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Clinical Thyroidology® for the Public

AMERICAN THYROID ASSOCIATION
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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 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 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:

- What is normal thyroid function in children with Down syndrome?
- Do we need a "new normal" for thyroid function test ranges?
- What should you expect after radioactive iodine therapy for Graves' disease?
- Is there a role for levothyroxine therapy in active surveillance of papillary thyroid microcarcinomas?
- Do patients with medullary microcarcinomas have a better outcome?
- What are the prognostic factors for anaplastic thyroid cancer?

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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THYROID FUNCTION

What is normal thyroid function in children with Down syndrome?

BACKGROUND

Down syndrome (DS) is a genetic condition where a baby is born with an extra chromosome (trisomy 13). Chromosomes are like small parts of our body's instruction manual, they carry genetic information. The extra information in children born with DS makes them look and grow differently. Children with DS are also at increased risk of having thyroid problems. Mild underactive thyroid (hypothyroidism) with high TSH and normal thyroid (free T4 and free T3) hormone levels can be seen up to 60% of children with DS. However, it is difficult to understand the thyroid function in children with DS because we do not have clear rules for what's normal. We don't know for sure if the TSH level is higher because thyroid works abnormally or whether this may be a normal level for a child with DS. Because we don't have clear levels for what's normal in this situation, the doctors may be checking the thyroid function too often or giving treatments too early.

The researchers planned this study to figure out the normal ranges for TSH, free T3 and free T4 in children with DS at different ages. They wanted to see how much these levels change over time and whether TSH levels could predict if the child would develop hypothyroidism later on.

THE FULL ARTICLE TITLE

Cattoni A et al 2023 Thyroid function tests in children and adolescents with trisomy 21: Definition of syndrome-specific reference ranges. J Clin Endocrinol Metab. Epub 2023 Jun 3. PMID: 37279507.

SUMMARY OF THE STUDY

Researchers studied the health records from a single hospital in Italy. They looked at thyroid test results collected over 30 years from children with DS between the ages of 0-18. Patients who were born with hypothyroidism (congenital hypothyroidism), who had autoimmune thyroid disease, abnormal thyroid structure, who were on thyroid hormone or medications that can affect the thyroid and who were exposed to radiation treatment were excluded from the study. The children had blood tests every 3–6 months during the first year and yearly after that. A total of 3748 TSH, 986 free T3, and 2974 free T4 results were included in the final analysis. Information was compared to normal ranges for children and adolescents without DS. The best TSH level that could predict the possibility of hypothyroidism in the future was identified. There were 548 patients in the study, 53% were boys and 47% were girls. The first tests were done when they were 0.9 to 3.3 years old, and the last evaluations were done when they were 5.4 to 12.5 years old. The average follow up was about 6 years. Many children with DS (44%) did not have associated health problems.

The average TSH level for children with DS was 4.6 uU/ml which was significantly higher than children without DS. About 30% of TSH levels during the first year of life and 21% between ages 11-18 were higher than 97.5% of TSH levels from children without DS. Free T3 levels were significantly lower in children with DS aged 0-11. Free T4 levels were higher in children with DS ages 0-6 but they decreased as the children got older and became lower than unaffected children after the age of 11.

TSH levels changed the most between measurements. However, if a single TSH level was greater than 75% of the TSH levels in children with DS, it predicted development of hypothyroidism in 15% of children at the next test. On the other hand, if a single TSH level was lower than 75% of the TSH levels, it predicted the next measurement would not show hypothyroidism in 91% of children with DS. The authors developed a web based tool to rank the values of TSH of children with DS, to help doctors make treatment decisions (https://b4-uni25-5627493duksfy852qr80fewbsn3986g43jkgkzie8.shinyapps.io/Percentile-Thyroid-ChildrenTrisomy21).

THYROID FUNCTION, continued

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The researchers conclude that the tests for thyroid function are different between children with and without DS. We don't know the reasons for this difference, but the findings from this study will help doctors make decisions when they test the thyroid in children with DS. The researchers point out that there wasn't very much information for very young children (0-29 days old) and doctors should still use same ranges used for children without DS for those. Mild hypothyroidism is very common in children with DS and sometimes the levels go back to normal without treatment. But if they don't get better, it is a condition that needs to be treated lifelong. The findings from this study are most helpful in this situation. The study identified a TSH level that can tell if a child will have hypothyroidism at the next test. This information and the online comparison tool will help doctors make better decisions and improve the care of children with DS.

— Ebru Sulanc, MD

ATA RESOURCES

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

ABBREVIATIONS & DEFINITIONS

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

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 organisms cells and pass genetic traits to offspring.

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.

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THYROID FUNCTION TESTS

The "new normal" for thyroid function test ranges

BACKGROUND

The normal range of thyroid function tests is determined by measuring Free T4 and TSH levels in a population of healthy adults with no thyroid problems. Those results in the middle 95% are considered the normal range; the 2.5% above these levels and the 2.5% below these levels are considered abnormal. The diagnosis of hyperthyroidism is made with the Free T4 levels is in the 2.5% above the normal range and the TSH is in the 2.5% below the normal range. Conversely, the diagnosis of hypothyroidism is made with the Free T4 levels is in the 2.5% below the normal range and the TSH is in the 2.5% above the normal range.

Determining the normal ranges this way does not take into consideration the risk of non-thyroid disease associated with thyroid hormone levels. There has long been known about an association between thyroid levels and heart disease and death. For example, in 2015, Dr. Cappola's group from University of Pennsylvania found that higher free T4 values even with the "normal" range might increase the risk of death in elderly patients. By contrast, a 2014 international study conducted at Johns Hopkins showed that free T4 levels on the lower end of the normal range might also increase risk of death in younger patients (average age 40).

This study was done to see if the normal range of thyroid function tests needs to be adjusted to better reflect patients' risk of heart disease and death.

THE FULL ARTICLE TITLE

Xu Y et al Thyroid Studies Collaboration 2023 The optimal healthy ranges of thyroid function defined by the risk of cardiovascular disease and mortality: Systematic review and individual participant data meta-analysis. Lancet Diabetes Endocrinol 11:743–754. PMID: 37696273.

SUMMARY OF THE STUDY

Studies from the Thyroid Studies Collaboration (1950-2020) and various online databases (2010-2017) were evaluated to determine TSH and Free T4 hormone levels and risk of death and heart disease on patients older than 18. Pregnant patients and patients with known thyroid or cardiac disease were not included in the analysis. A total of 134,346 participants were followed for an average of 11.5 years. Half of the participants were female, and their average age was 59. Only 4.3% of the group were on thyroid medication. The normal range of Free T4 and TSH were divided into 10 equal groups (percentiles) for analysis.

Individuals with free T4 levels within the 20th to 40th percentile for normal free T4 value ranges had the least risk of death and heart disease. When the 80th to 100th percentile group for the normal free T4 value range was compared to this 20th to 40th percentile group, their risk of heart disease-related death was 57% higher, any type of death was 34% higher, heart disease was 22% higher, and both heart disease and any type of death was 20% higher. For female patients above the age of 70 who had a free T4 value above the 85th percentile of the normal range, their absolute risk of death and having heart disease was greater than 5%. For male patients above the age of 70 who had a free T4 value above the 75th percentile of the normal range, their absolute risk of death and having heart disease was greater than 5%.

Participants who fell within the 60th to 80th percentile for normal TSH value ranges had the least risk of death and heart disease. When the 0 to 20th percentile group for the normal TSH value range was compared to this 60th to 80th percentile group, their risk of heart disease-related death was 7% higher, any type of death was 9% higher, and both heart disease and any type of death was 7% higher.

THYROID FUNCTION TESTS, continued

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Especially in the elderly population, higher percentiles of the free T4 reference range of lower percentiles of the TSH reference range were associated with higher rates of deaths from any reason as well as specifically cardiac reasons. The 60th to 80th percentile for normal TSH value ranges and 20th to 40th percentile for normal free T4 value ranges were determined to be the healthy ranges with the least association with death and heart disease. This study suggests that the "normal" thyroid function reference ranges might not be suitable for the elderly and men. However, it is not known whether treating individuals in the upper and lower percentiles of the "normal" reference range would affect the disks of heart disease and/or death. However, this study raises the possibility that clinicians should consider changing the "normal" Free T4 and TSH reference ranges for patients as they age, to help decrease the risk of heart disease.

— Pinar Smith, MD

ATA RESOURCES

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

ABBREVIATIONS & DEFINITIONS

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

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.

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.

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

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HYPERTHYROIDISM

Long term outcomes of patients with Graves' Disease

BACKGROUND

Graves' disease is the most common cause of hyperthyroidism in the United States. Graves' disease is caused by an antibody that attacks and turns on the thyroid. As such, it is an autoimmune disorder. Graves' disease calso can be associated with other conditions like thyroid eye disease (TED), and occasionally, skin issues known as dermopathy. It is also linked to various other autoimmune disorders. When treating Graves' disease, the first priority is to normalize thyroid hormone levels using antithyroid drugs (ATD) such as methimazole or propylthiouracil. While these drugs are first-line treatment in many places, they come with some side effects, and ~50% of patients may experience a recurrence of Graves' disease after stopping the drug. Consequently, more definitive treatments like radioactive iodine therapy or thyroidectomy may be necessary.

Patients frequently ask their physician how long they will need to take anti-thyroid medications or whether they will have Graves' disease forever. Unfortunately, the long-term behavior of Graves' disease remains unknown. This study examines the clinical outcomes of individuals with Graves' disease more than 20 years after their initial diagnosis and treatment. The researchers explore the progression of the disease, the impact on quality of life, and factors that influence the likelihood of disease remission or relapse.

THE FULL ARTICLE TITLE

Meling Stokland AE et al Outcomes of patients with Graves disease 25 years after initiating antithyroid drug therapy. 2023 J Clin Endocrinol Metab. Epub 2023 Sep 25. PMID: 37747433.

SUMMARY OF THE STUDY

The researchers examined a group from Norway who had participated in a two-year trial in the late 1990s, comparing different medical treatments for Graves' disease. In 2021, more than two decades after their initial diagnosis, these patients were contacted again to assess their long-term outcomes. Surprisingly, the researchers successfully re-enrolled 155 of the 195 patients still alive from the original study. The records of 23 patients who had passed away during the intervening years and 4 patients who could not be reached were also included, resulting in 182 cases for analysis. Participants were asked to complete questionnaires about their medical history and quality of life. Where available, blood samples in storage from the original study were re-examined for thyroid hormone levels, TSH-receptor antibodies, as well as other inflammatory markers like gastric parietal cell antibodies (linked to autoimmune gastritis and pernicious anemia) and transglutaminase antibodies (associated with celiac disease).

Following the initial 2-year study, 82 patients (45%) had a relapse of their Graves' disease. 20 years later only 11% of those that had relapsed were able to maintain normal thyroid function. The remaining 89% needed definitive treatment, either with radioactive iodine therapy or thyroid surgery. Some still used ATDs, while others had developed hypothyroidism. Among the 78 patients (43%) who achieved remission after the initial study, 62% had normal thyroid homone levels in the long term follow-up, with 14% having received definitive treatment. Hypothyroidism was more prevalent in this group (21%), and those with hypothyroidism experienced a reduced quality of life. Among the 22 patients (12%) who did not complete the initial study, only 18% had normal thyroid levels in the follow-up. Overall, only 34% of all patients were in remission at the 20-year follow-up.

The levels of inflammatory markers in the blood did not offer much useful information about the overall course of the disease. In the first study, 43% had TED. Over the next two decades, an additional 10 patients (7%) developed TED, with 7 of these cases occurring after radioactive iodine treatment. By the end of the follow-up, 47% of all patients had developed another autoimmune disease, including vitamin B12 deficiency (26%) and rheumatoid arthritis (5%).

HYPERTHYROIDISM, continued

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This research shows that Graves' disease is a challenging condition with unpredictable long-term results. Many patients go through a persistent or recurring pattern and need either decisive treatment or prolonged use of antithyroid medications. Additionally, many develop other autoimmune disorders or thyroid eye disease. Given the relatively frequent rate of disease reccurrence, even in those who initially achieved remission, long term monitoring of thyroid function is necessary.

— Phillip Segal, MD

ATA RESOURCES

Goiter: https://www.thyroid.org/goiter/

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

Thyroid Eye Disease: https://www.thyroid.org/thyroid-eye-disease/

ABBREVIATIONS & DEFINITIONS

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.

Thyroid eye disease (TED): also known as Graves ophthalmopathy. TED is most often seen in patients with Graves' disease but also can be seen with Hashimoto's thyroiditis. TED includes inflammation of the eyes, eye muscles and the surrounding tissues. Symptoms include dry eyes, red eyes, bulging of the eyes and double vision.

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*).

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THYROID CANCER

Is there a role for levothyroxine therapy in active surveillance of papillary thyroid microcarcinomas?

BACKGROUND

Papillary thyroid cancer is common and overall has an excellent prognosis. This is especially true of small papillary thyroid cancers (< 1 cm), called papillary thyroid microcarcinomas. These small cancers can often be monitored without the need for surgery or other treatment. This is called active surveillance. We know that in some patients, the small cancers will grow and surgery may eventually be needed.

One question is whether there is a role of levothyroxine therapy in the management of papillary thyroid microcarcinomas undergoing active surveillance. It is clear that levothyroxine therapy to keep TSH levels in the low normal to low range in patients that have undergone surgery for papillary thyroid cancer improves prognosis. Also, previous studies have suggested that a low normal TSH level may be associated with less cancer growth in younger patients with papillary thyroid microcarcinomas. However, to date, there is no study examining the use of levothyroxine therapy in papillary thyroid microcarcinomas undergoing active surveillance.

The current investigators looked back at their extensive experience in patients with papillary thyroid microcarcinomas undergoing active surveillance to evaluate the effect of levothyroxine therapy to decrease TSH levels to see how this influenced cancer growth.

THE FULL ARTICLE TITLE

Yamamoto M et al 2023 Active surveillance outcomes of patients with low-risk papillary thyroid microcarcinoma according to levothyroxine treatment status. Thyroid 33:1182–1189. PMID: 37310904.

SUMMARY OF THE STUDY

The authors identified 2,509 patients with papillary thyroid microcarcinomas undergoing active surveillance who were ≥20 years of age and had undergone at least four ultrasound neck surveillance studies. Patients were first divided into two groups. *Group I* – not on thyroid hormone at the time of diagnosis and *Group II* – on thyroid hormone at the time of diagnosis and remained on it. Group I was further subdivided into *IA* – those who remained off thyroid hormone and *IB* – those who were started on thyroid hormone during active surveillance. Disease progression was defined as growth of the papillary thyroid microcarcinoma of at least 3 mm compared to baseline or the development of spread to the lymph nodes. Group II (322 patients) were younger, had larger cancers and had a higher baseline TSH than Group I (2,187 patients). Group II had a lower rate of surgery during follow up (4% vs 8.3%).

There were 252 patients who began levothyroxine treatment during observation (Group IA) while 1,935 patients remained off levothyroxine (Group IB). Group IA patients had significantly larger cancers, faster cancer growth and higher TSH levels. The percentage of patients in Group IA with cancer growth decreased from 26.8% to 12.5% after starting levothyroxine and cancer regression was seen in 59.8% vs 41.7% before starting levothyroxine. TSH levels by themselves did not predict disease progression or development of spread to the lymph nodes.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The authors concluded that levothyroxine treatment of patients with papillary thyroid microcarcinomas decreased the rate of disease progression and may be useful in following patients with active surveillance. However, if we think that the mechanism of levothyroxine slowing disease progression is to decrease TSH, we would expect to see lower TSH levels in patients with slower growth. This was not identified. There is no information on TSH goals to guide treatment. While this is an interesting study, further studies will be needed to determine whether the routine use of levothyroxine is warranted in patients with papillary thyroid microcarcinomas undergoing active surveillance.

— Marjorie Safran, MD

THYROID CANCER, continued

ATA RESOURCES

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

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

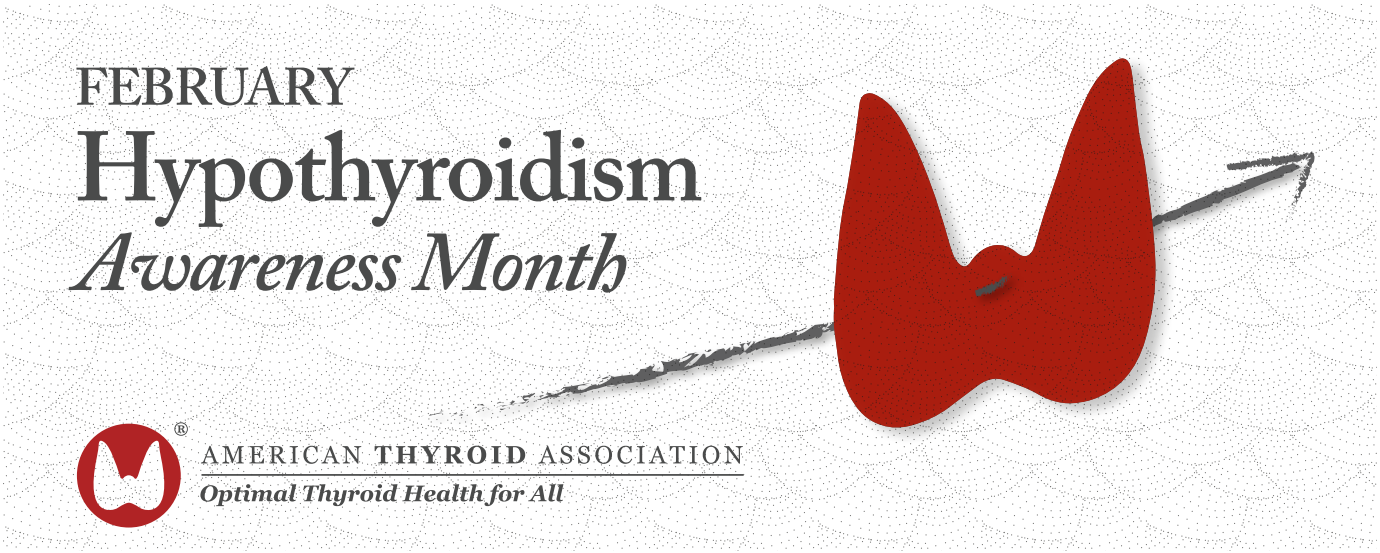
ABBREVIATIONS & DEFINITIONS

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

Active Surveillance: following a known thyroid cancer by ultrasound monitoring rather than surgery

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.

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



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THYROID CANCER

Small medullary thyroid cancer: predictive factors and outcomes

BACKGROUND

Medullary thyroid cancer (MTC) is a relatively rare form of thyroid cancer. MTC arises from Parafollicular or C cells in the thyroid. These cells produce the hormone calcitonin and the cancer marker carcinoembryonic antigen (CEA). This is contrast to the far more common papillary and follicular cancers that arise from the thyroid follicular cells that make thyroid hormone. Calcitonin and CEA are used to follow treatment of MTC and persistent levels indicate persistent cancer cells. Further, the rate of increase of calcitonin, also known as doubling time, is helpful to determine prognosis using the International Medullary Thyroid Carcinoma Grading System. This system uses the characteristics of the cancer cells as well as the Ki67 protein, which is associated with cell growth.

The goal of this study was to determine the factors that help predict outcomes in small medullary thyroid cancers, also known as medullary microcarcinomas (<1 cm), as there studies that suggest they may have very different outcomes than larger cancers.

THE FULL ARTICLE TITLE

Kesby N et al. Natural history and predictive factors of outcome in medullary thyroid microcarcinoma. J Clin Endocrinol Metab 108:2626–2634. PMID: 36964913

SUMMARY OF THE STUDY

This study included patients with an MTC ≤1 cm treated surgically between 1995 and 2022 who were in a endocrine surgery database in Australia. Patients with hereditary diseases were excluded. Details of their surgery, the surgical specimen, follow-up clinical information, cancer markers, and imaging were collected. Prognostic factors included in this study were primary cancer size, cancer grade, spread to the lymph nodes and postoperative calcitonin levels. There were 42 patients for inclusion in the final analysis. The average age was 60 years.

Patients who had MTC <0.5 mm were less likely to have spread to the lymph nodes or to be high grade, compared to those with MTC 0.5 to 1 cm. Patients with high-grade MTC were more likely to have larger cancers, higher serum calcitonin levels, and spread to the lymph nodes than were those with low-grade cancers. The rate of recurrence for cancers <0.5 cm was not significantly different from that for cancers 0.5 to 1 cm. All low-grade cancers showed no risk of recurrence within 5 years, where as in high grade cancers, recurrences occurred within 5 years in 50% of cases. The prognosis was also worse for those with high grade MTC than for those with low-grade MTC. Recurrence was more common in patients with spread to the lymph nodes and survival was also worse than those with no spread to the lymph nodes. Increased postoperative calcitonin levels were associated with more cancer recurrence. The extent of thyroid surgery did not significantly affect recurrence risks.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Patients with small, low-grade MTC have very good outcomes, particularly if they achieve a normal post-operative calcitonin level. This study indicates that these patients will likely not need any further treatment and suggests that extensive follow-up after diagnosis may be unnecessary. It is very important for patients to understand the particular characteristics of their thyroid cancer that determine their prognosis so they can be engaged with their care plan and sensibly proceed with their decision-making. Thyroid cancers are NOT all created equal.

— Maria Brito, MD, ECNU

THYROID CANCER, continued

ATA RESOURCES

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

ABBREVIATIONS & DEFINITIONS

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

Thyroidectomy: surgery to remove the 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*.

Calcitonin: a hormone that is secreted by cells in the thyroid (C-cells) that has a minor effect on blood calcium levels. Calcitonin levels are increased in patients with medullary thyroid cancer.

Calcitonin doubling time (CDT): the rate at which the calcitonin level doubles, usually reported in years. The CDT is related to prognosis in medullary thyroid cancer.

Carcinoembryonic antigen (CEA): a protein that can be made by certain cancers such as colorectal cancer and medullary thyroid cancer. CEA may be measured with a blood test.

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THYROID CANCER

Prognostic factors for anaplastic thyroid cancer

BACKGROUND

The most common types of thyroid cancer (papillary and follicular) have an excellent prognosis, with response and/or cure rates reaching 95%. This is due to, in part, excellent treatment options, including surgery and radioactive iodine therapy. In contrast, anaplastic thyroid carcinoma (ATC) is a very rare and aggressive type of thyroid cancer with a poor prognosis. This is due predominantly to the fact that we do not have good, effective treatment options for ATC. Indeed, the average survival of a patient with ATC is 9.5 months, which makes it one of the most deadly cancers.

Prior studies have reported several factors that can affect the prognosis of ATC patients, including the disease stage, pathological type, type of treatment and the patients' performance status. For example, ATC patients who received combination therapy (surgery followed by a combination of chemotherapy and radiotherapy), targeted therapy or immunotherapy had an improved survival. The goal of this study was to evaluate prognostic factors in a large group of patients with ATC from a care center network in France.

THE FULL ARTICLE TITLE

Jannin, A et al ENDOCAN-TUTHYREF Network 2023 Factors associated with survival in anaplastic thyroid carcinoma: A multi-center study from the ENDOCAN-TUTHYREF Network. Thyroid 33:1190–1200. PMID: 37855745

SUMMARY OF THE STUDY

This multicenter study included 360 ATC patients who received treatment at a network of 19 care centers in France between 2010 and 2020. The average age was 72 years with 61% of patients being women. Most patients (60%) had mild symptoms at diagnosis, with European Cooperative Oncology Group (ECOG) scores of 0-1. Overall, 41% of patients had neck compressive symptoms at diagnosis, including hoarseness, swallowing and breathing difficulty. The average time from the onset of compressive symptoms to the cancer diagnosis was 56 days, only 28% of patients being diagnosed within 30 days. At diagnosis, the cancer stage was advanced in all patient: stage IVa in 15 (4%), IVb in 102 (28%), IVc in 231 (64%), and unknown in 12 (4%) patients. Only 54% of patients had molecular testing, the most frequent mutation found being *TP53* (64% of patients). A total of 62% of patient had ATC consisting of only ATC cells, 27% had ATC including a combination of ATC and other thyroid cancer cells and 5% had transformed ATC, when ATC developed in patients with a prior diagnosis of thyroid cancer. A total of 18% of patients received only supportive care. Among the treated patients, 71% received chemotherapy and 59% received radiation therapy. Only 19% underwent thyroidectomy. Second-line treatments, including targeted therapy and immunotherapy were administered to 32% of patients.

Overall survival (OS) was defined as the time from the date of the ATC diagnosis to death from any cause. The average OS was 6.8 months, with disease progression being the main cause of death (68% of patients). The average OS rate at 6 months, 1 year, and 2 years was 53%, 33% and 20%. Based on the cancer stage, the average OS was not achieved in patients with stage IVa disease (more than 50% of patients were still alive at the end of the study) and was 11.4 months in those with stage IVb and 4.6 months in those with stage IVc disease. Based on the cancer type, patients with the combination of ATC and another thyroid cancer had a longer OS (14.7 months) compared to those with ATC developing in patients with an existing thyroid cancer (6 months) and with ATC alone (3.7 months). After an average follow-up of 52 months, 15 patients (4%) with an average age of 59 years were disease free. Of these, 33.3% had stage IVa and 67% had stage IVb disease. Overall, 7 (46%) patients had ATC alone and 8 (53.3%) had ATC in combination with other thyroid cancer. All but 1 patient (93%) underwent surgery, all underwent radiotherapy, and 80% underwent chemotherapy. Multimodal treatment improved survival, while age and gender did not affect survival.

THYROID CANCER, continued

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Although ATC is very aggressive with an advanced stage at initial diagnosis and overall poor prognosis, there is heterogeneity in prognosis among patients based on several factors, including the cancer stage and type, treatment modality, and the patient's performance status. Patients with lower performance status, advanced stage, and "pure" compared to "mixed" ATC had lower survival rates. The prognosis of ATC patients could be improved by reducing the time to diagnosis and using a multimodal treatment with early molecular testing to guide a more personalized treatment approach.

— Alina Gavrila, MD, MMSC

ATA RESOURCES

Anaplastic Thyroid Cancer: https://www.thyroid.org/anaplastic-thyroid-cancer/

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

ABBREVIATIONS & DEFINITIONS

Molecular markers: these are different types of molecules, such as DNA (genes), RNA, proteins present in the cancer cells that can provide information regarding the cancer, such as prognosis and prediction of the cancer response to a certain treatment.

Cancer-associated genes: these are genes that are normally expressed in cells. Cancer cells frequently have alterations (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. The presence of a mutation in the TP53 gene indicates a more aggressive type of thyroid cancer.

Targeted therapy: cancer treatment targeting the gene changes (mutations) that transform normal cells into cancer without affecting normal cells.

Immunotherapy: treatment that boosts the patient's own immune system to fight and destroy cancer cells.

European Cooperative Oncology Group (ECOG) Performance Status Scale: standard criteria to measure how cancer impacts a patient's level of functioning regarding the ability to care for themself, to perform daily activities and physical ability.

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

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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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