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Clinical Thyroidology® for the Public

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

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Clinical Thyroidology® for the Public

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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,* 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.

June is Differentiated Thyroid Cancer Awareness Month.

In this issue, the studies ask the following questions:

- Does surgery without radioactive iodine therapy affect outcomes in low-risk thyroid cancer?
- Does radioactive iodine therapy change outcomes in low-to-intermediate risk papillary thyroid cancers?
- How do additional high-risk features change patient survival for large thyroid cancers?
- Can lobectomy be enough surgery for treatment of medullary thyroid cancer?
- Can Graves' disease be treated with just medication?
- Does the addition of low-dose methotrexate improve remission rates in Graves' disease?

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

— Alan P. Farwell, MD

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THYROID CANCER

Does surgery without radioactive iodine therapy affect outcomes in low-risk thyroid cancer?

BACKGROUND

Thyroid cancer is common and usually has an excellent prognosis. This is largely because we have very effective treatments. Surgery is the usually first option. Historically, surgery was usually a total thyroidectomy to remove the entire thyroid and was often followed by radioactive iodine therapy to destroy all remaining thyroid cancer cells. More recently, a less aggressive approach is recommended, especially with small thyroid cancers with low-risk features. Radioactive iodine therapy is not an option with a lobectomy (removing 1 lobe of the thyroid, leaving the other lobe intact). Even in patients that undergo a total thyroidectomy, radioactive iodine is used less often and is reserved for patients with higher risk thyroid cancers.

Radioactive iodine therapy does cause side effects. It may damage the salivary glands, causing permanent dry mouth (xerostomia), and radiation may raise the risk of developing other cancers later in life. Thus, limiting its use to only patients that would benefit is important. Studies have suggested that patients with low-risk thyroid cancer do not benefit from radioactive iodine therapy. Indeed, the American Thyroid Association now recommends against using radioactive iodine therapy in low-risk patients. Still, there hasn't been enough long-term data proving that skipping radioactive iodine therapy is safe.

This study was done to examine the long-term results of omitting radioactive iodine therapy in treating patients with low-risk thyroid cancer.

THE FULL ARTICLE TITLE

Leboulleux S et al. Thyroidectomy without radioiodine in patients with low-risk thyroid cancer: 5 years of follow-up of the prospective randomised ESTIMABL2 trial. Lancet Diabetes Endocrinol,. 2025;13(1):38-46; doi: 10.1016/S2213-8587(24)00276-6.

SUMMARY OF THE STUDY

This was a trial of 730 patients aged 18 to 75 with low-risk thyroid cancer. "Low-risk" meant the cancer was smaller than 2 cm, showed no aggressive features, and hadn't spread to the lymph nodes or other parts of the body. Participants were randomly assigned to one of two groups: one group had only a total thyroidectomy, and the other group had the same surgery followed by a low dose of radioactive iodine therapy. Researchers compared how many patients in each group were cancer-free after 5 years—called disease-free survival. They also looked at side effects and patient's overall quality of life.

After 5 years, 698 patients remained in the study and 93.2% of the surgery-only group were cancer-free and 94.8% of the surgery-plus-radioactive iodine therapy group were cancer-free. This small difference was not statistically significant. Recurrence rates were very low and nearly the same — 6 in the surgery-only group vs. 5 in the radioactive iodine therapy group. No one in either group developed distant cancer, and overall survival rates were the same. However, those who did not receive radioactive iodine therapy reported better quality of life, with fewer issues like fatigue, and salivary gland problems.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study provides strong evidence that surgery alone is enough for patients with low-risk thyroid cancer. Adding radioactive iodine therapy doesn't improve outcomes and can lower quality of life. These findings support the growing trend to reduce aggressive treatment in low-risk thyroid cancer, because in some cases, the treatment may do more harm than good.

— Phillip Segal, MD

THYROID CANCER, continued

ATA RESOURCES

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

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

ABBREVIATIONS & DEFINITIONS

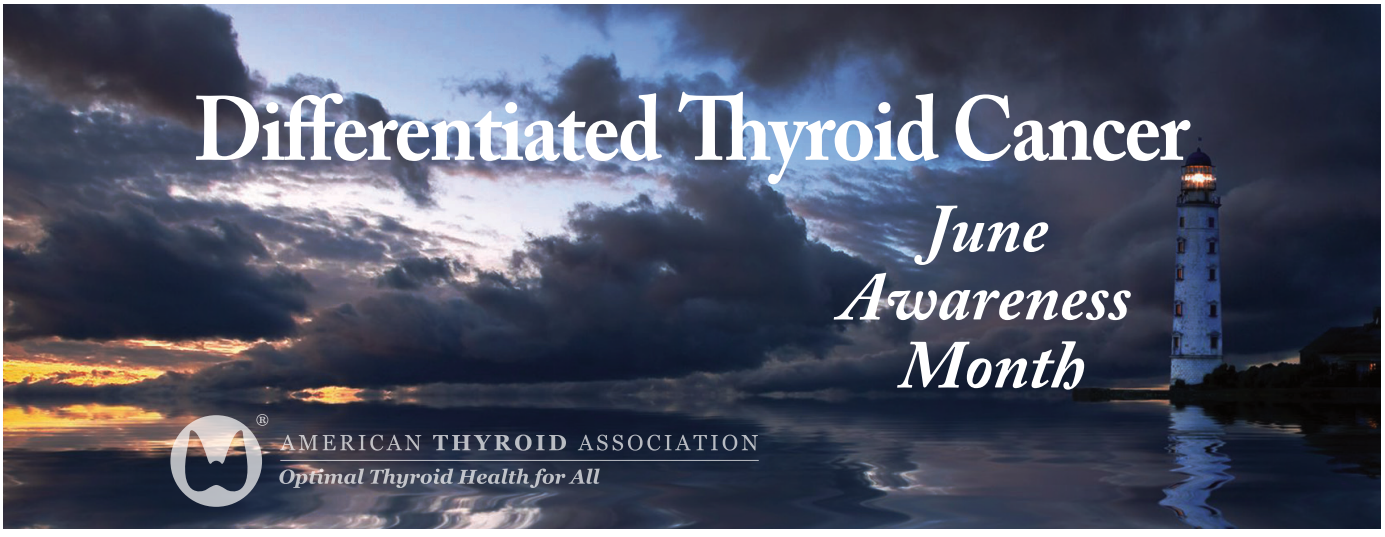
Radioactive iodine (RAI): this plays a valuable role in diagnosing and treating thyroid problems since it is taken up only by the thyroid gland. I-131 is the destructive form used to destroy thyroid tissue in the treatment of thyroid cancer and with an overactive thyroid. I-123 is the non-destructive 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).

Overt Hyperthyroidism: where the thyroid gland produces excessive thyroid hormones, leading to clear symptoms such as weight loss, rapid heartbeat, and sweating. It is diagnosed by low TSH levels and high free T3 and/or T4 levels in the blood

Xerostomia: dry mouth due to lack of saliva, frequently observed after radiation to the head and neck and after radioactive iodine therapy.

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.



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THYROID CANCER

Does radioactive iodine therapy change outcomes in low-to-intermediate risk papillary thyroid cancers?

BACKGROUND

Thyroid cancer is common and papillary thyroid cancer is the most common type of thyroid cancer. Papillary thyroid cancer has an excellent prognosis, particularly in patients <55 years of age. As such, papillary thyroid cancer is usually classified according to the risk of the cancer returning after initial treatment rather than the likelihood of dying of the cancer. This risk is rated as low, intermediate and high. Since the vast majority (>90%) of patients with papillary thyroid cancer, especially those with low and intermediate risk, do not die of their cancer, it can be difficult to evaluate the effect of treatment on overall survival in patients with low to intermediate risk papillary thyroid cancer. For example, while most studies show little effect of the presence of the spread of the cancer to lymph nodes in the neck on overall survival, their presence does increase both persistence and recurrence of the cancer.

Spread of the cancer to lymph nodes in the neck is common in papillary thyroid cancer, ranging from a low of 20% of patients to up to 90% of patients when neck dissections are performed as part of initial surgery. When spread of the cancer to lymph nodes in the neck is discovered during the initial surgery, radioactive iodine therapy is usually recommended.

This study was performed to evaluate whether the use of radioactive iodine therapy can improve survival in patients with low-to-intermediate risk papillary thyroid cancer that have spread of the cancer to lymph nodes in the neck at the time of surgery.

THE FULL ARTICLE TITLE

Palacardo F, et al. The impact of radioactive iodine on disease-specific survival in low-to-intermediate risk N1b papillary thyroid carcinoma. Ann Surg Oncol. Epub 2024 Nov 6; doi: 10.1245/s10434-024-16388-1. PMID: 39505729.

SUMMARY OF THE STUDY

The authors used a major database (SEER) to identify patients ≥18 years, diagnosed with papillary thyroid cancer from 2004-2015 who underwent total thyroidectomy with any lymph nodes resected during the initial operation. The average follow up was 7.5 years. They looked at predictors of survival such as age, sex, cancer size, race, risk, lymph node involvement and cancer extension outside the thyroid. Patients ≥55 years were analyzed separately. A total of 4601 adults were evaluated, of whom 78.6% received radioactive iodine therapy and 21.4% did not.

While overall there was improvement in survival with radioactive iodine therapy, on subgroup analysis it was only seen in patients ≥55 years and not seen in the group of younger patients. Other factors in the ≥55 group associated with worse survival were larger cancer size and any invasion into or beyond the thyroid capsule. The only factor associated with improved outcome in the younger group was female sex with improved survival.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study suggests that radioactive iodine therapy is associated with improved survival in patients with intermediate-risk papillary thyroid cancer and age ≥ 55 years, but not in patients with otherwise low-risk features. This information can help to limit radioactive iodine therapy treatment to those who are more likely to benefit from it and avoid potential side effects when radioactive iodine therapy may not be helpful.

— Marjorie Safran, MD

THYROID CANCER, continued

ATA RESOURCES

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

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

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

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

How do additional high-risk features change patient survival for large thyroid cancers?

BACKGROUND

Thyroid cancer is common and usually has an excellent prognosis. This is largely because we have very effective treatments. Surgery to remove all (total thyroidectomy) or part (lobectomy) is the usual first treatment option. Many thyroid cancers are low risk, so lobectomy is often the best option. Total thyroidectomy is better option if a thyroid cancer has high risk features. One high risk feature is the size of the cancer. The ATA guidelines recommend total thyroidectomy rather than a lobectomy for thyroid cancers larger than 4 cm due to worse reported patient outcomes. However, there is limited research data available looking at the cancer size as a prognostic factor for thyroid cancer. The goal of this study is to evaluate: 1. whether a cancer size larger than 4 cm is associated with worse outcomes in the absence of other markers of aggressive disease, 2. whether the presence of other high-risk features affect the prognosis of large cancers, and 3. whether a cancer size of 4 cm is the best cut off for risk stratification in thyroid cancer.

THE FULL ARTICLE TITLE

Ginzberg SP, et al. Revisiting the relationship between tumor size and risk in well-differentiated thyroid cancer. Thyroid 2024;34(8):953-1063; doi: 10.1089/thy.2023.0327. PMID: 38877803.

SUMMARY OF THE STUDY

The study included 193,133 patients from the National Cancer Database (NCDB), who were diagnosed with thyroid cancer between 2010 and 2015. A smaller group of 5,011 patients from the SEER database was used for comparison. Patient demographic, clinical and treatment data were used for analysis. The study compared the overall survival for patients with cancer sizes larger vs smaller than 4 cm, with and without the presence of other markers of aggressive disease. The average follow-up time was 87 months, with data available until 2020.

Most patients were white females (76% female, 76% white) with an average age of 50 years. The average cancer size was 1.3 cm, with 8% of patients having cancers larger than 4 cm. At least one marker of aggressive disease was present in 28% of patients with cancers 4 cm or smaller vs 61% with cancers larger than 4 cm. Total thyroidectomy was performed in 90% vs 88%, while radioactive iodine treatment was given to 67% vs 43% of patients with cancers smaller or larger than 4 cm, respectively. The overall 5-year survival was 96% in the entire group, with a decreased 5-year survival of 92% in patients with cancers larger than 4 cm as compared to 96% in patients with cancers 4 cm or smaller. Further analysis to adjust for differences between the two patient groups confirmed that a cancer size larger than 4 cm is associated with significantly worse overall survival compared to smaller cancers.

The presence of additional markers of aggressive disease worsened the prognosis. Patients with cancers larger than 4 cm had a greater risk of death if they had at least one additional risk factor. Patients with cancers larger than 4 cm and no additional risk factors had a similar survival with those with smaller cancers and additional risk factors. A higher number of high-risk features worsened survival, with a steeper increase of risk for cancers larger than 4 cm as compared to smaller cancers.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Patients with thyroid cancers larger than 4 cm have worse survival as compared to smaller cancers, and the presence of other features of aggressive disease further reduces survival. There was an increased risk of death at the 2 cm and 5 cm cancer size cutoffs, but not at the 4 cm cutoff, which is used in current guidelines. These findings support a more individualized risk assessment approach in thyroid cancer patients for adequate treatment and follow-up. While a total thyroidectomy for a cancer larger than 4 cm with one or more associated high-risk features would be recommended, the cut off for lobectomy could be increased to 5 cm for cancers without other high-risk features.

— Alina Gavrila, MD, MMSC

THYROID CANCER, continued

ATA RESOURCES

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

ABBREVIATIONS & DEFINITIONS

Thyroid Cancer: includes papillary thyroid cancer (PTC), the most common type of thyroid cancer and follicular thyroid cancer (FTC), the second most common type of thyroid cancer.

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 as 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. 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*).

NCDB (National Cancer Database): contains data on common cancers from ~ 1500 institutions in the United States.

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

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THYROID CANCER (MEDULLARY)

Can lobectomy be enough surgery for treatment of medullary thyroid cancer?

BACKGROUND

Medullary thyroid cancer (MTC) only accounts for 4% of all thyroid cancer diagnoses. However, it accounts for a larger proportion of thyroid cancer-related deaths compared to papillary thyroid cancer, the most common type of thyroid cancer that accounts for 84% of all thyroid cancer diagnoses. Complete surgical removal of cancer is the best option for cure. However, this may be more difficult in MTC, which can spread more easily outside the thyroid gland and in which many patients have cancer already spread to neck lymph nodes at the time of diagnosis. Total thyroidectomy with central neck dissection, where the thyroid gland is entirely removed and lymph nodes in the neck are dissected and examined, is the currently recommended initial surgery for MTC. However, this approach can lead to post-surgical complications such as damaged to recurrence of laryngeal nerve and parathyroid gland, and subsequent decreased quality of life related to vocal cord problems, permanent hypocalcemia, and hypothyroidism requiring lifelong thyroid hormone replacement. Therefore, there has been interest in assessing whether a lobectomy, where only the lobe with cancer is removed, would be enough in cases of small MTC without leading to cancer-related death or cancer recurrence.

This study aimed to investigate whether total thyroidectomy and lobectomy would result in different outcomes related to cancer-related death or recurrence in early-stage MTC that is smaller than 2 cm in size and limited to thyroid gland.

THE FULL ARTICLE TITLE

Jishu JA, et al. Limited thyroidectomy achieves equivalent survival to total thyroidectomy for early localized medullary thyroid cancer. Cancers (Basel) 2024;16(23):4062; doi: 10.3390/cancers16234062. PMID: 39682246.

SUMMARY OF THE STUDY

Information on 398 patients diagnosed with stage T1 MTC (cancer size is ≤ 2cm and cancer is only in the thyroid gland) from 2000 to 2019 were collected from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry, which records cancer-related information in about 28% of the U.S. population. The patients were on average 51 years old, with 65% women and 86% White race, and followed on average for 8.9 years. Among these patients, 221 patients (56%) had cancer ≤ 1cm in size (stage T1a) and 177 patients (44%) had cancer 1-2cm in size (stage T1b). A total of 280 patients (70%) had no cancer found in lymph nodes.

Of the patients who underwent surgery, 304 patients (85%) had a total thyroidectomy and 39 patients (10%) had a lobectomy. Only 46 patients (13%) had lymph node dissection, the majority of whom had total thyroidectomy. Patients who had total thyroidectomy were more likely to have lymph node involvement (35% vs 10%) and to receive chemotherapy afterwards (35% vs 10%). When comparing patients who underwent total thyroidectomy and lobectomy, there were no significant differences in MTC recurrence (0.3% vs 0%), overall death rate (13% vs 13%), and cancer-related death rate (6% vs 8%).

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The study reported that there were no differences in risks of cancer death or recurrence between lobectomy and total thyroidectomy as the initial surgical treatment for small MTC (≤ 2cm in size without distant metastasis). There have been several other studies that suggest that lobectomy in patients with early stage MTC may be a reasonable option rather than total thyroidectomy, without increased risks of death or recurrence. Since TSH suppression or radioactive iodine therapy are not a part of routine treatment of MTC unlike in papillary thyroid cancer, total thyroidectomy does not need to be considered for

THYROID CANCER (MEDULLARY), continued

these reasons. Therefore, lobectomy can be considered in certain patients with MTC after careful multidisciplinary discussion as well as shared decision making with patients. Still, long-term studies assessing impact on survival and recurrence rate as well as impact on quality of life would be needed to better inform the appropriate options for initial surgical approach for MTC. Regardless of the extent of surgery, patients with MTC should be monitored regularly with biochemical and imaging evaluation.

— Sun Y. Lee, MD

ATA RESOURCES

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

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

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

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.

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

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.

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

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

Parathyroid Glands: usually four small glands located around the thyroid that secrete parathyroid hormone (PTH) which regulates the body's calcium levels.

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.

THYROID CANCER (MEDULLARY), continued

ABBREVIATIONS & DEFINITIONS, continued

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

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.

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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GRAVES' DISEASE

Can Graves' disease be treated with just medication?

BACKGROUND

Graves' disease is the most common cause of an overactive thyroid gland (hyperthyroidism) and results from an antibody (Thyroid stimulating immunoglobulin) that turns on the thyroid gland. The initial treatment of Graves' disease is usually anti-thyroid drugs (methimazole or PTU) to control the hyperthyroidism and return the thyroid levels to normal. Once the thyroid levels are normal, the treatment options include 1) continuing the antithyroid medication in the hope that the antibody will go away and the Graves' disease will go into remission or 2) definitive treatments to destroy the thyroid gland (radioactive iodine therapy or surgery). Unfortunately, half of the patients will become hyperthyroid again once anti-thyroid drugs are stopped. For patients who have a high likelihood of becoming hyperthyroid again after stopping the anti-thyroid drugs, radioactive iodine or total thyroidectomy may be better options. If we can identify the patient characteristics that will make them more or less likely to stay in remission after completing the recommended course of anti-thyroid drugs, we will be able to offer patients more suitable treatment options and prevent recurrences of hyperthyroidism.

The goal of this study is to identify patient characteristics that will make them more likely to become hyperthyroid again after the anti-thyroid drugs are stopped.

THE FULL ARTICLE TITLE

El Kawkgi O, et al. A predictive model for Graves' disease recurrence after antithyroid drug therapy: a retrospective multicenter cohort study. Endocr Pract. Epub 2024 Dec 16; doi:10.1016/j.eprac.2024.12.011. PMID: 39694327.

SUMMARY OF THE STUDY

Patients above the age of 18 treated at University of Arkansas for Medical Sciences (UAMS), Mayo Clinic, and University of Florida (UF) were included in the study. These patients had a first-time diagnosis of Grave's disease and were treated initially with anti-thyroid drugs. If the patients were pregnant, treated with thyroidectomy or radioactive iodine initially, or diagnosed with other forms of hyperthyroidism, they were not included in the study. The age, sex, smoking status, family history, lab work (TSH and TSI antibodies), body mass index, presence of thyroid eye disease and goiter, imaging studies, and type of anti-thyroid drugs were studied for patients treated from 2002 to 2021 at Mayo Clinic, 2013 to 2019 at University of Florida, and 2009 to 2019 at University of Arkansas for Medical Sciences.

A recurrence of the Graves' disease was defined as a patient needing more anti-thyroid drugs, radioactive iodine, or a thyroidectomy within a year of stopping the anti-thyroid drugs. Of the 523 patients studied, 75.66% were women, and the average age was 48.6 years. Among these, 211 patients (40.3%) discontinued anti-thyroid drugs after their hyperthyroidism was treated successfully, with 142 patients (67.3%) having ≥12 months of follow-up for reporting purposes. Unfortunately, of these 142 patients, 79 (55.6%) of them experienced a Graves' Disease recurrence.

Elevated baseline FT4 levels (1.47 x more likely per 2.0 ng/dl increase) and early anti-thyroid drug discontinuation (if discontinued before 12 months; 2.7 x more likely) were significant predictors of recurrence. Older age (1.31 x more likely per 10 years older) and higher baseline FT4 levels (1.65 x more likely per 2.0 ng/dL increase) were independently associated with recurrence. Longer anti-thyroid drug therapy showed a trend toward reduced recurrence risk (15% less likely per 6 months longer use).

Using these statistics, a tool was developed to predict risk of recurrence after a certain duration of anti-thyroid drug therapy. For example, a 40-year-old female smoker with a freeT4 of 4 ng/dl and using anti-thyroid drugs for 12 months has a 70% recurrence risk of hyperthyroidism after stopping her anti-thyroid drugs. Another example is a 20-year-old nonsmoking male with a free T4 of 2 ng/dl and 24 months of anti-thyroid drug use has a 30% risk of hyperthyroidism recurrence after stopping his anti-thyroid drugs.

GRAVES' DISEASE, continued

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Although anti-thyroid drugs are effective, there is a chance that the patient will become hyperthyroid again after stopping the medications. If the patient has a high free T4 hormone level, is older, or has taken the anti-thyroid drug for only a short time, the chance that the patient will become hyperthyroid again after stopping the drug is higher. Only 142 of the patients studied had follow up 12 months after stopping their anti-thyroid drugs, which might limit the ability of the study to make conclusions.

A tool that predicts risk of hyperthyroidism recurrence can help the physician offer patients the best option to treat their hyperthyroidism: anti-thyroid drugs, radioactive iodine, or thyroidectomy. Future research is needed to improve the accuracy of this tool. Other similar tools to predict response to hyperthyroidism treatment include "10-point GREAT+ score" that even incorporates genetic data and "Clinical Severity Score (CSS)" that incorporates goiter size, free T4 levels, and presence/ absence of thyroid eye disease.

— Pinar Smith, MD

ATA RESOURCES

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

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.

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. 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).

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.

GRAVES' DISEASE, continued

ABBREVIATIONS & DEFINITIONS, continued

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

Thyroid Stimulating Immunoglobulin (TSI): antibodies often present in the serum of patients with Graves' disease that are directed against the TSH receptor, that cause stimulation of this receptor resulting in increased levels of thyroid hormones in the blood and hyperthyroidism

Antibodies: proteins that are produced by the body's immune cells that attack and destroy bacteria and viruses that cause infections. Occasionally the antibodies get confused and attack the body's own tissues, causing autoimmune disease.

Goiter: a thyroid gland that is enlarged for any reason is called a goiter. A goiter can be seen when the thyroid is overactive, underactive or functioning normally. If there are nodules in the goiter it is called a nodular goiter; if there is more than one nodule it is called a multinodular goiter.

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GRAVES' DISEASE

Does the addition of low-dose methotrexate to antithyroid drugs improve remission rates in Graves' disease?

BACKGROUND

Graves' disease is the most common type of hyperthyroidism. It is caused by antibodies the body makes that tell the thyroid cells to overproduce thyroid hormone. Those antibodies are called thyroid stimulating immunoglobulins (TSI) or thyrotropin receptor antibodies (TRAbs) because they stick to the TSH receptor in thyroid cells and turn on the cells to become overactive. Graves' disease is an autoimmune disease, since the antibodies the body produces attack normal cells rather than infections like bacteria and viruses. Methotrexate is a drug that decreases the immune response and is an effective treatment for other autoimmune diseases, such as rheumatoid arthritis.

Graves' disease is frequently treated with antithyroid drugs (Methimazole or PTU) to control the thyroid. Continuing the antithyroid drugs for 12-18 months may produce a remission of the Graves' disease, allowing the antithyroid drugs to be stopped. The likelihood of remission of Graves' disease after a course of antithyroid drugs is in the 25-30% range. Patients who have high levels of TRAbs relapse more frequently, so adding medications that could lower the immune response, such as methotrexate could help increase the likelihood of remission.

This study examined the effect of adding low dose methotrexate to antithyroid drugs on the remission rates in patients with Graves' disease.

THE FULL ARTICLE TITLE

Xie P, et al. Effects of low-dose methotrexate with methimazole in patients with Graves' disease: results of a randomized clinical trial. J Clin Endocrinol Metab 2025;110(2):489-497; doi: 10.1210/clinem/dgae472. PMID: 38994582.

SUMMARY OF THE STUDY

This study from China looked at 144 patients with Graves' disease. Half of the patients were treated with methimazole alone and the other half were treated with methimazole plus methotrexate. About 75% of patients in both groups were women, and the average age was 40 years in both groups. The medications were stopped after 12-18 months if both TSH and TRAb levels became normal. After 18 months of treatment, the group of patients that received methimazole plus methotrexate had a higher chance of being off the medications (56%) as compared to the group that received methimazole only (39%). The levels of TRAb went down faster and more often in the patients who received methimazole plus methotrexate as compared to the patients who received methimazole only: 88% vs 33% had negative TRAbs, respectively. Thyroid levels were similar in both groups and the side effects were mild and similar in both groups.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study suggests that the combination of methimazole plus methotrexate can help lower the Graves' antibodies faster and more often, and in this way be more successful at allowing stopping antithyroid drugs in patients with Graves' disease. Methotrexate was well tolerated and safe. Methotrexate may be a helpful for those patients with Graves' disease who have higher chances of relapse. However, it remains to be seen what the chances of relapse are in the long run after stopping both medications.

— Susana Ebner, MD

GRAVES' DISEASE, continued

ATA RESOURCES

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

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.

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.

Methotrexate: a drug that decreases the immune response and lowers antibody levels and is an effective treatment for autoimmune diseases, such as rheumatoid arthritis.

TRAb: antibodies often present in the serum of patients with Graves' disease that are directed against the TSH receptor, often causing stimulation of this receptor with resulting hyperthyroidism.

Thyroid Stimulating Immunoglobulin (TSI): antibodies often present in the serum of patients with Graves' disease that are directed against the TSH receptor, that cause stimulation of this receptor resulting in increased levels of thyroid hormones in the blood and hyperthyroidism.

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

MCT8 – AHDS Foundation
mct8.info
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Thyca: Thyroid Cancer Survivors' Association, Inc.
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