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Pilot Study for the Treatment of Papillary Thyroid Carcinoma with Radiofrequency Ablation

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IRB Greater Than Minimal Risk Protocol

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Study Title: Pilot study for the Treatment of Papillary Thyroid Carcinoma with Radiofrequency Ablation

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Research Question and Aims

Hypothesis:
RFA can control or eliminate small papillary thyroid carcinoma.

Aims, purpose, or objectives:
We aim to study the changes in primary tumor volume, development of lymph node involvement, development of distant metastasis and changes in serum thyroid hormone levels in patients with papillary thyroid carcinoma following RFA therapy. We will also assess the stability of these changes (need for repeat therapy) and the safety of the RFA procedure.

General Background:
US population has a high prevalence of thyroid nodules, with 50% of individuals after the age of 50% having at least one such lesion if ultrasound studies are performed. About 5-8% of these lesions harbor a thyroid cancer of which 80% are differentiated papillary thyroid carcinoma.
The incidence of diagnosed papillary thyroid carcinoma (PTC) has increased over the recent decades and this diagnosis is typically followed by partial or total thyroidectomy. In a minority of these patients when the tumor size is < 10-15 mm the necessity of intervention is less clear. The majority of these cases are treated surgically, with a minority observed and few treated with intra-lesional ethanol injection.

Surgery implies removal of (at least) half of the thyroid with risk of surgical complications, a neck scar and a high likelihood of developing hypothyroidism (50-80%) with subsequent lifelong thyroid hormone therapy. However for these patients RFA opens new horizons. It has the ability to destroy the cancerous lesion (ref review (1) and avoids the development of hypothyroidism (none noted in our series of RFA therapy for much larger benign thyroid nodule (2). Adding to that the benefit of avoiding surgical complications and a scar on the neck is a powerful motivator for patients to seek this therapy.

Background on Radiofrequency Ablation (RFA)
During the past ten years, radiofrequency ablation (RFA) has been shown to be a promising and well-tolerated new approach to benign TNs by inducing tissue necrosis and fibrosis through heat (3). Randomized trials in Italy and South Korea reported a 50% to 80% volume reduction in treated TNs, with sustained results 3 years after the intervention (3-6). In the United States, RFA is commonly used for percutaneous treatment of tumors in the lung, liver, kidney and bone (7). Yet until recently this intervention has not been validated for treating

benign or malignant TNs in North American Population. A year ago we have reported on our significant positive results with RFA on benign and toxic thyroid nodules in the past. Our results indicate substantial volume reduction of TNs by approximately 45% at 3 to 6 months, alleviation of compressive symptoms, and improvement in aesthetic appearance while preserving normal thyroid function.
Owing to advantages such as less invasiveness, reduced morbidity, lower complication rates, suitability for real-time imaging guidance and the ability to be performed in outpatient settings, RFA is gaining popularity in Asia to treat PTC and recurrence. Literature review to date has documented at least 150 patients who have undergone RFA for PTC, with reported 100% efficacy of tumor volume reduction ratio (VRR) ≥ 50% (8-9). In a most recent report from Jeong et al, (9) RFA has produced excellent local tumor control for papillary macro- and microcarcinomas. In addition to the advantages listed above, complications of RFA are rare with only two cases related to vocal cord effects reported in literature so far, possibly attributed to nerve injuries during the ablation process; none life-threatening complications are reported.

Therefore we aim to assess the effectiveness of RFA on eliminating small papillary thyroid carcinomas, its ability for preservation of normal thyroid function and the overall safety of RFA procedure.

Rationale:

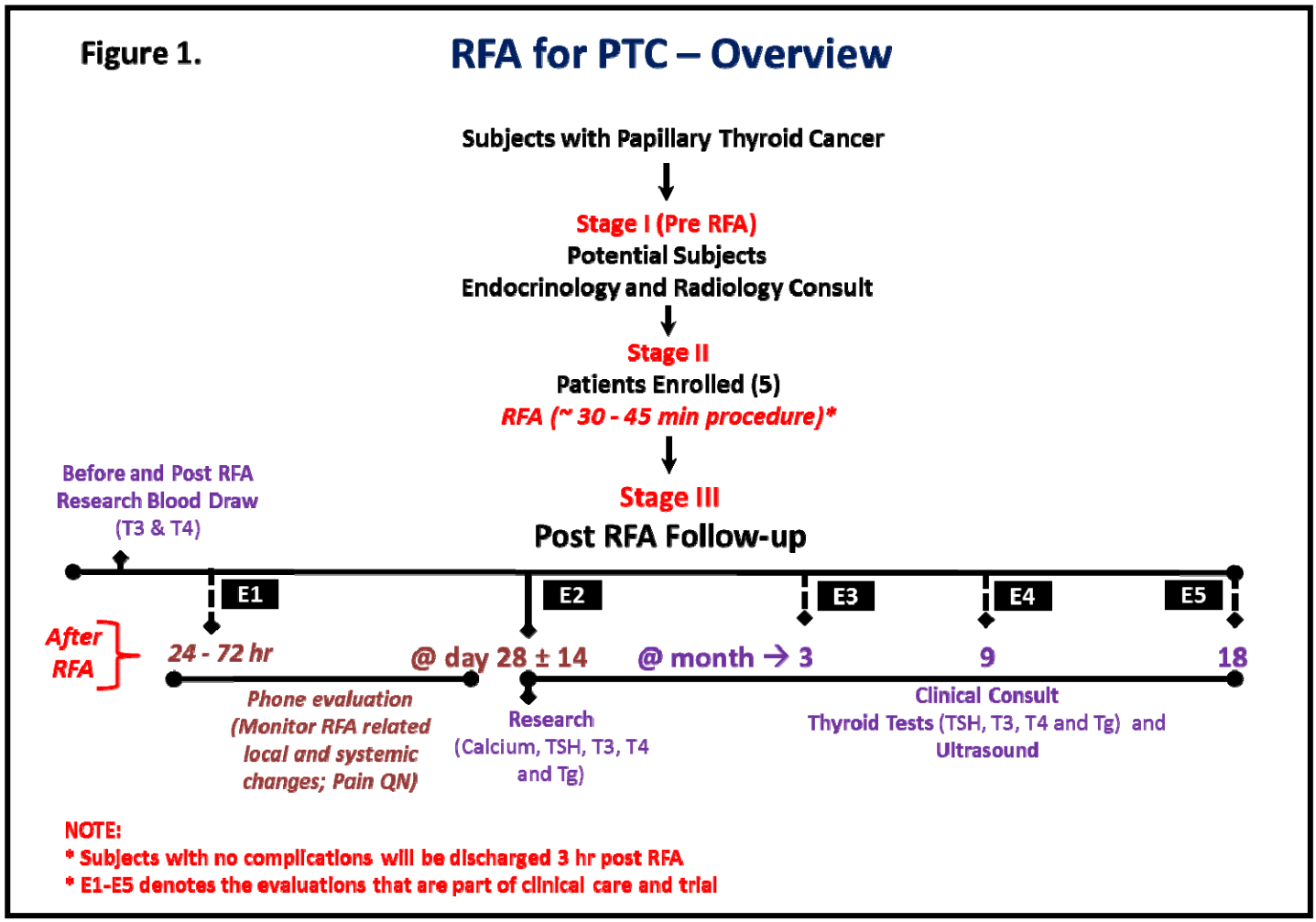
RFA delivers a large yet focused amount of energy to an area of thyroid tissue that becomes “charred” and thus nonfunctional and nonviable. The residual tissue is slowly resorbed by the surrounding normal tissue, which leads to the resulting shrinkage of the original thyroid nodule (2, 10). Therefore this effect would be very desirable for a cancerous lesion, if it can be achieved safely. Our experience confirms that ultrasound-guided RFA is a clinically effective and safe outpatient treatment in patients with symptomatic or steadily growing benign, large, predominantly solid TNs. With appropriate expertise and world class infrastructure at Mayo Clinic this technique can be extended to treat papillary thyroid carcinomas and has the potential to become an alternative for the management of cancerous papillary thyroid nodules. Hence this pilot study is planned to test this hypothesis and secondarily to identify the safety of RFA for PTC, reveal factors predicting greater response, comparing the performance of RFA with other procedures, and timing of the additional RFA sessions, if needed.

MAYO CLINIC

Study Design and Procedure

STUDY DESIGN

This will be an open-label clinical trial that will target patients diagnosed with small papillary thyroid carcinoma (<1.5 cm) interested in RFA therapy. They will be assessed clinically and if they are considered candidates for non-surgical choices (observation or percutaneous ethanol injection) these patients will then be offered also the option of RFA therapy. We will treat them with RFA therapy of the PTC lesion and monitor the clinical response through changes in nodule size as measured by ultrasound (> 50% volume shrinkage at 18



months considered positive outcome) and/or development of cervical or distant metastatic disease. We expect that an individual will be thus in the study for a total of 18 months. The schematic depiction of the sequence of events during the trial is presented in figure 1.

The safety of the procedure will be also part of the primary objective, both local reactions as well as complications from RFA. We plan to enroll 5 patients. The study will take place at Mayo Clinic in Rochester, MN. We expect that we would be able to identify 15 cases/year that would qualify for this trial. Given the potential acceptance to enrollment we expect that it would take 18-24 months for the trial completion.

PROCEDURE:
Enrolled patients will undergo RFA in a single session and then be followed for efficacy and safety of the procedure for 18 months.

Ultrasonography will be performed using a 6- to 15-MHz probe with the GE Logiq E9 ultrasound system. Nodule volume and the percentage of volume reduction are calculated using the following equations: volume= length x width x depth x 0.525; volume reduction percentage = [(initial volume - final volume) x 100%] /initial volume.

Patients will be sedated with general anesthesia during the procedure. General anesthesia is preferred in light of the improved pain control, and the desire to avoid any motion interference that could compromise the accuracy of the technique. A radiofrequency generator (Cool-tip; Covidien) and an 18-gauge, 15-cm electrode with a 1- or 2-cm active tip will be used in the procedure. All radiofrequency procedures will be performed by designated operators under ultrasonographic control with the same scanner model as used for the initial diagnostic evaluation.

For electrode placement, an in-plane oblique approach will be employed as opposed to directly entering the TN using the shortest pathway. The longer oblique pathway is chosen to lengthen the distance between the skin and the active tip of the RF electrode to reduce the chance of skin burns. Steps will be taken to protect extrathyroidal structures from generated thermal energy including selection of needle path, continuous ultrasound monitoring, and potential hydro-dissection if needed to generate a safe margin. Nodules will be selected for treatment that can be expected to be treated with technical success without the zone of ablation extending beyond the margin of the thyroid. Subcapsular lesions may be treated if the thyroid can be confidently isolated from adjacent structures with hydro-dissection. Safety will be paramount. The active tip of the electrode will be kept at a safe distance to prevent a skin burn.
The size and number of RF electrodes, total energy delivered, and total ablation times will be different according to target size and location. Patients will be intensively monitored during RFA and then closely observed for approximately 3 hours after the procedure and released home thereafter, unless adverse effects developed (11, 12).

To evaluate safety and efficacy of RFA procedure, post discharge from hospital, patients will be asked to fill-in a pain questionnaire to assess any level of pain or discomfort post RFA procedure and contacted by phone in the first 72 hours to assess for the presence of any adverse effects related to the procedure. Moving forward, patients will be contacted in a similar manner approximately every 2 weeks for the first 3 months for the purpose of detecting any adverse effects. Patients will have a face-to-face visit 1 month after the procedure for safety assessment as well. During this visit patients will provide blood sample for laboratory tests (Calcium and thyroid tests TSH, T3, T4, and Tg). Next face-to-face visit will happen at 3 month after the procedure; at this visit patients will provide a small volume of blood to test thyroid receptor antibody. Further in the process, patients will be monitored clinically for up to 18 months post RFA procedure.

Note: For laboratory research a small volume of blood (5 ml) will be drawn from patient prior to and post RFA in the OR. Blood will be processed for Mass Spectrometry analysis to evaluate if high temperature generated from RFA would impart any conformational changes to thyroid hormones and impact biological functions.

Concomitant Interventions

Allowed Interventions
TSH suppression as deemed clinically necessary.

Required Interventions
There are no required medications or interventions during this trial
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Prohibited Interventions
There are no prohibited medications or interventions during this trial

Adherence Assessment
Not applicable

Resources: We have the commitment of the Division of Endocrinology and Department of Radiology of Mayo Clinic Rochester that they will support this study. These 2 areas have worked collaboratively in a similar project that has led to the adoption of our current RFA protocol for benign thyroid nodules. We have enlisted the collaboration of a company manufacturing RFA devices, StarMed, with some of the single use RFA instrumentation and partial financial support. The procedure cost will be submitted for clinical cost. Additional support for the project is through a ***Richard F. Emslander Career Development Award in Endocrinology and Nutrition*** Grant awarded to Dr. Marius Stan that will be utilized for covering cost of laboratory tests, partial financial support for travel expenses for the patients and PI and study coordinator dedicated time to the project.

Subject Information

Target accrual is 5 patients. To achieve this number of subjects, we will access medical records for about 100 patients.

Subject population: Adults (≥ 18 years of age) who undergo evaluation at Mayo Clinic, Rochester for thyroid nodules.

Inclusion Criteria:

We will enroll patients that meet the following criteria:

a. Nodule with Papillary thyroid carcinoma
   i. Diagnosed by FNA cytology.
   ii. Size < 1.5 cm
   iii. Non-surgical therapy is considered acceptable by the treating physician
   iv. Radiology evaluation deems the lesion amenable to RFA therapy with minimal risk of complication

Safety will be primordial and therefore the Interventional Radiology evaluation will influence decision to treat.

Exclusion Criteria:

All candidates meeting any of the following exclusion criteria at baseline will be excluded from study participation:

1. Clinical evidence for a multifocal papillary thyroid malignancy
2. Clinical evidence for local or distant metastatic disease
3. Pregnancy
4. Vocal cord paralysis on contralateral side
5. Coagulopathy or patients on anticoagulation therapy
6. Patients with prior neck surgery or neck radiation
7. Patients with neck anatomy that precludes easy access by RFA
8. Patients with comorbidities deemed too high of a risk for general anesthesia
9. Treatment with another investigational drug or intervention (within 6 weeks of planned RFA).
10. Current drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.
11.

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. X **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the study design and procedure section)

2. X **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. X **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the study design and procedure section)

5. X **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☐ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC).

Biospecimens – Categories 2 and 3

(2) Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

   Blood samples will be obtained; Volume10 cc per visit.

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
   No blood samples will be obtained.

(3) Prospective collection of biological specimens other than blood: NONE

Review of medical records, images, specimens – Category 5

For review of existing data: provide a date range or an end date for when the data was generated. The end date can be the date this application was submitted to the IRB. Example: *01/01/1999 to 12/31/2015* or all records through *mm/dd/yyyy*.

Date Range: All records through 9/15/2019
Check all that apply (data includes medical records, images, specimens).

☐ (5a) No data will be collected beyond the IRB submission date.

X (5b) The study involves data that exist at the time of IRB submission **and** data that will be collected after IRB submission. Include this activity in the study design section.

- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☐ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name	X	
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	X	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data		
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. Note: Recording a year only is not a unique identifier.	X	
Social Security number		
Medical device identifiers and serial numbers	X	
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		

Street address, city, county, precinct, zip code, and their equivalent geocodes	X	
Phone or fax numbers	X	
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	X None

Data Analysis

Power analyses and study endpoints are not required for minimal risk research, pilot or feasibility studies.

☐ No statistical information. *If checked, please explain*:

Data Analysis Plan:
Sample size has not been calculated as analysis will only include descriptive statistics. Results for continuous variables will be expressed as median and interquartile range, and for categorical variables as proportions.

References:

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