AMERICAN THYROID ASSOCIATION
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Clinical Thyroidology® for the Public

VOLUME 12 | ISSUE 1 | JANUARY 2019

Too many thyroid ultrasound exams lead to an increase in the diagnosis of low-risk thyroid cancer

Increased medical imaging of any sort will lead to an increase in the diagnosis of small, potentially harmless thyroid nodules. More imaging may result in an increase in the diagnosis of low risk thyroid cancers that may not harm patients, whereas the treatment (surgery for example) may be more harmful than the disease. This study looks to see if more imaging leads to the diagnosis of more low risk thyroid cancers in patients over the age of 65.

Haymart MR et al 2018 Thyroid ultrasound and the increase in diagnosis of low-risk thyroid cancer. J Clin Endocrinol Metab. Epub 2018 Oct 16.

Combining cancer staging systems and patient age improves survival predictions for thyroid cancer

Cancer staging systems are used to determine the extent to which a cancer has invaded and spread. Knowing the stage of one's cancer provides information about prognosis (the lower the stage the better the prognosis) and potential treatments. The goal of the current study was to determine whether combining 2 updated classification systems would provide a more accurate estimate of survival for the various subsets of patients with thyroid cancer who are < 55-years-old.

Ghaznavi SA et al 2018 Using the American Thyroid Association risk-stratification system to refine and individualize the American Joint Committee on Cancer eighth edition disease-specific survival estimates in differentiated thyroid cancer. Thyroid. Epub 2018 Aug 2.

Advanced thyroid cancer patients can have a prolonged response to lenvatinib

While most patients with thyroid cancer do very well with current therapy, 3-5% of thyroid cancer patients have progressive cancer after the initial treatment, therefore, requiring alternative therapies. On such drug is Lenvatinib, which showed that this medication stopped the cancer progression for a longer time as compared to no drug. The aim of this study was to evaluate the duration of response to lenvatinib.

Gianoukakis AG et al 2018 Prolonged duration of response in lenvatinib responders with thyroid cancer. Endocr Relat Cancer 6:699–704. PMID: 29752332

Hypothyroidism during cancer therapy with tyrosine kinase inhibitors.

Hypothyroidism is often seen in patients being treated with TKI drugs for non-thyroidal cancers. Interestingly, the development of hypothyroidism during cancer treatment of non-thyroid cancer may be linked to improved survivals. This study examined the development of hypothyroidism in patients receiving TKI drugs for non-thyroid cancer and the effect on survival.

Lechner MG et al. 2018. Hypothyroidism during tyrosine kinase inhibitor therapy is associated with longer survival in patients with advanced nonthyroidal cancers. Thyroid 28:445–453. PMID: 29652597.

A high proportion of serum rT_3 tests are ordered by a relatively small number of providers in the United States

Reverse T_3 (rT_3) is not one of the primary hormones produced by thyroid gland. The production of T_3 and rT_3 is exactly opposite. Because of this relationship, and the fact that rT_3 is inactive, most clinicians do not use measurement of rT_3 for assessing thyroid function. Still, some providers continue to order rT_3 in the assessment of thyroid function. This study was done to identify the ordering pattern of serum rT_3 by clinicians.

Schmidt RL et al. Does reverse triiodothyronine testing have clinical utility? An analysis of practice variation based on order data from a national reference laboratory. Thyroid 2018 Jul; 28(7): 842-848.

Adding mycophenolate to infusions of methylprednisolone improves treatment of Graves' eye disease.

Severe Graves' eye disease is usually associated with poor clinical outcomes and impaired quality of life. Treatment currently is intravenous methylprednisolone, but response is often limited and there are significant side effects to high dose steroids. This study aimed to compare the efficacy and safety of combination therapy of the immunosuppressive medication mycophenolate and methylprednisolone to the standard regimen of methylprednisolone alone.

Kahaly GJ et and the European Group on Graves' Orbitopathy (EUGOGO). Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial. Lancet Diabetes Endocrinol. 2018 Apr;6(4):287-298. doi: 10.1016/S2213-8587(18)30020-2. Epub 2018 Jan 31.

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EDITOR'S COMMENTS

Happy New Year and welcome to another year and 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, ThyCa: Thyroid Cancer Survivors' Association, Thyroid Cancer Canada, Thyroid Cancer Alliance* and *Thyroid Federation International*.

The American Thyroid Association (ATA) extends its appreciation to all of the patients and their families that are part of the ATA community — our **Friends of the ATA**. It is for you that the 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.

As we think of all those who make a difference in our lives this holiday season, we thank you for being part of the ATA family and for 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 editorial board of CTFP, the ATA Board of Directors, Members, and ATA Headquarters Staff, wish you the best this season and look forward to being part of your thyroid network in 2019.

January is Thyroid Awareness Month.

In this issue, the studies ask the following questions:

- Is the increased use of ultrasound the cause of the increase in diagnosis of thyroid cancer?
- Does combining cancer staging systems with patient age improve survival predictions for thyroid cancer?
- How effective is levatinib in treating patients with advanced thyroid cancer?
- Does developing hypothyroidism while taking tyrosine kinase inhibitor drugs for non-thyroidal cancer increase survival?
- Who orders rT_3 testing in the United States?
- Is combination therapy effective for severe Graves' eye 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, FACE

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Clinical Thyroidology® for the Public

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THYROID CANCER

Too many thyroid ultrasound exams lead to an increase in the diagnosis of low-risk thyroid cancer

BACKGROUND

Thyroid cancer is common and is more common in older patients. Indeed thyroid cancer is the fastest rising cancer in women. Despite this increase, death from thyroid cancer remains low and is unchanged. One reason for the increase in the diagnosis of thyroid cancer is the increased use of imaging studies that include the neck, as increased medical imaging of any sort will lead to an increase in the diagnosis of small, potentially harmless nodules. Up to 50% of individuals that have an imaging study of the neck will be noted to have a thyroid nodule. More imaging may result in an increase in the diagnosis of low risk thyroid cancers that may not harm patients, whereas the treatment (surgery for example) may be more harmful than the disease. This is called overdiagnosis, where increased detection of a disease does not help a population in terms of decreased harm from that disease. This study looks to see if more imaging leads to the diagnosis of more low risk thyroid cancers in patients over the age of 65.

THE FULL ARTICLE TITLE

Haymart MR et al 2018 Thyroid ultrasound and the increase in diagnosis of low-risk thyroid cancer. J Clin Endocrinol Metab. Epub 2018 Oct 16.

SUMMARY OF THE STUDY

The authors studied two databases of Medicare patients (age over 65) and looked at the years 2002-2013. One database gave information about the number of thyroid ultrasounds performed and the other gave information about thyroid cancer detection. The authors used statistical methods to compare the rate of imaging with the discovery of new thyroid cancers.

The average patient age was 76 years old and most were white women from metro areas. The rate of ultrasound testing increased about 20% per year each year of the study. Patients who had more medical problems were more likely to get a thyroid ultrasound. About 1 out of 3 thyroid cancers discovered were smaller than 1 centimeter. The authors estimate that if the number of ultrasounds performed remained the same as in 2002, about 1800 fewer thyroid cancers would be detected.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The authors conclude that the increase in thyroid ultrasound results in the diagnosis of more low risk thyroid cancers. This is important to patients because sometimes the treatment for a disease is more harmful than the disease itself. In an older patient with other medical problems, a thyroid surgery for a small low risk thyroid cancer may cause more harm than benefit. In order to reduce harm from treatment after identifying low-risk thyroid cancer, there needs to be a focus on decreasing unnecessary thyroid ultrasounds and to focus on the risk of a thyroid nodule to better guide care. The current American Thyroid Association guidelines have addressed this by recommending that small thyroid nodules should be observed and not biopsied. Further, many are recommending that small thyroid cancers can be observed and do not require surgery.

— Joshua Klopper, MD

ATA THYROID BROCHURE LINKS

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

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

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THYROID CANCER, continued

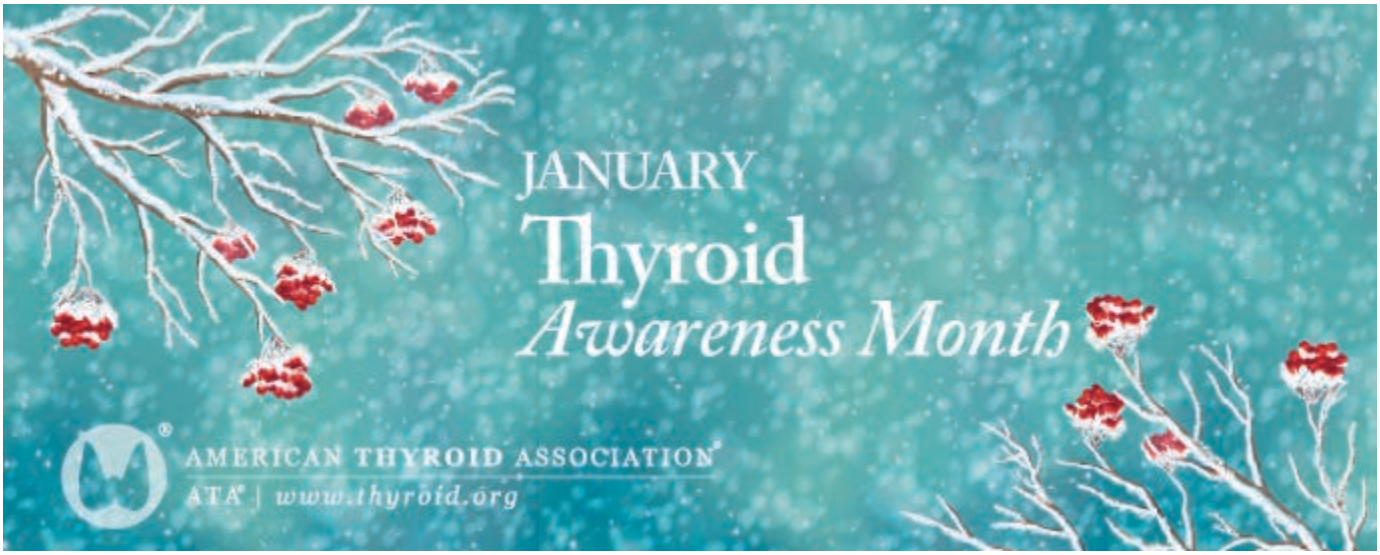
ABBREVIATIONS & DEFINITIONS

Thyroid nodule: an abnormal growth of thyroid cells that forms a lump within the thyroid. While most thyroid nodules are non-cancerous (Benign), ~5% are cancerous.

Thyroid Ultrasound: a common imaging test used to evaluate the structure of the thyroid gland. Ultrasound uses soundwaves to create a picture of the structure of the thyroid gland and accurately identify and characterize nodules within the thyroid. Ultrasound is also frequently used to guide the needle into a nodule during a thyroid nodule biopsy.

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).

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



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THYROID CANCER

Combining cancer staging systems and patient age improves survival predictions for thyroid cancer

BACKGROUND

Cancer staging systems are used to determine the extent to which a cancer has invaded and spread. Knowing the stage of one's cancer provides information about prognosis (the lower the stage the better the prognosis) and potential treatments. The American Joint Committee on Thyroid Cancer/Tumor Node Metastasis (AJCC) is the most commonly used staging system for thyroid cancer. Like other cancers, this system incorporates the size of the cancer (T), the spread to lymph nodes in the neck (N) and the presence or absence of spread of the cancer to other organs, to provide an estimate of disease specific survival (DSS) and cancer recurrence. But unlike other cancers, survival in thyroid cancer is also highly dependent on age. Until recently everybody less than 45 years old (< 45) was automatically classified as having low risk stage I disease unless there was evidence of spread of the cancer to other organs, in which case they were considered to have stage II disease.

Recently the AJCC system was revised to reflect a greater understanding of the behavior of thyroid cancer. One of the most important changes of this update was to adjust the age cut-off from 45 to 55 years. With this change, up to 1/3 of all thyroid cancer patients now fit into lower risk categories based solely on their age. Consequently, this new < 55-year-old group with supposedly excellent survival rates now includes patients with a much wider spectrum of cancer than before - from small papillary microcarcinomas to large cancers that have invaded into major structures in the neck and other organs in the body. As a result, the optimistic AJCC survival rates that have been previously quoted for younger patients with thyroid cancer may not be accurate any more.

The goal of the current study was to determine whether combining the AJCC classification with the American Association initial risk stratification system (ATA-IRS) would provide a more accurate estimate of DSS for the various subsets of patients with thyroid cancer who are < 55-years-old.

THE FULL ARTICLE TITLE

Ghaznavi SA et al 2018 Using the American Thyroid Association risk-stratification system to refine and individualize the American Joint Committee on Cancer eighth edition disease-specific survival estimates in differentiated thyroid cancer. Thyroid. Epub 2018 Aug 2.

SUMMARY OF THE STUDY

The authors studied 10-year survival in 4881patients less than 55-years-old with papillary or follicular thyroid cancer who were treated at the Memorial Sloan Kettering Cancer Centre between 1980 and 2016. Patients were first assigned to a stage based on the revised AJCC system (I or II). Then they were further divided into age group at diagnosis (younger = < 45 years; older = 45-55 year). Finally, the ATA-IRS recurrence risk stratification system (low, intermediate or high) was applied to the subgroups to see if a more refined and accurate estimate of DSS could be calculated.

Overall, there were 122 (2.5%) disease specific deaths in the entire < 55-year-old age group. By integrating the AJCC system with the ATA system, the authors were able to identify six different subgroups with differing outcomes: (i) stage I/ATA low risk, younger and older, 100% DSS; (ii) stage I/ATA intermediate risk, younger and older, 98% DSS; (iii) stage I/ATA high risk, younger, 95% DSS; (iv) stage I/ATA high risk, older, 89% DSS; (v) stage II/ATA high risk, younger, 78% DSS; and (vi) stage II/ATA high risk, older, 61% DSS.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Not everybody less than 55 years old with thyroid papillary or follicular thyroid cancer has the same prognosis. A composite staging approach that integrates two different cancer staging systems (AJCC and ATA) identifies six distinct subgroups with progressively worse DSS and provides a more individualized estimate of survival. This will allow identification of patients that would benefit form more aggressive treatment of their thyroid cancer.

— Phillip Segal, MD

THYROID CANCER, continued

ATA THYROID BROCHURE LINKS

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

ABBREVIATIONS & DEFINITIONS

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

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

Follicular thyroid cancer: the second most common type of thyroid cancer.

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

Disease specific survival: The percentage of people who have not died from a specific disease during a defined period. People who died from causes other than the disease being studies are not counted in this measurement.

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THYROID CANCER

Advanced thyroid cancer patients can have a prolonged response to lenvatinib

BACKGROUND

Most patients with thyroid cancer respond to the standard treatment consisting of surgery followed by radioactive iodine therapy and have excellent results, with 10 year survival rates in the 95+% range. However, 3–5% of thyroid cancer patients have progressive cancer after the initial treatment, requiring alternative therapies. Until recently, there was little to offer these patients in terms of chemotherapy. However, 2 chemotherapy drugs from the tyrosine kinase inhibitor (TKI) group, sorafenib and lenvatinib, have been shown to delay the cancer progression and have been approved to be used for patients with persistent and progressive thyroid cancer not responding to radioactive iodine therapy. The TKI therapy is promising, despite many significant side effects. Importantly, patients taking lenvatinib appear to have a lower risk to develop resistance to treatment as compared to sorafenib. Therefore, this medication may remain effective for a prolonged period.

Lenvatinib was approved based on the results of the SELECT clinical trial, which showed that this medication stopped the cancer progression for a longer time as compared to no drug (18 vs. 4 months). Additional data was collected in the SELECT study over the next three years of follow-up to update the initial analysis of the effect of lenvatinib. The aim of this study was to evaluate the duration of response to lenvatinib, which is defined as the time from when the cancer responded to treatment to when the disease started to progress again.

THE FULL ARTICLE TITLE

Gianoukakis AG et al 2018 Prolonged duration of response in lenvatinib responders with thyroid cancer. Endocr Relat Cancer 6:699–704. PMID: 29752332

SUMMARY OF THE STUDY

The SELECT study included 392 patients with thyroid cancer not responding to radioactive iodine therapy and progressing within the previous 13 months. Patients were randomly assigned 2:1 to receive 24 mg of oral lenvatinib daily (261 patients) or no drug (placebo, 131 patients) until the cancer started to progress, the patients developed an unacceptable toxicity to the treatment, or the patients withdrew from the study. The data collected prior to November 15, 2013 was used for the initial analysis. After this, the patients in the placebo group who had progressive cancer could choose to receive lenvatinib treatment.

Additional data collected over the next three years until September 1, 2016 was used for the current study. A total of 157 patients (60%) had a complete or partial response to the levantinib treatment. The patients who responded to lenvatinib had stable disease for an average of 30 months. The duration of the response to treatment appeared to be shorter in patients with large cancer and for patients with spread of the cancer to the liver or brain. The duration of the response to treatment was similar for patients who had received one prior cancer therapy and those who had never received therapy prior to the study. A total of 80% of lenvatinib-treated patients experienced serious treatment-related adverse events, most of them occurring early in the course of treatment.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This updated analysis confirmed that lenvatinib can delay the progression of thyroid cancer in patients not responding to radioactive iodine therapy and further showed that the patients who responded to lenvatinib could have a prolonged, durable effect, lasting for approximately 30 months. More than half of patients may respond to this treatment. Since most patients experienced side effects from the levantinib, early recognition and adequate treatment of the side effects is especially important to allow treatment continuation.

— Alina Gavrila, MD, MMSC

THYROID CANCER, continued

ATA THYROID BROCHURE LINKS

Papillary and Follicular Thyroid Cancer: https://www.thyroid.org/thyroid-cancer/
Radioactive Iodine: https://www.thyroid.org/radioactive-iodine/

ABBREVIATIONS & DEFINITIONS

Thyroid cancer: includes papillary and follicular cancer and overall has a favorable prognosis.

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.

Tyrosine kinases: proteins that are overactive in many of the pathways that cause cells to be cancerous. Tyrosine kinase inhibitors (TKIs) are medications that block the action of these proteins, thus preventing cancer progression.

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

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

Randomized study: a study in which the participants are divided by chance into groups to receive the treatment under investigation (test group) versus standard or placebo treatment (control group). This ensures that the groups are similar and allows a fair evaluation of the effects of a new treatment as compared to the standard treatment or no treatment (placebo) group.

Placebo: an inactive substance like water or sugar, which is given to study patients in the control group instead of the real medication to better evaluate the effects of a new medication and separate these effects from the natural disease progression without treatment.

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HYPOTHYROIDISM

Hypothyroidism during cancer therapy with tyrosine kinase inhibitors.

BACKGROUND

Thyroid function can be affected by cancer chemotherapy drugs given to treat non-thyroid cancers. Hypothyroidism is more common than hyperthyroidism. This is especially true with some of the newer drugs that affect the immune system. One class of cancer chemotherapy drugs is tyrosine kinase inhibitors (TKI), of which there are >20 TKI drugs. TKI drugs are active against a variety of solid cancers, especially kidney cancers and some GI cancers. They are also active against progressive thyroid cancer, although thyroid cancer patients are already hypothyroid after thyroidectomy and radioactive iodine therapy. Interestingly, the development of hypothyroidism during cancer treatment of non-thyroid cancer may be linked to improved survivals.

This study examined the development of hypothyroidism in patients receiving TKI drugs for non-thyroid cancer and the effect on survival.

THE FULL ARTICLE TITLE

Lechner MG et al. 2018. Hypothyroidism during tyrosine kinase inhibitor therapy is associated with longer survival in patients with advanced nonthyroidal cancers. Thyroid 28:445–453. PMID: 29652597.

SUMMARY OF THE STUDY

Data on more than a 1000 patients who received one of 6 TKI drugs was collected and reviewed. Almost half of the patients studied had renal cell cancer. Those patients who had TSH levels done before and within 6 months after the day the TKI was started were included. Patients with pre-existing thyroid disease or thyroid cancer were not included in the study. Data was also collected regarding treatment with levothyroxine for those patients who did develop hypothyroidism.

Women were more likely to become subclinically or overtly hypothyroid (53%) compared to men (34%). Of the 538 patients in the study, subclinical hypothyroidism developed in 71 (13%), and overt hypothyroidism in 144 (27%). Hyperthyroidism was detected in 18 patients who subsequently became hypothyroid. Most cases of hypothyroidism developed within 6 months but some took up to 18 months. The average survival time for those who remained with normal thyroid function was 685 days, but for those who became subclinically hypothyroid, it was 1005 days, and for those who became overtly hypothyroid it was 1643 days. Almost all the patients had advanced disease and about half had been treated with at least two TKIs. Hypothyroidism was also more frequent in patients with renal-cell cancer and GI stromal cancers.

More than 90% of those with overt hypothyroidism received levothyroxine replacement therapy (132 of 144). Patients who were given levothyroxine for a TSH above 5 and below 10 mIU/L generally had symptoms such as fatigue, depression, or worsening functional status. The 27 patients given replacement levothyroxine for a TSH between 5 and 10 mIU/L survived longer than the 83 patients who were not treated.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study showed that new hypothyroidism—sometimes preceded by a hyperthyroid phase—developed after TKI drugs in ~40% of patients, and they survived longer. Hypothyroid patients treated with levothyroxine seemed to have a longer overall survival than those not given levothyroxine. It is not clearly understood as to why many patients who receive the TKI therapy for non-thyroidal cancer develop hypothyroidism. However, this study suggests that thyroid function tests should be measured before treatment with TKIs and then periodically after for at least for the first 6 months and especially in women. However, it appears that patients who develop this condition may have an improved survival. Further studies are needed to better understand the survival benefit and to determine if thyroid function on TKIs are a real prognostic factor.

—Vibhavasu Sharma, MD

HYPOTHYROIDISM, continued

ATA THYROID BROCHURE LINKS

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

ABBREVIATIONS & DEFINITIONS

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

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.

Overt Hypothyroidism: clear hypothyroidism an increased TSH and a decreased T_4 level. All patients with overt hypothyroidism are usually treated with 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.

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.

Tyrosine kinases: proteins that are overactive in many of the pathways that cause cells to be cancerous. Inhibiting these proteins with drugs known as tyrosine kinase inhibitors are effective chemotherapy drugs for cancers, including advanced thyroid cancer

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THYROID FUNCTION TESTS

A high proportion of serum rT_3 tests are ordered by a relatively small number of providers in the United States

BACKGROUND

Different types of laboratory tests are available for evaluation of thyroid disorders. These tests are used mainly to measure either hormones (like TSH, T_4 and T_3) or thyroid antibodies. Extensive clinical studies have been done to guide clinicians to choose the most effective test in every clinical situation.

Reverse T_3 (rT_3) is not one of the primary hormones produced by thyroid gland. It is mostly produced inside the cells in other tissues from the breakdown of T_4. The normal pathway is that T_4 is broken down to T_3, which is the active hormone. T_4 can also be broken down to rT_3, which is an inactive hormone. The production of T_3 and rT_3 is exactly opposite: the higher the T_3 level, the lower the rT_3 level; the lower the T_3 level, the higher the rT_3 level. Because of this relationship, and the fact that rT_3 is inactive, most clinicians do not use measurement of rT_3 for assessing a patient for hypothyroidism or hyperthyroidism. Still, some providers continue to order rT_3 in the assessment of thyroid function. This study was done to identify the ordering pattern of serum rT_3 by clinicians.

THE FULL ARTICLE TITLE

Schmidt RL et al. Does reverse triiodothyronine testing have clinical utility? An analysis of practice variation based on order data from a national reference laboratory. Thyroid 2018 Jul; 28(7): 842-848.

SUMMARY OF THE STUDY

The data from the National Reference Laboratory was used to conduct this study. The authors reviewed all the thyroid related tests that had been ordered from November 2015 to November 2016. They studied the records to find out the ordering pattern of the tests based on hospital types (for example, community versus academic hospitals) and providers (type of specialty). They also reviewed the published medical articles about rT_3 and did a Google search to identify the information available in internet to public about rT_3.

They found that relatively small proportion of providers had ordered majority of rT_3 tests. Of the 100 providers who had ordered rT_3 the most, 60% were practitioner of functional medicine and 40% conventional medicine (thyroid specialists, internal medicine, family medicine and gynecologist). Functional medicine was defined as a form of alternative medicine often based on complementary and holistic treatment techniques.

The review of medical articles about this topic showed that 90% were published before 2000 and provided limited evidence to support measuring rT_3 for evaluation of regular thyroid disorders like hypothyroidism and hyperthyroidism. Most of the publications were about the effect of medications, medical conditions other than thyroid disease and severe illness on rT_3 level.

The Google search showed mostly links to published articles in medical journals. Most of the webpages that discussed the use of rT_3 level for clinical purposes were 8-fold more associated with functional medicine than conventional medicine.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study suggests that the majority of rT_3 tests are ordered by a relatively small proportion of clinicians, mostly providers practicing functional medicine. The review of medical literature does not support routine measurement of rT_3 in clinical care of a patient with hypothyroidism and hyperthyroidism. This is important for patients who have thyroid disease and would like to be involved in decision making regarding their care. This might be especially important for patients who have to pay or share the cost of their laboratory tests.

— Shirin Haddady, MD

THYROID FUNCTION TESTS, continued

ATA THYROID BROCHURE LINKS

Thyroid Function Tests: https://www.thyroid.org/thyroid-function-tests/
Hypothyroidism (Underactive): https://www.thyroid.org/hypothyroidism/
Hyperthyroidism (Overactive): https://www.thyroid.org/hyperthyroidism/
Thyroid Disease and Complementary and Alternative Medicine (CAM): https://www.thyroid.org/thyroid-disease-cam/

ABBREVIATIONS & DEFINITIONS

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

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.

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

Reverse Triiodothyronine (rT3): the inactive thyroid hormone produced from thyroxine in various tissues in the body. Levels of T_3 and rT_3 are exactly opposite each other.

Thyroid Awareness Monthly Campaigns

The ATA will be highlighting a distinct thyroid disorder each month and a portion of the sales for Bravelets™ will be donated to the ATA. The month of **January** is **Thyroid Awareness Month** and a bracelet is available through the **ATA Marketplace** to support thyroid cancer awareness and education related to thyroid disease.

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THYROID EYE DISEASE

Adding mycophenolate to infusions of methylprednisolone improves treatment of Graves' eye disease.

BACKGROUND

Thyroid eye disease is most often associated with Graves' disease, so much so that it usually referred to as Graves' ophthalmopathy (GO). GO is an autoimmune disorder that ranges from mild to severe disease. In its' most severe form, GO causes bulging of the eyes, blurry or double vision, pain and swelling around the eyes and altered eye movement. Moderate-to-severe GO is usually associated with poor clinical outcomes and impaired quality of life as treatment is limited. GO is currently treated with a course of steroids, particularly intravenous methylprednisolone, but response is often limited and there are significant side effects to high dose steroids. Mycophenolate is an immunosuppressive medication that showed clinical efficacy in GO treatment in previous studies. This study aimed to compare the efficacy and safety of combination therapy of mycophenolate and intravenous methylprednisolone to the standard regimen of methylprednisolone alone.

THE FULL ARTICLE TITLE

Kahaly GJ et and the European Group on Graves' Orbitopathy (EUGOGO). Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial. Lancet Diabetes Endocrinol. 2018 Apr;6(4):287-298. doi: 10.1016/S2213-8587(18)30020-2. Epub 2018 Jan 31.

SUMMARY OF THE STUDY

This study compared combined mycophenolate with intravenous methylprednisolone therapy versus intravenous methylprednisolone alone in active moderate-to-severe GO. A total of 81 out of 164 patients from four European centers received treatment with methylprednisolone alone (weekly infusions for 3 months) and 83 received combination of methylprednisolone with mycophenolate (weekly infusions for 3 months and twice daily tablet for 6 months).

Response to therapy was defined as improvement in eye findings. Symptoms measured by a standardized clinical activity score and severity of GO were assessed at 3, 6 and 9 months. Patients also filled out quality of life questionnaire at 3, 6 and 9 months. Relapse defined as worsening of symptoms that occurred after a response was assessed at 6 and 9 months. Safety of the medications was monitored during time of the study.

Response to therapy was observed in 36 of 73 (49%) patients in the methylprednisolone alone group and 48 of 76 (63%) patients in the combination group. At 6 months, 38 of 72 (53%) patients on methylprednisolone and 53 of 75 (71%) patients on combination therapy responded to treatment. At 9 months, 46% of patients on methylprednisolone compared to 67% on methylprednisolone with mycophenolate continued to respond to therapy. At 6 months, relapse occurred in 4 of 38 (11%) patients in the monotherapy group and 4 of 53 (8%) patients in the combination group. At 9 months, relapse occurred in additional 3 (8%) patients in the monotherapy group and 2 (4%) patients in the combination group. Drug-related adverse events were similar in both groups.

Although no significant difference was seen in the response rate at 3 months or relapse rate at 6 and 9 months, advanced analysis suggested that addition of mycophenolate to treatment with methylprednisolone improved response rate to therapy by 6 months in patients with active and moderate-to-severe GO.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study suggests that combination therapy of mycophenolate and methylprednisolone compared to methylprednisolone alone is more efficient in treatment of moderate-to- severe GO. This is an important result as moderate-to-severe GO is usually associated with poor clinical outcomes as treatment is limited. Indeed, this study shows that been in the group that responded the best, 30-40% of patients did not respond to treatment. More effective therapy is needed but this study is encouraging for patients with moderate-to-severe GO.

—Valentina D. Tarasova, MD

THYROID EYE DISEASE, continued

ATA WEB BROCHURE LINKS:

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

ABBREVIATION AND DEFINITIONS:

Clinical Activity Score: a scoring system used to evaluate patients with Graves' ophthalmopathy, and is based on classical signs of inflammation (pain, redness, swelling and function) and that helps predict which patients will benefit from immunosuppressive treatment

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.

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

Steroids/Glucocorticoids: general anti-inflammatory and immunosuppressive drugs that are commonly used for the treatment of many autoimmune diseases associated with inflammation

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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.

WHO WE ARE (in alphabetical order)

AMERICAN THYROID ASSOCIATION
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"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.