Title
MAPS trial – Molecular Analysis for Precision Surgery in Thyroid Cancer, a Pilot Feasibility Study

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PROJECT TITLE

Routine Preoperative Molecular Analysis to Guide Extent of Surgery in Thyroid Cancer, a Pilot Feasibility Study

SUMMARY

Ideal surgical extent for differentiated thyroid cancer remains unclear. Routine use of molecular analysis in biopsy-proven thyroid cancer could provide important prognostic information to help guide extent of surgery – thyroid lobectomy versus total thyroidectomy. This is a pilot feasibility study for the use of routine molecular analysis in Bethesda V and VI thyroid cancers, with randomization of the intermediate-molecular risk subgroup to thyroid lobectomy and total thyroidectomy. We hypothesize that patients will 1) agree to preoperative molecular analysis, and 2) 50% of intermediate-risk patients will agree to and follow through with randomization. This will be a pilot study for a future randomized controlled trial (RTC) to compare between the two surgical approaches in intermediate-molecular risk thyroid cancer.

BRIEF DESCRIPTION OF STUDY KEY WORDS

RAI	Radioactive iodine
PTC	Papillary thyroid cancer
NIFTP	Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
ATA	American Thyroid Association
FNA	Fine needle aspiration
PTH	Parathyroid hormone
TSH	Thyroid stimulating hormone
Tg	Thyroglobulin
EMR	Electronic Medical Record

2. ABSTRACT

Every year, ~45,000 individuals in the United States develop a new diagnosis of thyroid cancer. Initial therapy for most patients involves surgical excision of the thyroid lobe containing the cancer (thyroid lobectomy) or removal of the entire gland (total thyroidectomy). Compared to thyroid lobectomy, total thyroidectomy carries double the risk of recurrent laryngeal nerve injury, adds the possibility of permanent hypoparathyroidism, and makes all patients dependent on lifelong thyroid hormone supplementation. We accept these additional risks because total thyroidectomy allows patients to receive postoperative radioactive iodine (RAI) therapy, which mitigates recurrence risk in high-risk patients. Thus, total thyroidectomy primarily benefits patients that require radioiodine remnant ablation. Unfortunately, the need for RAI ablation relies on postoperative pathology findings and cannot be reliably predicted preoperatively. **The current problem** is that some patients in this system receive overly aggressive care, undergoing the additional risk of total thyroidectomy but ultimately not requiring radioactive iodine. Others may receive overly conservative initial treatment, needing reoperation for a completion thyroidectomy after initial thyroid lobectomy. Thus, there is a clear, unmet need for preoperative prognostic risk stratification to determine ideal surgical treatment for thyroid cancer.

One potential solution is to risk-stratify thyroid cancer patients based on molecular testing. Currently, molecular analysis is used to differentiate benign nodules from potentially cancerous nodules but it is not utilized for prognostic purposes. Several studies have determined that high-risk mutation profiles, such as *TERT* and *TP53*,[1,2] predict metastatic and recurrent disease. As such, if mutation status was known preoperatively, these patients could be directed to undergo a total thyroidectomy. Conversely, lower risk lesions could be directed to thyroid lobectomy. There would still be a large area of uncertainty among intermediate molecular-risk lesions, such as isolated *BRAF,*[3] for which there are no recommendations on extent of treatment.

To date, no randomized control trial exists comparing extent of surgery based on preoperative molecular data. We envision a future clinical trial where thyroid cancer patients undergo risk stratification with molecular testing, and subsequently intermediate-molecular risk patients get randomized to thyroid lobectomy versus total thyroidectomy. To determine how to adequately power this endeavor, we propose a pilot randomized clinical trial as an initial feasibility study. *We **hypothesize** that 1) patients with papillary thyroid cancer will agree to preoperative molecular testing, and 2) 50% of intermediate molecular-risk patients will agree to randomization to thyroid lobectomy versus total thyroidectomy and complete treatment as assigned.*

Patients referred to our Endocrine Surgery Clinic with new diagnosis of papillary thyroid cancer (Bethesda V or VI on cytology) will be enrolled and undergo routine molecular testing. We will exclude patients with hard indications for total thyroidectomy on ultrasound imaging (nodal or distant metastases, extrathyroidal extension). Patients' thyroid cancer molecular profile will be classified as low, intermediate, or high molecular-risk based on previous published data.[4] There is equipoise between thyroid lobectomy and total thyroidectomy for intermediate risk molecular profile thyroid cancers. Thus, we will randomize those patients to thyroid lobectomy or total thyroidectomy. Endpoints are related to feasibility of a future trial. We will assess percentage of patients who 1) agree to randomization, and 2) complete treatment as assigned.

We will simultaneously create a registry tracking the final surgical pathology and clinical results of low and high molecular-risk patients. Postoperative pathologic findings following thyroid surgery will be obtained using chart review. We will determine whether certain mutations and molecular risk profiles predict the need for RAI treatment. Additionally, we will track postoperative cancer surveillance outcomes, including biochemical and structural evidence of recurrence.

3. STUDY RATIONALE

Incidence of thyroid cancer has substantially increased in the past decade.4 Papillary thyroid cancers (PTC), typically follow a very indolent course. Although approximately 45,000 patients are diagnosed with thyroid cancer each year, only 2,000 patients die from it with a 5-year survival of over 98%.[4] Thus, there has been a movement to de-escalate care to reduce unnecessary surgical morbidity, and current guidelines recommend consideration of thyroid lobectomy over total thyroidectomy when appropriate.[5] At this time, it is unclear when thyroid lobectomy would be more beneficial than total thyroidectomy. A systematic review of guidelines and expert consensuses from 2009 to 2019 for PTC 1-4 cm in size found that 11 studies recommended total thyroidectomy, recommended thyroid lobectomy, and recommended patient-centered decision making.[6] Improved preoperative risk stratification can play a significant role in determining ideal surgical treatment of thyroid cancer.

Currently, molecular testing is used to determine the risk of malignancy in indeterminate thyroid biopsies. However, these tests have not been used for prognostic purposes in biopsy-proven thyroid cancer. Recent studies have demonstrated that the molecular profile of thyroid cancer is predictive of recurrent disease.[2,7] Certain high-risk mutation combinations such as BRAFV600E and TERT are associated with increased risk of recurrence and fatal disease.[1,7] Therefore, molecular testing can offer valuable prognostic information to guide treatment.

This proposal is intended to be a feasibility study to assess whether patients will agree to routine preoperative molecular testing and whether patients would complete assigned treatment following randomization. The results of this pilot randomized control trial will inform the design of a future multicenter trial. Demonstrating that molecular profile can be used to dictate initial therapy for thyroid cancer will have an immediate and dramatic impact on the field. It can accomplish our goal of reducing overtreatment and its associated morbidity in the treatment of thyroid cancer.

4. BACKGROUND

Diagnosis of thyroid cancer. Patients with thyroid nodules that look concerning for malignancy on ultrasound undergo fine needle aspiration biopsy. The cytology is classified into the Bethesda Category based on risk of malignancy. Bethesda I is non-diagnostic and repeat biopsy is required, and Bethesda II is benign. Bethesda III and IV are indeterminate nodules with a 5-30% risk of malignancy. Bethesda V and VI have an 85-100% risk of malignancy, so those patients require operative resection. Molecular testing was first employed in Bethesda III and IV lesions to better delineate the risk of malignancy.[5] However, we have not yet used these molecular tests on Bethesda V or VI lesions for prognostic purposes.

Thyroseq molecular analysis. As mentioned above, patients with indeterminate thyroid nodules undergo molecular analysis of the biopsy sample to determine risk of malignancy based upon mutations and gene alterations that are present. In this proposal, we plan to utilize Thyroseq for the analysis, which is a DNA- and RNA-based next generation sequencing model of 112 genes.[8] Molecular analysis models were trained with machine learning algorithm on both pathologies that were confirmed to be benign (Bethesda II) and malignant (Bethesda V and VI) to analyze which genes and mutations are associated with malignancy.[9] It reports the analysis in six different categories that range from negative to presence of high-risk mutation (Figure 1). Based on Thyroseq's risk stratification, nodules with certain combinations of TERT/TP53 with BRAF mutations are considered high risk for recurrence,[2] and total thyroidectomy is recommended. Conversely, RAS-like mutations are associated with non-invasive follicular thyroid neoplasm with

papillary-like nuclear features (NIFTP), or a very low-risk variant of papillary thyroid cancer.[10] Thus, a thyroid lobectomy is recommended for these low-risk cases. However, there exists a gray area in the appropriate management of intermediate-molecular risk mutations, such as Hurthle cell-type mutation and BRAF-type mutation, where thyroid lobectomy or total thyroidectomy are both considered adequate

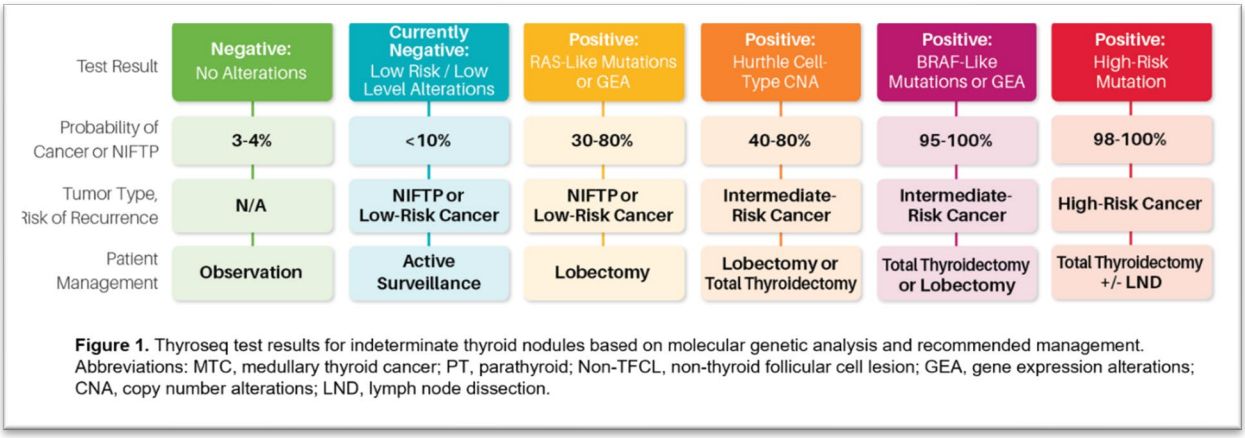


Figure 1. Thyroseq test results for indeterminate thyroid nodules based on molecular genetic analysis and recommended management. Abbreviations: MTC, medullary thyroid cancer; PT, parathyroid; Non-TFCL, non-thyroid follicular cell lesion; GEA, gene expression alterations; CNA, copy number alterations; LND, lymph node dissection.

treatments.

Thyroidectomy for thyroid cancer. Most patients can either undergo thyroid lobectomy or total thyroidectomy as initial surgical treatment of their thyroid cancer. For patients with disease involving the lymph nodes or soft tissues of the neck, total thyroidectomy is indicated so that patients can receive postoperative treatment with RAI. Thus, it is important for patients with diagnosed thyroid cancer to undergo ultrasound of the neck to assess for sonographic evidence of extrathyroidal spread and lymph node metastasis.5 For cancers < 1 cm limited to the thyroid, thyroid lobectomy is sufficient because those patients do not benefit from RAI. However, those who fall in the middle with nodules between 1 cm and 4 cm without evidence of disease spread, which accounts for most thyroid cancer patients, the ideal extent of surgery is uncertain and frequently debated. Since total thyroidectomy has a higher risk of recurrent laryngeal nerve injury and hypoparathyroidism, and renders all patients hypothyroid, it should be avoided if there is no clinical benefit.

Postoperative RAI for high-risk disease on pathology. Patients who ultimately end up with high-risk disease on pathology (extrathyroidal extension, numerous lymph node involvement, high-risk histologic features, etc.) undergo RAI therapy. In order to receive RAI, patients must have a total thyroidectomy. Those who initially had thyroid lobectomy and pathology returns with high-risk disease undergo reoperation for completion thyroidectomy – removal of the remaining thyroid gland – prior to starting RAI. The response to therapy is then assessed based on thyroglobulin levels, which are proteins secreted by thyroid tissues. Complete response would mean patients have undetectable serum thyroglobulin levels. As such, patients can be monitored for disease recurrence by serially checking thyroglobulin levels.

Molecular analysis and associated with aggressive disease. Commercially available molecular testing was first developed to discriminate benign from malignant thyroid nodules when cytology was indeterminate. Over time, there has been a growing understanding that certain molecular profiles are associated with worse clinical outcomes. Yip et al. verified a method of risk stratification of thyroid cancers based on their molecular profile by performing a propensity-matched retrospective molecular analysis of 62 differentiated thyroid cancers with distant metastases to those without distant metastases.[11] They found that high-

molecular risk profiling had a strong association with distant metastases (odds ratio 25.1, 95% confidence interval [CI] 3.07 – 204.4) and no patients with low-molecular risk had metastatic disease. In this instance, molecular profile predicted clinical behavior, which led us to hypothesize that molecular risk could be used to dictate therapy in thyroid cancer. This molecular risk stratification is utilized by Thyroseq (Figure 1).

Most recently, our group published a retrospective study of molecular profiles of 100 Bethesda V and VI thyroid nodules and assessed their associated risk of recurrence. Majority of the nodules in this population harbored an intermediate molecular-risk profile (6 low-risk, 88 intermediate-risk, and 6 high-risk).[12] Similar to the study by Yip et al., high-molecular risk patients had higher rates of recurrence at 67% compared to intermediate-risk at 7%, and no recurrence in the low-risk cohort. High-risk molecular profile was associated with risk of disease recurrence in the 5-year follow-up period (hazard ratio 1.36, 95% CI 1.02 – 1.80). Based upon this data, it appears that total thyroidectomy can be reserved for high-risk individuals and thyroid lobectomy in low-risk patients. However, the ideal extent of initial surgery in intermediate-risk disease remains unclear.

5. STUDY OBJECTIVE

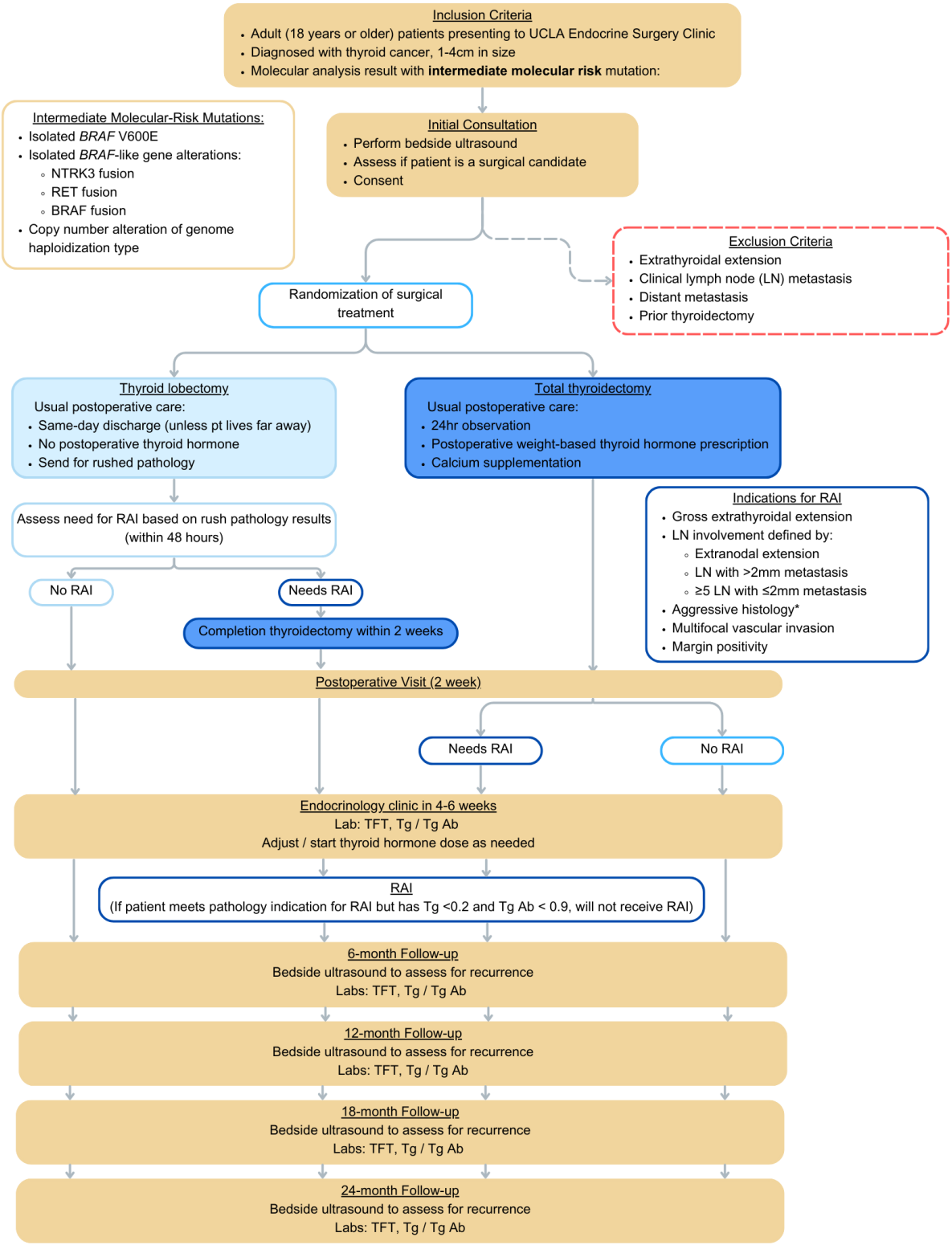
Aim 1. Determine feasibility of a future multi-center prospective trial of routine preoperative molecular testing for papillary thyroid cancers to guide extent of therapy. Patients with a new diagnosis of papillary thyroid cancer will undergo routine molecular testing with Thyroseq genomic classifier. Inclusion criteria include age over 18 years and cytology consistent with papillary thyroid cancer. We will exclude patients with hard indications for total thyroidectomy on ultrasound imaging (nodal or distant metastases, extrathyroidal extension). Patients' thyroid cancer molecular profile will be classified as low-, intermediate-, or high-risk based on previous published data.[11,12] Endpoints are related to feasibility of a future trial, including enrollment rate among eligible patients and drop-out rate among enrolled patients.

Aim 2. Determine the percent of eligible patients that undergo randomization to thyroid lobectomy versus total thyroidectomy and complete assigned treatment. There is equipoise between thyroid lobectomy and total thyroidectomy for intermediate risk molecular profile thyroid cancers. Thus, we will randomize those patients to thyroid lobectomy or total thyroidectomy. However, many patients may object to randomization or may not be willing to undergo treatment as randomized. Thus, we will assess percentage of patients who 1) agree to randomization, and 2) complete treatment as assigned.

Aim 3. Determine whether preoperative molecular testing predicts postoperative clinicopathologic findings by creating a registry tracking the final surgical pathology and clinical results.

6. SCHEMA

MAPS: Molecular Analysis for Precision Surgery in Thyroid Cancer, a Pilot Study



*Aggressive histology includes diffuse sclerosing, insular, Hurthle cell, solid, hobnail, columnar cell variant, and high-grade follicular cancer

7. METHODS

7.1 STUDY DESIGN
Prospective, randomized pilot feasibility study

7.2 CRITERIA FOR SUBJECT ELIGIBILITY
Population
Adult patients with biopsy-proven papillary thyroid cancer presenting to UCLA Endocrine Surgery Clinic for surgical consultation

7.2.1 Inclusion Criteria:
- Patients aged 18 years or older at the time of enrollment,
- Biopsy proven differentiated thyroid cancer measuring 1cm to 4cm in diameter, defined as:
    - Bethesda V or VI thyroid nodule, OR
    - Bethesda III or IV thyroid nodule with molecular analysis showing mutation consistent with malignancy
- Molecular analysis result with **intermediate molecular risk** mutation:
    - Isolated *BRAF* V600E
    - Isolated *BRAF*-like gene alteration
        - NTRK3 fusion
        - RET fusion
        - BRAF fusion
    - Copy number alteration of genome haploidization type

7.2.2 Exclusion Criteria:
- Prior thyroid operation
- Extrathyroidal extension or lymph node metastases seen on ultrasound
- Distant metastatic disease

7.2.3 Subject Identification and Recruitment
Recruitment and screening method
Subjects for potential recruitment for participation in the study will be identified by screening of the medical record. Identification of eligible patients related to their thyroid cancer will be done by review of the medical record for patients to be seen at the UCLA Endocrine Surgery Clinic. A waiver of HIPAA research authorization is requested for screening using medical records. Patients who meet inclusion criteria on the initial chart review will be introduced to the study during their clinic visit and either consented during the clinic visit or via phone/zoom following their clinic visit. The physician will ask the patient if he/she is willing to hear about the research study, and if the patient agrees, they will then introduce the study to the patient. This will be done in a private clinic office.

Enrolment of study participants
Potential study subjects identified by recruitment procedures will be further screened for eligibility and exclusion criteria by direct patient interview and ultrasound by study physician. If after the interview or

ultrasound the physician determines that the patient has met an exclusion criterion, the patient will be informed that he/she is not eligible for the study.
If after the interview or ultrasound, the physician determines that the patient may still be eligible for the study, however molecular test results needed to determine inclusion criteria are still pending, the physician will introduce the study to the patient in person at the time of the clinic visit. If the patient is interested in learning more about the study, the study team will enroll interested patients who are waiting for results. Once results are returned, if they are not eligible, they will be withdrawn from enrollment. If they are eligible, the study team will contact the patient over the phone or via zoom to conduct the consent process and have the patient complete the consent forms via DocuSign for an electronic signature prior to their surgery.

Process for informed consent
Initial contact will be made with potential subjects by a study physician during the scheduled endocrine surgery visit. During this conversation, physicians will inform the patient about the study and the opportunity to participate in a private clinic room with doors closed.

The physician will ask the patient if he/she is willing to hear about the research study, and if the patient agrees, the physician will then introduce and explain the study to the patient. If the subject chooses to participate, the physician will obtain informed consent. The consent documentation will be sent to the patient, reviewed, and electronically signed in person via DocuSign. Patients will receive a copy of the signed consent documents. Once the document is signed, it will be electronically uploaded to the patient's electronic medical record.

If the patient is potentially eligible for participation but is awaiting results to determine all eligibility criterion are met, the physician will ask the patient if he/she is willing to hear about the research study, and if the patient agrees, the physician will then introduce and explain the study. If the subject is interested in participating, the physician will enroll the interested patient. Once obtained, if the results determine the patient is not eligible, they will be withdrawn from enrollment. If the results confirm eligibility, the study team will contact the patient over the phone or via zoom to conduct the consent process. The consent documentation will be sent to the patient, reviewed, and electronically signed over the phone/zoom via DocuSign. Patients will receive a copy of the signed consent documents and a signed copy will be electronically uploaded to the patient's electronic medical record. We will conduct the same consent procedures for patients who meet all eligibility criteria in clinic, are potentially interested in participating after their physician presents the study in person, but would like more time to consider participating. These patients will be given additional time to consider consenting and will be enrolled but contacted at a later date via phone or zoom by the study team to conduct the consent process.

In other rarer cases, the patient may have their initial consult visit via telehealth with their physician. In such cases, the physician will proceed with the same activities as listed above to determine eligibility. If the patient is interested in hearing about the study, the physician will present the study in their private clinic room via telehealth. If the patient is interested in participating in the study, the physician will either enroll them using DocuSign at the time of the telehealth visit or if additional results are required OR the patient would like more time to consider participating, the patient will be enrolled and our study team will contact them at a later date to conduct the consent process.

During the consent process, investigators will inform the patient about his or her rights, the purpose of the study, the procedures to be undergone, and the potential risks and benefits of participation. It will be emphasized that participation in the study is voluntary and if they choose not to participate, they will receive equal standard of care. Study team members have undergone human subjects research and HIPAA training through the CITI courses, and will further be trained about the specific aspects of this study consent prior to enrollment of subjects. The informed consent is attached below (see attachment A)

7.2.4 Privacy

The research team will obtain informed consent in a private room. The interview, ultrasound, and medical procedures will be conducted in a medical examination room or private inpatient setting such as an operating room.

7.2.5 Target Enrollment

For feasibility studies of randomized control trials, a sample size of 24 to 50 patients is recommended.[13] We hypothesize that 50% of intermediate-risk patients will agree to and complete the treatment as assigned. Therefore, in order to end with a total of 50 patients in the randomization cohort, we will need 100 patients with intermediate-risk disease. The UCLA Endocrine Center is a high-volume tertiary referral center, performing 300 thyroid operations annually. Of these patients, approximately 200 patients per year have localized disease eligible for this study. Based on our clinical volume, this is achievable in a one-year enrollment period.

- Total goal enrollment N = 100
- Total goal enrollment of intermediate molecular risk patients into randomization cohort N = 50

7.2.6 Location

University of California Los Angeles (UCLA) endocrine surgery clinic
UCLA Health Westwood Ambulatory Surgery Center
UCLA Ronald Reagan Medical Center
UCLA Santa Monical Medical Center

7.3 INTERVENTION

7.3.1 Duration of Participation

Subjects will participate until they conclude a 24-month follow-up visit.

7.3.2 Schedule of Activities

Procedure	Screening Day -7 to -1	Enrollment / First clinic visit Visit 1, Day 1	Surgery	*Completion Thyroidectomy Postop day 7 to 14*	Follow-up Visit 3, Postop Day 14 +/- 7 days	Endocrine Visit Visit 4, Postop Day 28 +/- 14 days	6-month ± 1 month F/u Visit 4	12-month ± 1 month F/u Visit 5	18-month ± 1 month F/uVisit 6	24-month ± 1 month F/uVisit 7
Informed Consent	X	X								
Demographics	X	X								
Medical history	X	X								
Adverse Event Review and Evaluation	X ----------X									
Physical Exam		X								
Ultrasound		X			X		X	X	X	X
Randomization		X								
Consent for surgery		X	X	X						
Surgery			X	X						
Lab work: Tg, Tg Ab, TSH						X	X	X	X	X
Assess need for postoperative RAI						X				
Biopsy concerning lesions seen on neck ultrasound							X	X	X	X

7.3.5 Randomization Protocol

Patients with intermediate molecular-risk thyroid nodules will be randomized to thyroid lobectomy or total thyroidectomy. We will perform a 1:1 randomization in a consecutive manner. Patients will be informed of what operation they will receive and providers will also be aware what operation was performed as it dictates care moving forward. Details of operative management will be discussed further.

7.3.6 Peri-operative Protocol

<u>Thyroid Lobectomy</u>

Patients undergoing thyroid lobectomy will have the thyroid lobe containing the cancer removed in the standard surgical technique. These operations will be performed at either the UCLA Health Westwood

Ambulatory Surgery Center, UCLA Ronald Reagan Medical Center, or UCLA Santa Monica Medical Center. Patients will undergo our usual postoperative care, which involves:

- Patient's pathology will be sent as "Rush Pathology," such that results return in 48 hours and not the usually 2-week period.
- Patients will have a 4-hour observation in the post-anesthesia care unit and if the operative site appears well, without signs of hematoma formation, they will be discharged the same day.
- If patients are coming from far away (>30 miles from the hospital) or does not have an adult who can stay with them for the next 24 hours, they will stay at the facility overnight for observation.
- Patients will not receive any postoperative thyroid hormone supplementation at this time.

Total Thyroidectomy and Completion Thyroidectomy

Patients undergoing total thyroidectomy will have their whole thyroid gland removed in the standard surgical technique. Patients undergoing a completion thyroidectomy will have their remaining thyroid lobe removed. These operations will be performed at UCLA Ronald Reagan Medical Center or UCLA Santa Monical Medical Center. Patients will undergo our usual postoperative care, which involves:

- If patients are coming from far away (>30 miles from the hospital) or does not have an adult who can stay with them for the next 24 hours, they will stay at the facility overnight for observation.
- Started on calcium carbonate 1g per mouth every 6 hours
- Parathyroid hormone (PTH) level checked 1-hour after operation
    - If PTH < 10: start calcitriol 0.25mcg per mouth every 6 hours and increase calcium carbonate to 1.5g per mouth every 6 hours
    - If PTH 10 – 15: start calcitriol 0.25mcg per mouth every 6 hours
    - If PTH > 15: no new medications
- Calcium level will be checked at 4am on postoperative day 1
- The morning after the operation, patients will be started on levothyroxine 1.8 x weight (kg), closest to the available doses (88, 100, 112, 125, 137, 150, 175, 200 mcg). Patients will be prescribed the same dosage on discharge.
- Patient's discharge medication, in addition to the levothyroxine, will be determined on the PTH level drawn previously
    - If PTH < 10: Calcium carbonate 2g by mouth THREE times a day and calcitriol 0.25mcg by mouth THREE times a day
    - If PTH 10 – 15: Calcium carbonate 2g by mouth TWO times a day and calcitriol 0.25mcg by mouth TWO times a day
    - If PTH > 15: Calcium carbonate 1g by mouth TWO times a day

7.3.7 Indications for Postoperative RAI and Completion Thyroidectomy

Indications Postoperative RAI

Patients who ultimately result with aggressive disease on histopathology will need postoperative RAI to reduce the risk of disease recurrence, which is in accordance with the 2015 ATA Guidelines. Indications include:

- Gross extrathyroidal extension of the cancer seen at time of operation
- Lymph node metastasis, which is defined as
    - 1 or more lymph node with a > 2mm metastasis
    - 5 or more lymph nodes with a ≤ 2mm metastasis
    - Extranodal extension of metastasis

- Aggressive histology (diffuse sclerosing, insular, Hurthle cell, solid, hobnail, columnar cell variant, and high-grade follicular cancer)
- Multifocal vascular invasion
- Microscopic margin positivity

Completion Thyroidectomy

Patients who initially underwent thyroid lobectomy and pathology ultimately return with the indications listed above for postoperative RAI need to undergo completion thyroidectomy. All patients who undergo thyroid lobectomy have their pathology sent for rush pathology, which will result 48 hours later. If patients need a completion thyroidectomy, the surgeon will call them with this information and book a second operation. The surgical team will perform informed consent for the operation on the day of the surgery and patients will receive the usual peri-operative care as listed above.

7.3.8 Postoperative RAI Dosing

At the visit with the endocrinologist 4-6 weeks postoperatively, patients will have the first set of thyroglobulin (Tg) and thyroglobulin antibody (Tb Ab) drawn. If patients initially met criteria for RAI based on pathology, but their Tg and Tg Ab ultimately return as undetectable, these patients will not receive RAI. Patients who ultimately need postoperative RAI will be dosed according to the 2015 ATA guidelines.[5] It recommends a low-administered activity of 30 mCi.

7.3.9 Goal TSH Suppression Levels

Postoperative thyroid hormone doses will need to be adjusted by endocrinologists corresponding to the ideal TSH level in accordance with the 2015 ATA Guideline.[5]
The ideal TSH levels will be as followed:

- If patient underwent RAI, goal TSH = 0.1 – 0.5
- If patient did not undergo RAI, goal TSH = 0.5 – 2.0

Initial labs, which include TSH, thyroid function test, Tg, and Tg antibody will be drawn 6-8 weeks postoperatively in time with the first postoperative endocrinology visit. During this visit is when thyroid hormone medication will be adjusted according to goal TSH and need for postoperative RAI will be determined.

7.3.10 Surveillance Protocol

All surveillance visits will be done at the UCLA Endocrine Surgery office. These visits are to assess for any evidence of early cancer recurrence. Visits will be done at 6-, 12-, 18-, and 24-months postoperatively. All surveillance visits will have a window of 1 month. The visit will include:

- History and physical exam
- In-clinic ultrasound assessing the postoperative thyroid bed, central neck, and lateral necks to assess for recurrence
- If there are any concern for disease recurrence on the ultrasound, an in-office FNA will be performed. Indications for FNA include
    - Lymph node >1cm in size
    - Thyroid-appearing tissue >1cm in size located in the postoperative thyroid bed
- Lab draw: TSH, thyroid function test, Tg, Tg antibody

7.4 DATA MANAGEMENT

7.4.1 Data Collection

Patient's data will be collected via review of the patient's electronic medical record (EMR), which will be reviewed weekly. Data points to be recorded include:

- Patient demographics: age, sex, BMI, date of birth
- Comorbid endocrine disease: concurrent hypo/hyperthyroid disease, parathyroid disease, neuroendocrine tumor
- Prior or current cancer diagnosis
- Medications
- Bethesda category of FNA
- ThyroSeq results (specific mutation(s) present, cancer risk classifier results)
- Type of operation (thyroid lobectomy, total thyroidectomy, completion thyroidectomy)
- Ultrasound imaging results
- Laboratory values (Tg, Tg antibody, TSH, Calcium, PTH)
- Pathology results
- RAI dosing
- Thyroid hormone medication dosing
- Presence of postoperative complications: neck hematoma, reoperation, hypocalcemia, recurrent laryngeal nerve injury, voice hoarseness, readmission, reason for readmission

7.4.2 Data Storage

Investigators will extract the above data points from review of the EMR. It will then be entered into a REDCap password protected web-based database. **A REDCap data collection form (see attachment C) is attached.

All information gathered during this study will be kept confidential. At the time of subject providing study consent, a unique numerical identifier (sequential in study) will be assigned to the subject in lieu of personal identifying information and this numerical identifier will be used to code all clinical data abstracted from the medical record. A key linking the patient name, date of birth, and medical record number to this study identifier will be created and maintained by the study principal investigator that will not be shared with non-study members. The key will be maintained on an encrypted, firewalled, and password protected computer file.

7.5 ASSESSMENT/EVALUATION PLAN

The primary outcome of this study will be to assess the feasibility of a future multicenter, randomized controlled trial. Outcomes that will be analyzed include:

- Rate of enrollment: # of patients enrolled / # of patients screened
-
- Drop-out rate for randomization: # of patients who do not finish treatment as assigned / # of patients randomized
- Rate of patients who require escalation of care: # of patients requiring completion lobectomy / # of patients in the thyroid lobectomy randomization arm

Secondary endpoints will be whether molecular-risk category predicts American Thyroid Association risk category[5] that incorporates histopathological findings, percentage of patients requiring thyroid hormone supplementation or replacement, short-term quality of life. Our study is designed as a feasibility study, and is under-powered to assess oncologic outcomes.

8 RISKS AND BENEFITS

8.1 Risks to Subjects and Mitigating Steps

If patients had their FNA performed at a facility outside of UCLA, we will not have their sample and therefore will need to undergo repeat FNA of the nodule to participate. Informed consent will be separately obtained for the FNA. Risks of FNA include <1% risk of bleeding, pain, infection, or damage to surrounding structures. To mitigate this risk, we will ensure that the FNA are performed by physicians who have had appropriate training. Standard procedures will include sterilization of the puncture site and use of sterile materials to minimize infection risk.

There is equipoise in performing a thyroid lobectomy or total thyroidectomy for intermediate molecular-risk thyroid cancer, and both are currently offered for these patients. Both operations carry risk of bleeding and infection. Total thyroidectomy has an increased risk of injury to the recurrent laryngeal nerve causing voice hoarseness compared to thyroid lobectomy and makes all patients dependent on thyroid hormone medication. Majority of patients who undergo thyroid lobectomy do not require thyroid hormone supplementation, but they carry a risk that the remaining lobe cannot produce enough hormone and thus will be dependent. Patients randomized to thyroid lobectomy may ultimately have high risk histopathology and need postoperative RAI. These patients will need a reoperation for completion thyroidectomy, or removal of the remaining thyroid lobe, and thus are at risk again for the operative complications listed above.

Other risk includes privacy and confidentiality violation with protected health information from unplanned disclosure of HIPAA-protected data. These risks are estimated to be <1%. Mitigating steps we will take are:

- Interviewing and obtaining consent in a secure, private setting
- Use of de-identified, numeric code once data collection is complete. The key for this code will be maintained as a single file under password protection and encryption by the study PI. It will not be shared with others outside of the institution or study, and will be destroyed at the completion of the study.

8.2 Benefits to Subjects

Preoperative molecular analysis data will provide improved prognostic information to help guide extent of surgery. Historically, patients in our inclusion criteria underwent thyroid lobectomy or total thyroidectomy based on nodule size and ultrasound characteristics. With preoperative molecular risk stratification, patients can evidence-based recommendations on thyroid lobectomy for low molecular-risk, which reduces unnecessary operative risk, and total thyroidectomy for high molecular-risk cancers, which reduces risk of recurrence. Additionally, patients randomized to thyroid lobectomy will have reduced perioperative risk as listed above.

8.3 Compensation for Participation
There is not compensation for participants.

8.4 Benefits to Society and Population
The study will help design a future multicenter randomized controlled trial of the same subject. It will greatly impact future guidelines and treatment considerations for patients with PTC that are 1-4cm in size, intrathyroidal, and without distant metastasis – which is a significant population of thyroid cancer patients. Demonstrating that molecular profile can be used to dictate initial therapy for thyroid cancer will have an immediate and dramatic impact on the field. It can reduce overtreatment and its associated morbidity in the treatment of thyroid cancer.

9. DATA SAFETY AND MONITORING PLAN

9.1 Serious Adverse Event Reporting
Incidence and information regarding serious, unanticipated problems related to the study (i.e. adverse events and violations) will be reported promptly to the JCCC DSMB. Additionally, the study investigators have outlined the following components of a data safety and monitoring plan.

9.2 Planned interim safety analysis
After enrollment of each interval of 10 subjects, the incidence of adverse events experienced or reported by subjects will be evaluated to ensure that it is in line with anticipated rates. Study procedures will be suspended and protocols amended if the rates are higher than expected or unforeseen adverse events are noted. A report of adverse events and serious adverse events will be reported to the DSMB every 3 months from the date of the first participant's enrollment.

9.3 Planned stopping rules for the study
The study will be stopped entirely or for a specific subgroup if there is greater than 50% incidence of serious adverse events due to study procedures, such as infection, as well as greater than 50% of thyroid lobectomy patients requiring completion thyroidectomies and early cancer recurrence in the low and intermediate risk group. The rate of completion thyroidectomies will be reviewed and calculated every 10 participants who were randomized to thyroid lobectomy.

9.4 Planed rules for withdrawing participants from study interventions
Subjects will be withdrawn from participation if they have a change in health status that excludes them from eligibility between time of consent to initial operation. All subjects may withdraw safely from the study at any time. Their medical and operative care will not be affected by the withdrawal.

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