

COMIRB Protocol

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
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Project Title: Evaluation of Thyroid Stunning from a Diagnostic Dose of I-123

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I. Hypotheses and Specific Aims:

Specific Aim: In a test-retest protocol, determine whether I-123 causes stunning.

Hypothesis: Pretreatment dosimetry with I-123 does not cause stunning of thyroid tissue and, therefore, does not reduce the benefit of subsequent therapeutic doses of I-131. Before I-123 can be used as the standard of comparison for other isotopes of radioiodine such as I-124, it must be proven that I-123 causes little or no stunning. We propose to address this question with the first prospective randomized intra-patient comparison of I-123 dosimetry by doing a I-123 imaging study twice, test-retest, before doing routine I-131 remnant ablation.

II. Background and Significance: The annual incidence of differentiated thyroid cancer in the United States is approximately 44,000 cases and the annual death rate is approximately 1,700 individuals (1). Although many patients do well with conventional therapy of surgery and remnant thyroid tissue ablation with I-131, a significant minority of patients develop regional and/or distant metastases. Initially, these metastases are differentiated and take up iodine and the standard of care is I-131 radioiodine therapy.

Currently, most hospitals treat patients with differentiated thyroid metastases with a fixed dose of 100 to 200 mCi of I-131 while a few university centers use individualized dosimetry to determine the maximum safe tolerable dose. The dosimetric approach is based on the assumption that a larger dose is more likely to ablate residual functioning thyroid cancer than a smaller dose. Although the dosimetric approach was described more than 45 years ago by Benua (2), there is still no consensus with respect to the advantage of the dosimetric approach over the fixed dose (3-9).

In the case of treatment with a fixed dose, the patient is usually treated with a therapeutic dose of I-131 without performing a preliminary biodistribution study. However, in the case of treatment with the maximum safe dose of I-131 based on dosimetry, it is necessary to give an initial small dose of radioiodine, usually I-131, to measure the biodistribution of radioiodine and in turn to calculate the maximum dose that the patient can safely tolerate. The dilemma is that there is significant, but controversial, evidence that the initial small dose of I-131 may stun the thyroid metastases and decrease the uptake of the subsequent therapeutic dose of I-131, thus defeating the purpose of dosimetrically determining the maximum safe dose (4,10-20).

The radioisotope of iodine, I-123, is a pure gamma emitter and is thought to be less likely to cause stunning than I-131. However, there are some reports that even I-123 can cause stunning (21-24).

If it is demonstrated that I-123 does not cause significant stunning, a follow-up separately funded prospective study can be designed to determine whether a dosimetrically determined dose of I-131 is superior to a fixed dose. If an individually calculated maximum dose is determined to be superior, it would suggest that the dosimetric approach, which is currently used in only a

small minority of patients, should be offered to all patients. This would represent a major advance in the treatment of patients with metastatic differentiated thyroid cancer. Alternatively, if a dosimetrically determined dose of I-131 is not superior to a fixed dose, all patients can be treated with the simpler less costly fixed dose regimen.

III. Preliminary Studies/Progress Report: N/A

IV. Research Methods

A. Outcome Measure(s): Difference in uptake of I-123 in the thyroid remnant in the neck in the two imaging studies. Greater than a 20% decrease from the first to second study will indicate evidence of stunning.

B. Description of Population to be Enrolled:

Inclusion criteria:

1. Patient must be 21-years-old or greater.
2. Patient must be status post near total thyroidectomy for differentiated thyroid cancer without known distant metastases and who are planning to undergo routine remnant thyroid tissue ablation with I-131.
3. Patients must qualify for thyroid ablation with I-131.

Exclusion criteria:

1. Women who are pregnant or breastfeeding.
2. Prior bovine TSH use.
3. Known metastatic thyroid cancer.
4. History of cardiovascular disease that may adversely affect patient participation at the discretion of the primary investigator.
5. Patients on hemodialysis.
6. Patients with acute serious illnesses at the discretion of the primary investigator.

C. Study Design and Research Methods: The proposed research will be the first study to perform test-retest studies in a group of patients to answer the long standing and fundamental question of whether diagnostic doses of I-123 cause stunning. Ten patients will be studied. If the patient elects to pursue participation in the study, the consent form will be explained to the patient

If the patient consents, the patient will undergo two I-123 whole body imaging studies prior to the I-131 thyroid remnant ablation.

Figure 1. General Scheme of Investigational Plan

The current standard of care is indicated in the solid black boxes and the additional research component is the dashed boxes.

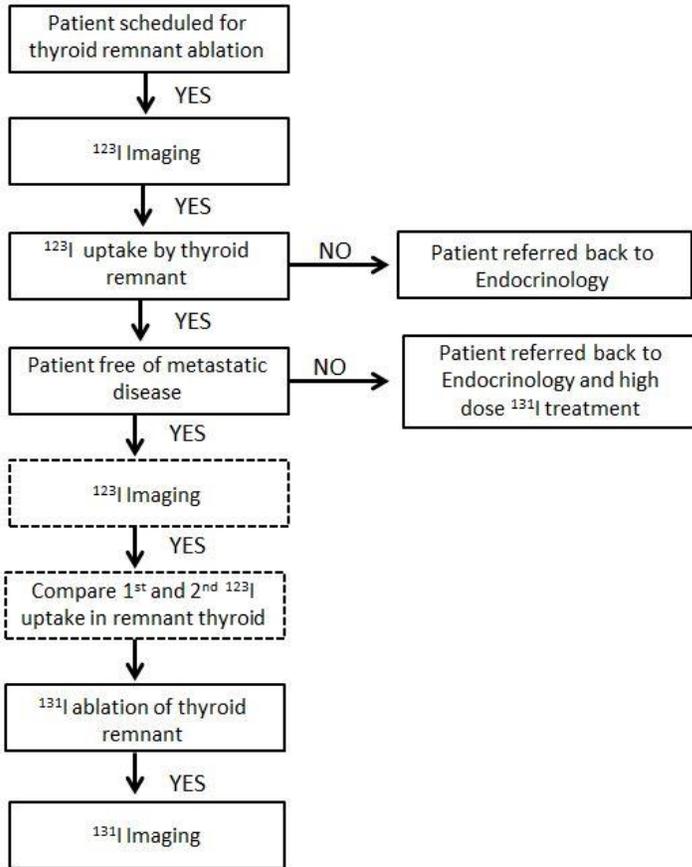
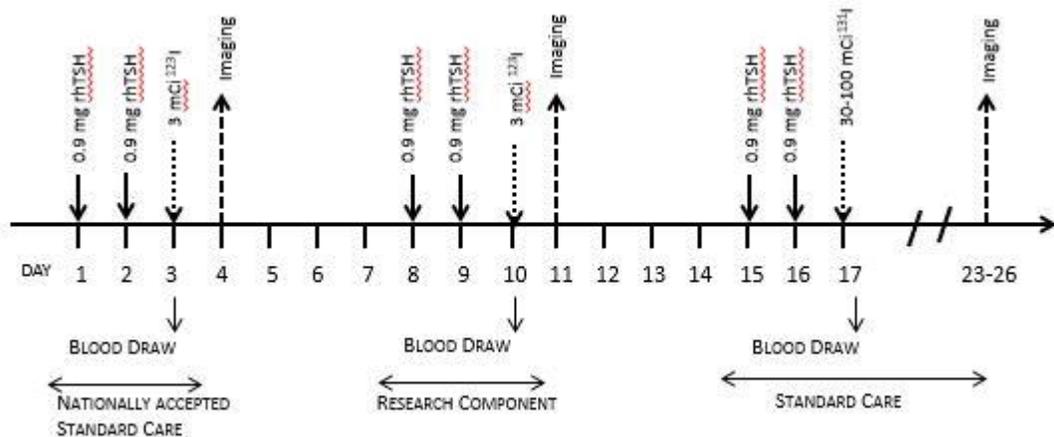


Figure 2. Timing of standard of care and research interventions for the study population.



Patient Preparation

Participants will be placed on a low iodine diet for 1 week before the dosimetry study and continue on this diet until 24 hours after the therapeutic dose of ^{131}I .

Patient is prepared for the study by receiving an intramuscular injection of rhTSH (Thyrogen). The patients are prepared for receiving radioiodine by receiving an intramuscular injection of rhTSH (Thyrogen) on days 1, 2, 8, 9, 15 and 16 in order to raise the blood level of TSH and maximally stimulate the residual thyroid tissue to take up iodine (25-27). The Thyrogen received on days 1, 2, 8 and 9 will be provided free of charge by Genzyme. The subject's vital signs will be monitored before and after each Thyrogen injection. The Thyrogen injection will be withheld if vital signs show significant alterations from the patient's baseline.

Female patients of reproductive age who have not undergone a hysterectomy will undergo serum pregnancy tests on days 3 and 17 prior to administration of radioiodine.

All patients will have blood samples taken on days 3, 10, and 17 in the morning, to document that rhTSH was given and that there was a rise in thyroglobulin level (TSH action on thyroid cells) prior to administration of radioiodine.

Diagnostic imaging with I-123

On days 3 and 10 the patient is given 3 mCi of ^{123}I orally in the morning. The participant will be asked to fast at least 4 hours before and 1 hour after the I-123 oral dose to control for interference with I-123 uptake.

Imaging with gamma camera from the top of the head to the thighs is performed on days 4 and 11.

In each of the I-123 whole body diagnostic imaging studies, one done for research purposes and the other as routine care, a region of interest will be placed over the I-123 uptake in the residual thyroid tissue and the number of counts will be recorded (28). Less than a 20% decrease in counts from the first to the second study will be considered no significant stunning (29). The Null hypothesis is that there will be less than a 20% decrease in I-123 in the thyroid remnant from the first to the second study.

In order to more accurately measure I-123 uptake in the residual thyroid tissue from the I-123 whole body diagnostic image, an I-123 standard will be placed in the field of imaging at the time of image acquisition. Use of I-123 standard is common practice for calibrating I-123 activity in the body. By using an I-123 standard, in addition to recording the number of counts in the residual thyroid tissue and comparing the count differences between the first and second study, percent uptake of I-123 in the residual thyroid tissue can be calculated for each study and compared. Less than a 20% decrease in percent uptake of I-123 in the residual thyroid tissue will be considered no significant stunning and provide additional supportive data to measuring counts in the residual thyroid tissue.

If thyroid cancer metastases are incidentally discovered in the patient with no known metastases, the patient will be removed from the study and referred back to Endocrinology.

Thyroid tissue ablation with I-131

On day 17, the patient is given a fixed therapeutic dose of ^{131}I determined by the endocrinologist and nuclear medicine physician (range 30-100 mCi ^{131}I).

Post-treatment imaging evaluation

Approximately 7 to 10 days after therapeutic dose of radioiodine (day 23-26), patient returns for routine, standard of care post ¹³¹I treatment imaging.

D. Description, Risks and Justification of Procedures and Data Collection Tools: A risk of participating in this research study is the relatively small additional radiation dose from second dosimetric study preceding the standard I-131 therapeutic ablation. Assuming a typical 30-100 mCi I-131 ablation dose, the one additional I-123 diagnostic study will increase the effective whole body dose by approximately 0.5%-1.6%. The small increase in radiation to the remnant thyroid tissue should be of no consequence since it will be ablated by the large therapeutic dose of I-131 one week later.

Another possible risk is that the radiation to the thyroid remnant from the initial experimental dosimetry studies will stun the remnant to the extent that it may not be effectively ablated. This is highly unlikely since the commonly used 30-100 mCi dose of I-131 is chosen for a significant margin of error so that very few remnants are not successfully ablated.

Patient Safety Monitoring Plan: Subject will remain in the clinical area for 20-30 minutes after each injection to be assessed for any acute adverse events. Symptoms will be recorded before and 20-30 minutes after injections. Subjects will be provided a primary phone number and an after-hours phone number to call with any questions or concerning symptoms. The most common reported side-effect symptoms are headache observed in 5% and nausea observed in 5% of patients. I-123 is a well-established FDA approved radiopharmaceutical used for diagnostic imaging of thyroid tissue and serious long term adverse events have not been reported. As a result, patients will be followed for potential adverse events until the completion of the routine standard of care treatment when the patient returns on days 23-26 for post-treatment imaging study.

The study Principle investigator, co-investigators and study coordinator will meet monthly to review preliminary data and discuss any safety related issues that may arise. The PI will be responsible for reporting any serious adverse events that are identified.

E. Potential Scientific Problems: None.

F. Data Analysis Plan: The primary endpoint will be measurement of thyroid remnant activity at 24 hours. We predict there will be less than a 20% reduction in the amount of I-123 in the thyroid remnant when the results of the second administered dose of I-123 is compared to the results from the first dose of I-123. The data will be analyzed statistically by the t-test and by the sign test. While we plan to study only 10 participants, this should be a sufficient number to determine whether there is any evidence of stunning by the sign test and, if there is stunning, whether there is more than a 20% stunning effect by the t-test. This is a pilot study, but it is likely to give results that are sufficiently definitive that it will not need to be repeated with larger numbers of participants. In addition, this is an internally funded research project that is intended to generate preliminary data to be

used in a larger NIH grant proposal that will compare fixed versus dosimetrically determined I-131 doses for treatment of patients with differentiated thyroid cancer with distant metastases.

G. Monitoring and Oversight

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs, UAPs and reportable AEs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs, UAPs and reportable AEs are to be reported to the DSMC within 5 business days of the sponsor investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The sponsor investigator will provide a DSM report to the CU Cancer Center DSMC on a six month basis. The DSM report will include a protocol summary; current enrollment numbers; summary of toxicity data to include specific SAEs, UAPs and AEs; any dose modifications; all protocol deviations; and protocol amendments. The DSM report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this six month report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

Quality Control and Quality Assurance

Site monitoring visits will be performed by the sponsor investigator's authorized representative on a regular basis, pursuant to the Monitoring Plan. During these visits, information recorded on the CRFs will be verified against source documents. Additional

computer programs that identify selected protocol deviations, out-of-range data, and other data errors within the electronic data entry may also be used to help monitor the study. As necessary, requests for data clarification or correction will be sent to the appropriate site PI.

Independent auditors from the sponsor investigator's authorized representative will be allowed by the site's PI to audit. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB.

- H. Summarize Knowledge to be Gained:** There will be no benefits to the human subjects in this research project. However, there is likely to be significant benefit to future patients with differentiated thyroid cancer.

If it is demonstrated that I-123 does not cause significant stunning, a follow up separately funded prospective study can be designed to determine whether a dosimetrically determined dose of I-131 is superior to a fixed dose. If an individually calculated maximum dose is determined to be superior, it would suggest that the dosimetric approach which is currently used in only a small minority of patients should be offered to all patients. This would represent a major advance in the treatment of patients with metastatic differentiated thyroid cancer. Alternatively, if a dosimetrically determined dose of I-131 is not superior to a fixed dose, all patients can be treated with the simpler less costly fixed dose regimen.

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