INSTITUTE: National Cancer Institute

STUDY NUMBER: 15-C-0105 PRINCIPAL INVESTIGATOR: Naris Nilubol, M.D.

STUDY TITLE: Randomized Controlled Trial of Total Thyroidectomy with and without Prophylactic Central Neck Lymph Node Dissection in Patients with Low-risk Papillary Thyroid Cancer

Continuing Review Approved by the IRB on 11/19/18

Amendment Approved by the IRB on 01/31/19 (G) Date posted to web: 02/13/19

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

In many cases, papillary thyroid cancer often spreads to the lymph nodes in the neck. Unfortunately, standard imaging techniques sometimes cannot detect if a person's cancer has spread to the lymph nodes. This study will compare whether removing lymph nodes in the neck when they do not yet show evidence of cancer, during thyroid surgery, is better and results in less recurrence of cancer than when only the thyroid is removed.

Why are you being asked to take part in this study?

You are being asked to take part in this trial because you have been diagnosed with papillary thyroid cancer or you have thyroid nodules that are suspicious for papillary thyroid cancer and there is no evidence that your disease has spread to other parts of your body.

How many people will take part in this study?

About 225 people at the NIH and Northshore University Health System will participate in this trial.

Description of Research Study

What will happen if you take part in this research study?

Before you begin the study

All research studies have specific criteria for entry to allow for valid interpretation of the study results and safety of participants, known as eligibility criteria. Before you begin this study you will need to have the following exams and tests to make sure you are eligible for this study. The exams and tests are part of regular cancer care and may be done even if you do not join the study. If you recently had some of the tests, they may not need to be repeated.

- History and physical examination, including vital signs (height, weight, blood pressure, heart rate, temperature, breathing rate)
- Standard blood tests to measure including a complete blood count, chemistry panel, tests to check the levels of certain hormones in your body e.g. thyroid stimulating hormone (TSH)
- Tumor biopsy (if not previously done)
- Ultrasound and/or CT scan of your thyroid and neck

If you meet the eligibility criteria for this study you will be offered the option of participating.

During the Study

This study is a randomized study. You will be placed into one of two groups by chance (like flipping a coin).

One group will undergo surgery to remove the thyroid gland only. During the surgery, if the investigator discovers that your cancer has spread to the lymph nodes in your neck, they will also be removed. If no evidence of cancer is found in your lymph nodes they will not be removed.

The second group will undergo surgery to remove the thyroid as well as the lymph nodes in your neck.

You will not be told during the trial which group you have been assigned to. This is called a blind. However, the blind may be broken if information is critical for your medical care. For example if you are assigned to group 1 and cancer is discovered in your lymph nodes, this will be discussed with you and you will be told if the lymph nodes in your neck have been removed.

Questionnaires

Before you undergo surgery, you will be asked to fill out 4 questionnaires so that we can find out about your quality of life, neck pain, if you are having problems with your voice or if you are having trouble swallowing before your surgery. This should take about 15 to 20 minutes. Additionally, you will undergo a flexible laryngoscopy (described below) so that we can look at how well your vocal cords work.

Pregnancy test

A pregnancy test will also be performed if you are a woman that can have children. If the test is positive, your surgery will be postponed.

Flexible Laryngoscopy

In flexible laryngoscopy, a thin, flexible viewing tube (called a laryngoscope) is passed through the nose and guided to the vocal cords. You will be asked to sit upright in an exam chair. A local anesthetic will be sprayed into the back of your nose and throat to numb these areas and suppress the gag reflex (however, you may still gag and feel some discomfort when the laryngoscope is first inserted). The study doctor will then insert the scope through one nostril and closely inspect your vocal cords. Photographs may be taken with a tiny camera attached to the scope. This procedure usually takes 5 to 10 minutes.

Surgery

Within 4 weeks after completing these tests, you will undergo surgery.

You will then be required to complete a few tests at 1 day, 2 weeks, 3 months, 6 months and 1 year after surgery. Some of these procedures are part of routine care for people with papillary thyroid cancer (people with this disease may have these procedures whether they are in a clinical trial or not). A brief description of what will be done at each time point is indicated below:

1 day after surgery

- Fill out 4 questionnaires so that we can find out about your quality of life, neck pain, if you are having problems with your voice or if you are having trouble swallowing before your surgery.
- Undergo a flexible laryngoscopy to look at your vocal cords
- Have some blood drawn for routine laboratory tests

2 weeks after surgery

- Fill out 4 questionnaires so that we can find out about your quality of life, neck pain, if you are having problems with your voice or if you are having trouble swallowing before your surgery.

- Have some blood drawn for routine laboratory tests
- If the study doctor believes it is necessary, you will undergo a flexible laryngoscopy to look at your vocal cords. Most patients do not require this.

3 months after surgery

- Fill out one questionnaire so that we can find out about your quality of life
- Have some blood drawn for routine laboratory tests
- Ultrasound of your thyroid and soft tissue in the neck
- All patients will need to either stop thyroid hormone treatment for 2 weeks or, if the study doctor believes that it's in your best interest, you will be offered recombinant thyroid hormone as part of standard of care in a preparation for a specific blood test. You will have the opportunity to discuss with doctors regarding these options.
- If necessary, as part of your standard care, you will be offered the opportunity to be treated with I^{131}, which is a radioactive form of iodine. I^{131} could destroy any remaining thyroid cancer cells or thyroid tissue present in your body. This is called remnant ablation. The study doctor will discuss with you whether this is in your best interest and you will be given the opportunity to decide on your treatment.
- If the study doctor believes it is necessary, a diagnostic whole body radioiodine scan (WBS) will be performed

To prepare for a WBS, you will be asked to swallow a capsule or liquid that contains a very small amount of radioactive iodine (RAI). This will be absorbed by any remaining thyroid cells in your body. You will then be asked to return for the scan in about 48 hours. This involves lying down under a large camera that scans for x-rays being emitted by any remaining radioactive iodine that may have been captured in your body. If any thyroid or thyroid cancer cells are present, they may show up as spots on the x-ray film.

6 months after surgery

- Fill out 4 questionnaires so that we can find out about your quality of life, neck pain, if you are having problems with your voice or if you are having trouble swallowing before your surgery.
- If a laryngoscopy showed that your vocal cords were not working well on day 1, you will undergo a flexible laryngoscopy to look at your vocal cords.
- Have some blood drawn for routine laboratory tests

- Ultrasound of your thyroid and soft tissue in the neck

1 year after surgery

If you underwent remnant ablation you will be given TSH for 2 consecutive days or if you have been taking thyroid hormone, undergo thyroid hormone withdrawal and then after 4 weeks have some blood drawn for routine tests.

If you did not undergo remnant ablation, you will receive TSH for 2 consecutive days and then have blood drawn for routine tests.

All study subjects will also be required to:

- Fill out one questionnaire so that we can find out about your quality of life
- Undergo a diagnostic whole body radioiodine scan (WBS)
- Have an ultrasound of your thyroid and soft tissue in the neck

If your bloodwork shows elevated serum thyroglobulin, this could be an indication that your cancer has metastasized (spread to other parts of your body) and we will need to perform additional standard tests to confirm or rule out the presence of metastatic disease.

We will continue to follow you to see if your cancer returns once each year for 10 years after surgery. You will have a detailed physical exam, blood drawn for routine laboratory tests and an ultrasound of the soft tissues in your neck or other imaging that the study doctor feels is in your best interest. At year 5 and year 10 after surgery, we will ask you to complete a questionnaire so that we may get some information about your quality of life.

Standard of Care Treatment

Treatments covered under this study may include a single medication or a combination of medications, surgery or radiation to treat your cancer. These treatments will not be experimental. Your doctors will describe your treatment plan to you in detail before asking you to sign this consent form. You may be asked to sign a separate consent form for any treatment procedures not outlined in this consent.

Birth Control

If you are a woman who can become pregnant, you will need to practice an effective form of birth control before starting study and for 3 months after surgery. If you think that you are pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)

- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

Blood Draw

Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

Surgery

The side effects from the surgery are the same as you would have if you received standard surgery for papillary thyroid cancer anyplace. You will have the risks of the surgery explained to you prior to the surgery and you will sign a separate consent for that procedure.

Ultrasound Guided Biopsy

A hollow needle is used to collect cell samples from your tumor using an ultrasound for guidance. The needle is put in 3 to 6 times to get the samples, or cores. This procedure usually causes only brief discomfort at the site from which the biopsy is taken and you will be offered medication to help numb the pain. Biopsy collection may cause bruising, bleeding, and occasional pain during swallowing but usually does not leave scars. Rarely infection may occur at the needle site.

You may experience significant discomfort from where the needle punctures the skin. If this occurs, pain medication will be provided to you.

Flexible Laryngoscopy

In some cases, local anesthesia medications (spray) can cause complications, such as irregular heartbeats and breathing problems. These complications are not common. Allergic reactions are also possible but not common. If they do occur, they typically develop within a few minutes after the anesthesia is given. The study doctors can provide immediate medical attention if that happens.

Whole Body Radiodine Scan

For this procedure a small amount of radiotracer is ingested. Nuclear medicine diagnostic procedures have been used for more than five decades, and there are no known long-term adverse effects from such low-dose exposure. In rare circumstances, it is possible to have an allergic reaction to the tracer.

Neck Ultrasound

For standard diagnostic ultrasound, there are no known harmful effects on humans.

You should talk to your study doctor about any symptoms that you experience while taking part in the study.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if removal of the lymph nodes in addition to the thyroid gland will result in less recurrence (tumor coming back) compared to removal of the thyroid gland alone. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits may include a lower rate of radioiodine use, a lower rate of recurrence, and improved quality of life. Because it is not proven that removal of the lymph nodes will have any additional benefit, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have papillary thyroid cancer.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options**:**

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Stopping Study Participation

In addition to completion of 10 years of follow up, your doctor may decide to remove you from this study for the following reasons:

- if he/she believes that it is in your best interest
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason that you are being removed from the study.

Participation in this study is voluntary. You may leave the study at any time. You will be given a copy of the consent form for your records. There are no penalties for leaving the study. If you choose not to participate in this study this will not affect your care or your ability to participate in other clinical trials at the NIH. If you decide to stop taking part in the study, we would like you to talk to the study doctor first.

If you leave the study, any remaining data of yours that have been obtained for the study can be destroyed at your written request. However, data that have already been distributed to other researchers or placed in the research databases can**not** be withdrawn.

You may ask our staff to answer any and all questions and we invite you to do so. Any new findings that relate to your participation will be discussed with you.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.

- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.

- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.

- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board

A description of this clinical trial will be available on http://www.Clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

- will be used for auditing or program evaluation internally by the NIH; or
- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Use of Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human diseases. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These data will be stripped of identifiers such as name, address or account number, so that it may be used for future research on any topic and shared broadly for research purposes. Your data will be used for research purposes only and will not benefit you. It is also possible that the stored

data may never be used. Results of research done on your data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If do not want your data used for future research, please contact us in writing and let us know; then we will not use your data for future research. However, it may not be possible to withdraw or delete data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Naris Nilubol, M.D., Building 10, Room 4-5952, Telephone: 240-760-6154. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM NOVEMBER 19, 2018 THROUGH DECEMBER 03, 2019

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____

Print Name _____ Print Name _____