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Impact of Near Infrared Autofluorescence (NIRAF) Detection for Identifying Parathyroid Glands during Parathyroidectomy

Research Protocol

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1.0 Background

Inability of the surgeon to identify or localize the diseased PG can occur in 5 – 10% of cases resulting in failed parathyroidectomies (1, 2). As a result, persistent hyperparathyroidism can occur in these patients resulting in unnecessary repeat surgeries that may be associated with increased morbidity and costs (3, 4). Ultrasound imaging, ^{99m}Technetium-sestamibi scintigraphy, and computed tomography (CT) have so far demonstrated variable efficacy in preoperative localization of diseased PGs (5, 6) and may not always correlate well with the surgical field of view as observed intraoperatively. Consequently, most surgeons rely on visual identification of PGs during surgery, whereby the accuracy of PG identification is eventually determined by her/his surgical skill and experience (7, 8). When in doubt, a surgeon routinely confirms the identity of PG tissue intraoperatively by sending the specimen for frozen section analysis (or PTH aspirate) that typically requires a wait time of 20–30 minutes per sample (9) and has additional costs.

By easily being able to distinguish parathyroid from other tissues intraoperatively, postsurgical complications and associated costs may be reduced. The unique discovery of near infrared autofluorescence (NIRAF) in parathyroid tissues demonstrated that optical modalities that detect NIRAF can be utilized for non-invasive and label-free identification of parathyroid tissues with an accuracy as high as 97%.(10, 11, 12, 13) Since then, several research groups have explored the feasibility of localizing parathyroid glands using NIRAF detection with reasonable success, resulting in FDA clearance for this optical technique (14). In this study, we plan to evaluate whether an FDA-cleared device called 'PTeye' ([redacted]) is beneficial or not, for the surgeon and patient during parathyroid operations. The results of such a study will help us to understand and assess the true impact of optical modalities such as PTeye on (i) improving the quality and efficiency of parathyroid surgeries and (ii) minimizing risk of postsurgical complications and related expenses.

2.0 Rationale and Specific Aims

The goal of this study is to assess whether using PTeye – a NIRAF detection modality – can reduce healthcare associated costs after parathyroid surgeries and improve patient outcomes. The specific aims of this study is to determine if PTeye is beneficial or not for (i) intraoperative identification of parathyroid tissues, (ii) improving efficiency of parathyroid surgeries, and (iii) minimizing risk of postsurgical complications.

By being able to quickly and definitively locate parathyroid glands while in the operating room, the duration of surgical procedure could be further reduced. In addition, the number of frozen section biopsy (or PTH aspirate) and associated costs can be minimized. Furthermore, repeat surgeries as a result of missing a diseased parathyroid gland at the time of the initial parathyroidectomy for hyperparathyroidism could potentially be avoided.

Primary Outcome Measure:

1. Number of frozen sections (or PTH aspirate) sent for analysis
    a. Number of frozen sections (or PTH aspirate) sent for analysis during the procedure to confirm potential parathyroid tissue [Time Frame: Immediate. During PTx procedure.]

Secondary Outcome Measure:

1. Persistent hyperparathyroidism (Immediate)

    a. Failure of intra-operative parathyroid hormone (PTH) to normalize (defined as failure of PTH to drop > 50% of its baseline value at final intra-operative PTH assay and/or failure of PTH to drop < 65 pg/ml or 6.9 pmol/L). [Time Frame: During parathyroidectomy (PTx) procedure]
2. Persistent hyperparathyroidism or hypercalcemia (transient)
    a. Elevated blood calcium levels (total blood calcium level > 10.5 mg/dL or 2.6 mmol/L) with/without elevated parathyroid hormone (PTH) (serum intact PTH > 65 pg/ml or 6.9 pmol/L) at first postoperative visit. [Time Frame: 5-14 days after PTx procedure]
3. Persistent hyperparathyroidism or hypercalcemia (failed parathyroidectomy)
    a. If blood calcium with/without parathyroid hormone (PTH) has not normalized at 1st post-operative visit, calcium and/or PTH is subsequently measured as necessary. Patient is defined to have a failed parathyroidectomy if hypercalcemia/hyperparathyroidism (defined as total blood calcium level > 10.5 mg/dL or 2.6 mmol/L, with/without elevated serum intact PTH > 65 pg/ml or 6.9 pmol/L) persists at or after the 6th postoperative month. [Time Frame: 6 months after PTx procedure]
4. Overall number of parathyroid glands identified
    a. Overall number of parathyroid glands identified (Experimental Group: Glands identified with naked eye + NIRAF;Control Group: Glands identified with naked eye) [Time Frame: Immediate. During PTx procedure.]
5. Number of parathyroid glands identified with NIRAF
    a. Number of parathyroid glands identified with NIRAF, which was not seen with surgeon's naked eye [Time Frame: Immediate. During PTx procedure.]
6. Number of diseased parathyroid glands identified versus preoperatively localized glands
    a. Number of diseased parathyroid glands identified intra-operatively versus glands localized preoperatively using sestamibi, CT or ultrasound [Time Frame: Preoperative to immediate during PTx procedure.]
7. Number of intra-operative parathyroid hormone (PTH) assays sent
    a. Number of intra-operative parathyroid hormone assays sent during the procedure [Time Frame: Immediate. During PTx procedure.]
8. Duration taken to identify first parathyroid gland
    a. Duration taken to identify 1st parathyroid gland in PTx procedure – timed from skin incision to finding PG. [Time Frame: Immediate. During PTx procedure.]
9. Duration taken to identify last parathyroid gland
    a. Duration taken to identify last parathyroid gland in PTx procedure – timed from skin incision to finding the last PG.[Time Frame: Immediate. During PTx procedure.]
10. Duration of parathyroidectomy (PTx) procedure
    a. Duration of PTx procedure – timed from skin incision until the surgeon notifies the anesthesia team to awaken the patient [Time Frame: Immediate. During PTx procedure.]
11. Duration taken for intraoperative parathyroid hormone (PTH) to normalize
    a. Time taken for PTH to attain cure criteria or normalize - timed from skin incision until the PTH levels drops > 50% of its baseline value and/or PTH drops < 65 pg/ml or 6.9 pmol/L. [Time Frame: Immediate. During PTx procedure.]
12. Number of nights spent in the hospital after parathyroidectomy
    a. Number of nights spent for postoperative recovery in the hospital after the surgical procedure. [Time Frame: 0-72 hours after PTx procedure.]
13. Number of 'false positive' tissues excised by surgeon
    a. Number of tissues that were excised by surgeon assumed to be parathyroid tissue, but is later validated as nonparathyroid tissue (false positive) by histology [Time Frame: Immediate to 10 days after PTx procedure.]
14. Number of doctor visits/emergency department visits or hospital admissions

a. Number of doctor visits/emergency department visits or hospital admissions due to persistent hypercalcemia and/or associated symptoms after parathyroidectomy procedure [Time Frame: Up to 6 months after PTx procedure.]

15. Number of patients who have had repeat parathyroidectomy (PTx) procedure
    a. Number of patients with repeat PTx procedure performed after the current procedure [Time Frame: 6 - 12 months after PTx procedure.]

3.0 Animal Studies and Previous Human Studies

Modalities that rely on NIRAF detection for label-free parathyroid identification have been successfully validated in several studies (15-18). FDA approval for this application was recently granted to Fluobeam (a commercially available imaging system) and PTeye (a commercial fiber probe-based system) in 2018 (14). Certain outcome studies have reported that imaging-based systems for NIRAF detection such as the PDE Neo II system was able to reduce the number of frozen sections (or PTH aspirate) required during parathyroid procedures (17). However, other studies have reported that they observed no benefit from imaging-based systems in parathyroid localization (19). In a recent study, Thomas *et al.* demonstrated that a fiber probe-based system – the PTeye – was more sensitive in parathyroid identification compared to the imaging-based system by PDE Neo II (20). To date, there has been no studies that determine the impact of a fiber probe-based system (i.e. PTeye) during parathyroid surgeries in minimizing a number of frozen sections (or PTH aspirate) obtained intraoperatively or postsurgical complications.

4.0 Inclusion/Exclusion Criteria

Inclusions:

- All adults (i.e., ≥ 18 years old) patients with primary hyperparathyroidism who will be undergoing parathyroid surgery
- All adults (i.e., ≥ 18 years old) patients with persistent primary hyperparathyroidism after having undergone a failed prior parathyroid surgery who will be undergoing repeat parathyroid surgery

Exclusion:

- Children and minors
- Pregnant women
- Patients with concurrent parathyroid and thyroid disease that require total thyroidectomy
- Patients with secondary or tertiary hyperparathyroidism

5.0 Enrollment/Randomization

The research will be designed as a single center study, where patient recruitment will be conducted by the participating surgeon at UCSF. The initial evaluation will be conducted while the surgeon is evaluating the patients. The final eligibility of each patient for participating in this study will be determined by the participating surgeon in accordance of his/her medical conditions. Following the exclusion criteria, the study will aim to accrue all eligible patients who are going to the OR as part of their standard surgical procedure.

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their

participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

1. On the date of procedure consent at clinic or the date of surgery, patients will be given a paper consent form detailing about the outcome study with PTeye in addition to the consent for the surgical procedure that will be performed.
2. The key study personnel will briefly describe the PTeye and its application to the patient.
3. If the patient is interested in participating, the key study personnel will provide the patient with a paper-based consent form.
4. The key study personnel or the surgeon assigned to the patient will be available to discuss the protocol with the patient (including, risks, benefits, alternatives, etc.). The patient will also be provided with the contact information of the principle investigator should they have any questions.
5. If the patient consents to be part of the study, a scan of their signed consent form will be stored digitally in the patient's medical record.

Prior to surgery, the patient will be assigned a unique ID (e.g. Para_001). The unique ID will be utilized for randomly allocating the patient to the experimental arm (where the surgeon will use PTeye) or a control arm (where the surgeon will not use PTeye). The allocation will be conducted by the study coordinator using 'Random Allocation Software' (http://mahmoodsaghaei.tripod.com/Softwares/randalloc.html).

6.0 Study Procedures

For patients assigned to the study arm, the surgeon will use the PTeye as an intraoperative tool to identify if a suspect tissue is a parathyroid or not, during the parathyroid surgery. The surgeon will first take 5 baseline NIRAF measurements on the thyroid gland (or neck muscle, if thyroid is absent) using the disposable sterile fiber probe that is connected to the PTeye console (see Figure 1), as per device functionality requirements. The subsequent step would involve touching the target tissue in the neck with the fiber optic probe, following which the PTeye will indicate to the surgeon if the tissue is parathyroid or not. Parameters which are displayed on the PTeye console – Baseline values, Detection Intensity, Parathyroid Detection Ratio – will be recorded for each patient enrolled in the study arm. PTeye indicates that a tissue is parathyroid if it displays the 'Parathyroid Detection Ratio' is greater than 1.2. The rest of the surgical procedure will follow according to standard protocol.

For patients assigned to the control arm, the surgeon will not use the PTeye and will proceed with the parathyroid surgery as usual, while relying solely on her/his surgical experience in identifying the parathyroid glands during the operations.

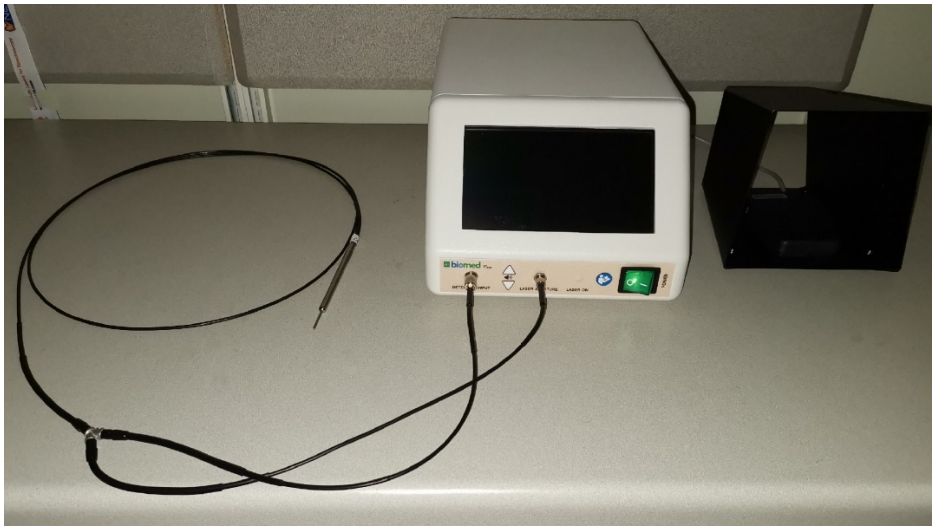

Figure 1. A commercial fiber probe-based system (PTeye, [redacted]) for detecting near infrared autofluorescence (NIRAF) utilized for intraoperative parathyroid gland identification. PTeye consists of 1) the console that has a display and indicates to the surgeon if a tissue is parathyroid or not, 2) a detachable fiber optic probe, and 3) a foot-pedal which is activated by the surgeon for tissue NIRAF measurements.

De-identified information regarding (i) patient demographics, (ii) duration of surgery, (iii) number of frozen section (or PTH aspirate) analysis performed, (iv) frozen section (or PTH aspirate) and permanent histology reports of all excised tissues, (v) blood calcium levels (before surgery, 5-14 days after surgery and 6 months after surgery), (vi) parathyroid hormone (PTH) levels (5-14 days after surgery and 6 months after surgery) and (vii) postsurgical complications, if any and history of ER visits or hospitalization or repeat surgeries due to high or altered calcium levels, will be compiled for all enrolled patients. These parameters would then be compared between the study arm and the control arm to truly gauge the impact or value of a device like PTeye for parathyroid surgeries.

7.0 Risks

The clinical site is responsible for protecting all participants involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the participants' rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

- The proposed study is designed to collect NIRAF measurements from neck tissues with a commercial device called PTeye during a parathyroidectomy. The device that will be used for NIRAF measurements is an FDA-cleared device.
- Each PTeye measurement takes less than 2 seconds, with the whole set of measurements not adding more than 5 minutes to the surgical procedure. Thus, there is a minimal increase of risk of surgery due to the potential five extra minutes

of anesthesia time associated with the study. In addition, the participating surgeon will evaluate the eligibility of the patient based on his or her medical condition. Patients with high anesthetic risks will not be asked to participate in the study.

- Since the power of near infrared light from PTeye will be extremely low, no side effects should be introduced to the patient.

- There should not be any discomforts, inconveniences, and/or risk resulting from this study.

- The study should not increase the risk of infection as a disposable sterile probe is used for each patient.

- The PTeye device used in this study has been FDA-cleared. The FDA clearance is granted based on the caveat that necessary precautionary measures will be taken by the surgeon to minimize the probable risks (as listed in the device brochure). The PTeye may be associated with unknown/unforeseen risks as with any other FDA-cleared medical devices used during surgical procedures.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Upon identification, adverse events resulting from this *in vivo* data acquisition procedure will be reported to the PI and' IRB immediately. The study will be immediately terminated and not resumed until the sources leading to the adverse events are identified.

9.0 Study Withdrawal/Discontinuation

The data acquisition procedure will be terminated if the medical conditions of the participant show some unexpected and adverse changes. The decision of terminating the study will be determined by the participating surgeon.

10.0 Statistical Considerations

Currently there are no comparable published randomized trials that have evaluated the effect of NIRAF detection for reducing intraoperative frozen section analysis (or PTH aspirate) during parathyroidectomies. Based on preliminary data obtained from a similar ongoing study at Vanderbilt University Medical Center over 123 patients, an 83% reduction in frozen section analysis was observed in the interventional group of 63 patients where NIRAF was used, compared to the control group of 60 patients where NIRAF was not used (unpublished). The mean frozen section analysis (FSA) obtained for the NIRAF group is 0.1 FSA/patient versus 0.6 FSA/patient obtained in the control group. Assuming, that an expected mean difference of 0.6 FSA/patient needs to be observed between the NIRAF and the control group, where the standard deviation of the enrolled study population is 0.8 (Standard Deviation obtained in VUMC study population is 0.78 FSA/patient), 47 patients would be required per group (for a 95% powered study). Since this study may involve patient follow-up for data up to 6 months after surgery, we will thus assume an approximate data attrition rate of 15%, thus requiring a recruitment of 55 patients per group. Therefore, a total of 110 patients (study and control arm) should be recruited per surgeon for this study at this study site. Overall, 110

patients need to be enrolled at this study site under a single surgeon to assess the impact of this technology.

Sample size	
2-side significance level	0.05
Power (1-beta)	0.95
Ratio of sample size, Control/NIRAF group	1
Expected mean in NIRAF group	0.7
Expected mean in Control group	0.1
Study population standard deviation	0.8
Result	
Sample Size - Control group	47
Sample Size - NIRAF group	47
Sample Size – Control group compensated for 15% attrition	55
Sample Size – NIRAF group compensated for 15% attrition	55
Total sample size	110

Analysis Plan:
Continuous variables will be reported using medians and interquartile ranges (IQRs). Categorical variables will be reported using counts, percentages, and their 95% confidence intervals (CIs). Comparisons of the NIRAF and control parathyroidectomy groups for primary and secondary outcomes will be done using (a) 1-sided $\chi 2$ or Fisher tests for categorical variables and (b) 2-tailed Student's t-test or Wilcoxon's test for continuous variables (depending on distribution of data). To analyze factors that influence the primary outcome assessed for this study, i.e., number of frozen sections specimens (or PTH aspirate) sent for analysis, a generalized linear mixed models will be used. The following variables will be considered as fixed effects for the study model: (i) nature of the intervention (NIRAF or control), (ii) age, (iii) BMI, (iv) number of intraoperative PTH assays, (v) number of diseased parathyroid glands seen, and (vi) type of parathyroid surgery (focused parathyroidectomy or bilateral neck exploration). The multivariate analysis based on this model will generate the respective odds ratios and their 95% CIs for the aforementioned factors that are being considered. A p-value ≤ 0.05 based on the statistical analysis for continuous/categorical variables under the primary and secondary outcomes measured in this study will be considered as significant.

11.0 Privacy/Confidentiality Issues

All study staff are required to complete the CITI Protection of Human Subjects Training Program. All data pertaining to this study will be stored in the HIPPA compliant REDcap data management program. Access to study data will be limited to the investigators listed on the study only. Only indirect identifiers such as medical record number (MRN) will be used. Participants' information, including his or her name and medical record number, will be available only to the PI and key study personnel. It will be stored in a password-protected computer and a locked file cabinet in the study coordinator's office where we also will store the consent forms. All records will only be available to the PI and key study

personnel. All information potentially identifying the participant will not be included in the data analysis or reporting of results therein.

Participants will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the participants' medical records, and each participant will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

12.0 Follow-up and Record Retention

The duration of the study is expected to be approximately two year and will depend on patient availability. The data acquired from this study will be preserved indefinitely, as it may influence the future development of the entire research project. However, the data will not be accessible to anyone other than the participants of this study. All original paper records, record sheets, preoperative and postoperative lab investigations, drug/medication history, post-surgical medical history, histopathological diagnoses of the investigated tissue samples, will be collectively retained by the PI or Key Study Personnel. The data of this study will be stored in a password protected computer, and only users with permission from the PI can access the data base.

The PI is required to prepare and maintain adequate records of the disposition of study materials and case histories that record all observations and other data pertinent to the investigation on each individual administered the materials in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all data entry forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed participant consent forms).

Source documents include all recordings of observations or notations and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

13.0 Study Management

13.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the PI will have written and dated approval from the Institutional Review Board for the protocol, informed consent form, subject recruitment materials, and any other written information to be provided to participants before any protocol related procedures are performed on any participants.

The PI must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable

regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

13.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant-facing materials related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB. Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review and Monitoring Committee (PRMC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

13.4 Changes to the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the PI and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to participants, an amendment may be implemented prior to IRB approval. In this circumstance, however, the PI must then notify the IRB according to institutional requirements.

The Study Chair and the UCSF study team will be responsible for updating any participating sites, if any.

13.5 Handling and Documentation of Study Supplies

The PI will maintain complete records showing the receipt, dispensation, return, or other disposition of all study materials. The date, code number, and the identification of patients to whom study materials have been dispensed by patient number and initials will be included.

13.6 Data Management

The PI and/or designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the investigation on each study participant. Specific study data will be entered into OnCore®, Eureka and/or REDCap. Study personnel will enter study data into the study database(s); the PI will review and approve the completed data entry forms. Screening data from the participating site will be reported and reviewed in aggregate with data from patients enrolled at the coordinating center, UCSF.

In accordance with federal regulations, the PI is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto study database(s).

At study completion, when the data have been declared to be complete and accurate, the database(s) will be locked. Any changes to the data entered into the database(s) after that time can only be made by joint written agreement among the Study Chair and the trial statistician.

13.7 Oversight and Monitoring Plan

This protocol is classified as a minimal risk level study and we do not anticipate the need for monitoring by the HDFCCC Data and Safety Monitoring Committee (DSMC) as per the NCI-approved Data and Safety Monitoring Plan (DSMP).

The UCSF Sponsor-Investigator will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress.

14.0 Protection of Human Subjects

14.1 Protection from Unnecessary Harm

The clinical site at UCSF is responsible for protecting all participants involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the participants' rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

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