Volume 13 | Issue 7 | July 2020

Clinical Thyroidology® for the Public

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

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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 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.

The Covid-19 pandemic has caused an unprecedented upheaval in our daily lives and presented extremely difficult challenges to our healthcare system. There is a lot of information circulating around. 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/)

July is Graves' Disease Awareness Month.

In this issue, the studies ask the following questions:

- What is the best treatment for Graves' disease?
- Does changing brands of levothyroxine alter thyroid function tests?
- Does the heart beat stronger with thyroid hormone treatment in older patients with mild hypothyroidism?
- Does amiodarone therapy increase the risk of developing thyroid storm?
- What are patient preferences for surgery in low risk thyroid cancer?
- Does extension of thyroid cancer outside of the thyroid impact response to therapy?

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

— Alan P. Farwell, MD, FACE

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GRAVES' DISEASE

Most patients with Graves' disease treated with antithyroid drugs eventually require additional therapies

BACKGROUND

Graves' disease is the most common cause of hyperthyroidism (overactive thyroid). It usually affects people between 30-60 years of age and is much more common in women than men. Patients with Graves' disease, often have enlarged thyroids (goiter) and bulging eyes (exophthalmos). There are three main options to treat Graves' disease: antithyroid drugs (ATDs), radioactive iodine therapy and surgery.

The most common ATDs in use are methimazole and PTU. ATDs work by decreasing the production of thyroid hormones. When ATDs are stopped, about half of the patients' thyroid levels remain normal and are then considered to be on remission. Many eventually return to their hyperthyroid state (relapse) and require further treatment. Some patients become hypothyroid (underactive thyroid), known as "burnt-out Graves', and require lifelong thyroid replacement therapy.

Surgery and radioactive iodine almost always resolve the hyperthyroidism. With surgery, all or nearly all thyroid tissue is removed and thyroid levels go down immediately. With radioactive iodine therapy, permanent damage to the thyroid cells occurs more gradually over several months. After both treatments, the majority of patients become hypothyroid and therefore will require lifelong thyroid replacement therapy.

This study examined the long-term effects of the three treatments (ATDs, radioactive iodine therapy and surgery) in Swedish patients diagnosed with Graves' disease.

THE FULL ARTICLE TITLE

Sjölin G et al 2019 The long-term compared outcomes of treatment for Graves' hyperthyroidism. Thyroid **29:**1545–1557

SUMMARY OF THE STUDY

This study examined the long-term effects of the three treatments (ATDs, radioactive iodine therapy and surgery) in Swedish patients diagnosed with Graves' disease between 2003 and 2005. The study included nearly 1200 patients who were asked questions about their symptoms and satisfaction with their treatment choice. In addition, and the medical records, with follow up for up to ten years, were reviewed. The patients' average age was 47 years and 82% were women.

The majority (65%) of the patients were initially treated with ATDs, while 27% were initially treated with radioactive iodine therapy and 4% were initially treated with surgery. Of the patients initially treated with ATDs, 23% did not complete this treatment and subsequently received radioactive iodine therapy or surgery. Of the remaining 77% who did complete the ATD treatment, approximately 59% remained on remission after 6-10 years and 41% relapsed. Of the patients who relapsed, 49% had a second course of ATDs and of those, 29% achieved remission. Of all patients treated with ATDs who remained in remission, 23% eventually became hypothyroid and required hormone replacement therapy. The hyperthyroidism was resolved in 82% of the patients who received radioactive iodine therapy and 96% of the patients who had surgery.

Unfortunately, around 25% of all patients reported that they did not feel fully recovered after their treatment, mostly due to persistent fatigue and eye symptoms. The proportion of patients who felt fully recovered was similar between the three treatment groups.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The authors conclude that patients who were first treated with ATDs for Graves' disease have around a 50% chance of remission with the medication alone. However, only 40% of these patients will end up with normal thyroid function; the rest of the patients will develop hypothyroidism and require thyroid hormone replacement. Surgery and radioactive iodine therapy are definitive treatments for the majority of patients, but almost all of these

GRAVES' DISEASE, continued

patients became permanently hypothyroid and require thyroid hormone replacement for life. Regardless of the treatment chosen, some patients have persistent symptoms of fatigue, particularly those who became hypothyroid, even though they were treated with thyroid hormone.

This study informs patients with Graves's disease about the chances of resolution of the hyperthyroidism associated with different treatment options.

— Susana Ebner MD

ATA THYROID BROCHURE LINKS

Graves' Disease: https://www.thyroid.org/graves-disease/
Radioactive Iodine Therapy: https://www.thyroid.org/radioactive-iodine/
Thyroid Surgery: https://www.thyroid.org/thyroid-surgery/

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.

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 thyroid cancer and with an overactive thyroid.

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HYPOTHYROIDISM

Switching levothyroxine brands frequently results in abnormal thyroid function tests

BACKGROUND

Hypothyroidism is a condition in which the thyroid gland is underactive and does not produce enough thyroid hormone. Hypothyroidism can be treated with levothyroxine, the main hormone secreted by the thyroid gland. There are different manufacturers that make levothyroxine. When levothyroxine is branded, for example Synthroid™, Levoxyl™ and Tirosint™ in the United States, Thyrax in Europe, every prescription filled is for that same brand. When levothyroxine is generic (non-branded), prescriptions may be filled with levothyroxine from different manufacturers. Because potency of levothyroxine between manufacturers is variable, there is a possibility that changing brands may affect thyroid function tests. However, there is limited data on the impact of changing brands on thyroid function.

In 2016, the manufacturer of the levothyroxine brand Thyrax experienced an interruption in production that required approximately 350,000 Dutch patients to change their levothyroxine supplier. The current study examined the effect of the shortage of the levothyroxine brand Thyrax in the Netherlands and subsequent switch to a different brand on thyroid stimulating hormone (TSH) levels.

THE FULL ARTICLE TITLE

Flinterman LE et al 2020 Impact of a forced dose-equivalent levothyroxine brand switch on plasma TSH: A cohort study. Thyroid. Epub 2020 Mar 18. PMID: 32188356

SUMMARY OF THE STUDY

Patient information in 2 databases representing more than 25% of the Dutch population were used for this study. Patients taking at least 25 mcg Thyrax daily for at least one year were included. Of these, 85% were women, and the average age was ~60 years. Two groups were included: a group of patients who switched from Thyrax to another brand and a group of patients who continued taking Thyrax. TSH levels were obtained at set intervals for patients in the same group receiving the same dose of levothyroxine. In the group of patients on <100 mcg levothyroxine who continued taking Thyrax daily and had a previously normal TSH, 19% had an abnormal TSH level in follow-up. In the group of patients on <100 mcg levothyroxine who were switched and had a previously normal TSH, 24% of the group had an abnormal TSH level in follow-up. For patients on >100 mcg of levothyroxine, there was a greater difference: 24% of the group taking Thyrax and 63% of those who switched brands had abnormal TSH levels. A low/suppressed TSH was more likely to occur in patients who switched brands than those who continued on Thyrax with no brand switch.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Changing to the same dose of a different brand levothyroxine was associated with abnormal TSH levels in more patients compared to those who continued on the brand Thyrax. These results suggest that switching levothyroxine brands may require a dose change in a larger number of patients.

— Priya Mahajan, MD

ATA THYROID BROCHURE LINKS

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

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

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

HYPOTHYROIDISM, continued

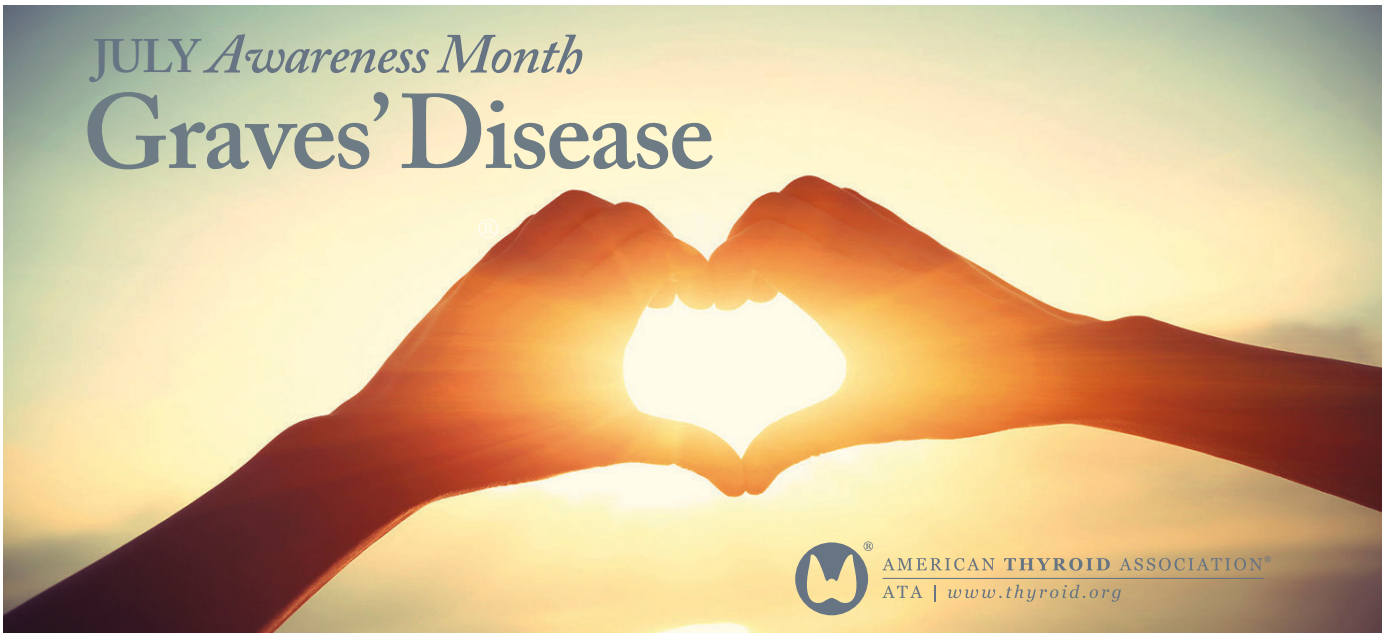
ABBREVIATIONS & DEFINITIONS

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

Levothyroxine (T4): 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.

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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HYPOTHYROIDISM

Does the heart beat stronger with thyroid hormone treatment in older patients with mild hypothyroidism?

BACKGROUND

Hypothyroidism is a condition where the thyroid gland cannot make enough thyroid hormone. Since every system in our bodies uses thyroid hormone to function, having an underactive thyroid can create a large variety of symptoms. Overt hypothyroidism is diagnosed when the TSH is elevated and free T_4 is low while mild/subclinical hypothyroidism is diagnosed with a high TSH and a normal free T_4 level. TSH levels may naturally increase with age and a mildly elevated level may not cause any ill effect in older adults. Researchers have been interested in the effect of thyroid hormone on heart muscle for a long time. Some studies showed that patients over 65 years of age with untreated subclinical hypothyroidism who had TSH levels over 10 mIU/L had greater risk of heart failure. There is information from a few small studies that suggest treatment with thyroid hormone my strengthen the heart muscle, but this may be risky in older patients.

The TRUST trial (Multi-Modal Effects of Thyroid Replacement for Untreated Older Adults with Subclinical Hypothyroidism) was designed as the largest multicenter randomized controlled trial comparing thyroid hormone treatment with no treatment in patients over 65 with subclinical hypothyroidism. This method is the best way to study a research question. This is a study that is a smaller part of the TRUST trial and the aim of this study was to show the effect of thyroid hormone treatment on heart function in patients over 65 years with subclinical hypothyroidism.

THE FULL ARTICLE TITLE

Gencer B et al 2020 The impact of levothyroxine on cardiac function in older adults with mild subclinical hypothyroidism: A randomized clinical trial. Am J Med. Epub 2020 Mar 11. PMID: 32171774.

SUMMARY OF THE STUDY

The study was done in Switzerland. A total of 185 patients who were over 65 years old with an elevated TSH level and normal free T_4 levels were studied. Patients were given either levothyroxine (thyroid hormone) or placebo (a pill without a medication). A total of 96 patients with TSH levels above 4.6 mIU/L received levothyroxine; only 4 of these patients had a TSH level above 10 mIU/L. A total of 89 patients were in the placebo group. The levothyroxine starting dose was 25 mcg or 50 mcg. The dose was increased slowly until the TSH was normal. The researchers evaluated the heart muscle function, strength, and stiffness using echocardiography at the end of the study.

After 18 months of treatment TSH levels decreased into normal range with levothyroxine and remained elevated around 5.29 mIU/L with placebo. There was no difference in ejection fraction (how well the heart pumps blood with each beat) or in the measures of stiffness (how well the heart relaxes between beats) between the 2 groups.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Thyroid hormone treatment did not have any effect on heart function in patients with mild/subclinical hypothyroidism who were over 65 years old. This is the largest study assessing the effects of thyroid hormone treatment on heart function in this age group. Based on the results of this study, treatment of patients over 65 years old with very mild TSH elevation, especially if less than 10 mIU/L, can be avoided. This approach would mean one less medication to take and it would protect these patients from the risks of taking thyroid hormone.

— Ebru Sulanc, MD

HYPOTHYROIDISM, continued

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.

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.

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

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

Levothyroxine (T4): 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.

Heart failure: A condition when the heart can't pump enough blood to meet the body's needs or cannot pump with enough force or cannot fill enough with blood.

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HYPERTHYROIDISM

Amiodarone was the most common cause of thyroid storm in French intensive care units

BACKGROUND

Thyroid hormone has a direct effect on heart function. Hyperthyroidism usually causes an increase in heart rate and occasionally causes the heart muscle to weaken. Hyperthyroidism is especially difficult in patients with underlying heart problems. Amiodarone - a medication used for irregular heart rhythms – contains a lot of iodine that can affect thyroid function. In Europe, amiodarone can often cause the development of hyperthyroidism (amiodarone-induced thyrotoxicosis), while in the United States, hypothyroidism is more common.

Thyroid storm, while rare, is the extreme result of an overactive thyroid and has a high risk of death even when recognized and treated appropriately. In this study, authors looked to evaluate the presentation, management and death rate of patients with thyroid storm causing admission to French intensive care units (ICUs).

THE FULL ARTICLE TITLE

Bourcier S et al 2019. Thyroid storm in the ICU: a retrospective multicenter study. Crit Care Med **48:**83–90. PMID: 31714398.

SUMMARY OF THE STUDY

The investigators reviewed all patients admitted to 31 intensive care units in France from 2000-2017 who were diagnosed with any type of hyperthyroidism. After reviewing the records, they selected those patients > 18 yr who had hyperthyroidism and at least one organ failure felt to be secondary to the hyperthyroid state. This comprised their group of patients with thyroid storm – which is diagnosed as severe hyperthyroidism resulting in central nervous system (CNS) abnormalities, temperature elevation, rapid pulse, congestive heart failure (CHF) and stomach problems. Among 270 patients admitted to the ICU's with elevated thyroid hormone levels, they identified 92 as having thyroid storm.

Amiodarone-induced thyrotoxicosis was the most common cause of thyroid storm (33%), followed by Graves' disease (26%). Autoimmune thyroiditis, toxic multinodular goiter, and toxic solitary thyroid adenoma were much less frequent causes (10%, 9%, and 6% respectively). In 16% of patients, a cause was not stated. Other than the use of amiodarone, other inciting factors were discontinuation of antithyroid drugs (14%), infection (10%), excess thyroid hormone medication (4%), pregnancy (2%), iodinated contrast administration (2%), and nonthyroid surgery in one patient. Approximately 1/3rd of patients had no identifiable precipitating factor.

At the time of admission to the ICU, clinical manifestations of CHF were present in 72% of the patients. CNS problems was noted in 53% of patients and stomach or liver problems occurred in 48%. About half of the patients had fever. Common treatments included antithyroid drugs (80%), beta-blockers (71%) and steroids (~50%) with other treatments used less commonly. Mortality in the ICU and 6 mo later was 17% and 22%, respectively.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Using fairly stringent criteria to diagnose thyroid storm and looking only at patients who required ICU admission, the risk of death remains quite high. While Graves' disease is the most common cause of hyperthyroidism overall, amiodarone was the most frequent cause of thyroid storm in this study. In patients who develop thyroid storm while on amiodarone, the risk of death is particularly high, likely due to the difficulty in treating amiodarone-induced thyrotoxicosis along with the patient's underlying cardiac issues. It is important that thyroid function be carefully followed in patients on amiodarone.

— Marjorie Safran, MD

HYPERTHYROIDISM, continued

ATA THYROID BROCHURE LINKS

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

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.

Amiodarone: an iodine-rich drug that is commonly used for the treatment of irregular heart rhythms. Amiodarone can cause thyroid problems, including both hypothyroidism and hyperthyroidism.

Amiodarone-induced Thyrotoxicosis: elevated thyroid hormone levels that can occur as a result of excessive iodine from amiodarone resulting in increased thyroid hormone production and secretion or to destruction of thyroid cells with release of thyroid hormone into the blood

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THYROID CANCER

Patient preferences for surgery for low-risk thyroid cancer

BACKGROUND

Thyroid nodules and thyroid cancer are common health problems. The routine use of ultrasound has led to finding thyroid nodules in 19-68% of randomly selected individuals, with higher frequency in women and in older adults. Thyroid cancer is found in 7-15% of thyroid nodules, depending on the patient's age, sex, family history and other factors. In the United States, the incidence of thyroid cancer has been reported to have increased significantly in the last 30 years and a study has predicted that thyroid cancer will become the 4th leading cancer diagnosis by 2030 in the United States.

The initial treatment for thyroid cancer is, almost always, surgery. The advice given to patients regarding the type of surgery needed has also changed in the last 10 years, when a total thyroidectomy was the recommended initial procedure for all patients with a thyroid cancer that was larger than 1 cm. More recently, however, several studies have shown that there is no decrease in expected survival for patients who elect to have a lobectomy (removal of the lobe containing the nodule/cancer) instead as their initial surgery. Also this surgery is associated with fewer complications such as low calcium levels, hoarseness or the need for tracheostomy because of nerve damage. However, in certain cases, after the initial surgery, the patient may need a second surgery to remove the remaining lobe if the final pathology evaluation shows a more aggressive cancer.

Although the most recent guidelines of the American Thyroid Association encourage doctors to take into account patient preferences when advising treatment, very few studies have been carried out to investigate what those preferences are. In the case of thyroid cancer, the death rate is very low (<5%), but many patients may overestimate the risk of death due to thyroid cancer, which may drive patient's willingness to undergo more aggressive treatments.

This study was done to assess patients views on the relative importance of the risks and benefits associated with the different extent of thyroid surgery. The goals were to determine which risks patients would accept before surgery when evaluating the benefits and harms of thyroid surgery (lobectomy vs thyroidectomy) and to quantify which trade offs among treatment-related side effects and clinical benefits associated with the two different surgical procedures would be more acceptable.

THE FULL ARTICLE TITLE

Ahmadi S et al 2020 Patient preferences around extent of surgery in low-risk thyroid cancer: A discrete-choice experiment. Thyroid. Epub 2020 Mar 6. PMID: 32143553.

SUMMARY OF THE STUDY

Adult patients who were diagnosed with thyroid nodules requiring surgery were prospectively enrolled over a two year period (2017-2018). People who were older than 18 years of age, who had a diagnosis of thyroid cancer less than 4 cm without evidence of extension outside of the thyroid, or who had a thyroid nodule that needed surgery because of symptoms or because of biopsy reports that had indeterminate reports and an abnormal ultrasound appearance were eligible to participate in the study. For the purpose of this study, participants were asked to imagine that they had just been diagnosed with thyroid cancer.

A total of 150 adult patients were enrolled. The majority (82%) were females with an average age of 58 years. Of these patients, 126 patients were scheduled to have surgery for a benign or indeterminate thyroid nodule, and the remaining 24 patients were having surgery to manage low risk thyroid cancer.

The study had two phases. In the first phase, the investigators gave the survey to 8 patients to make sure that the format and content were understood well and based on those results, corrections to the questions were made. In the second phase, the participants were provided with information about the surgeries, including descriptions of a lobectomy and a total thyroidectomy. They were

THYROID CANCER, continued

asked to select between different treatment-related pairs of hypothetical management options with estimated varying levels of risk. Treatment associated complications included risk of hypocalcemia (0%, 3% or 8%), risk of voice change (1%, 9% or 14%), need for daily thyroid hormone replacement therapy (yes or no), risk for needing a second surgery (0% or 40%) and risk of 5 year thyroid cancer recurrence (1%, 3% or 5%). The treatment preferences were analyzed using statistical methods.

The survey found that the average patient favored a lobectomy over total thyroidectomy as long as the chance of needing a second surgery after the initial lobectomy remained less than 30%. Patients also would accept a risk of recurrence of 1.6% if the risk for having a low calcium could be reduced from 3% to 0% and a risk of recurrence of 2.6% if the risk for change of voice could be lowered from 9% to 1%

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study is important to patients because it helps understand what outcomes are most concerning to them. It also shows that it is very important to have a careful evaluation and discussion with the patient before the surgery, so that all the information is available to help patients make better decisions regarding their care.

— Jessie Block-Galarza, MD

ATA THYROID BROCHURE LINKS

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

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

ABBREVIATIONS & DEFINITIONS

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.

Completion thyroidectomy: surgery to remove the remaining thyroid lobe in thyroid cancer patients who initially had a lobectomy.

Hypocalcemia: low calcium levels in the blood, a complication from thyroid surgery that is usually short-term and relatively easily treated with calcium pills. If left untreated, low calcium may be associated with muscle twitching or cramping and, if severe, can cause seizures and/or heart problems.

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.

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THYROID CANCER

Extra-thyroidal extension in papillary thyroid cancer has an impact on the risk of recurrence and response to therapy

BACKGROUND

Doctors use different staging systems to predict the prognosis of patients with cancer. One of the most widely used staging systems is the AJCC system which predicts the risk of death from cancer based on the size of the cancer, if it has spread to the lymph nodes and if it has spread to other parts of the body. In general, stages I and II have a very low risk of death. The risk of death increases in stage III and is the highest in stage IV.

Most patients with thyroid cancer fall into stage I or II. One factor that resulted in an increase to stage III was whether the cancer was seen extending out from the thyroid into the neck muscles at the time of surgery (gross extra-thyroidal extension) or if this was seen only by examining the cancer under the microscope (minimal extra-thyroidal extension). With the AJCC update in 2017, patients with minimal extra-thyroidal extension were downgraded to stage II and only patients with gross extra-thyroidal extension were included in stage III.

The current study was done to compare the risk of recurrence and response to treatment between patients with gross extra-thyroidal extension and those with minimal extra-thyroidal extension.

THE FULL ARTICLE TITLE

Danilovic DLS et al 2020 Is there a difference between minimal and gross extension into the strap muscles for the risk of recurrence in papillary thyroid carcinoma? Thyroid. Epub 2020 Mar 17. PMID: 32059626.

SUMMARY OF THE STUDY

This study was conducted in Universidade de São Paulo in São Paulo, Brazil. The authors reviewed the medical records of patients with thyroid cancer who had follow up there from 2012 to 2018. A total of 596 patients with papillary thyroid cancer were included and patients with other types of thyroid cancers and those with advanced papillary thyroid cancer were excluded. Of these, 88% of patients were female with an average age of ~50 years. Overall, 87% of patients had stage I and 13% had stage II thyroid cancer. A total of 191 had minimal extra-thyroidal extension and 65 had gross extra-thyroidal extension. About 14% of patients with minimal extension had recurrence while the recurrence in the group of patients with gross extension was about 25%. At the time of final evaluation, the proportion of patients who were free of cancer was significantly higher in the group with microscopic extension.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The extent of local spread of thyroid cancer to adjacent structures in the neck changes the risk of recurrence for patients with papillary thyroid cancer. Based on this finding, patients with gross extra-thyroidal extension need closer and, possibly, more aggressive treatment while those with minimal extra-thyroidal extension can be treated more conservatively.

— Shirin Haddady, MD

ATA THYROID BROCHURE LINKS

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

THYROID CANCER, continued

ABBREVIATIONS & DEFINITIONS

Cancer recurrence: this occurs when the cancer comes back after an initial treatment that was successful in destroying all detectable cancer at some point.

Papillary thyroid carcinoma: 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).

Extra-thyroidal extension: cancer that extends out from the thyroid into the neck muscles. If this is visible at the time of surgery, it is termed gross extra-thyroidal extension. If it is only seen by examining the cancer under the microscope, it is termed minimal extra-thyroidal extension.

American Joint Committee on Cancer (AJCC) staging system: predicts the risk of death from cancer based on the size of the cancer, if it has spread to the lymph nodes and if it has spread to other parts of the body. In general, stages I and II have a very low risk of death. The risk of death increases in stage III and is the highest in stage IV.

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

Bite Me Cancer
www.bitemecancer.org
info@bitemecancer.org

Graves' Disease and Thyroid Foundation
www.gdatf.org
(Toll-free): 877-643-3123
info@ngdf.org

Light of Life Foundation
www.checkyourneck.com
info@checkyourneck.com

MCT8 – AHDS Foundation
mct8.info
Contact@mct8.info

Thyca: Thyroid Cancer Survivors' Association, Inc.
www.thyca.org
(Toll-free): 877-588-7904
thyca@thyca.org

Thyroid Cancer Alliance
www.thyroidcanceralliance.org
www.thyroidcancerpatientinfo.org
Rotterdam, The Netherlands

Thyroid Cancer Canada
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AMERICAN THYROID ASSOCIATION®

Optimal Thyroid Health for All

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JOIN US

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

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

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

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

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

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

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

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

Graves' Disease

WHAT IS THE THYROID GLAND?

The thyroid gland is a butterfly-shaped endocrine gland that is located in the lower front of the neck. The thyroid makes thyroid hormones, which are secreted into the blood and then carried to every tissue in the body. Thyroid hormones help the body use energy, stay warm and keep the brain, heart, muscles, and other organs working appropriately.

WHAT IS GRAVES' DISEASE?

Graves' disease is an autoimmune disease that leads to a generalized overactivity of the entire thyroid gland (*hyperthyroidism*). It is the most common cause of hyperthyroidism in the United States. It is named after Robert Graves, an Irish physician, who described this form of hyperthyroidism about 150 years ago. It is 7-8 times more common in women than men.

WHAT CAUSES GRAVES' DISEASE?

Graves' disease is triggered by a process in the body's immune system, which normally protects us from foreign invaders such as bacteria and viruses. The immune system destroys foreign invaders with substances called antibodies produced by blood cells known as lymphocytes. Sometimes the immune system can be tricked into making antibodies that cross-react with proteins on our own cells. In many cases these antibodies can cause destruction of those cells. In Graves' disease these antibodies (called the thyrotropin receptor antibodies (TRAb) or thyroid stimulating immunoglobulins (TSI) do the opposite – they cause the cells to work overtime. The antibodies in Graves' disease bind to receptors on the surface of thyroid cells and stimulate those cells to overproduce and release thyroid hormones. This results in an overactive thyroid (*hyperthyroidism*).

WHAT ARE THE SYMPTOMS OF GRAVES' DISEASE?

- *Hyperthyroidism*

  The majority of symptoms of Graves' disease are caused by the excessive production of thyroid hormones by the thyroid gland (see *Hyperthyroidism brochure*). These may include, but are not limited to, racing heartbeat, hand tremors, trouble sleeping, weight loss, muscle weakness, neuropsychiatric symptoms and heat intolerance.

- *Eye disease*

  Graves' disease is the only kind of hyperthyroidism that can be associated with inflammation of the eyes, swelling of the tissues around the eyes and bulging of the eyes (called *Graves' ophthalmopathy or orbitopathy*). Overall, a third of patients with Graves' disease develop some signs and symptoms of Graves' eye disease but only 5% have moderate-to-severe inflammation of the eye tissues to cause serious or permanent vision trouble. Patients who have any suggestion of eye symptoms should seek an evaluation with an eye doctor (an ophthalmologist) as well as their endocrinologist.

  Eye symptoms most often begin about six months before or after the diagnosis of Graves' disease has been made. Seldom do eye problems occur long after the disease has been treated. In some patients with eye symptoms, hyperthyroidism never develops and, rarely, patients may be hypothyroid. The severity of the eye symptoms is not related to the severity of the hyperthyroidism.

  Early signs of trouble might be red or inflamed eyes, a bulging of the eyes due to inflammation of the tissues behind the eyeball or double vision. Diminished vision or double vision are rare problems that usually occur later, if at all. We do not know why, but problems with the eyes occur much more often and are more severe in people with Graves' disease who smoke cigarettes.

- *Skin disease*

  Rarely, patients with Graves' disease develop a lumpy reddish thickening of the skin in front of the shins known as pretibial myxedema (called Graves' dermopathy). This skin condition is usually painless and relatively mild, but it can be painful for some. Like the eye trouble of Graves' disease, the skin problem does not necessarily begin precisely when the hyperthyroidism starts. Its severity is not related to the level of thyroid hormone.

Graves' Disease

HOW IS THE DIAGNOSIS OF GRAVES' DISEASE MADE?

The diagnosis of hyperthyroidism is made on the basis of your symptoms and findings during a physical exam and it is confirmed by laboratory tests that measure the amount of thyroid hormones (thyroxine, or T4, and triiodothyronine, or T3) and thyroid-stimulating hormone (TSH) in your blood (see the *Hyperthyroidism brochure*). Clues that your hyperthyroidism is caused by Graves' disease are the presence of Graves' eye disease and/or dermopathy (see above), a symmetrically enlarged thyroid gland and a history of other family members with thyroid or other autoimmune problems, including type 1 diabetes, rheumatoid arthritis, pernicious anemia (due to lack of vitamin B12) or painless white patches on the skin known as vitiligo.

The choice of initial diagnostic testing depends on cost, availability and local expertise. Measurement of antibodies, such as TRAb or TSI, is cost effective and if positive, confirms the diagnosis of Graves' disease without further testing needed. If this test is negative (which can also occur in some patients with Graves' disease), or if this test is not available, then your doctor should refer you to have a radioactive iodine uptake test (RAIU) to confirm the diagnosis.

Also, in some patients, measurement of thyroidal blood flow with ultrasonography may be useful to establish the diagnosis if the above tests are not readily available.

HOW IS GRAVES' DISEASE TREATED?

The treatment of hyperthyroidism is described in detail in the *Hyperthyroidism brochure*. All hyperthyroid patients should be initially treated with beta-blockers. Treatment options to control Graves' disease hyperthyroidism include antithyroid drugs (generally methimazole [Tapazole®], although propylthiouracil [PTU] may be used in rare instances such as the first trimester of pregnancy), radioactive iodine and surgery.

Antithyroid medications are typically preferred in patients who have a high likelihood of remission (women, mild disease, small goiters, negative or low titer of antibodies). These medications do not cure Graves' hyperthyroidism, but when given in adequate doses are effective in controlling the hyperthyroidism.

If methimazole is chosen, it can be continued for 12-18 months and then discontinued if TSH and TRAb levels are normal at that time. If TRAb levels remain elevated, the chances of remission are much lower and prolonging treatment with antithyroid drugs is safe and may increase chances of remission. Long term treatment of hyperthyroidism with antithyroid drugs may be considered in selected cases.

If your hyperthyroidism due to Graves' disease persists after 6 months, then your doctor may recommend definitive treatment with either radioactive iodine or surgery.

If surgery (thyroidectomy) is selected as the treatment modality, the surgery should be performed by a skilled surgeon with expertise in thyroid surgery to reduce the risk of complications.

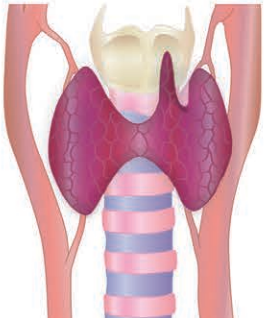
Your doctor should discuss each of the treatment options with you including the logistics, benefits and potential side effects, expected speed of recovery and costs. Although each treatment has its advantages and disadvantages, most patients will find one treatment plan that is right for them. Hyperthyroidism due to Graves' disease is, in general, controllable and safely treated and treatment is almost always successful.

WHAT WILL BE THE OUTCOME OF TREATMENT?

If you receive definitive treatment for your Graves' hyperthyroidism (such as radioactive iodine or surgery), you will eventually develop hypothyroidism (underactive thyroid). Even if you are treated with antithyroid drugs alone, hypothyroidism can still occur. Your doctor will check your *thyroid function tests* frequently to assess thyroid function following treatment. When hypothyroidism occurs, you will need to take a thyroid hormone tablet once a day at the right dose (see *Hypothyroidism brochure*).

OTHER FAMILY MEMBERS AT RISK

Graves' disease is an autoimmune disease and has a genetic predisposition. However, no specific gene has been identified for screening to date.



FURTHER INFORMATION

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

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