening. As explained above, currently available imaging modalities including FDG PET/CT have poor capability for this differentiation. ^{68}Ga-citrate PET/CT by the mean of its functional nature has the potential to overcome this shortage in patient care.

4. Statistical Analysis:

For each subject, we will record the presence and location of abnormal uptake. For the PET/CT images, we will generate a region-of-interest (ROI) around each area of morphologic abnormality to calculate a mean standardized uptake value (SUV), a maximum SUV, and a target-to-background ratio. A target-to-background ratio of at least 2.0 will be used to score a particular ROI as positive. These values will be compared quantitatively with those of contralateral normal joint. Radiotracer uptake pattern on each modality will be classified according to known methods (29). Then, we will descriptively and quantitatively correlate ^{68}Ga-citrate PET/CT findings with those of ^{18}F-FDG PET/CT. Using the macroscopic intraoperative and later tissue histology and culture as the gold standard, sensitivity, specificity, and positive and negative predictive values of Ga and FDG PET will be calculated and compared with each other. We will also review the PET/CT images for multifocal involvement, if any.

Statistical Analysis:
Primarily, all variables will be analyzed and overall, descriptively, as follows:

- Mean. standard deviation, median and range for continuous variables
- Median, range and frequency distribution for discrete (ordinal) variations

- The results of the imaging modalities (PET, CT and MRI) will be classified as true positive (TP), true negative (TN), false positive (FP), or false negative (FN) according to the reference standard.
- The McNemar test of correlated properties will be used to statistically compare the imaging results of ^{68}Ga-citrate and ^{18}F-FDG PET with MRI and diagnostic CT.
- The student t-test will be used to statistically compare the quantitative findings of ^{68}Ga-citrate and ^{18}F-FDG scans.
- Analysis will be done on a lesion basis and on a patient basis.
- All P values, <0.05 will be considered significant.
- Cohen's k-statistic with 95% confidence intervals will be calculated to show the degree of association between the techniques.

5. Reporting Results

The study was previously supported by the research grant from New Jersey Health Foundation (NJHF). As per the requirement of the NJHF an interim report on the progress of the project and a final narrative report have to be submitted to NJHF. In addition, NJHF Vice President of Communications should be consulted before any communications activities, including but not limited to such media as organization publications, trade publications, newspapers, magazines, radio and television.

6. Bibliography

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