Evaluation of ^{99m}Tc Sestamibi Scans In Patients who have Differentiated Thyroid Cancer, Elevated Serum Thyroglobulin Levels, and Negative Diagnostic Imaging Studies

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Introduction

This is a prospective, informed consent study to evaluate a diagnostic radioisotope scan for evaluation of a selected group of patients who have differentiated thyroid cancer, elevated serum thyroglobulin levels indicating the presence of disease, but negative

diagnostic imaging studies. The following two sections are a layman's and medical overview of this study, respectively.

Layman's Overview

One of the major problem areas in the management of patients who have thyroid cancer that is differentiated (DTC) is when their blood levels of the tumor marker for this cancer (thyroglobulin) increase. Yet, despite all the efforts of the physician with physical exam and the standard diagnostic imaging studies, the physician is unable to find the site of metastases that is causing this patient's tumor marker to increase.

One type of scan performed with an isotope called ^{99m}Tc sestamibi was evaluated in the 1990s and 2000s in such patients and was found useful. However, this scan was replaced with multiple superior imaging modalities such as Computer Tomography (CT) scan and ^{18}F fluorodeoxyglucose positron emission tomography (PET) scan. Unfortunately, these scans do not always identify the site of the metastases causing the patient's tumor marker to increase. To date we are unaware of any one who has evaluated ^{99m}Tc sestamibi when all these other standard and extensive imaging scans are also negative. The purpose of this study is to determine if ^{99m}Tc sestamibi may have a role in localizing the tumor in the patients who have an elevated tumor marker with all standard diagnostic scans negative.

Medical Overview

Patients who have differentiated thyroid cancer with a positive or rising serum thyroglobulin level (Tg) and negative standard diagnostic imaging studies (NSDIS)* or negative extensive diagnostic imaging studies (NEDIS)** represent a diagnostically problematic group of patients. The positive or rising Tg typically indicates the presence of recurrent metastatic DTC; however, with either NSDIS or a NEDIS, no structural or functional recurrent or metastatic disease accounting for the positive or rising Tg can be identified. As a result, potential local treatment of a specific site of metastases is not an option and deciding whether to continue active surveillance or to perform a "blind" I-131 treatment is not resolvable by the data available.

As a result, the physicians, in order to make a management decision, must use less than satisfactory factors such as patient age, level of Tg, doubling time of Tg, past patient history, patient co-morbidities, patient desires, etc. Accordingly, additional methods to identify the source of the elevated or rising Tg levels are desirable.

^{99m}Tc sestamibi has been previously used in the evaluation of differentiated thyroid cancer and is taken up by mitochondria in differentiated thyroid cancer cells **[1-11].** Although good overall sensitive and specificity has been shown using ^{99m}Tc sestamibi, it is not routinely used because other standard diagnostic imaging studies have superior sensitivity, specificity, and/or localization of DTC cells. However, to our knowledge no study has been published to evaluate the utility of ^{99m}Tc sestamibi when the other SDCIS or EDCIS are negative. The objective of this study is to evaluate the utility of ^{99m}Tc sestamibi when either all SDIS or EDIS are negative.

*Negative **STANDARD** diagnostic clinical imaging studies (NSDCIS) = negative ultrasound (US), diagnostic radioiodine scan (DRS), chest-x-ray (CXR), computer tomography with or without contrast (CT), and ^{18}F-Fluoro-deoxyglucose positron emission computer tomography scan (^{18}F-FDG PET).

Negative neck structural imaging at least one of the following studies, (i.e., ultrasound, CT with or without contrast, MRI scan) was performed and all performed imaging studies must be negative.

Negative chest structural imaging at least one of the following studies (i.e., x-ray, CT, MRI) must be performed, and all performed imaging studies must be negative.

Negative abdominal structural imaging at least one of the following studies (i.e., ultrasound, CT, MRI) must be performed and all performed imaging studies must be negative.

Negative diagnostic radioiodine whole-body scan.

Negative FDG PET/CT scan.

Negative **EXTENSIVE diagnostic clinical imaging studies (NEDCIS) = all of the above plus negative ^{18}F-sodium fluoride positron emission computer tomography scan (^{18}F NaF PET) or ^{99m}Tc methylene diphosphonate bone scan (^{99m}Tc MDP), **AND** negative brain CT or magnetic resonance (MR).

OBJECTIVE OF THE STUDY

The primary objective of this prospective study is to:

1. **Perform a pilot study of the utility of the ^{99m}Tc sestamibi scans in patients who have differentiated thyroid cancer, positive serum thyroglobulin levels, and negative SDCIS* or negative EDCIS**.**

STUDY DESIGN AND METHODS

This will be a prospective informed consent study. Medical records of the patients with histologically documented differentiated thyroid carcinoma (DTC) in follow-up at MedStar Washington Hospital Center will be reviewed via the electronic medical records systems such as Centricity and Amalga. The subjects meeting the following eligibility criteria may be included in the study.

INCLUSION CRITERIA

- ≥ 18 years of age;
- Diagnosed with differentiated thyroid carcinoma;
- At least one prior I-131 therapy, which may be remnant ablation, adjuvant treatment, and treatment of distant metastases,
- Elevated suppressed or stimulated thyroglobulin level (Tg) ≥ 5 ng/ml WITHOUT thyroglobulin antibodies,
- Any measurable suppressed or stimulated thyroglobulin (Tg) level WITH positive thyroglobulin antibodies,

- All NEGATIVE standard diagnostic clinical imaging studies (NSDCIS) = negative ultrasound (US), diagnostic radioiodine scan (DRS), chest-x-ray (CXR), computer tomography with or without contrast (CT), and ^{18}F-Fluoro-deoxyglucose positron emission computer tomography scan (^{18}F-FDG PET) within the last 24 months.
    - Negative neck structural imaging at least one of the following studies (i.e., ultrasound, CT with or without contrast, MRI scan) was performed and all performed imaging studies must be negative.
    - Negative chest structural imaging at least one of the following studies (i.e., x-ray, CT, MRI) must be performed, and all performed imaging studies must be negative.
    - Negative abdominal structural imaging at least one of the following studies (i.e., ultrasound, CT, MRI) must be performed and all performed imaging studies must be negative.
    - Negative diagnostic radioiodine whole-body scan.
    - Negative ^{18}F FDG PET/CT scan.

- If EDCIS (extensive diagnostic clinical imaging studies) of 18F-sodium fluoride positron emission computer tomography scan (18F NaF PET) or 99mTc methylene diphosphonate bone scan (99mTc MDP), AND brain CT or magnetic resonance (MR) are performed, these are also negative.

- OR meets all of the above prior criteria, but has stable indeterminate nodule on CT for 6 months. Stable defined by Recist Criteria version 1.1 as “Neither sufficient shrinkage to qualify for partial response (30% decrease) nor sufficient increase to qualify for progressive disease (20% increase), taking as reference the smallest sum diameters while on study.

EXCLUSION *CRITERIA*

- < 18 years of age;
- Pregnant or breast feeding
- Any SDCIS or EDCIS that is positive and/or suggestive of recurrent and/or distant metastases secondary to DTC. If a study is indeterminate, this will be forwarded to a committee for review and resolution.

DOCUMENTATION OF PREGNANCY TESTING OR WAIVER

Potential female subjects of childbearing age will undergo either pregnancy testing with blood or urine HCG levels prior to study enrollment.

Alternatively, female subjects can opt to sign a pregnancy waiver form if she rejects undergoing pregnancy testing prior to study enrollment. Pregnancy waiver form will be submitted to the IRB for approval.

Per Cardinal Health Sestamibi Package Insert: “Pregnancy Category C. Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc 99m Sestamibi. It is also not known whether Technetium Tc 99m Sestamibi can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc 99m Sestamibi should be given to a pregnant woman only if clearly needed.”

STUDY POPULATION: GENDER AND ETHNIC INCLUSION

No potential participants will be excluded from participating in this study solely based on gender, ethnic origin, or socioeconomic status.

SUBJECT RECRUITMENT AND SCREENING

The patient's will be identified by referring endocrinologists and nuclear medicine physicians. For potential candidates identified from referring endocrinologists, these will be referred for screening through either Tasha Peterson, Dr. Di Wu, Dr. Cristiane Lima, Shari Moreau, and/or Dr. Douglas Van Nostrand. Potential candidates identified by the "reading desk" nuclear medicine physician will again be screened by Dr. Cristiane Lima, Shari Moreau, and/or Dr. Douglas Van Nostrand. For potential candidates identified by the "reading desk" nuclear medicine physician that meet the criteria, the referring physician will be contacted regarding our desire to speak with the patient regarding this study.

After the endocrinologists supports the patient potentially participating in the study and after confirming that the patient passes the first screening step, the patient will be contacted to explain the study. If the patient is interested, the staff will give the patient an informed consent, and then a discussion with the patient will follow. After final confirmation that the patient meets all inclusion criteria without any exclusion criteria, informed consent will be obtained. This study is being submitted as an exempt study (e.g. waiver of informed consent).

IRB APPROVAL

The study will submitted to the IRB and initiated only after IRB approval of all documents including the protocol, informed consent and HIPPA form.

PATIENT DATA

The demographic, pathological, laboratory, imaging, therapy data, outcome data, etc. will be obtained using the electronic medical records systems such as Centricity, Amalga, and other patient charts such as the charts in the Division of Nuclear Medicine of MedStar Washington Hospital Center. Examples of data include the following:

Demographics

1. Age at diagnosis
2. Gender

Initial Diagnosis

3. TNM at the time of diagnosis + AJCC thyroid cancer stage
4. Histological type

Initial Treatment

5. Date of initial surgery
6. Extent of initial surgery (total or subtotal)
7. Histological subtype
8. Post-operative Tg levels (suppressed and stimulated, when available) and thyroglobulin antibody
9. Results of any other imaging studies including ultrasound, radioiodine scan, etc.
10. Prescribed activity of any I-131 therapy

11. Post I-131 therapy scan

Six-month to one year follow-up results after initial treatment (patient history prior to sestamibi procedure)

1. Follow up Tg levels (suppressed and stimulated, when available)
2. Results of all other imaging studies including ultrasound, radioiodine scan, etc.

Subsequent therapies

3. Sequence and details of subsequent therapies.

Additional information

4. Number of prior I-131 therapies.
5. Total cumulative prescribed activity (mCi) of I-131 received prior to the consideration of a "blind I-131 treatment."
6. Past imaging results (e.g. ultrasound, chest-x-ray, CT, MR, PET scan, etc.)
7. Date, prescribed activity, and results of the most immediate prior I-131 therapy and post-therapy scan.
8. Results of dosimetry and dosimetric scan

Performance of ^{99m}Tc Sestamibi Study.

A. Procedure: The following is the procedure for the ^{99m}Tc sestamibi study
   a. Intravenous injection of 20-30 mCi of ^{99m}Tc sestamibi
   b. Waiting period of approximately 1 hour
   c. Lying supine on a standard nuclear medicine gamma camera table for approximately 45 minutes
   d. Use of parallel hole low energy collimator
   e. Acquisition time: 45 minutes
   f. Review of images by nuclear medicine physician for any extra views
   g. If necessary, either extra spot view, pinhole view, or SPECT (single photon emission computer tomography) image.
   h. Review of images by nuclear medicine physician.
   i. Release of patient.

Radiation safety

   j. This study has been submitted to the Radiation Safety Committee
   k. Radiation Exposure: Two routes
      i. From the 99mTc sestamibi:

2.2 Radiation Dosimetry

The radiation doses to organs and tissues of an average patient (70 Kg) per 1110 MBq (30 mCi) of Technetium Tc99m Sestamibi injected intravenously are shown in Table 1.0.

Table 1.0. Radiation Absorbed Doses from Tc99m Sestamibi

	Estimated Radiation Absorbed Dose			
	REST			
	2.0 hour void		4.8 hour void	
Organ	rads/ 30 mCi	mGy/ 1110 MBq	rads/ 30 mCi	mGy/ 1110 MBq
Breasts	0.2	2.0	0.2	1.9
Gallbladder Wall	2.0	20.0	2.0	20.0
Small Intestine	3.0	30.0	3.0	30.0
Upper Large Intestine Wall	5.4	55.5	5.4	55.5
Lower Large Intestine Wall	3.9	40.0	4.2	41.1
Stomach Wall	0.6	6.1	0.6	5.8
Heart Wall	0.5	5.1	0.5	4.9
Kidneys	2.0	20.0	2.0	20.0
Liver	0.6	5.8	0.6	5.7
Lungs	0.3	2.8	0.3	2.7
Bone Surfaces	0.7	6.8	0.7	6.4
Thyroid	0.7	7.0	0.7	7.0
Ovaries	1.5	15.5	1.6	15.5
Testes	0.3	3.4	0.4	3.9
Red Marrow	0.5	5.1	0.5	5.0
Urinary Bladder Wall	2.0	20.0	4.2	41.1
Total Body	0.5	4.8	0.5	4.8

ii. From the low-dose localization CT of the SPECT.

1. The PI submits that the decision by the nuclear medicine physician to perform an extra view, namely the SPECT-CT image, is arguably a clinical decision based on findings on the ^{99m}Tc sestamibi research scan. Any finding on the research scan that is not initially interpreted as Grade 1 (physiologic activity) or Grade 2 (probably physiologic activity) should be evaluated further based on the clinical indication to try to determine where this activity is precisely located in anticipation of potential treatment.

   However, the PI has included this in as part of the research study. Accordingly, there is additional radiation exposure from the low dose CT. The reason this is a low dose CT is because this CT is not a diagnostic CT but is only used for attenuation correction of the SPECT and localization of findings on the 99mTc sestamibi image. When the CT is used for attenuation correction and localization, the exposure is significantly reduced from a diagnostic CT.

For this study and to the estimate the percent additional radiation exposure to the volunteer, the data from Mhiri et al. has been used with the key table attached below **[12]**

Table 3: The Percentage Increase of Effective Dose by the Inclusion of the CT

Type of Study	No of Patients	% Increase of Effective dose by the inclusion of the CT
^{99m}Tc-MDP	30	83%
^{99m}Tc-MIBI parathyroid	20	28%
^{111}In-octreotide	10	27%
^{131}I post therapy scan	30	0,15%
^{123}I-MIBG	10	125%

The percent increase of the effective dose by the inclusion of the CT is 28%. This is based on the ^{99m}Tc-MIBI parathyroid data above. ^{99m}Tc-MIBI is the abbreviation for ^{99m}Tc-sestamibi, and a CT used with ^{99m}Tc-MIBI for a parathyroid scan involves only one extra view. In this case, when an SPECT-CT is requested by the interpreting physician for one of the subjects in this study, there is only one extra view. Thus, ^{99m}Tc-MIBI parathyroid datum is a good surrogate for estimating the percent increase for a patient having a SPECT-CT in this study. The only difference is instead of evaluating for possibly differentiated thyroid cancer, one is evaluating for parathyroid adenoma and that does not change the estimated increase in radiation dose.

Side Effects of ^{99m}Tc sestamibi

I. The prescribed information is attached in Appendix A.

----------ADVERSE REACTIONS----------

• The following adverse reactions have been reported in ≤ 0.5% of patients: signs and symptoms consistent with seizure occurring shortly after administration of the agent; transient arthritis, angioedema, arrythmia, dizziness, syncope, abdominal pain, vomiting, and severe hypersensitivity characterized by dyspnea, hypotension, bradycardia, asthenia, and vomiting within two hours after a second injection of Technetium Tc99m Sestamibi. A few cases of flushing, edema, injection site inflammation, dry mouth, fever, pruritis, rash, urticaria and fatigue have also been attributed to administration of the agent.

Contraindication of ^{99m}Tc sestamibi

- None known per Prescribing Information.

Exemption from a Sestamibi IND per 21 CFR 312.2(b)

^{99m}Tc sestamibi is an approved FDA (Food and Drug Administration) radioisotope for the imaging of

coronary artery disease (Cardiolite®) and breast lesions (Miraluma®). This study has no intentions to support a new indication or any other significant change in the labeling of the drug. There is no intention to support a change in the advertising for sestamibi. This study team has no intention to promote or commercialize sestamibi.

The ^{99m}Tc sestamibi is commercially purchased from Cardinal Health or other available commercial entities that ensure labeling requirements are met. The study team does not utilize their own cyclotron to produce the sestamibi. The route of administration and activity (dose) of sestamibi are the same as that allowed in FDA indications. This study is under IRB review and patients provide signed informed consent prior to sestamibi scan.

Exemption from a DSMB

^{99m}Tc sestamibi is an approved FDA (Food and Drug Administration) radioisotope for the imaging of coronary artery disease (Cardiolite®) and breast lesions (Miraluma®). Literally hundreds of thousands of doses have been administered, and the adverse effects are minimal and infrequent. As a result, the safety concerns are not unusually high and are very low. Specifically and based on the Guidance for Clinical Trial Sponsors , Establishment and Operation of Clinical Trial Data Monitoring Committees, OMB Control No. 0910-5810, Expiration Date 12/31/2018, there is no *a priori* reasons for a particular safety concern, no serious toxicity, no elevated risk of death/serious outcome, and the patient population is not fragile or vulnerable. As a result, a DSMB not be required for this study.

Data Safety Monitoring Plan

Close cooperation between the designated members of the Research Team will occur to evaluate and respond to individual adverse events in a timely manner. Designated team members (Principal Investigator, Associate Investigators, and Study Coordinator,) will review the summary study safety data reports on a quarterly basis.

I. Study Agent Accountability

Documentation

The radiopharmacist/technologist will be responsible for maintaining an accurate record of the prescription number, inventory, and an accountability record of supplies for this study. Electronic documentation with dose manager as well as paper copies will be used.

Disposition

The empty vials and the unused portion of a vial will be discarded according to the policies of the Radiation Safety Division of the Washington Hospital Center.

II. Adverse Event Reporting

a. Adverse Events

An adverse event is any unfavorable or unintended change in body structure, body function or laboratory result associated temporally with the use of study treatment, whether or not

considered related to the study treatment.

b. Serious Adverse Events

The term “Serious Adverse Drug Experience” is defined in 21 CFR 312.32 as follows: “Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.”

c. Adverse Event Reporting

Information on adverse events is collected by the principal investigator and other clinic staff and entered into a computer database. These data are reviewed on an ongoing basis by the study coordinator and the principal investigator. Adverse experiences that meet Serious Adverse Event (SAE) Reporting Requirements must be reported by the clinical site to the IRB.

Briefly summarized, events requiring completion of an SAE report form include the following and these are to be reported regardless of assessed relationship to study agent:

- Death
- Permanent disability/incapacity
- Hospitalization (other than for elective reasons and the planned I-131 treatment)
- Grade 4 adverse events

In addition, any event, regardless of grade, which in the judgment of a site investigator represents a serious adverse event, may be reported.

For the purposes of this study, a Serious Adverse Event is defined as either (1) any Grade 3 or Grade 4 adverse untoward event as defined by the NCI criteria and/or (2) any event, which is considered in the opinion of the PI to be a serious adverse event. The PI will report SAE’s within seven (7) days to the IRB.

The patient will be tracked for SAE’s after the administration of the tracer prescribed activity of sestamibi up to the time of the patient’s release after completion of sestamibi scan. The Serious Adverse Events form is attached (Appendix B).

d. Adverse Event Reporting to the Institutional Review Board

Adverse event reporting requirements to the MHRI Institutional Review Board (IRB) for this

protocol are as follows:

- Investigators will submit a completed serious adverse event report to the MRI IRB within 7 days after becoming aware of a subject death, a potentially life-threatening (grade 4) serious adverse event that is possibly, probably or definitely related to investigational agent, an inpatient hospitalization (other than elective or the I-131 treatment), a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

- Investigators will submit a completed serious adverse event report to the MHRI IRB within 15 days after becoming aware of any Grade 3 (severe) adverse event that is possibly, probably or definitely related to investigational agent.

- Investigators will report within 15 days on any other event or condition regardless of grade, which in their judgment represents an event reportable to the IRB.

- A summary of all adverse events will be reported to the MHRI IRB with submission of a request for continuing review.

Interpretation of ^{99m}Tc Sestamibi Study.

A. A team of two nuclear medicine physicians will interpret the ^{99m}Tc sestamibi, and any area of radioactivity will be graded as by a standard nuclear medicine grading system:
   1. Normal physiological activity
   2. Probably physiological activity
   3. Indeterminate activity
   4. Probably metastatic disease
   5. Metastatic disease

B. Criteria for "final determination" regarding whether a finding represents physiological activity or metastatic disease:
   a. For findings graded as 1 or 2, they will be defined for this study as physiological activity.
   b. For findings graded as 3, or 4, the following will be required:
      i. **Biopsy;** however, this will only be performed if clinically indicated.
         1. **Follow-up:** It is anticipated that very few biopsies will be performed and because the criteria for entering this study is NDCIS or NECIS, the only alternative for confirming whether or not a foci of ^{99m}Tc sestamibi uptake on a scan is metastases will be follow up, which will be performed on a clinical bases depending on the patient's treating physicians' decisions. The study team will follow up through telephone at 1, 3, 6 and 12 months after the sestamibi scan and/or until diagnosis of the metastatic site. The purpose of the telephone follow-up is to enquire on what, if any, blood tests, imaging studies or biopsies were ordered by the patient's treating physician. However, if on follow up any of the following occur, then the focus will be categorized as a metastases (true positive).
            a. Subsequent biopsy,

b. Subsequent clinical imaging study(s) (For example, although a lytic bone lesion in the area of interested was not present initially on the CT, a lytic lesion indicative of metastases may subsequently develop in that area, and for this study this will be defined as evidence of metastases of DTC (true positive).

ii. **Blind I-131 treatment****: with or without a prefatory scan: If a "blind" I-131 treatment" is clinically selected and the post I-131 therapy scan demonstrates uptake in the same areas as the ^{99m}Tc sestamibi, then the finding on the ^{99m}Tc sestamibi will be classified for this study as a metastases of DTC.

c. Grade 5 is not anticipated, because unlike I-131, which can have patterns that are very specific for DTC, ^{99m}Tc sestamibi patterns are not specific for DTC.

** A "blind I-131 treatment" is a potential therapeutic option, and this term means that the treating physician or team cannot identify the source of the patient's elevated Tg, but because of factors such as the level of elevated Tg, the rate of rise of the Tg, and the patient's clinical situation, a therapeutic administration of I-131 is give despite being "blind" to the source of the Tg.

Patient Numbers

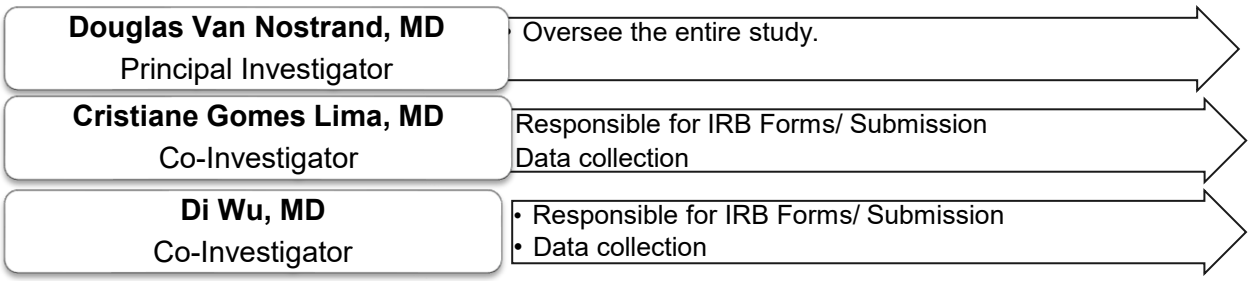
a. As noted in the objective of this study, this is a pilot study. As a pilot study, the present plan is to perform 15 patients. If no findings of Grade 3, 4, or 5 are identified on the first fifteen ^{99m}Tc sestamibi scans, then the study will be terminated.
b. If Grade 3, 4, or 5 findings are observed, then the study will continue with the follow-up of those patients with those findings to determine as best as reasonably possible whether or not the findings represent metastatic disease from DTC. However, no further patients will be recruited for ^{99m}Tc sestamibi scanning until that data become available and reviewed.
c. At this time, I am unable to establish what would be criteria to reinitiate ^{99m}Tc sestamibi scanning or completely terminate the study.

Statistical analysis:

1. I have initiated a conversation with Mihriye Mete regarding what additional statistical analysis may be reasonable for such a pilot study.

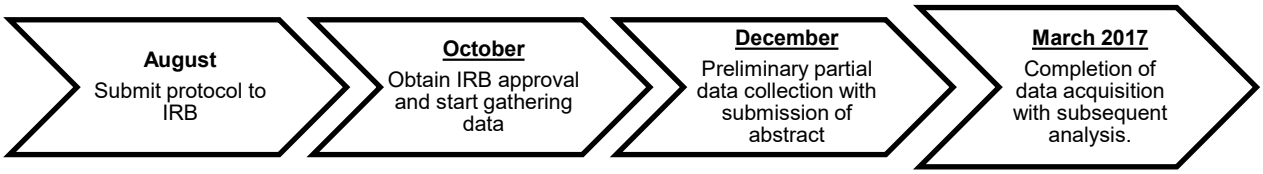
PROJECT ORGANIZATION

Organizational Flowchart



- An authorization chart delegating various functions is being developed.

Project timetable



DATA HANDLING AND RECORD KEEPING

Confidentiality

The Principal Investigator will ensure that subjects' anonymity is maintained. Subjects will not be identified in any reports on this study. All records will be kept confidential to the extent required by federal, state and local law.

Study Documentation and Storage

The Principal Investigator is responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from the MHRI, IRB, FDA, and/or applicable regulatory authorities.

In addition, all original submission documentation will be maintained and be readily available at InfoEd. All essential documentation should be retained by the institution for the same period of time required for medical records retention. No study document should be destroyed without prior written agreement between the MHRI and the Principal Investigator. Should the investigator wish to assign the study records to another party or move them to another location, MHRI must be notified in writing of the new responsible person and/or the new location.

All data will be coded, and the data and the code document will be on computer in a secure file with password on a secure computer with password.

Problems/weaknesses: The very nature of this study in regard to inclusion criteria, namely negative standard or extensive clinically diagnostic imaging scans, is problematic in determining "truth" regarding whether or not a foci of 99mTc sestamibi is secondary to metastatic DTC. But that problem should not stop one from performing such a study evaluation for these problematic patients.

Risk/Benefit Assessment: The risk/benefit assessment for this study is very low. The risk of side effects is typically <1%, and if they occur they are minor. The likelihood of benefit is not known and is the objective of the study; however, if the source of the patient's elevated serum thyroglobulin is identified, this could have significant potential benefit because of the potential for earlier treatment and avoidance of complications from the site of metastases later.

Study Population-Gender/Ethnic Inclusion: The selection of the study population is not based on gender or ethnicity.

Data Management: As noted above, confidentiality will be maintained by coding each patient, and all of the patient's identifiers will be stored on the principal investigator's computer in which the file and the computer are password protected.

Subject Identification: All patients will be identified in the Division Nuclear Medicine at the MedStar Washington Hospital Center.

Participation of Children: Children of less than 18 years of age are not eligible to participate in this clinical trial.

Compensation Plan for Subjects: None

Informed Consent: Attached

Vertebrate Animals: Not applicable

Consultants—None

Budget:

The work will be performed by Douglas Van Nostrand (DVN) and Cristiane Lima (CL) and subsequently Di Wu (DW), future research assistant, who will be added to the study on arrival. DVN works without salary or compensation and Cl's and DW's salary will be paid from the research fund for thyroid cancer research.

For expenses related to abstract submission, poster presentation, travel for presentations, etc. will be paid from the research fund for nuclear medicine thyroid cancer.

For the 99mTc Sestamibi radioisotope and scan, per Wayne Dunkle, the expense is $295.94 for the 78801 scan code, which includes ^{99m}Tc tetrafosmin. Because we will be using ^{99m}Tc sestamibi, there is an additional $10.00 surcharge.

Item	Charge	Units	Subtotal
78801 scan	$295.94	15	$4439.10
Surcharge for ^{99m}Tc Sestamibi	$10	15	$150.00
Poster preparation, travel, lodging for	$1900	1	$1900

Presentation of initial results			
Poster preparation, travel, lodging for Presentation of final results	**$1900**	**1**	**$1900**
Manuscript preparation and submission including journal fees, etc.	**$1800**	**1**	**$1800**
Statistical analysis and support	**$1500**	**1**	**$1500**
Miscellaneous expenses			**$1200**
Cristiane Lima			**Salary already covered**
Di Wu			**Salary already covered**
D Van Nostrand			**Pro bono**

Appendices

Appendix A: Prescribing Information, which will be uploaded separately to InfoEd.
Appendix B: Adverse events form.

ADVERSE EVENTS

Protocol #		ALL VISITS
	Subject Initials ___ Subject # ___	

List adverse events. ☐ CHECK IF NONE

#	Adverse Event	Start Date *mm/dd/yyyy*	Start Date *mm/dd/yyyy*	If < 24 hours, record duration HH/MM.	SAE: 1=Yes* 2=No	Grade: 1 2 3 4 5	Outcome: 1=Resolved 2=Residual Effect 3=Ongoing 4=Death† 5=Unknown	Relationship to Study Procedure: 1=Not related 2=Possible Related 3=Definitely Related

*This is a Serious Adverse Event. Notify the IRB as specified in the protocol.

Page ___ of ___
☐ Check if last page in series

Investigator Signature: _____ Date: _____

SUPPLEMENTAL COMMENT PAGE

Protocol #		Visit Time
	Subject Initials ___ Subject # ___	_____

Comments

Investigator Signature: _____ Date: _____

REFERENCES

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