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Clinical Thyroidology® for the Public

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

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Is levothyroxine enough during menopause in hypothyroid women?

Some hypothyroid patients treated with levothyroxine report persistent cognitive symptoms such as "brain fog" and difficulty concentrating despite normal TSH blood levels. Similar cognitive symptoms can be seen during menopause. This study aimed to investigate whether levothyroxine-treated hypothyroidism is associated with a more significant decline in cognitive function in women during the menopausal transition

Ettleson MD et al. The association between hypothyroidism and cognitive function change in women across the menopause transition: the study of women's health across the nation. Thyroid 2024;34(10):1205-1213; doi: 10.1089/thy.2024.0358. PMID: 39225158.

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Treatment preferences in patients with hypothyroidism

The standard of care for the treatment of hypothyroidism is L-T4 administered at doses to normalize TSH levels. The goal of this study was to review and analyze the results of clinical trials that evaluated patient preference in adults with hypothyroidism comparing treatments using L-T4 monotherapy with those using T4 and T3 in the form of either T4/T3 combination therapy or DTE.

de Lima Beltrão FE et al Treatment preferences in patients with hypothyroidism: an analysis of eleven randomized controlled trials. J Clin Endocrinol Metab. Epub 2024 Sep 18:dgae651; doi: 10.1210/clinem/dgae651. PMID: 39290156.

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Thyroid hormone levels change with age

TSH and FT4 tests are commonly ordered to evaluate patients for possible thyroid problems. Currently, laboratories use the same normal range for TSH and FT4 for all adults, regardless of age. However, some research suggests that TSH and FT4 levels may change with age. The goal of this study was to establish age-specific normal reference ranges for TSH and FT4.

Jansen HI et al. Age-specific reference intervals for thyroid-stimulating hormones and free thyroxine to optimize diagnosis of thyroid disease. Thyroid. Epub 2024 Sep 30

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Cancer risks of patients with Graves' disease who received antithyroid drugs as initial treatment

Some studies have shown that patients with hyperthyroidism have an increase chance to develop several types of cancer. Other studies looking at the link between hyperthyroidism and cancer only looked at those patients who were treated with radioactive iodine therapy, since radiation is a risk factor for cancer. The goal of this study is to shed some light about the risk of cancer in patients with Graves' disease who are treated with ATDs.

Lee JY, et al. Cancer risks of patients with Graves' disease who received antithyroid drugs as initial treatment: a nationwide population-based analysis. Thyroid 2024;34(10):1271-1279; doi: 10.1089/thy.2024.0178. PMID: 39228052.

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Are thyroid nodules in the isthmus different from nodules in the thyroid lobes?

Some studies suggest that isthmus nodules, while less frequent than nodules within the thyroid lobes, may carry a higher risk of cancer than nodules in either thyroid lobe. A recent study suggested potential differences in gene mutations found in thyroid cancer between the isthmus and the lobes. This study examines the cytologic and molecular marker differences between nodules and papillary thyroid cancer based on whether the cancer is in the isthmus or the thyroid lobes.

Jasim S, et al. Cytologic and molecular assessment of isthmus thyroid nodules and carcinomas. Thyroid. Epub 2024 Nov 11; doi: 10.1089/thy.2024.0254. PMID: 39527399.

THYROID CANCER. 13

Effect of thyroidectomy on survival outcomes for medullary thyroid cancer with distant metastasis at diagnosis

Medullary thyroid cancer (MTC) is a more aggressive thyroid cancer and is more likely to spread outside the thyroid into the neck. As such, there is limited data regarding the potential benefit of thyroidectomy on survival in patients with spread of the MTC outside of the neck when the cancer is diagnosed. This study 1) evaluates the prognosis based on the presence of what organs and how many contain MTC cells, 2) evaluates whether thyroidectomy is beneficial in these patients, and (3) identifies the best candidates for thyroidectomy in patients with metastatic MTC at diagnosis.

Liu C-Q, et al. Survival outcome and optimal candidates of primary tumor resection for patients with metastatic medullary thyroid cancer. J Clin Endocrinol Metab 2024;109(11):2979-2985; doi: 10.1210/clinem/dgae214. PMID: 38570918.

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Editor's Comments

Welcome to another issue of *Clinical Thyroidology for the Public* and Happy New Year!!! 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 X (previously known as 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 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:

- Is levothyroxine enough during menopause in hypothyroid women?
- Do hypothyroid patients prefer T3-containing therapies?
- How much do thyroid levels change as we age?
- Is there an increased risk of cancer in patients with Graves' disease treated with antithyroid drugs?
- Are thyroid nodules in the isthmus different from nodules in the thyroid lobes?
- Does thyroidectomy increase survival in patients with medullary thyroid cancer if the cancer has already spread outside of the neck??

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

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HYPOTHYROIDISM

Is levothyroxine enough during menopause in hypothyroid women?

BACKGROUND

Hypothyroidism is common and affects many more women than men. Many symptoms of hypothyroidism are nonspecific and, while most patients note improvement in their symptoms once started on thyroid hormone replacement, most commonly levothyroxine, as many as 10% of hypothyroid patients continue to have symptoms. For example, some hypothyroid patients treated with levothyroxine report persistent cognitive symptoms such as "brain fog" and difficulty concentrating despite normal TSH blood levels. This has led to the discussion of alternative treatment options for hypothyroidism (combination T4/T3 therapy, desiccated thyroid extract).

Similar cognitive symptoms can be seen during menopause. The menopause transition occurs on average at the age of 51, and estrogen levels decrease during this time. The Study of Women's Health Across the Nation (SWAN) is a longitudinal study tracking health outcomes in women through midlife. This study aimed to investigate whether levothyroxine-treated hypothyroidism is associated with a more significant decline in cognitive function in women during the menopausal transition.

THE FULL ARTICLE TITLE

Ettleson MD et al. The association between hypothyroidism and cognitive function change in women across the menopause transition: the study of women's health across the nation. Thyroid 2024;34(10):1205-1213; doi: 10.1089/thy.2024.0358. PMID: 39225158.

SUMMARY OF THE STUDY

Data was gathered from the SWAN by following the patients from the beginning and comparing cognitive testing to other patients with similar characteristics (age, race, education level, menopausal status, and other health conditions) except the presence of thyroid disease. Of the 2,033 patients followed, 227 had hypothyroidism treated with levothyroxine, and 1,806 had no thyroid disease. Women with a history of thyroid cancer, other thyroid disease without the use of levothyroxine, or the use of other thyroid hormone replacement such as liothyronine or desiccated thyroid extract were not included in the study. At several points throughout the 15 years, the women were tested on processing speed, working memory, and episodic memory and were asked to fill out a survey at the end about how well they were able to concentrate.

Although not different enough to be significant, the processing speed and working memory of women taking levothyroxine were better at the initial assessment. Over the entire 15-year time, there was no difference in processing speed, working memory, or episodic memory between the women on levothyroxine and those not on levothyroxine. This finding held true even when they took into consideration abnormal TSH blood levels in both groups. There was also no difference in the ability to concentrate reported between the two groups on the survey conducted at the end.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study suggests that cognitive functioning in hypothyroid women taking levothyroxine during menopause is the same as in women who are not hypothyroid. Interestingly, hypothyroid women taking levothyroxine appeared to be slightly better in the processing speed and working memory of women than those without hypothyroidism, although the differences were not significant. These results also suggest that, despite some persistent symptoms in concentrating, actual cognitive function is normal. Finally, this study suggests that levothyroxine is sufficient for treatment of hypothyroidism and its cognitive symptoms in the menopausal female population. To help sort out causes and treatment of persistent cognitive symptoms in hypothyroid women, future studies might be able to incorporate more ways of testing concentration, documentation of whether the patient has antibodies against his/her thyroid gland, and the differences in patients' response to levothyroxine medication.

— Pinar Smith, MD

HYPOTHYROIDISM, continued

ATA RESOURCES

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 (T4): the major hormone produced by the thyroid gland and available in pill form as Synthroid™, Levoxyl™, Tyrosint™ 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.

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

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™.

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HYPOTHYROIDISM

Treatment preferences in patients with hypothyroidism

BACKGROUND

Hypothyroidism is common and is diagnosed by elevated levels of TSH and low levels of thyroxine (T4). T4 is the main hormone secreted from the thyroid gland. T4 is converted to the active thyroid hormone, T3, mostly in peripheral tissues. Most, if not all, of the actions of the thyroid are mediated by T3. Symptoms of hypothyroidism are also very common and nonspecific, including fatigue/decreased energy, difficulty concentrating, weight gain, feeling cold and constipation. The standard of care for the treatment of hypothyroidism is synthetic thyroxine (L-T4) administered at doses to normalize TSH levels. The expectation is that T3 levels will also be returned to normal by the conversion of L-T4 to T3.

While L-T4 monotherapy is effective in relieving symptoms in most hypothyroid patients, ~10% of patients continue to have symptoms that they attribute to hypothyroidism. Because of this, alternative treatment options are proposed, including combining levothyroxine with T3 (combination T4/T3 therapy) and desiccated thyroid extract (DTE), produced from animal thyroid gland that also contain T4 and T3. DTE was the only treatment for hypothyroidism until thyroxine was isolated and able to be mass produced. Some studies have reported better outcomes with T4/T3 combination therapy as comparted to levothyroxine monotherapy, although this has been inconsistently demonstrated and thus remains controversial.

The goal of this study was to review and analyze the results of clinical trials that evaluated patient preference in adults with hypothyroidism comparing treatments using L-T4 monotherapy with those using T4 and T3 in the form of either T4/T3 combination therapy or DTE.

THE FULL ARTICLE TITLE

de Lima Beltrão FE et al Treatment preferences in patients with hypothyroidism: an analysis of eleven randomized controlled trials. J Clin Endocrinol Metab. Epub 2024 Sep 18:dgae651; doi: 10.1210/clinem/dgae651. PMID: 39290156.

SUMMARY OF THE STUDY

A total of 11 clinical trials were included, with a total of 1135 patients (543 on L-T4 and 592 on combination therapy). Overall, the majority of these studies (6 of 11) showed no difference between the treatment groups while 5/11 showed a preference for combination therapy. Combining all of the studies together (call a meta-analysis) suggested there was an overall preference for combination therapy over L-T4 monotherapy. Overall, 52% of patients preferred combination therapy (T4/T3 or DTE), 24% preferred L-T4 monotherapy, and 24% had no preference.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This meta-analysis of 11 clinical trials of treatment options for hypothyroidism suggests that a slight majority of patients preferred combination therapy that included some form of T4 and T3. This is valuable insight as we continue to try to provide the best options for treating patients with hypothyroidism. This also provides options to address the continued symptoms of ~10% of hypothyroid patients who do not feel completely well on L-T4 monotherapy.

— Alan P. Farwell, MD

ATA RESOURCES

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

HYPOTHYROIDISM, continued

ABBREVIATIONS & DEFINITIONS

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

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. 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™.

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.

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HYPOTHYROIDISM

Thyroid hormone levels change with age

BACKGROUND

Thyroid function tests are commonly ordered to evaluate patients for possible thyroid problems. In particular, hypothyroidism is often screened for due to common nonspecific symptoms such as fatigue and weight gain. Thyroid-stimulating hormone (TSH) levels are the most common thyroid test ordered, followed by free thyroxine (FT4) measurements of the TSH is abnormal. If TSH levels are high and FT4 levels are low, it indicates overt hypothyroidism, which is usually treated with lifelong thyroid hormone therapy using levothyroxine. If FT4 levels are normal but TSH levels are high, it is called subclinical hypothyroidism. There is ongoing debate about whether subclinical hypothyroidism should be treated.

Currently, laboratories use the same normal range for TSH and FT4 for all adults, regardless of age. However, some research suggests that TSH and FT4 levels may change with age. In particular, TSH levels appear to increase in older patients, so a TSH level that seems abnormal in a young adult might be normal for an older adult. This could lead to some people being treated unnecessarily, even when their test results are appropriate for their age.

The goal of this study was to establish age-specific normal reference ranges for TSH and FT4.

THE FULL ARTICLE TITLE

Jansen HI et al. Age-specific reference intervals for thyroid-stimulating hormones and free thyroxine to optimize diagnosis of thyroid disease. Thyroid. Epub 2024 Sep 30

SUMMARY OF THE STUDY

The authors analyzed lab data from 13 medical institutions in the Netherlands, collected from patients between 2008 and 2022. This data included over 7.6 million TSH measurements and 2.2 million FT4 measurements. They calculated age-specific normal ranges for TSH and FT4 levels using advanced statistical methods.

They discovered that TSH levels are naturally higher in children compared to adults. In adults, TSH levels tend to increase with age, especially after 50 in women and 60 in men. For example, the upper normal limit for TSH in 50-year-old women was 4.0 mIU/L, but by age 90, it increased by 50% to 6.0 mIU/L. In contrast, Free T4 levels stayed relatively stable throughout adulthood.

The study also found that using these age-specific normal ranges could significantly reduce the number of people diagnosed with subclinical hypothyroidism. Among women aged 50-60, the rate of subclinical hypothyroidism would drop from 13.1% to 8.6%. In women aged 90-100, it would decline from 22.7% to 8.1%. Similar decreases were seen in men, with the diagnosis of subclinical hypothyroidism falling from 10.9% to 7.7% in men aged 60-70 and from 27.4% to 9.6% in those aged 90-100.

The impact on overt hypothyroidism was smaller but still noticeable. Among women aged 50-60, the diagnosis rate would decrease from 3.0% to 2.2%, while in men, it would drop from 1.7% to 1.4%.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The results of this study show that it is normal for levels of TSH increase with age in adults, starting at age 50 for women and age 60 for men. Using age-specific reference ranges for normal thyroid function can help avoid over-diagnosing and over-treating both subclinical and overt hypothyroidism.

— Phillip Segal, MD FRCPC

HYPOTHYROIDISM, continued

ATA RESOURCES

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

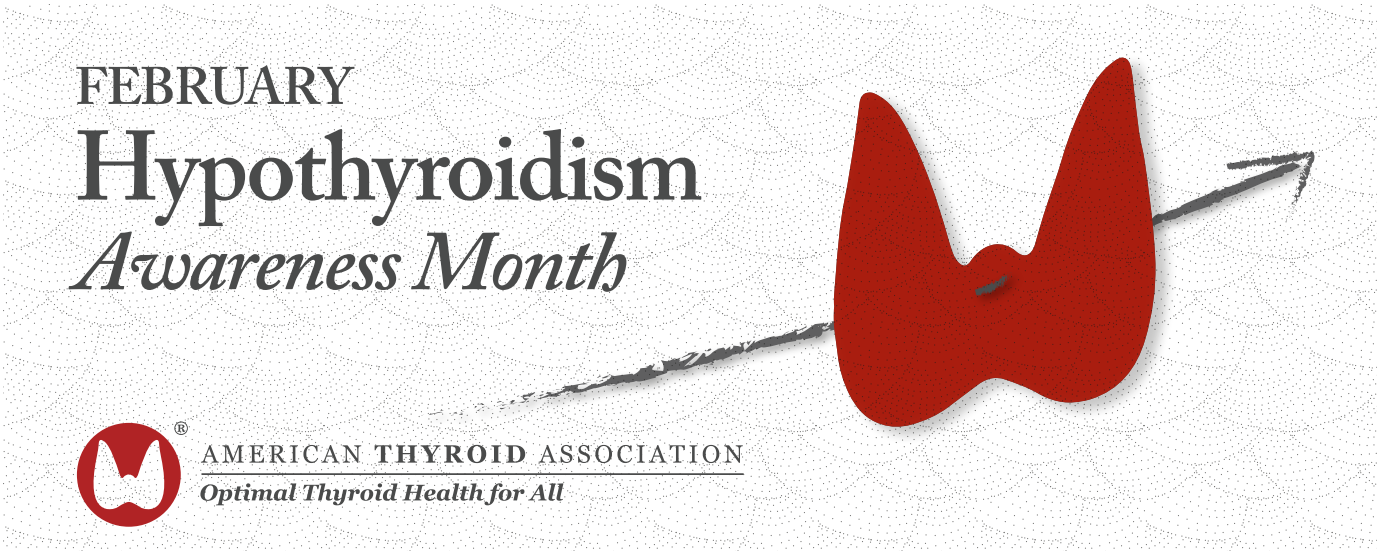
Hypothyroidism (Underactive): https://www.thyroid.org/hypothyroidism/

ABBREVIATIONS & DEFINITIONS

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 T4 level. All patients with overt hypothyroidism are usually treated with thyroid hormone pills.

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.



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HYPERTHYROIDISM

Cancer risks of patients with Graves' disease who received antithyroid drugs as initial treatment

BACKGROUND

Graves' disease is the most common type of hyperthyroidism. Treatment options include antithyroid drugs (ATDs) that control the hyperthyroidism and definitive treatments that destroy the thyroid (radioactive iodine therapy and surgery). The ATDs currently in use in the United States are methimazole and propylthiouracil. In recent years and for many reasons, ATDs have become the first line of treatment for patients with Graves' disease.

Because of the many effects of thyroid hormone on cells, including increasing cell growth, there is the possibility that thyroid hormones may help cancer cells to grow. Some studies have shown that patients with hyperthyroidism have an increase chance to develop cancer, such as breast, lung, prostate and thyroid cancer. A major problem with most of those studies is that they did not consider important personal risk factors for cancer, such as smoking and obesity. Other studies looking at the link between hyperthyroidism and cancer only looked at those patients who were treated with radioactive iodine therapy, since radiation is a risk factor for cancer.

The goal of this study is to shed some light about the risk of cancer in patients with Graves' disease who are treated with ATDs.

THE FULL ARTICLE TITLE

Lee JY, et al. Cancer risks of patients with Graves' disease who received antithyroid drugs as initial treatment: a nationwide population-based analysis. Thyroid 2024;34(10):1271-1279; doi: 10.1089/thy.2024.0178. PMID: 39228052.

SUMMARY OF THE STUDY

The authors looked at health information from a South Korea data base. They studied almost 30,000 patients with Graves' disease who were treated with ATDs from 2003 to 2022. They looked at how many of these patients were also diagnosed with several types of cancer. They compared the rate of cancer on these patients with that of a control group of similar age and risk factors for cancer but without Graves' disease. They found that patients with Graves' disease treated with ATDs have higher chances of biliary, pancreatic, prostate and ovarian cancer as compared to the control group. The risks for those cancers were small but significant. For thyroid cancer, there was a very significant increased risk in patients with Graves' disease, particularly within 1-2 years after starting ATDs.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Patients with Graves' disease treated with ATDs may have higher chances of cancer as compared to healthy controls. It is possible that this increase cancer risk is due to being hyperthyroid rather than to the specific type of treatment for Graves' disease, but this study cannot definitively answer that question. More studies are needed to clarify the relationship of hyperthyroidism, ATDs and cancer.

— Susana Ebner MD

ATA RESOURCES

Hyperthyroidism (Overactive): https://www.thyroid.org/hyperthyroidism/

Graves' Disease: https://www.thyroid.org/graves-disease/

HYPERTHYROIDISM, continued

ABBREVIATIONS & DEFINITIONS

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.

Graves' disease: the most common cause of hyperthyroidism in the United States. It is caused by antibodies that attack the thyroid and turn it on.

Methimazole: an antithyroid medication that blocks the thyroid from making thyroid hormone. Methimazole is used to treat hyperthyroidism, especially when it is caused by Graves' disease.

Propylthiouracil (PTU): an antithyroid medication that blocks the thyroid from making thyroid hormone. Propylthiouracil is used to treat hyperthyroidism, especially in women during pregnancy.

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THYROID NODULES

Are thyroid nodules in the isthmus different from nodules in the thyroid lobes?

BACKGROUND

Thyroid nodules are very common and found in up to 50% of individuals with imaging studies that include the neck. The concern about any thyroid nodule is whether they are a thyroid cancer. Fortunately, only 5-6% of thyroid nodules are cancers and the most common cancer by far is papillary thyroid cancer. The best way to determine if a nodule is a cancer is to perform a biopsy of nodules. The analysis of the cells in the biopsy sample (cytology) can make a diagnosis of benign (no cancer), at risk for cancer and cancer and help determine which patients should undergo thyroid surgery.

The thyroid is separated into right and left lobes connected by the isthmus. Some studies suggest that isthmus nodules, while less frequent than nodules within the thyroid lobes, may carry a higher risk of cancer than nodules in either thyroid lobe. There may be several reasons for this based on the anatomy of the thyroid. However, recently a study suggested potential differences in gene mutations found in thyroid cancer between the isthmus and the lobes. These gene mutations are identified using molecular marker analysis that is done on thyroid biopsies to determine the risk for a nodule being a cancer.

This study examines the cytologic and molecular marker differences between nodules and papillary thyroid cancer based on whether the cancer is in the isthmus or the thyroid lobes.

THE FULL ARTICLE TITLE

Jasim S, et al. Cytologic and molecular assessment of isthmus thyroid nodules and carcinomas. Thyroid. Epub 2024 Nov 11; doi: 10.1089/thy.2024.0254. PMID: 39527399.

SUMMARY OF THE STUDY

This study examined two groups of thyroid biopsy results obtained from a molecular marker company's thyroid nodule data base (Afirma™). The molecular marker group included 177,227 samples while the thyroid pathology group included 583 samples of classic papillary thyroid cancer and 194 of a follicular subtype of papillary thyroid cancer.

There were 8527 (4.8%) isthmus nodules identified in the AfirmaTM database, with the remainder from the thyroid lobes. Isthmus nodules were twice as likely to have cytology that was suspicious for cancer or cancer (8.2% vs. 4.3%) and had twice the frequency of the molecular marker *BRAF* V600E (21% vs. 10.6%), an increased frequency of the more aggressive ALK/*NTRK/RET* fusions (4.6% vs. 2.5%) and a decreased frequency of the less aggressive *NRAS* mutations (7.8% vs. 13.2%). Despite these differences, analysis of clinical outcomes from 454 samples did not show differences in the aggressiveness of the cancers on pathology analysis or spread of the cancer to the lymph nodes

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study shows that isthmus nodules were more likely to be cancer and to have increased rates of higher-risk molecular mutations compared to nodules in the lobes. Despite these changes, the cancers identified did not appear to be more aggressive in the isthmus vs the lobes. While interesting, more studies are needed to confirm these findings before changing recommendations for the management of isthmus thyroid nodules.

— Alan P. Farwell, MD

THYROID NODULES, continued

ATA RESOURCES

Thyroid Cancer (Papillary and Follicular): https://www.thyroid.org/thyroid-cancer/
Fine Needle Aspiration Biopsy of Thyroid Nodules: https://www.thyroid.org/fna-thyroid-nodules/
Thyroid Nodules: https://www.thyroid.org/thyroid-nodules/

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.

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.

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.

Mutation: A permanent change in one of the genes.

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, ALK/*NTRK*/*RET* fusions and RAS.

BRAF gene: this is gene that codes for a protein that is involved in a signaling pathway and is important for cell growth. Mutations in the *BRAF* gene in adults appear to cause cancer.

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THYROID CANCER

Effect of thyroidectomy on survival outcomes for medullary thyroid cancer with distant metastasis at diagnosis

BACKGROUND

Medullary thyroid cancer (MTC) is rare type of thyroid cancer that often runs in families. MTC is a more aggressive thyroid cancer and is more likely to spread outside the thyroid into the neck and to other parts of the body (distant metastasis) than the usual type of thyroid cancer (papillary thyroid cancer). Standard thyroid cancer treatment with radioactive iodine is not effective in MTC as the cancer cells to not take up iodine. Patients with MTC that has not spread outside of the neck undergo thyroidectomy to remove the thyroid and removal of the lymph nodes located close to the thyroid in the hope for a potential cure. However, there is limited data regarding the potential benefit of thyroidectomy on survival in patients with spread of the MTC outside of the neck when the cancer is diagnosed. This is seen in ~10% of patients with MTC and is associated with a poor prognosis (10-year survival rates of 40%).

This study used a population-based registry to 1) evaluate the prognosis based on the presence of what organs and how many contain MTC cells, 2) evaluate whether thyroidectomy is beneficial in these patients, and (3) identify the best candidates for thyroidectomy in patients with metastatic MTC at diagnosis.

THE FULL ARTICLE TITLE

Liu C-Q, et al. Survival outcome and optimal candidates of primary tumor resection for patients with metastatic medullary thyroid cancer. J Clin Endocrinol Metab 2024;109(11):2979-2985; doi: 10.1210/clinem/dgae214. PMID: 38570918.

SUMMARY OF THE STUDY

The study included 186 patients from the Surveillance, Epidemiology, and End Results (SEER) database diagnosed with MTC with distant metastasis between 2010 and 2020. The following information was extracted from the database for analysis: demographics (age, gender, race), cancer characteristics (grade, size, lymph node metastasis, distant metastasis), and type of treatment (thyroidectomy, neck dissection, radiation, and chemotherapy). The SEER database has data on five metastatic sites: lung, bone, liver, brain, and distant lymph nodes. The authors compared the survival outcomes of the thyroidectomy versus non- thyroidectomy group, including the overall survival (OS) and cancer-specific survival (CSS).

The average age at diagnosis of the study patients was 56 years, 56.5% being males. The percentage of patients with metastases was, as follows: bone 46%, liver 40%, lung 37%, distant lymph nodes 22%, and brain 5%. Overall, 58%, 30%, 10%, and 2% of the patients had 1,2,3, and 4 metastatic organs at diagnosis. Half of the patients had cancer spread to multiple organs. Slightly more than half of the patients (56.5%) underwent thyroidectomy. There was no difference between the thyroidectomy and non-thyroidectomy groups regarding age, gender, cancer size, metastatic organs and the number of organs involved. More patients in the non-thyroidectomy group had lung metastases, while more patients with lymph node involvement underwent thyroidectomy. More patients who underwent thyroidectomy also received chemotherapy.

Patients with single-organ metastasis had better OS and CSS as compared to those with 2 metastases, while there was no difference between patients with 3-5 organ-metastases. The presence of brain metastasis indicated a significantly poorer OS and CSS as compared to other metastatic organs.

Overall, the thyroidectomy group showed improved OS and CSS as compared to the non-thyroidectomy group. The thyroidectomy group had ~1/3rd of overall risk of death and cancer-specific death than the non-thyroidectomy group. Patients with lung, bone, liver, and distant lymph node but not brain metastases had a better

THYROID CANCER, continued

survival if they underwent thyroidectomy compared to the non- thyroidectomy group. Overall, chemotherapy and radiation did not improve survival.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Overall, this study suggests that thyroidectomy may improve prognosis in MTC patients who have distant metastasis at diagnosis. Thyroidectomy may improve survival in MTC patients with a one- or two-organ metastases in the bone, lung, liver or distant lymph nodes at diagnosis. The survival may not improve in patients with brain metastases, who have a worse prognosis overall. Therefore, thyroidectomy may confer survival benefits in selected patients with metastatic MTC at diagnosis. Additional research is needed to confirm these findings before implementing them in the current guidelines for metastatic MTC treatment.

— Alina Gavrila, MD, MMSC

ATA RESOURCES

Thyroid Cancer (Medullary): https://www.thyroid.org/medullary-thyroid-cancer/

ABBREVIATIONS & DEFINITIONS

Medullary thyroid cancer (MTC): a relatively rare type of thyroid cancer that often runs in families. Medullary cancer arises from the C-cells in the thyroid.

Cancer metastasis: spread of the cancer from the initial organ where it developed to other organs, such as the lungs and bone.

Lymph node: bean-shaped organ that plays a role in removing what the body considers harmful, such as infections and cancer cells.

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.

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 papillary 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).

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/

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info@checkyourneck.com

MCT8 – AHDS Foundation
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Thyca: Thyroid Cancer Survivors' Association, Inc.
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www.thyroidcancerpatientinfo.org
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