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VOLUME 11 | ISSUE 2 | FEBRUARY 2018

Many clinicians and laboratories check TSH alone as the initial test for thyroid problems and then only add a Free T_4 measurement if the TSH is abnormal, referred to as "reflex" testing. The goal of this study was to evaluate different TSH cutoffs leading to reflex Free T_4 testing, with the purpose to determine whether a widened normal range could decrease the need for additional Free T_4 testing and not lead to missing cases of thyroid problems.

Henze M et al. Rationalizing thyroid function testing: Which TSH cutoffs are optimal for testing Free T_4?. J. Clin Endocrinol. Metab. 2017. 102 (11): 4235-4241.

Thyroid nodules are common and the vast majority of thyroid nodules are benign. While the genetic mutations in papillary thyroid cancer have been well-characterized, the genetic characteristics of benign thyroid nodules are not well understood. The aim of this study was to define the genetic characteristics of benign thyroid nodules, in contrast to papillary thyroid cancer.

Ye L et al The genetic landscape of benign thyroid nodules revealed by whole exome and transcriptome sequencing. Nature Commun 2017;8:15533.

Follicular variant of papillary carcinoma is a common type of papillary thyroid cancer. Encapsulated forms of the follicular variant with the absence of certain adverse features has led to another variant termed noninvasive follicular neoplasm with papillary-like nuclear features (NIFTP), which is currently considered to not be a cancer. The goal of this study is to evaluate the molecular profile of NIFTPs in comparison to benign follicular adenomas and the invasive follicular variant of papillary thyroid carcinoma.

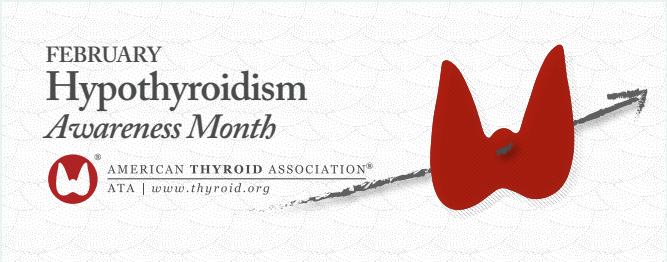
Giannini R et al. Identification of two distinct molecular subtypes of non-invasive follicular neoplasm with papillary-like nuclear features by digital RNA counting. Thyroid 2017;27:1267-76. Epub September 5, 2017.

Because small papillary thyroid cancers are common and are overall low risk, observation (known as active surveillance) has been recommended as an option over surgery. In prior studies, only 10-15% of patients with small thyroid cancers have demonstrated cancer growth. The goal of the study was to evaluate growth of small papillary thyroid cancers over time to better determine treatment, monitoring and timing of surgery if necessary of these patients.

Tuttle RM et al. Natural history and tumor volume kinetics of papillary thyroid cancers during active surveillance. JAMA Otolaryngol Head Neck Surg. August 31, 2017 [Epub ahead of print].

Papillary thyroid cancer makes up about 85% of all thyroid cancers and overall has a good prognosis. It is not completely clear whether multifocal Papillary thyroid cancer is more aggressive and is more associated with chance of recurrence or spread outside of the neck than unifocal Papillary thyroid cancer. This current study has been done to evaluate the effect of multifocality on the outcome of Papillary thyroid cancer.

Wang F et al The Prognostic Value of Tumor Multifocality in Clinical Outcomes of Papillary Thyroid Cancer. J Clin Endocrinol Metab 2017; 102: 3241-50



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Clinical Thyroidology® for the Public

VOLUME 11 | ISSUE 2 | FEBRUARY 2018

EDITOR'S COMMENTS

Welcome to another issue of *Clinical Thyroidology for the Public*. In this journal, we will bring to you the most up-to-date, cutting edge thyroid research. We also provide even faster updates of late-breaking thyroid news through Twitter at @thyroidfriends and on Facebook. Our goal is to provide patients with the tools to be the most informed thyroid patient in the waiting room. Also check out our friends in the Alliance for Thyroid Patient Education. The Alliance member groups consist of: the *American Thyroid Association, Bite Me Cancer, the Graves' Disease and Thyroid Foundation, the Light of Life Foundation, ThyCa: Thyroid Cancer Survivors' Association, Thyroid Cancer Canada, Thyroid Cancer Alliance* and *Thyroid Federation International.*

We invite all of you to join our Friends of the ATA community. It is for you that the American Thyroid Association (ATA) is dedicated to carrying out our mission of providing reliable thyroid information and resources, clinical practice guidelines for thyroid detection and treatments, resources for connecting you with other patients affected by thyroid conditions, and cutting edge thyroid research as we search for better diagnoses and treatment outcomes for thyroid disease and thyroid cancer. We thank all of the Friends of the ATA who support our mission and work throughout the year to support us. We invite you to help keep the ATA mission strong by choosing to make a donation that suits you – it takes just one moment to give online at: www.thyroid.org/donate and all donations are put to good work. The ATA is a 501(c)3 nonprofit organization and your gift is tax deductible.

February is Hypothyroidism Awareness Month.

In this issue, the studies ask the following questions:

- Should TSH testing for thyroid disease become standardized?
- Can molecular testing help identify benign nodules?
- Can NIFTP be diagnosed without surgery?
- Can low risk small papillary cancer be followed without surgery?
- Is multifocal papillary thyroid cancer a risk factor for more aggressive disease?

We welcome your feedback and suggestions. Let us know what you want to see in this publication. I hope you find these summaries interesting and informative.

— Alan P. Farwell, MD, FACE

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Clinical Thyroidology® for the Public

FEBRUARY 2018 | VOLUME 11 | ISSUE 2

THYROID HORMONE TESTS

Determination of optimal TSH ranges for reflex Free T_4 testing

BACKGROUND

TSH measurement is generally regarded as the most sensitive initial laboratory test for screening individuals for thyroid hormone abnormalities. This is due to the fact that small changes in Free T_4 levels result in larger changes in TSH values. Many clinicians and laboratories check TSH alone as the initial test for thyroid problems and then only add a Free T_4 measurement if the TSH is abnormal (outside the laboratory normal reference range). When the laboratory adds the Free T_4 test to the blood sample automatically based on an abnormal TSH result, it referred to as "reflex" testing. Although laboratories vary, most report a normal TSH reference range between 0.4-0.5 mU/L on the lower end and 4-5.5 mU/L on the upper end of the range. The goal of this study was to evaluate different TSH cutoffs leading to reflex Free T_4 testing, with the purpose to determine whether a widened normal range could decrease the need for additional Free T_4 testing and not lead to missing cases of thyroid problems.

THE FULL ARTICLE TITLE

Henze M et al. Rationalizing thyroid function testing: Which TSH cutoffs are optimal for testing Free T_4?. J. Clin Endocrinol. Metab. 2017. 102 (11): 4235-4241.

SUMMARY OF THE STUDY

These investigators evaluated TSH and Free T_4 measurements in two populations. One group of 120,403 individuals (named the clinical group) had thyroid tests performed in a single laboratory in Western Australia over a 12 year period of time. This group was compared to community group of 4568 individuals participating in the Busselton Health Study. All individuals had both TSH and Free T_4 measured. They excluded people with known pituitary disease, thyroid disease and other factors known to affect thyroid function tests. These investigators quantified the number of individuals at different TSH values that had high, low or normal Free T_4 levels. They measured the effect of changing the TSH reference range cutoffs on the number of reflex Free T_4 tests. They determined how many times an abnormally high or low Free T_4 would have gone undetected if the TSH cutoffs for reflex testing had been changed. The normal reference range for the TSH was 0.4-4 mU/L in this study. They found in the clinical group that if the TSH normal range that led to reflex Free T_4 testing was changed to from 0.4-4 mU/L to 0.3-5 mU/L, this would have led to a 22% reduction in the number of Free T_4 tests performed. As expected, if the TSH normal reference range was widened even more to 0.2-6 mU/L, even fewer reflex Free T_4 tests would have been done. They then examined how many of those Free T_4 levels that would not have been done were abnormal. When the TSH lower limit was reduced from 0.4 to 0.2 mU/L, a high Free T_4 would have been missed in 4.2% of people who had a TSH between 0.2 and 0.4 mU/L. When the TSH upper limit was raised from 4 to 6 mU/L, a low Free T_4 would have been missed in 2.5% of the people who had a TSH between 4 and 6 mU/L.

The authors noted that this was a relatively small number of people that would have been missed and that the majority had only very slight abnormalities of Free T_4. They suggested that these mild abnormalities were unlikely to be associated with clinically important overt hyper- or hypothyroidism. The vast majority of people (97%) with a TSH in the normal range of 0.4-4 mU/L also had normal Free T_4 values. The findings were similar but of lesser magnitude in the smaller community group of patients. The authors concluded that the TSH reference range leading to reflex Free T_4 testing could likely be widened to decrease the number of unnecessary Free T_4 measurements performed. This would reduce overall costs to the medical system without likely causing negative consequences in terms of missing the detection of people with thyroid hormone abnormalities.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

These results indicate that by widening the normal reference range for TSH, the need for additional reflex testing for Free T_4 values could be reduced. The authors suggested that fewer unnecessary Free T_4 measurements would be performed and thus these changes would be cost saving for the health care system. The results indicated that the TSH normal reference range could be altered with minimal clinical effects. In other words, few cases of overt

THYROID HORMONE TESTS, continued

hyper- or hypothyroidism would go undetected if the TSH cutoffs leading to reflex Free T_4 testing were only slightly changed. It is important to note, that this study refers to the finding of overt thyroid disease and does not address the concept of "subclinical" or mild thyroid disorders. Additionally it is important to remember that TSH testing alone is inadequate or misleading in some conditions (such as central hypothyroidism or other abnormal thyroid conditions). This study primarily addresses the utility of isolated TSH measurements when screening people for new thyroid disease. When screening the general population for thyroid disease, the majority of people with a TSH in the normal reference range will also have a normal Free T_4, making the new diagnosis of a thyroid disorder unlikely when a person has a normal TSH.

— Whitney W. Woodmansee MD

ATA THYROID BROCHURE LINKS

Thyroid Function Tests: https://www.thyroid.org/thyroid-function-tests/
Hypothyroidism (Underactive): https://www.thyroid.org/hypothyroidism/
Hyperthyroidism (Overactive): https://www.thyroid.org/hyperthyroidism/

ABBREVIATIONS & DEFINITIONS

TSH: thyroid stimulating hormone — produced by the pituitary gland that regulates thyroid function; also the best screening test to determine if the thyroid is functioning normally.

Thyroxine (T4): the major hormone produced by the thyroid gland. T_4 gets converted to the active hormone T_3 in various tissues in the body.

Hypothyroidism: a condition where the thyroid gland is underactive and doesn't produce enough thyroid hormone. Treatment requires taking thyroid hormone pills.

Subclinical Hypothyroidism: a mild form of hypothyroidism where the only abnormal hormone level is an increased TSH. There is controversy as to whether this should be treated or not.

Overt Hypothyroidism: clear hypothyroidism an increased TSH and a decreased T_4 level. All patients with overt hypothyroidism are usually treated with thyroid hormone pills.

Hyperthyroidism: a condition where the thyroid gland is overactive and produces too much thyroid hormone. Hyperthyroidism may be treated with antithyroid meds (Methimazole, Propylthiouracil), radioactive iodine or surgery.

Subclinical Hyperthyroidism: a mild form of hyperthyroidism where the only abnormal hormone level is a decreased TSH.

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FEBRUARY 2018 | VOLUME 11 | ISSUE 2

THYROID NODULES

The genetic characteristics of benign thyroid nodules

BACKGROUND

Thyroid nodules are common, occurring in 1/3rd to ½ of individuals that have imaging studies of the neck. The vast majority of thyroid nodules are not cancerous (benign). Thyroid nodules are typically evaluated by neck ultrasound, and depending on the imaging features, thyroid biopsy. Testing of biopsy specimens for molecular markers is sometimes considered, especially if the biopsy is indeterminate (unable to make a diagnosis based on cytology alone). The genetic mutations in the most common type of thyroid cancer, papillary thyroid cancer, have been well-characterized and, if present in a biopsy specimen, usually leads thyroid surgery. However, the genetic characteristics of benign thyroid nodules are not well understood. The aim of this study was to define the genetic characteristics of benign thyroid nodules, in contrast to papillary thyroid cancer.

THE FULL ARTICLE TITLE

Ye L et al The genetic landscape of benign thyroid nodules revealed by whole exome and transcriptome sequencing. Nature Commun 2017;8:15533.

SUMMARY OF THE STUDY

The authors analyzed DNA and RNA from thyroid tissue samples from thyroid surgery specimens from 21 individuals who had both papillary thyroid cancer and benign thyroid nodule(s) as well as 8 individuals who had benign thyroid nodule(s) without papillary thyroid cancer. Thyroid tissue samples were matched for each individual. The genetic mutations identified in this study were evaluated in 328 fresh-frozen benign thyroid nodule tissues from 259 patients.

Using a laboratory technique of whole-exome sequencing and/or transcriptome sequencing techniques, the authors detected the following mutations, according to diagnosis: papillary thyroid cancer - BRAF (22/32 papillary thyroid cancer specimens but no benign nodule specimens), benign nodules - mutations in SPOP (4/38 benign nodules but not papillary thyroid cancer), ZNF148 (6/38 benign nodules but not papillary thyroid cancer) and EZH1 (3/38 benign nodules but not papillary thyroid cancer). In a separate study group including 328 benign thyroid nodules from 259 patients, the authors identified mutually exclusive SPOPP94R, EZH1Q571R and ZNF148 mutations in 24.3% of specimens.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The authors concluded that there were distinct genetic expression patterns in benign thyroid nodules compared to papillary thyroid cancer and they suggested that papillary thyroid cancer evolved independently from matched benign nodules within the same patients. Although larger confirmatory studies are needed, these data are important to inform our understanding of the molecular profile of benign thyroid nodules.

— Anna M. Sawka, MD, PhD, FRCPC

ATA THYROID BROCHURE LINKS

Thyroid Nodules: https://www.thyroid.org/thyroid-nodules/

Thyroid Cancer (Papillary and Follicular): https://www.thyroid.org/thyroid-cancer/

ABBREVIATIONS & DEFINITIONS

Thyroid nodule: an abnormal growth of thyroid cells that forms a lump within the thyroid. While most thyroid nodules are non-cancerous (Benign), ~5% are cancerous.

Thyroid Ultrasound: a common imaging test used to evaluate the structure of the thyroid gland. Ultrasound uses soundwaves to create a picture of the structure of the thyroid gland and accurately identify and

THYROID NODULES, continued

characterize nodules within the thyroid. Ultrasound is also frequently used to guide the needle into a nodule during a thyroid nodule biopsy.

Thyroid biopsy: a simple procedure that is done in the doctor's office to determine if a thyroid nodule is benign (non-cancerous) or cancer. The doctor uses a very thin needle to withdraw cells from the thyroid nodule. Patients usually return home or to work after the biopsy without any ill effects.

Indeterminate thyroid biopsy: this happens a few atypical cells are seen but not enough to be abnormal (atypia of unknown significance (AUS) or follicular lesion of unknown significance (FLUS)) or when the diagnosis is a follicular or hurthle cell lesion. Follicular and hurthle cells are normal cells found in the thyroid. Current analysis of thyroid biopsy results cannot differentiate between follicular or hurthle cell cancer from noncancerous adenomas. This occurs in 15-20% of biopsies and often results in the need for surgery to remove the nodule.

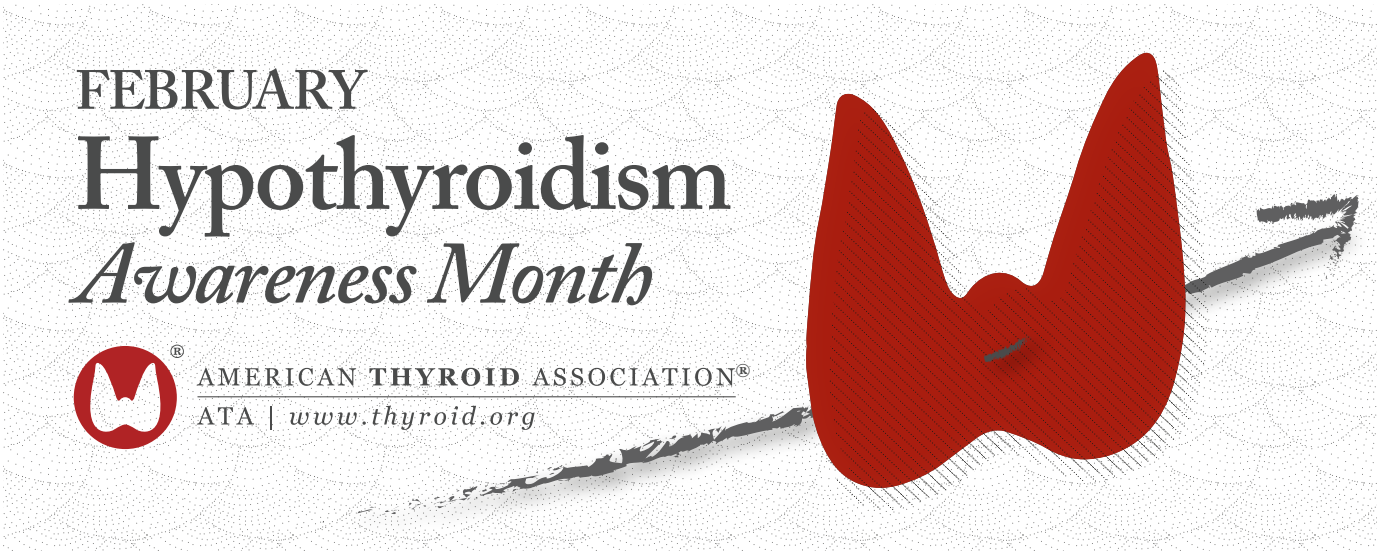
Mutation: A permanent change in one of the genes.

Genes: a molecular unit of heredity of a living organism. Living beings depend on genes, as they code for all proteins and RNA chains that have functions in a cell. Genes hold the information to build and maintain an organism's cells and pass genetic traits to offspring.

Papillary thyroid cancer: the most common type of thyroid cancer.

Molecular markers: genes and microRNAs that are expressed in benign or cancerous cells. Molecular markers can be used in thyroid biopsy specimens to either to diagnose cancer or to determine that the nodule is benign. The two most common molecular marker tests are the AfirmaTM Gene Expression Classifier and ThyroseqTM

Cancer-associated genes: these are genes that are normally expressed in cells. Cancer cells frequently have mutations in these genes. It is unclear whether mutations in these genes cause the cancer or are just associated with the cancer cells. The cancer-associated genes important in thyroid cancer are BRAF, RET/PTC, TERT and RAS.



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FEBRUARY 2018 | VOLUME 11 | ISSUE 2

THYROID CANCER

Multiple Variants of Noninvasive Follicular Neoplasm with Papillary-like Nuclear Features (NIFTP)

BACKGROUND

Papillary cancer is the most common type of thyroid cancer. Follicular variant of papillary thyroid carcinoma represents 30% of all papillary thyroid cancers and, like the classic type of papillary cancer, has a good prognosis overall. The follicular variant can be further divided into encapsulated (better prognosis) and invasive (worse prognosis) types. Although encapsulated follicular variant of papillary thyroid carcinoma has a good prognosis overall, further characterization with the absence of certain adverse features on examining these cancers under the microscope has led to another variant termed noninvasive follicular neoplasm with papillary-like nuclear features (NIFTP), which is currently considered to not be a cancer. At present, the diagnosis of NIFTP is a pathologic one, meaning that it can only be diagnosed after surgery with review under a microscope. The goal of this study is to evaluate the molecular profile of NIFTPs in comparison to benign follicular adenomas and the invasive follicular variant of papillary thyroid carcinoma.

THE FULL ARTICLE TITLE:

Giannini R et al. Identification of two distinct molecular subtypes of non-invasive follicular neoplasm with papillary-like nuclear features by digital RNA counting. Thyroid 2017;27:1267-76. Epub September 5, 2017.

SUMMARY OF THE STUDY:

The study included 62 patients diagnosed with follicular adenomas and follicular variant of papillary thyroid carcinoma who underwent thyroid surgery at the University of Pisa, Italy between 2013 and 2015. The thyroid cancer samples were re-evaluated by two pathologists and reclassified as follicular adenomas, encapsulated follicular variant of papillary thyroid carcinoma and invasive follicular variant of papillary thyroid carcinomas. Among the 30 encapsulated follicular variant of papillary thyroid carcinomas, 26 cases did not have adverse features and were classified as NIFTPs. The study evaluated the differences in the gene expression of 75 genes, most of them involving thyroid hormone synthesis, and for the presence of BRAF and RAS gene mutations in 18 follicular adenomas, 18 invasive follicular variant of papillary thyroid carcinomas and 26 NIFTPs.

Follicular adenomas and invasive follicular variant of papillary thyroid carcinomas had different and distinct gene expression profiles. The 26 NIFTPs showed either follicular adenoma-like gene expression profile (13 cases) or invasive follicular variant of papillary thyroid carcinoma-like gene expression profile (13 cases). A total of 13 NIFTPs showed predominantly RAS but also BRAF mutations, the mutations being more common in NIFTPs with invasive follicular variant of papillary thyroid carcinoma-like gene expression (11 of 11) than in those with follicular adenoma-like gene expression (2 of 13). Most BRAF mutations in NIFTPs were noted at V601 locus, while V600 locus mutations are usually seen in invasive thyroid cancer.

Among the NIFTP tumors with invasive follicular variant of papillary thyroid carcinoma-like gene expression, 5 had a NRAS Q61R gene mutation, 2 had a HRAS Q61R gene mutation, 3 had a BRAF k601E gene mutation and one had a BRAF V600E gene mutation. Among the NIFTP tumors with a follicular adenoma-like gene expression, one had an HRAS Q61R gene mutation and another had an NRAS Q61R gene mutation.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This is the first study that reports the presence of two different gene expression profiles in patients with NIFTP tumors. The NIFTP tumors with follicular variant of papillary thyroid carcinoma-like gene expression showed more frequent RAS and BRAF gene mutations as compared to tumors with follicular adenoma-like gene expression, so these may be precursors of thyroid cancer. Currently, NIFTP tumors need to be removed surgically for diagnosis and this study does not change this. Further studies are needed to define a list of genes that characterize NIFTPs, which could be used to identify these lesions by thyroid biopsy cytology and result in less invasive diagnostic procedures.

— Alina Gavrila, MD, MMSC

THYROID CANCER, continued

ATA THYROID BROCHURE LINKS

Thyroid Cancer (Papillary and Follicular): https://www.thyroid.org/thyroid-cancer/

ABBREVIATIONS & DEFINITIONS

Papillary thyroid cancer (PTC): the most common type of thyroid cancer. There are 4 variants of papillary thyroid cancer: classic, follicular, tall-cell and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).

Follicular variant of papillary thyroid cancer (FVPTC): one of the subtypes of papillary thyroid carcinoma, which has been classified to two different forms with different prognostic: encapsulated or well-demarcated and invasive.

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): a new term has been used to describe a type of papillary thyroid cancer which is non-invasive. These cancers behave less aggressively than typical papillary thyroid cancer and have been shown to have low risk for recurrence and low risk for spread outside of the thyroid.

Follicular Adenoma (FA): benign (non-cancerous) tumor of the thyroid gland.

Molecular profile: genes and microRNAs that are expressed in benign or cancerous cells. Molecular markers can be used in thyroid specimens to either diagnose cancer or determine that the nodule is benign.

Mutation: A permanent change in one of the genes.

Genes: a molecular unit of heredity of a living organism. Living beings depend on genes, as they code for all proteins and RNA chains that have functions in a cell. Genes hold the information to build and maintain an organism's cells and pass genetic traits to offspring.

Cancer-associated genes: these are genes that are normally expressed in cells. Cancer cells frequently have mutations in these genes. It is unclear whether mutations in these genes cause the cancer or are just associated with the cancer cells. The cancer-associated genes important in thyroid cancer are BRAF, RET/PTC, TERT and RAS.

Thyroid fine needle aspiration biopsy (FNA): a simple procedure that is done in the doctor's office to determine if a thyroid nodule is benign (non-cancerous) or cancer. The doctor uses a very thin needle to withdraw cells from the thyroid nodule. Patients usually return home or to work after the biopsy without any ill effects.

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FEBRUARY 2018 | VOLUME 11 | ISSUE 2

THYROID CANCER

Ultrasound monitoring of small papillary thyroid carcinomas shows low rate of cancer growth

BACKGROUND

The increase in thyroid cancer incidence has been attributed in large part due to small papillary thyroid cancers measuring less than 2 cm in size. Because other studies have shown a low risk for growth of these small cancers over time, the American Thyroid Association has supported observation as opposed to surgery as an option in these low risk papillary thyroid cancers. This is known as active surveillance. Little is known about how these small cancers grow and change over time, though only 10-15% of these patients have demonstrated cancer growth in the previous studies. This study was done to demonstrate the rate and magnitude of growth of small papillary thyroid cancers over time in a group of patients in the US. The goal of the study was to evaluate growth of small papillary thyroid cancers over time to better determine treatment, monitoring and timing of surgery if necessary of these patients.

THE FULL ARTICLE TITLE

Tuttle RM et al. Natural history and tumor volume kinetics of papillary thyroid cancers during active surveillance. JAMA Otolaryngol Head Neck Surg. August 31, 2017 [Epub ahead of print].

SUMMARY OF THE STUDY

A total of 291 patients at Memorial Sloan Kettering Cancer Center in New York who were being followed by active surveillance for papillary thyroid carcinoma measuring 1.5 cm or smaller were included. Of these, 75.3% of the patients were women, average age was 51 year old and 79.7% had cancers under 1cm in size. Patients had normal TSH values, no evidence on ultrasound for extension of the lesion beyond the thyroid or region metastases (specifically lymph node metastases) and no evidence for spread of the cancer beyond the neck. Patients were monitored by ultrasound every 6 months for two years, then annually. If the cancer increased by 3 mm or more in greatest dimension from the pre-biopsy ultrasound measurements or if there was suggestion of spread of the cancer outside of the thyroid capsule, or if the spread of the cancer to lymph nodes was found, surgery was suggested. Measurements of the cancer volume was performed prior to the fine needle aspiration and at each time point, using ultrasound measurements of height, width, and length of the nodule. Percentage change in volume was considered significant if greater than 50% increase from baseline.

After a follow-up of an average of 25 months, 279 patients (95.9%) remained on active surveillance. A total of 5 patients had surgery after growth of 3 mm or more, 5 patients elected surgery and 2 were lost to follow-up. A total of 11 patients had cancer growth of 3 mm or more, but 6 of them declined surgery. Volume increased more than 50% in 36 patients, stable in 229 patients, and decreased by more than 50% in 19 patients, and was not available in 7 patients. Volume increase of more than 50% occurred approximately 8.2 months before the 3 mm cancer diameter increase in those patients with tumor growth. Patients under age 50 years were more likely to have cancer growth. Cancer size at the onset did not predict future growth.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study supports findings of previous studies showing that a 10-15% of small papillary thyroid cancers grow over a short period of active surveillance. Using cancer volume increase of more than 50% occurs earlier than growth of more than 3 mm. Expanding the size for observation to up to 1.5 cm seems to show similar risk for growth to cancers under 1cm. This confirms that the low risk for progression over this short interval is consistent with previous studies and has been a safe option for patients who are able and willing to undergo close follow-up. It also suggests that cancer growth can be predicted based upon measurements of the volume of the nodule over time, rather than waiting for 3 mm growth in diameter.

— Julie Hallanger Johnson, MD

THYROID CANCER, continued

ATA THYROID BROCHURE LINKS

Thyroid Cancer (Papillary and Follicular): https://www.thyroid.org/thyroid-cancer/

ABBREVIATIONS & DEFINITIONS

Papillary thyroid cancer: the most common type of thyroid cancer. There are 4 variants of papillary thyroid cancer: classic, follicular, tall-cell and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).

Papillary microcarcinoma: a papillary thyroid cancer smaller than 1 cm in diameter.

Active surveillance: this refers to the observation of small thyroid cancers with ultrasound and physical examination as opposed to surgery as an option in certain low risk cancers.

Thyroid Ultrasound: a common imaging test used to evaluate the structure of the thyroid gland. Ultrasound uses soundwaves to create a picture of the structure of the thyroid gland and accurately identify and characterize nodules within the thyroid. Ultrasound is also frequently used to guide the needle into a nodule during a thyroid nodule biopsy.

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FEBRUARY 2018 | VOLUME 11 | ISSUE 2

THYROID CANCER

Multifocality is not an independent risk factor for recurrence of papillary thyroid cancer

BACKGROUND

There are four different types of thyroid cancers: Papillary, Follicular, Medullary and Anaplastic. The most common type of thyroid cancer is Papillary thyroid cancer and makes up about 85% of all thyroid cancers and overall has a good prognosis. At the time of diagnosis, Papillary thyroid cancer can be seen only in one area in the thyroid gland (called unifocal) or can be seen in more than one area (called multifocal). It is not completely clear whether multifocal Papillary thyroid cancer is more aggressive and is more associated with chance of recurrence or spread outside of the neck than unifocal Papillary thyroid cancer. The most recent published guideline by American Thyroid Association for treatment of thyroid cancer, does not consider multifocality as a risk factor for higher recurrence rate. This current study has been done to evaluate the effect of multifocality on the outcome of Papillary thyroid cancer.

THE FULL ARTICLE TITLE

Wang F et al The Prognostic Value of Tumor Multifocality in Clinical Outcomes of Papillary Thyroid Cancer. J Clin Endocrinol Metab 2017; 102: 3241-50

SUMMARY OF THE STUDY

A total of 11 medical centers from 6 countries participated in this study. A total of 2638 patients with Papillary thyroid cancer entered the study with and average age of 46 years and average follow up time of 58 months after their surgery. Of these, 76% of study subjects were women. The authors also added 89,680 patients from SEER database from 2004 to 2013.

About 38% of Papillary thyroid cancer cases were multifocal. Patients with multifocal cancer had more extension of the cancer outside of the thyroid, more spread of the cancer to the lymph nodes in the neck and more advanced staging. More patients with multifocal cancers had radioactive iodine therapy and received a higher dose of radioactive iodine.

After considering all the known risk factors causing higher recurrence into analysis, the patients with multifocal cancers did not have a higher rate of recurrence of the cancer or spread of the cancer outside of the neck and did not have a higher death rate. In analysis of 89,680 patients fro SEER database also showed that multifocal thyroid cancers did not have a higher death rate.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The conclusion of this study was that multifocal Papillary thyroid cancer is not associated with a higher death rate, recurrence or spread outside of the neck. Based on this finding, a higher dose of radioactive iodine and more aggressive treatment is not indicated for patients with multifocal Papillary thyroid cancer.

— Shirin Haddady, MD

ATA THYROID BROCHURE LINKS

Thyroid Cancer (Papillary and Follicular): https://www.thyroid.org/thyroid-cancer/

Radioactive Iodine: https://www.thyroid.org/radioactive-iodine/

ABBREVIATIONS & DEFINITIONS

Papillary thyroid cancer: the most common type of thyroid cancer.

Cancer recurrence: this occurs when the cancer comes back after an initial treatment that was

THYROID CANCER, continued

successful in destroying all detectable cancer at some point.

SEER: Surveillance, Epidemiology and End Results program, a nation-wide anonymous cancer registry generated by the National Cancer Institute that contains information on 26% of the United States population. Website: http://seer.cancer.gov/

Radioactive iodine (RAI): this plays a valuable role in diagnosing and treating thyroid problems since it is taken up only by the thyroid gland. I-131 is the destructive form used to destroy thyroid tissue in the treatment of thyroid cancer and with an overactive thyroid. I-123 is the non-destructive form that does not damage the thyroid and is used in scans to take pictures of the thyroid (Thyroid Scan) or to take pictures of the whole body to look for thyroid cancer (Whole Body Scan).

Thyroid Awareness Monthly Campaigns

The ATA will be highlighting a distinct thyroid disorder each month and a portion of the sales for Bravelets™ will be donated to the ATA. The month of **February** is **Hypothyroidism Awareness Month** and a bracelet is available through the **ATA Marketplace** to support thyroid cancer awareness and education related to thyroid disease.

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FEBRUARY 2018 | VOLUME 11 | ISSUE 2

ATA Alliance for Thyroid Patient Education

GOAL

The goal of our organizations is to provide accurate and reliable information for patients about the diagnosis, evaluation and treatment of thyroid diseases.

We look forward to future collaborations and continuing to work together toward the improvement of thyroid education and resources for patients.

WHO WE ARE (in alphabetical order)

AMERICAN THYROID ASSOCIATION
www.thyroid.org
ATA Patient Resources:
http://www.thyroid.org/thyroid-information/
Find a Thyroid Specialist: www.thyroid.org
(Toll-free): 1-800-THYROID
thyroid@thyroid.org

BITE ME CANCER
http://www.bitemecancer.org
info@bitemecancer.org

GRAVES' DISEASE AND THYROID FOUNDATION
www.gdatf.org
(Toll-free): 877-643-3123
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LIGHT OF LIFE FOUNDATION
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THYCA: THYROID CANCER SURVIVORS' ASSOCIATION, INC.
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thyca@thyca.org

THYROID CANCER CANADA
www.thyroidcancercanada.org
416-487-8267
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THYROID FEDERATION INTERNATIONAL
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tfi@thyroid-fed.org

AMERICAN THYROID ASSOCIATION
FOUNDED 1923

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"The ATA was a valuable resource for our family when my dad was diagnosed with Anaplastic Thyroid Cancer. When you're faced with a detrimental diagnosis where even a few days can make the difference in life or death, understanding your options quickly is critical. The ATA website offers a one-stop shop for patients and caregivers to find specialists, current clinical trials, general thyroid cancer information, and links to other patient support groups and information."

Mary Catherine Petermann
- Father who was diagnosed with Anaplastic Thyroid Cancer in 2006
- He was treated at Mayo Clinic
- He has clean scans as of October 2016

PLEASE JOIN OUR JOURNEY TO ADVANCED DISCOVERIES AND TREATMENT FOR THYROID DISEASE AND THYROID CANCER

As patients with thyroid disease navigate the challenges to their quality of life and researchers and physicians look for more effective directions, we at the ATA have our own destination– **funding for critical thyroid research, prevention, and treatment.** For 94 years, the ATA has led the way in thyroidology. It's a daily obstacle course to find new drugs, better treatments, advanced surgical methods, and more rapid diagnoses for the 20 million Americans who have some form of thyroid disease.

The ATA has paved the way with management guidelines for clinicians who diagnose and treat thyroid disease. For physicians treating pregnant women diagnosed with thyroid disease, our recent publication presents 97 evidence-based recommendations making sure that best practices are implemented with the latest, most effective treatment.

Through your generous support and donations, research takes the lead and hope is on the horizon. **Will you join us** in our campaign to raise **$1.5 million** for thyroid research, prevention, and treatment? Your compassionate, tax-deductible gift will provide funds for:

- Research grants that pave the way for 1,700 ATA physicians and scientists who have devoted their careers to understanding the biology of and caring for patients affected by thyroid disease.
- Patient education for individuals and families looking for life-changing clinical trials, the best thyroid specialists, and cutting edge treatment and drugs.
- Professional education that offers a wealth of knowledge and leading-edge research for trainees and practitioners.
- A website that is the go-to resource for thyroid information for patients and practitioners alike. In 2016 alone, there were more than 3,700,000 website views of ATA's library of online thyroid information patient brochures.

Donations **of all sizes** will change the future for thyroid patients. You will make a direct impact on patients like Mary Catherine's father as he deals with Anaplastic Thyroid Cancer. You will help scientists like ATA Associate Member Julia Rodiger, Ph.D., a scientist at the National Institutes of Health, as she analyzes thyroid hormones for intestinal stem cell development.

Hypothyroidism

WHAT IS THE THYROID GLAND?

The thyroid gland is a butterfly-shaped endocrine gland that is normally located in the lower front of the neck. The thyroid's job is to make thyroid hormones, which are secreted into the blood and then carried to every tissue in the body. Thyroid hormone helps the body use energy, stay warm and keep the brain, heart, muscles, and other organs working as they should.

WHAT IS HYPOTHYROIDISM?

Hypothyroidism is an underactive thyroid gland. Hypothyroidism means that the thyroid gland can't make enough thyroid hormone to keep the body running normally. People are hypothyroid if they have too little thyroid hormone in the blood. Common causes are autoimmune disease, such as *Hashimoto's thyroiditis*, surgical removal of the thyroid, and radiation treatment.

WHAT ARE THE SYMPTOMS?

When thyroid hormone levels are too low, the body's cells can't get enough thyroid hormone and the body's processes start slowing down. As the body slows, you may notice that you feel colder, you tire more easily, your skin is getting drier, you're becoming forgetful and depressed, and you've started getting constipated. Because the symptoms are so variable and non-specific, the only way to know for sure whether you have hypothyroidism is with a simple blood test for TSH.

KEEPING OTHER PEOPLE INFORMED

Tell your family members. Because thyroid disease runs in families, you should explain your hypothyroidism to your relatives and encourage them to get periodic TSH tests. Tell your other doctors and your pharmacist about your hypothyroidism and the drug and dose with which it is being treated. If you start seeing a new doctor, tell the doctor that you have hypothyroidism and you need your TSH tested every year. If you are seeing an endocrinologist, ask that copies of your reports be sent to your primary care doctor.

WHAT CAN YOU EXPECT OVER THE LONG TERM?

There is no cure for hypothyroidism, and most patients have it for life. There are exceptions: many patients with viral thyroiditis have their thyroid function return to normal, as do some patients with thyroiditis after pregnancy.

Hypothyroidism may become more or less severe, and your dose of thyroxine may need to change over time. You have to make a lifetime commitment to treatment. But if you take your pills every day and work with your doctor to get and keep your thyroxine dose right, you should be able to keep your hypothyroidism well controlled throughout your life. Your symptoms should disappear and the serious effects of low thyroid hormone should improve. If you keep your hypothyroidism well-controlled, it will not shorten your life span.

WHAT CAUSES HYPOTHYROIDISM?

There can be many reasons why the cells in the thyroid gland can't make enough thyroid hormone. Here are the major causes, from the most to the least common.

- *Autoimmune disease.* In some people's bodies, the immune system that protects the body from invading infections can mistake thyroid gland cells and their enzymes for invaders and can attack them. Then there aren't enough thyroid cells and enzymes left to make enough thyroid hormone. This is more common in women than men. Autoimmune thyroiditis can begin suddenly or it can develop slowly over years. The most common forms are *Hashimoto's thyroiditis* and atrophic thyroiditis.
- *Surgical removal of part or all of the thyroid gland.* Some people with *thyroid nodules*, *thyroid cancer*, or *Graves' disease* need to have part or all of their thyroid removed. If the whole thyroid is removed, people will definitely become hypothyroid. If part of the gland is left, it may be able to make enough thyroid hormone to keep blood levels normal.
- *Radiation treatment.* Some people with Graves' disease, nodular goiter, or thyroid cancer are treated with *radioactive iodine* (I-131) for the purpose of destroying their thyroid gland. Patients with Hodgkin's disease, lymphoma, or cancers of the head or neck are treated with radiation. All these patients can lose part or all of their thyroid function.

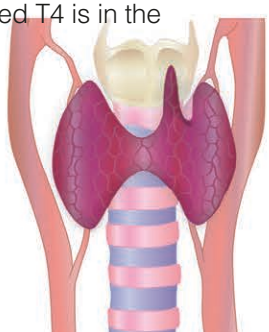
Hypothyroidism

- *Congenital hypothyroidism (hypothyroidism that a baby is born with).* A few babies are born without a thyroid or with only a partly formed one. A few have part or all of their thyroid in the wrong place (ectopic thyroid). In some babies, the thyroid cells or their enzymes don't work right.
- *Thyroiditis.* *Thyroiditis* is an inflammation of the thyroid gland, usually caused by an autoimmune attack or by a viral infection. Thyroiditis can make the thyroid dump its whole supply of stored thyroid hormone into the blood at once, causing brief hyperthyroidism (too much thyroid activity); then the thyroid becomes underactive.
- *Medicines.* Medicines such as amiodarone, lithium, interferon alpha, and interleukin-2 can prevent the thyroid gland from being able to make hormone normally. These drugs are most likely to trigger hypothyroidism in patients who have a genetic tendency to autoimmune thyroid disease.
- *Too much or too little iodine.* The thyroid gland must have iodine to make thyroid hormone. Iodine comes into the body in food and travels through the blood to the thyroid. Keeping thyroid hormone production in balance requires the right amount of iodine. Taking in too much iodine can cause or worsen hypothyroidism.
- *Damage to the pituitary gland.* The pituitary, the "master gland," tells the thyroid how much hormone to make. When the pituitary is damaged by a tumor, radiation, or surgery, it may no longer be able to give the thyroid instructions, and the thyroid may stop making enough hormone.
- *Rare disorders that infiltrate the thyroid.* In a few people, diseases deposit abnormal substances in the thyroid and impair its ability to function. For example, amyloidosis can deposit amyloid protein, sarcoidosis can deposit granulomas, and hemochromatosis can deposit iron.

HOW IS HYPOTHYROIDISM DIAGNOSED?

The correct diagnosis of hypothyroidism depends on the following:

- *Symptoms.* Hypothyroidism doesn't have any characteristic symptoms. There are no symptoms that people with hypothyroidism always have and many symptoms of hypothyroidism can occur in people with other diseases. One way to help figure out whether your symptoms are due to hypothyroidism is to think about whether you've always had the symptom (hypothyroidism is less likely) or whether the symptom is a change from the way you used to feel (hypothyroidism is more likely).
- *Medical and family history.* You should tell your doctor:
  - about changes in your health that suggest that your body is slowing down;
  - if you've ever had thyroid surgery;
  - if you've ever had radiation to your neck to treat cancer;
  - if you're taking any of the medicines that can cause hypothyroidism— amiodarone, lithium, interferon alpha, interleukin-2, and maybe thalidomide;
  - whether any of your family members have thyroid disease.
- *Physical exam.* The doctor will check your thyroid gland and look for changes such as dry skin, swelling, slower reflexes, and a slower heart rate.
- *Blood tests.* There are two blood tests that are used in the diagnosis of hypothyroidism.
- *TSH (thyroid-stimulating hormone) test.* This is the most important and sensitive test for hypothyroidism. It measures how much of the thyroid hormone thyroxine (T4) the thyroid gland is being asked to make. An abnormally high TSH means hypothyroidism: the thyroid gland is being asked to make more T4 because there isn't enough T4 in the blood.
- *T4 tests.* Most of the T4 in the blood is attached to a protein called thyroxine-binding globulin. The "bound" T4 can't get into body cells. Only about 1%–2% of T4 in the blood is unattached ("free") and can get into cells. The free T4 and the free T4 index are both simple blood tests that measure how much unattached T4 is in the blood and available to get into cells.



FURTHER INFORMATION

Further details on this and other thyroid-related topics are available in the patient thyroid information section on the American Thyroid Association® website at *www.thyroid.org*.

For information on thyroid patient support organizations, please visit the *Patient Support Links* section on the ATA website at *www.thyroid.org*

Hypothyroidism

HOW IS HYPOTHYROIDISM TREATED?

THYROXINE (T4) REPLACEMENT.

Hypothyroidism can't be cured. But in almost every patient, hypothyroidism can be completely controlled. It is treated by replacing the amount of hormone that your own thyroid can no longer make, to bring your T4 and TSH levels back to normal levels. So even if your thyroid gland can't work right, T4 replacement can restore your body's thyroid hormone levels and your body's function. Synthetic thyroxine pills contain hormone exactly like the T4 that the thyroid gland itself makes. All hypothyroid patients except those with severe myxedema (life-threatening hypothyroidism) can be treated as outpatients, not having to be admitted to the hospital. For the few patients who do not feel completely normal taking a synthetic preparation of T4 alone, the addition of T3 (Cytomel®) may be of benefit.

SIDE EFFECTS AND COMPLICATIONS.

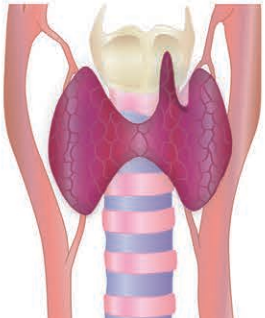
The only dangers of thyroxine are caused by taking too little or too much. If you take too little, your hypothyroidism will continue. If you take too much, you'll develop the symptoms of hyperthyroidism—an overactive thyroid gland. The most common symptoms of too much thyroid hormone are fatigue but inability to sleep, greater appetite, nervousness, shakiness, feeling hot when other people are cold, and trouble exercising because of weak muscles, shortness of breath , and a racing, skipping heart. Patients who have hyperthyroid symptoms at any time during thyroxine replacement therapy should have their TSH tested. If it is low, indicating too much thyroid hormone, their dose needs to be lowered.

FOLLOW-UP

You'll need to have your TSH checked 6 to 10 weeks after a thyroxine dose change. You may need tests more often if you're pregnant or you're taking a medicine that interferes with your body's ability to use thyroxine. The goal of treatment is to get and keep your TSH in the normal range. Babies with hypothyroidism must get all their daily treatments and have their TSH levels checked as they grow, to prevent mental retardation and stunted growth. Once you've settled into a thyroxine dose, you can return for TSH tests about once a year.

YOU NEED TO RETURN SOONER IF ANY OF THE FOLLOWING APPLY TO YOU:

- Your symptoms return or get worse.
- You want to change your thyroxine dose or brand, or change taking your pills with or without food.
- You gain or lose a lot of weight (as little as a 10-pound difference for those who weren't overweight to begin with).
- You start or stop taking a drug that can interfere with absorbing thyroxine (such as certain antacids, calcium supplements and iron tablets), or you change your dose of such a drug. Medications containing estrogen also impact thyroxine doses, so any change in such a medication should prompt a re-evaluation of your thyroxine dose.
- You start or stop taking certain medicines to control seizures such as phenytoin or tegretol, as such medicines increase the rate at which thyroxine is metabolized in your body, and your dose of thyroxine may need to be adjusted.
- You're not taking all your thyroxine pills. Tell your doctor honestly how many pills you've missed.
- You want to try stopping thyroxine treatment. If ever you think you're doing well enough not to need thyroxine treatment any longer, try it only under your doctor's close supervision. Rather than stopping your pills completely, you might ask your doctor to try lowering your dose. If your TSH goes up, you'll know that you need to continue treatment.



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