

# Clinical Thyroidology® for the Public



AMERICAN THYROID ASSOCIATION  
Optimal Thyroid Health for All



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Beltrão FEL et al 2021 Thyroid hormone levels during hospital admission inform disease severity and mortality in COVID-19 patients. *Thyroid*. Epub 2021 Sep 9. PMID: 34314259.

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Shakir MKM et al 2021 Comparative effectiveness of levothyroxine, desiccated thyroid extract, and levothyroxine + liothyronine in hypothyroidism. *J Clin Endocrinol Metab*. Epub 2021 Jun 29. PMID: 34185829.

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Ylli D et al 2021 Biotin interference in assays for thyroid hormones, thyrotropin and thyroglobulin. *Thyroid* 31:1160–1170. PMID: 34042535.

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The Bethesda System for Reporting Thyroid Cytopathology is often used in adults to determine the chance a thyroid nodule is cancerous. Little is known about the use of the Bethesda system for thyroid nodules in children and adolescents. This study investigates the use of the Bethesda system in pediatrics.

Vuong HG et al 2021 The use of the Bethesda System for reporting thyroid cytopathology in pediatric thyroid nodules: A meta-analysis. *Thyroid* 31:1203–1211. PMID: 33504264.

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Ahn HS et al 2021 Diagnostic performance of core needle biopsy as a first-line diagnostic tool for thyroid nodules according to ultrasound patterns: Comparison with fine-needle aspiration using propensity score matching analysis. *Clin Endocrinol (Oxf)* 94:494–503. PMID: 32869866.

## THYROID CANCER .....13

### The presence of minimal extension of thyroid cancer outside of the thyroid does not predict initial response to treatment but can help determine prognosis

Minimal extrathyroidal extension (ETE) means that a small amount of thyroid cancer is found extending outside of the thyroid gland after examining the cancer under the microscope. This study was done to look at the impact of minimal ETE in predicting initial treatment response in papillary thyroid cancer, with and without treatment with radioactive iodine therapy.

Forleo R et al. 2021 Minimal extrathyroidal extension in predicting 1-year outcomes: A longitudinal multicenter study of low-to-intermediate-risk papillary thyroid carcinoma (ITCO#4). *Thyroid*. Epub 2021 Sept 19. PMID: 34541894.



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### Clinical Thyroidology for the Public

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## Editor's Comments

Happy New Year and 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*, *MCT8 – AHDS 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](http://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.

The COVID-19 pandemic has caused an unprecedented upheaval in our daily lives and presented extremely difficult challenges to our healthcare system. We at the American Thyroid Association would like to make sure that you all have access to most accurate, reliable, fact-based and updated information. (<https://www.thyroid.org/covid-19/>)

January is [Thyroid Awareness Month](#).

In this issue, the studies ask the following questions:

- Can thyroid hormone levels predict outcomes in patient hospitalized with severe COVID infection?
- Are either desiccated thyroid extract or combination therapy with L-T4 and L-T3 better than L-T4 alone in treating hypothyroidism?
- What are the effects of biotin on thyroid levels?
- Is the Bethesda system for classifying thyroid biopsies accurate in children with thyroid nodules??
- Is core needle biopsy better than fine needle biopsy in evaluating thyroid nodules?
- Does extrathyroidal extension in thyroid cancer increase the risk of cancer recurrence??

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,



## THYROID AND COVID

### Can thyroid hormone levels help us recognize which patients with COVID-19 will have more severe disease in the hospital?

#### BACKGROUND

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2 virus infection. It was first detected in December 2019 and has become the fifth documented pandemic since the 1918 flu pandemic. It has led to more than 248 million cases and 5 million deaths worldwide. COVID-19 mostly effects the respiratory system, but many patients also develop changes in thyroid function tests. These changes are like the changes that occur in any life-threatening illness and known as non-thyroidal illness syndrome (NTIS). Serum triiodothyronine (FT3), serum thyroxine (FT4) levels decrease and reverse triiodothyronine (rT3) levels increase. There have been reports showing an association with low FT3 levels with COVID-19 severity, 28-day death rate, and hospitalization expenses in the intensive care unit. However, there were weaknesses in the previous studies, such as small number of patients, design of the study, and inconsistent collection of thyroid function tests.

We need to understand the factors that may help us recognize which patients may develop more severe illness to treat them successfully. Currently we use several proinflammatory markers for this purpose. These are molecules made by immune system that can promote inflammation. This study was designed to evaluate thyroid hormone levels and presence of NTIS in patients admitted with COVID-19 and to investigate whether thyroid hormone levels were associated with pro-inflammatory markers and COVID-19 severity and death rate.

#### THE FULL ARTICLE TITLE

Beltrão FEL et al 2021 Thyroid hormone levels during hospital admission inform disease severity and mortality in COVID-19 patients. *Thyroid*. Epub 2021 Sep 9. PMID: 34314259.

#### SUMMARY OF THE STUDY

The researchers studied 245 patients who were admitted with COVID-19 to a referral hospital (Metropolitan

Hospital Dom Jose Maria Pires) in Brazil from June to August 2020. SARS-Cov-2 infection was confirmed in all patients by PCR testing. NTIS was defined as serum FT3 levels <2 pg/ml, FT4 and TSH levels within or below the normal reference ranges. All patients had a chest CT (computed tomography) scan when they were admitted. Researchers calculated severity scores based on the extent of disease in the lungs. Noncritical infection was defined as breathing <30 breaths per minute, oxygen saturation <93% at rest, > 50% lung injury as estimated by CT scan. Critical infection was defined as respiratory failure requiring a machine to help with breathing (mechanical ventilation), sudden drop in blood flow and pressure (shock), or organ failure requiring treatment in intensive care unit (ICU). Blood samples were collected within 48 hours of admission and prior to any treatment that may affect thyroid hormone or inflammatory marker levels.

The average age was 62 years (range, 49-74.5) and 145 (59.1%) were men. The average hospital stay was 8.3 days. A total of 58 (23.6%) patients were admitted to the ICU and 41 (16.7%) of these patients later died. Only 54 (22%) patients had normal thyroid hormone levels while 154 (62.8%) had elevated rT3 levels and 18 had only high serum fT4 levels. Only 6.5% of patients had NTIS. Critically ill patients had lower serum fT3 and high normal rT3 levels while rT3 levels were higher in noncritical patients. Serum fT3, rT3, and the product of fT3 x rT3 showed strong association with COVID-19 severity and death rate. Overall, 8 of the 11 inflammation markers (IL-6, D-dimer, lactate dehydrogenase, albumin, CRP, neutrophils, neutrophil/lymphocyte ratio, and hemoglobin) predicted disease severity and death rate. The strongest predictors of death rate and length of stay were fT3 x rT3, neutrophil/lymphocyte ratio, CRP, neutrophil count and serum fT3.



## THYROID AND COVID, continued

### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The findings from this study are important for several reasons. This was one of the largest studies that reported thyroid tests of patients hospitalized with COVID-19. Serum fT3, rT3 and the product of fT3 x rT3 were able to help recognize which patients were likely to have more severe disease or die from it. It is the first study that inves-

tigated whether the product of rT3 x fT3 would show an association with disease severity. This marker was better as a predictor than the currently used methods.

These are promising findings that can help the management of patients hospitalized for COVID-19 but need to be confirmed with other large, carefully designed studies.

— Ebru Sulanc, MD

### ATA THYROID BROCHURE LINKS

Thyroid Function Tests: <https://www.thyroid.org/thyroid-function-tests/>

Novel Coronavirus (COVID-19) and the Thyroid: <https://www.thyroid.org/covid-19/coronavirus-frequently-asked-questions/>

### ABBREVIATIONS & DEFINITIONS

**Non-thyroidal illness syndrome (NTIS):** changes in thyroid function that are a response to illness affecting other parts of the body and not related to a thyroid disorder. The hallmark of NTIS is a low T3 level with normal or low levels of FT4 and TSH

**Thyroxine (T4):** the major hormone produced by the thyroid gland. T4 gets converted to the active hormone T3 in various tissues in the body.

**Triiodothyronine (T3):** the active thyroid hormone, usually produced from thyroxine, available in pill form as Cytomel™.

**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.

**Reverse T3 (rT3):** is metabolically inactive form of T3. It is made from thyroxine (T4) like T3, but when it enters the cell it does not cause any effect.



## HYPOTHYROIDISM

### Comparison of levothyroxine, desiccated thyroid extract, and combination levothyroxine + liothyronine for hypothyroidism

#### BACKGROUND

The thyroid gland mainly produces the thyroid hormone thyroxine (T<sub>4</sub>), which is converted in other tissues to the active hormone triiodothyronine (T<sub>3</sub>). The thyroid is regulated by the hormone TSH. Hypothyroidism occurs when the thyroid gland is underactive and doesn't produce enough thyroid hormone. This is diagnosed with an increase in TSH levels and a decrease in the T<sub>4</sub>. The symptoms of hypothyroidism include being tired, cold, constipated, having decreased energy and gaining weight. Hypothyroidism is usually treated by levothyroxine (L-T<sub>4</sub>) which usually resolves the thyroid-related symptoms. However, the symptoms of hypothyroidism are not specific and may be caused by any other disorders. This may complicate the treatment of hypothyroidism, as some patients continue to have symptoms despite the return of the thyroid hormone and TSH levels to the normal range.

For patients with continued symptoms on treatment with L-T<sub>4</sub> alone, alternative treatment options with desiccated thyroid extract (DTE) or combination therapy (L-T<sub>4</sub> with liothyronine, L-T<sub>3</sub>) have been used with some success. Indeed, a few small studies suggest that some patients seem to prefer regimens that include L-T<sub>3</sub>. The current study aimed to evaluate the clinical effects of DTE, L-T<sub>4</sub>, and combination therapy (L-T<sub>4</sub> and L-T<sub>3</sub>) in patients with hypothyroidism.

#### THE FULL ARTICLE TITLE

Shakir MKM et al 2021 Comparative effectiveness of levothyroxine, desiccated thyroid extract, and levothyroxine + liothyronine in hypothyroidism. *J Clin Endocrinol Metab*. Epub 2021 Jun 29. PMID: 34185829.

#### SUMMARY OF THE STUDY

This was a randomized, double-blind crossover study. A total of 75 patients participated in the study. These patients were beneficiaries of the U.S. military health care system, between the age of 18 and 65 years, diagnosed

with hypothyroidism, and on a stable dose of L-T<sub>4</sub> (or an equivalent dose for combination therapy or DTE) for at least 6 months. A majority of the study population was Caucasian (77.3%) and female (77.3%), with an average age of 50 years. At the time of enrollment, greater than 90% were on L-T<sub>4</sub> therapy alone.

Participants were randomly assigned to one of three treatment groups: L-T<sub>4</sub>, L-T<sub>4</sub>+L-T<sub>3</sub>, or DTE for a 22-week period. After the first 6 weeks on the treatment, a serum TSH level was checked and the dose was adjusted accordingly. Once the TSH level was at goal, patients continued the medication for an additional 16 weeks. Thereafter, the participant was crossed over to the next treatment group. Measurements were obtained at baseline and at the end of each study period. Memory testing was performed using the Wechsler Memory Scale Fourth Edition (WMS-IV). Hypothyroidism symptoms were assessed with the 12-Item General Health Questionnaire (GHQ-12), a thyroid symptom questionnaire (TSQ-36), and the Beck Depression Inventory (BDI). The primary outcomes included performance on memory testing, mood, quality of life, and symptoms.

Analyses at the end of the study period showed no differences in the TSQ-36 and GHQ-12 questionnaires or in the BDI and WMS-IV test assessments between treatment groups. No significant difference was noted in serum TSH levels between the treatment groups. In those who took a T<sub>3</sub>-containing preparation, the serum total T<sub>3</sub> was 30 to 50% higher and the serum T<sub>4</sub> 30% lower than in those on L-T<sub>4</sub> alone group. In the overall study population, there was no significant difference in treatment preference.

Subgroup analysis of the top 20 of the most symptomatic patients showed a strong preference for treatments containing L-T<sub>3</sub> and improved performance on TSQ-36, GHQ-12, BDI, and visual memory index. The treatments were all tolerated well, with no reported adverse effects.





## HYPOTHYROIDISM, continued

### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

In patients with hypothyroidism, no major differences were found between L-T<sub>4</sub> therapy, DTE or combination therapy with regard to symptomatic control, quality of life, treatment preference, or serum TSH levels. A subgroup analysis of the most symptomatic patients did

reveal improved performance on memory testing and improvement in quality of life, with a preference for T<sub>3</sub>-containing treatments. Importantly, there were no adverse effects in any of the treatment groups. Further larger studies are indicated.

— Alan P. Farwell, MD

### ATA THYROID BROCHURE LINKS

Hypothyroidism (Underactive): <https://www.thyroid.org/hypothyroidism/>

Thyroid Hormone Treatment: <https://www.thyroid.org/thyroid-hormone-treatment/>

### ABBREVIATIONS & DEFINITIONS

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

**Levothyroxine (T<sub>4</sub>):** the major hormone produced by the thyroid gland and available in pill form as Synthroid™, Levoxyl™, Tirosint™ and generic preparations.

**Thyroid hormone therapy:** patients with hypothyroidism are most often treated with Levothyroxine in order to return their thyroid hormone levels to normal. Replacement therapy means the goal is a TSH in the normal range and is the usual therapy. Suppressive therapy means that the goal is a TSH below the normal range and is used in thyroid cancer patients to prevent growth of any remaining cancer cells.

**Desiccated thyroid extract:** thyroid hormone pill made from animal thyroid glands. Currently desiccated thyroid extract is made from pig thyroids and is available as Armour Thyroid™ and Nature-Throid™.

**Triiodothyronine (T<sub>3</sub>):** the active thyroid hormone, usually produced from thyroxine, available in pill form as Cytomel™ or Liothyronine.

**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.



## THYROID FUNCTION TESTS

### Biotin use can interfere with the management of thyroid diseases, including thyroid cancer

#### BACKGROUND

Biotin is a dietary supplement that belongs to vitamin B family. Although not proven, large doses of biotin are taken by some for purposes like improving hair and nail quality. Further, some skin doctors also recommend biotin for these issues. Biotin has no effect on thyroid hormone levels or thyroid function in the body. However, biotin can interfere with the measurement of hormone levels in the laboratory, making them inaccurate. This is because biotin is added as a reagent during some of the laboratory methods. The hormone measurements that can be affected are thyroxine, triiodothyronine, TSH and thyroglobulin. This effect may falsely change the results and lead to an incorrect diagnosis. Precise measurement of thyroid hormones and TSH is important for diagnosis of thyroid disorders. Similarly, an accurate testing of thyroglobulin is vital for patients with thyroid cancer, as it can serve as a cancer marker.

This study has been done to compare the effect of biotin intake on hormone levels from 4 different laboratories used in diagnosis of thyroid disorders. Biotin is added as a reagent in the assays from Roche and Siemens but is not used in the assays from Abbot or when done using mass spectrography (LC-MS/MS).

#### THE FULL ARTICLE TITLE

Ylli D et al 2021 Biotin interference in assays for thyroid hormones, thyrotropin and thyroglobulin. *Thyroid* 31:1160–1170. PMID: 34042535.

#### SUMMARY OF THE STUDY

The authors recruited 13 volunteers to participate in the study; 9 women and 4 men with an average age of 45 years (range: 28–67). Of the participants, 10 had no thyroid disease and 3 had prior thyroid surgery and had

to take Levothyroxine on daily basis. All had normal levels of thyroid hormone, TSH and thyroglobulin at the time of study. They were asked to take 10,000 mcg of biotin daily for 8 days. Blood tests were done before and in 2 and 5 hours after taking biotin on day 1 and day 8. Thyroid hormones were measured by Roche Cobas 6000, Abbott architect and LC-MS/MS and thyroglobulin was measured by Siemens Immulite 2000. Their levels were compared on day 1 and day 8, before and after taking Biotin.

A significant decrease in TSH and significant increases in FT4 and TT3 concentrations were observed between baseline at day 1 and all time points but baseline at day 8 after taking biotin when Roche Cobas 6000 was used. Thyroglobulin levels were found to be falsely lower after taking biotin with the Siemens Immulite 2000 assay. No change in hormone levels were noted after biotin when measured by the Abbott assay or the LC-MS/MS, although the TSH was falsely lower 2 h after taking biotin with the Abbott assay.

#### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study shows that taking a 10,000 mcg daily dose of Biotin (a commonly used dose) may falsely change the result of the blood test for TSH, Free T4, total T3 and thyroglobulin. This change does not happen with all types of laboratory methods; it mostly occurs when biotin is used in the process of hormone measurement. Additional factors like, the dose of biotin and the time of the blood test from intake of biotin are also important. Patients and clinicians should be aware of this effect. In general, patients taking biotin should stop the supplement for at least 3–5 days before getting thyroid levels tested.

— Shirin Haddady, MD, MPH



## THYROID FUNCTION TESTS, continued

### ATA THYROID BROCHURE LINKS

Thyroid Function Tests: <https://www.thyroid.org/thyroid-function-tests/>

### ABBREVIATIONS & DEFINITIONS

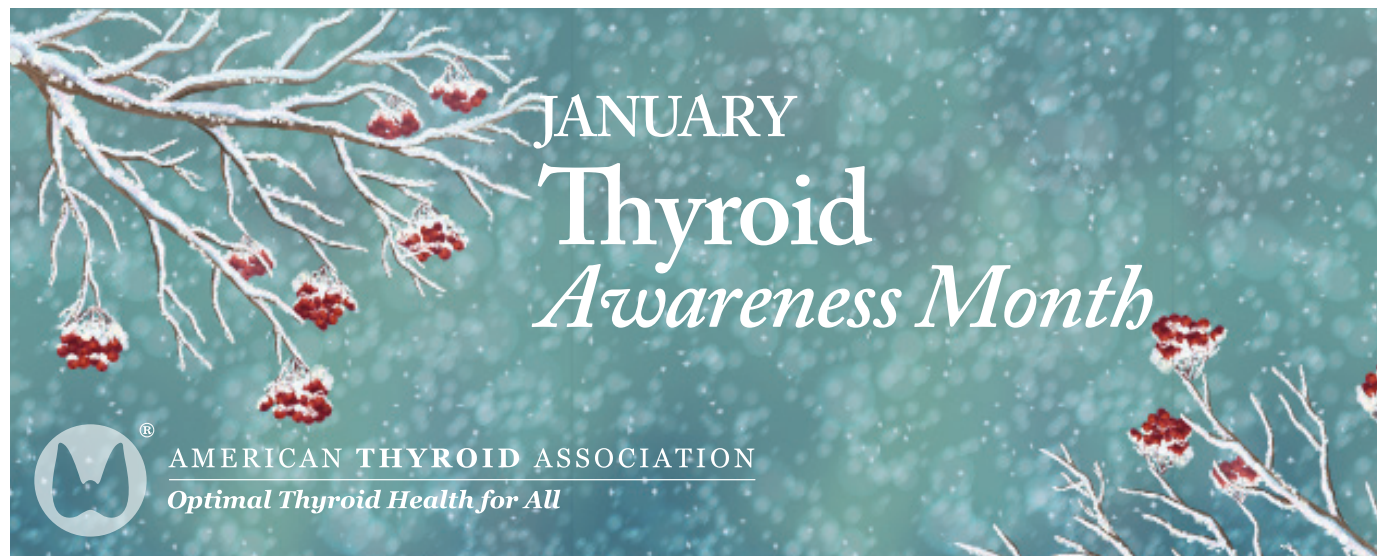
**TSH: thyroid stimulating hormone** — produced by the pituitary gland that regulates thyroid function; also the best screening test to determine if the thyroid is functioning normally.

**Thyroglobulin:** a protein made only by thyroid cells, both normal and cancerous. When all normal thyroid tissue is destroyed after radioactive iodine therapy in patients with thyroid cancer, thyroglobulin can be used as a thyroid cancer marker in patients that do not have thyroglobulin antibodies.

**Levothyroxine (T4):** the major hormone produced by the thyroid gland and available in pill form as Synthroid™, Levoxyl™, Tirosint™ and generic preparations.

**Thyroxine (T4):** the major hormone produced by the thyroid gland. T4 gets converted to the active hormone T3 in various tissues in the body.

**Triiodothyronine (T3):** the active thyroid hormone, usually produced from thyroxine.







## THYROID NODULES

### How useful is the Bethesda system for reporting cytology results in children and adolescents with thyroid nodules?

#### BACKGROUND

A thyroid nodule is an abnormal growth of thyroid cells that form a lump within the thyroid. Thyroid nodules are uncommon in children and therefore little is known about the diagnostic characteristics and outcomes of pediatric thyroid nodules. The Bethesda System for Reporting Thyroid Cytopathology is often used in adults to determine the chance a thyroid nodule is cancerous. A biopsy of the thyroid nodule in which cells from the thyroid nodule are obtained, can often help establish if the thyroid nodule is a cancer or not. The Bethesda system is used to report six categories of cytology results (diagnostic information after cells are examined from the fine needle aspiration biopsy). Bethesda system categories include: nondiagnostic, benign (not cancer), atypia of uncertain significance/follicular neoplasm of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), suspicious for malignancy, and malignant (cancer). The chance that a thyroid nodule is cancer in a child or adolescent is much higher than in adults. Little is known about the use of the Bethesda system for thyroid nodules in children and adolescents. This study investigates the use of the Bethesda system in pediatrics.

#### THE FULL ARTICLE TITLE

Vuong HG et al 2021 The use of the Bethesda System for reporting thyroid cytopathology in pediatric thyroid nodules: A meta-analysis. *Thyroid* 31:1203–1211. PMID: 33504264.

#### SUMMARY OF THE STUDY

This analysis involved reviewing articles published between 2007 and 2020 using PubMed or Web of Science. Articles included in the analysis included the Bethesda system or an equivalent reporting system and pediatric cases with thyroid biopsy, surgery and final pathology. A total of 17 articles including a total of 3687 pediatric thyroid nodules were analyzed. Of the 3687 thyroid nodules, 1426 (38.7%) were removed by surgery and 683 (47.9%) of those were cancerous. The most common cancer found was papillary thyroid carcinoma (88.4%). Rates of surgical resection (where thyroid tissue is removed) in children and adolescents were greater than those for adults in all Bethesda system categories, except the nondiagnostic group. However, the risk for cancer was similar for pediatric and adult thyroid nodules in all Bethesda system categories.

#### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The Bethesda system is a useful tool to make decisions for children and adolescents with thyroid nodules. Compared to adults, pediatric patients with benign and indeterminate thyroid nodules had a higher surgery rate but the risk for having cancer was not statistically different. Therefore, there may be a potential to over treat children and adolescents. Establishing treatment guidelines and risk stratification tools are needed to identify which children need thyroid surgery.

— Priya Mahajan, MD

#### ATA THYROID BROCHURE LINKS

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

Thyroid Surgery: <https://www.thyroid.org/thyroid-surgery/>

Fine Needle Aspiration Biopsy of Thyroid Nodules in Children and Adolescents: <https://www.thyroid.org/fna-thyroid-nodules-children-adolescents/>



## THYROID NODULES, continued

### 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 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.

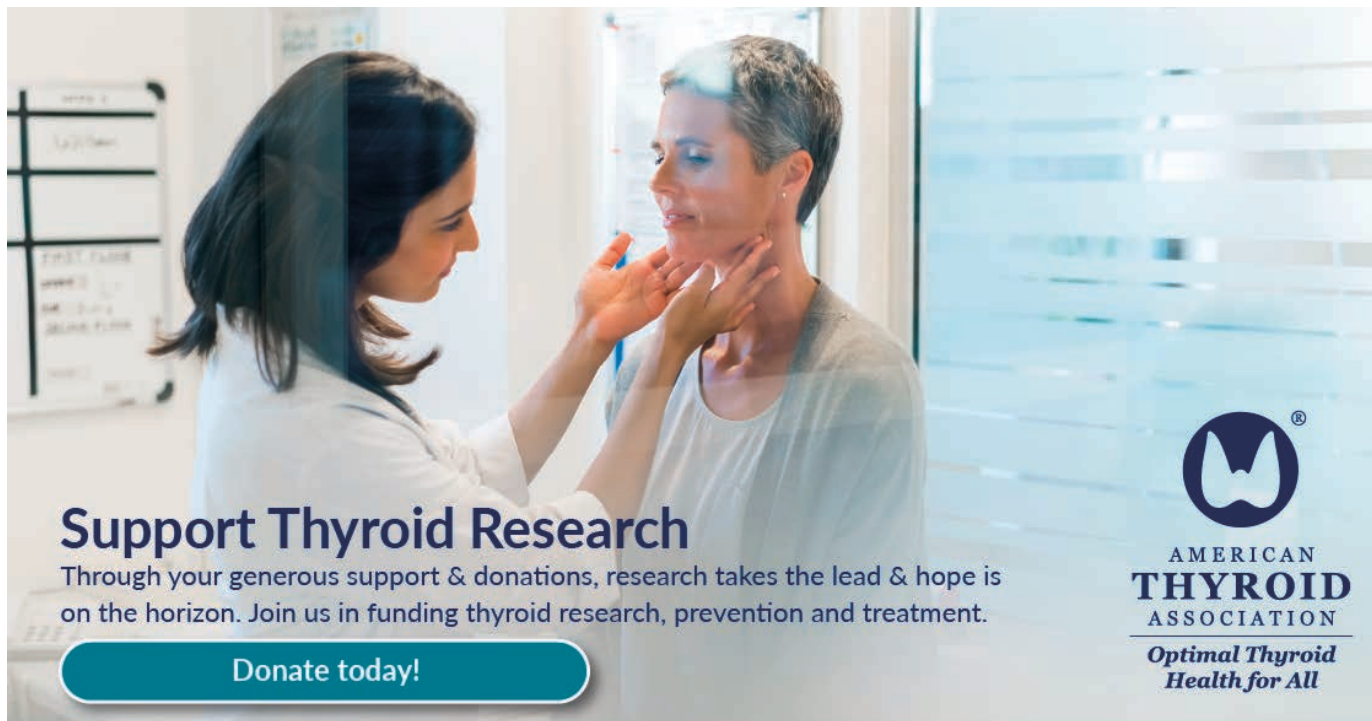
**Non-diagnostic thyroid biopsy:** this happens when some atypical cells are found but not enough to provide a diagnosis. This occurs in 5-10% of biopsies. This often results in the need to repeat the biopsy.

**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.

**Atypical thyroid biopsy:** this happens when there are some abnormal/atypical cells in the biopsy sample but not enough to diagnose a cancer. However, because there are abnormal cells in the biopsy sample, the specimen cannot be called benign. Sometimes a repeat biopsy may be helpful but often surgery is recommended to remove the nodule.


**Suspicious thyroid biopsy:** this happens when there are atypical cytological features suggestive of, but not diagnostic for malignancy. Surgical removal of the nodule is required for a definitive diagnosis.



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ASSOCIATION  
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Health for All



## THYROID NODULES

### Core needle biopsy for evaluation of thyroid nodules

#### BACKGROUND

Thyroid nodules are very common and identified in up to 50% of the population. Only about 5-6% are cancers and the rest are benign (noncancerous), so most patients will not need surgery of these nodules unless they have symptoms. Thyroid biopsy is the main test used to determine whether a given nodule needs to be removed. Thyroid biopsy is usually done with a thin needle (fine needle biopsy) and is a well-tolerated procedure with minimal to no complications and can be done in the office. However, up to 10% of thyroid fine needle biopsies will not have enough cells for a diagnosis. In addition, as many as 25% will be indeterminate, meaning they can't tell if the cells are normal or abnormal. There are 3 indeterminate categories: 1) atypia of unknown significance or follicular lesion of unknown significance (AUS/ FLUS), 2) follicular or hürthle cell lesion and 3) suspicious for papillary cancer. AUS/ FLUS is the most common indeterminate finding and additional testing such as repeat biopsy and the use of molecular markers is often used to determine the cancer risk.

An alternative method to evaluate thyroid nodules is a core needle biopsy (CNB). This procedure uses a large needle and requires an experienced operator with specific training. CNB also has a higher risk of complications than a fine needle biopsy, including injuries to the trachea and carotid artery.

Many organizations have supported the use of CNB as a second line test when a fine needle biopsy is not diagnostic. However, in Asia, many institutions recommend the use of CNB as an initial test because of its reported lower incidence of non-diagnostic results. This study was performed to compare the use of CNB vs a fine needle biopsy as a first option in the evaluation of thyroid nodules.

#### THE FULL ARTICLE TITLE

Ahn HS et al 2021 Diagnostic performance of core needle biopsy as a first-line diagnostic tool for thyroid nodules according to ultrasound patterns: Comparison with fine-needle aspiration using propensity score matching analysis. Clin Endocrinol (Oxf) 94:494–503. PMID: 32869866.

#### SUMMARY OF THE STUDY

This study compares the results of CNB, used as the initial test in one institution, to the results of a fine needle biopsy from two other institutions in Korea. In the first institution CNB was used as an initial test in 705 patients whose ultrasound predicted the likelihood of a non-diagnostic fine needle biopsy. This was compared to a second group of 583 patients from the other two institutions where a fine needle biopsy was the initial testing. Ultrasound features of the thyroid nodules were categorized according to the Korean Thyroid Imaging Reporting and Data System (K-TIRADS). Nodules were considered cancerous either by result of CNB or a fine needle biopsy, or by the evaluation of the nodule after surgery. Nodules were considered benign if there were two benign results on CNB or a fine needle biopsy, or one benign result on CNB or a fine needle biopsy and no evidence of indeterminate or cancer results in initial or repeat biopsy or in a surgical pathology result.

CNB was less likely to result in a nondiagnostic, AUS/ FLUS or suspicious for malignancy cytology diagnosis than was a fine needle biopsy. CNB also had a higher frequency of cancer cytology findings than a fine needle biopsy. The fine needle biopsy group had a small number of false negative results (2 of 244 nodules) and one false positive result (1 of 141 nodules). There were no false negative or false positive results in the CNB group.

There were no complications in the fine needle biopsy group. A total of 5 patients in the CNB group developed local bleeding treated just with manual pressure. The authors concluded that CNB was superior to a fine needle biopsy in the initial evaluation of thyroid nodules.

#### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study suggests that increased use of CNB may be able to decrease the incidence of inadequate or indeterminate results when a fine needle biopsy is used. While a number of studies have shown similar results, there are



## THYROID NODULES, continued

others suggesting no difference in performance using the two techniques. In addition, the increased training needed for CNB and slight increase in complications may limit its use as an initial method of evaluation. However, it does suggest the need for additional study to compare

the usefulness of these two diagnostic techniques. It also suggests an alternative to using molecular markers when a fine needle biopsy is non-diagnostic – although a cost comparison would need to be performed.

— Marjorie Safran, MD

### ATA THYROID BROCHURE LINKS

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

Fine Needle Aspiration Biopsy of Thyroid Nodules: <https://www.thyroid.org/fna-thyroid-nodules/>

### ABBREVIATIONS & DEFINITIONS

**Thyroid fine needle aspiration 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.

**Core needle biopsy (CNB):** a procedure that uses a large needle and requires an experienced operator with specific training. CNB has a higher risk of complications than a fine needle biopsy, including injuries to the trachea and carotid artery.

**Inadequate/Insufficient biopsy:** this happens with not enough cells are obtained during the biopsy to provide a diagnosis. This occurs in 5-10% of biopsies. This often results in the need to repeat the biopsy.

**Non-diagnostic thyroid biopsy:** this happens when some atypical cells are found but not enough to provide a diagnosis. This occurs in 5-10% of biopsies. This often results in the need to repeat the biopsy.

**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.

**Atypical thyroid biopsy:** this happens when there are some abnormal/atypical cells in the biopsy sample but not enough to diagnose a cancer. However, because there are abnormal cells in the biopsy sample, the specimen cannot be called benign. Sometimes a repeat biopsy may be helpful but often surgery is recommended to remove the nodule.

**Suspicious thyroid biopsy:** this happens when there are atypical cytological features suggestive of, but not diagnostic for malignancy. Surgical removal of the nodule is required for a definitive diagnosis.

**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 Afirma™ Gene Expression Classifier and Thyroseq™





## THYROID CANCER

### The presence of minimal extension of thyroid cancer outside of the thyroid does not predict initial response to treatment but can help determine prognosis

#### BACKGROUND

Thyroid cancer is the fastest rising cancer in recent years. Most patients with thyroid cancer are at low risk of cancer recurrence after the initial surgery to remove the cancer. However, there are some features found on pathology after surgery that increases the risk of the thyroid cancer returning. One such feature is minimal extrathyroidal extension (ETE) which means that a small amount of thyroid cancer is found extending outside of the thyroid gland after examining the cancer under the microscope. This finding was removed from the current thyroid cancer staging guidelines because it is not associated with increased likelihood of death. However, it is still important and may be associated with an increased risk of the thyroid cancer coming back (recurrence).

Most patients at low risk of thyroid cancer recurrence are usually just treated with surgery then thyroid hormone. Patients with an increased risk of the thyroid cancer returning based on the results of the initial surgery usually are treated additionally with radioactive iodine therapy. This study was done to look at the impact of minimal ETE in predicting initial treatment response in papillary thyroid cancer, with and without treatment with radioactive iodine therapy.

#### FULL ARTICLE TITLE

Forleo R et al. 2021 Minimal extrathyroidal extension in predicting 1-year outcomes: A longitudinal multicenter study of low-to-intermediate-risk papillary thyroid carcinoma (ITCO#4). *Thyroid*. Epub 2021 Sept 19. PMID: 34541894.

#### SUMMARY OF THE STUDY

This study looked at the Italian Thyroid Cancer Observatory (ITCO), a web-based database started in 2013, which includes 9000 patients with thyroid cancer from 49 thyroid cancer centers. Of these, 2237

subjects met all the criteria to be included in this study. Initial treatment was classified as thyroid lobectomy (partial thyroid removal) or total thyroidectomy (total thyroid removal) and if radioactive iodine therapy was given following total thyroidectomy. Risk of recurrence was classified based on the 2015 American Thyroid Association guidelines for thyroid nodules and thyroid cancer, and response to initial treatment was classified based on diagnostic scans and blood thyroglobulin and thyroglobulin antibody levels at the 1-year follow-up visit.

Of the 2237 subjects included in the analysis, 1,153 (51.5%) patients received radioactive iodine therapy and minimal ETE was documented in 470 patients (21%). According to the American Thyroid Association risk classification system, 1632 (73%) were classified as low risk of recurrence and 605 (27%) as intermediate risk of recurrence. At the 1-year follow-up, there was no difference in initial therapy response rates between patients with and without minimal ETE. Other factors, including cancer size, aggressive thyroid cancer types and age at diagnosis were also looked at. Only the combination of minimal ETE with a cancer size of >2 cm showed a difference in treatment response.

Among the 470 patients with minimal ETE, 370 had received radioactive iodine therapy. Subjects who received radioactive iodine therapy were more likely to have an excellent response initially but there was no difference in the response once the investigators corrected for the other variables.

#### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Minimal ETE is not an independent prognostic marker in predicting the initial response to therapy in patients with papillary thyroid cancer who do not have spread of the cancer to the lymph nodes. However, the





## THYROID CANCER, continued

combination of minimal ETE and cancer size >2 cm can predict worse outcomes. Knowing this information is important for patients with thyroid cancer to understand the management decisions that are being made to treat

their cancer, as these decisions are dependent on factors associated with their prognosis.

— Maria Brito, MD

### ATA THYROID BROCHURE LINKS

Thyroid Surgery: <https://www.thyroid.org/thyroid-surgery/>

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

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).

**Thyroidectomy:** surgery to remove the entire thyroid gland. When the entire thyroid is removed it is termed a total thyroidectomy. When less is removed, such as in removal of a lobe, it is termed a partial thyroidectomy.

**Lobectomy:** surgery to remove one lobe of the thyroid.

**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).

**Thyroglobulin antibodies:** these are antibodies that attack the thyroid instead of bacteria and viruses, they are a marker for autoimmune thyroid disease, which is the main underlying cause for hypothyroidism and hyperthyroidism in the United States.

**Thyroglobulin:** a protein made only by thyroid cells, both normal and cancerous. When all normal thyroid tissue is destroyed after radioactive iodine therapy in patients with thyroid cancer, thyroglobulin can be used as a thyroid cancer marker in patients that do not have thyroglobulin antibodies.



# Clinical Thyroidology® for the Public

## 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.



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Survivors' Association, Inc.™  
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MCT8 - AHDS  
Foundation

THYROID CANCER  
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Thyroid Cancer Canada  
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Thyroid  
Federation  
International

### American Thyroid Association

[www.thyroid.org](http://www.thyroid.org)

ATA Patient Resources:

[www.thyroid.org/thyroid-information/](http://www.thyroid.org/thyroid-information/)

Find a Thyroid Specialist: [www.thyroid.org](http://www.thyroid.org)

(Toll-free): 1-800-THYROID

[thyroid@thyroid.org](mailto:thyroid@thyroid.org)

### Bite Me Cancer

[www.bitemecancer.org](http://www.bitemecancer.org)

[info@bitemecancer.org](mailto:info@bitemecancer.org)

### Graves' Disease and Thyroid Foundation

[www.gdatf.org](http://www.gdatf.org)

(Toll-free): 877-643-3123

[info@ngdf.org](mailto:info@ngdf.org)

### Light of Life Foundation

[www.checkyourneck.com](http://www.checkyourneck.com)

[info@checkyourneck.com](mailto:info@checkyourneck.com)

### MCT8 – AHDS Foundation

[mct8.info](http://mct8.info)

[Contact@mct8.info](mailto:Contact@mct8.info)

### Thyca: Thyroid Cancer Survivors' Association, Inc.

[www.thyca.org](http://www.thyca.org)

(Toll-free): 877-588-7904

[thyca@thyca.org](mailto:thyca@thyca.org)

### Thyroid Cancer Alliance

[www.thyroidcanceralliance.org](http://www.thyroidcanceralliance.org)

[www.thyroidcancerpatientinfo.org](http://www.thyroidcancerpatientinfo.org)

Rotterdam, The Netherlands

### Thyroid Cancer Canada

[www.thyroidcancer canada.org](http://www.thyroidcancer canada.org)

416-487-8267

[info@thyroidcancer canada.org](mailto:info@thyroidcancer canada.org)

### Thyroid Federation International

[www.thyroid-fed.org](http://www.thyroid-fed.org)

[tfi@thyroid-fed.org](mailto:tfi@thyroid-fed.org)

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