AMERICAN THYROID ASSOCIATION
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Clinical Thyroidology® for the Public

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Radioactive iodine therapy has been available as a treatment option for patients with hyperthyroidism since the 1940s. The CTTFS has been following >35,000 patients with hyperthyroidism who were treated with radioactive iodine therapy between 1946 and 1964 and previously reported no increased risk of dying of cancer in this group. In the current study, the authors extend analysis of the previous CTTFS by including an additional 24+ years of patient follow-up in order to assess the associations between radioactive iodine therapy for the treatment of hyperthyroidism and overall death from cancer.

Kitahara C et al 2019 Association of radioactive iodine treatment with cancer mortality in patients with hyperthyroidism. JAMA Intern Med. Epub 2019 Jul 1. PMID: 31260066.

Prior studies have shown that obesity is a risk factor for several cancers and may contribute to the risk of developing thyroid cancer. Obesity is one aspect of metabolic health, which also includes blood sugar, lipids and blood pressure. This study examined the effect of obesity on the incidence of thyroid cancer according to metabolic health status.

Kwon H et al 2019 Metabolic Obesity Phenotypes and Thyroid Cancer Risk: A Cohort Study. Thyroid 29:349-358.

Bariatric surgery is becoming more common and is the most effective treatment for severely obese individuals. Since levothyroxine is absorbed in the small intestine, the amount of levothyroxine required may change after bariatric surgery in patients who have hypothyroidism. This study was done to compare changes in levothyroxine dose in the first 2 years after the 2 most common types of bariatric surgery.

Julià H et al. 2019 Changes in Thyroid Replacement Therapy after Bariatric Surgery: Differences between Laparoscopic Roux-en-Y Gastric Bypass and laparoscopic Sleeve Gastrectomy. Obes Surg doi. 10.1007/s11695-019-03890-9 [Epub ahead of print]

Medullary thyroid cancer arises from the C-cells in the thyroid that produce the hormone calcitonin. After surgery, calcitonin can be used as a cancer marker to help determine if any cancer cells are remaining. This study was designed to check how long it takes calcitonin to normalize after successful medullary thyroid cancer surgery.

Machens A et al 2019 Time to calcitonin normalization after surgery for node-negative and node-positive medullary thyroid cancer. Br J Surg 106:412-418. Epub 2019 Feb 6. PMID: 30725475.

While radioactive iodine therapy is usually very effective, advanced thyroid cancer can become resistant to radioactive iodine. A few, small studies have showed that targeted therapy with drugs that inhibit BRAF and MEK may restore the ability of the thyroid cancer cells to take up radioactive iodine. This study evaluated whether the radioactive iodine sensitivity is restored in patients with advanced, radioactive iodine resistant thyroid cancer treated with either a single drug or a combination of BRAF and/or MEC inhibitors.

Jaber T et al 2018 Targeted therapy in advanced thyroid cancer to resensitize tumors to radioactive iodine. J Clin Endocrinol Metab 103:3698–3705. PMID: 30032208.

Measuring molecular markers, which are gene mutations that are seen in cancer, allows the identification of indeterminate biopsies as benign and, thus, to avoid surgery. There are 3 such companies offering measurement of molecular markers in thyroid biopsy specimens. The 3 papers reviewed report the performance of these assays in evaluating Bethesda III and IV indeterminate biopsies.

Steward DL et al Performance of a multigene genomic classifier in thyroid nodules with indeterminate cytology: a prospective blinded multicenter study. JAMA Oncol. Epub 2018 Nov 8. PMID: 30419129.

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★★★★ CHARITY NAVIGATOR Four Star Charity

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, 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.

August is Thyroid and Pregnancy Awareness Month.

In this issue, the studies ask the following questions:

- Does radioactive iodine therapy for Graves' disease cause cancer?
- Is obesity a risk factor for thyroid cancer?
- Does bariatric surgery change levothyroxine dose requirements?
- Are calcitonin measurements helpful in following patients with medullary thyroid cancer after surgery?
- Can cancer drugs make radioactive iodine-resistant thyroid cancer responsive to radioactive iodine again?
- How well do current molecular marker tests identify benign nodules that have indeterminate biopsy results?

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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HYPERTHYROIDISM

Does radioactive iodine therapy for Graves' disease cause cancer?

BACKGROUND

Graves' disease is the most common cause of hyperthyroidism. Radioactive iodine therapy has been available as a treatment option for patients with hyperthyroidism since the 1940s. While very high doses of radioactive iodine (>400 mCi) have been associated with increasing the risk for cancer, the relatively low doses typically used to treat hyperthyroidism (5-20 mCi) have been thought to result in minimal, if any, increased cancer risk. To address this concern, the Cooperative Thyrotoxicosis Therapy Follow-up Study (CTTFS) has been following >35,000 patients with hyperthyroidism (due to either Graves' disease or overactive thyroid nodules) in the United States and the United Kingdom who were treated with radioactive iodine therapy between 1946 and 1964. In 1998, data from this study demonstrated that radioactive iodine therapy for hyperthyroidism was not associated with an increased risk of dying of cancer. In the current study, the authors extend analysis of the previous CTTFS by including an additional 24+ years of patient follow-up and by using a new method to examine exposure of the body to radioactive iodine, in order to assess the associations between radioactive iodine therapy for the treatment of hyperthyroidism and overall death from cancer.

THE FULL ARTICLE TITLE

Kitahara C et al 2019 Association of radioactive iodine treatment with cancer mortality in patients with hyperthyroidism. JAMA Intern Med. Epub 2019 Jul 1. PMID: 31260066.

SUMMARY OF THE STUDY

The CTTFS included patients who received radioactive iodine therapy for hyperthyroidism at 24 U.S. medical centers and 1 U.K. site between 1946 and 1964. Patients were followed through 1968 with office visits and laboratory measurements; subsequent clinical follow-up was obtained from medical records, patient questionnaires, and national databases that included the U.S. Social Security Administration and the U.S. National Death Index. Of the 35,630 patients in the CTTFS, only the 18,805 radioactive iodine-treated patients with complete records and who did not have a cancer diagnosis prior to radioactive iodine therapy were included in the current analysis.

Of the 18,805 patients analyzed, the average age at study entry was 49 years, 78% were female and 93.7% had Graves' disease. The average total dose of radioactive iodine was 10.1 mCi for patients with Graves' disease and 17.6 mCi for patients with autonomous thyroid nodules; 34.1% of the patients received two or more radioactive iodine treatments. During the average follow-up of 26 years, there appeared to be a statistically significant dose-response relationship for death from breast cancer (12% increased risk) and from all solid cancers combined (5% increased risk). In subgroup analyses, the increased mortality risk from all solid cancers persisted in patients receiving only 1 dose of radioactive iodine but was no longer significant for breast cancer. There was no statistically increased risk for deaths related to leukemia, non-Hodgkin lymphoma, multiple myeloma, or thyroid cancer. The authors estimate that 14% of breast cancer deaths and 7% of all other solid-cancer deaths were attributed to radioactive iodine exposure in this group.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This is an important study as it suggests that there is indeed an increased risk of some solid cancers after radioactive iodine therapy for hyperthyroidism, something that prior studies failed to show. While there is data to show a slight increase in cancers in patients treated with high dose radioactive iodine therapy for thyroid cancer, this is the 1st study to suggest there is an increased risk after low dose radioactive iodine therapy. Additional studies are needed to confirm this study and to clarify the risks and benefits of low dose radioactive iodine therapy for hyperthyroidism, especially as compared to medical therapy with anti-thyroid drugs and surgery.

— Alan P. Farwell, MD, FACE

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HYPERTHYROIDISM, continued

ATA THYROID BROCHURE LINKS

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

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.

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).

mCi: millicurie, the units used for I-131. Typical doses for hyperthyroidism are 5-15 mCi, while doses for thyroid cancer range from 30-200 mCi.

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THYROID CANCER

Is obesity a risk factor for thyroid cancer?

BACKGROUND

Thyroid cancer has been the fastest rising cancer in women over the past few decades, although this more recently has reach a steady level. A major cause of this increase is likely due to increased detection of small, low-risk thyroid cancers due to more frequent imaging tests. However, the number of larger cancers has also increased. Thus, it is clear that other factors are involved. Some of these other factors may include lifestyle and environmental factors. Prior studies have shown that obesity is a risk factor for several cancers and may contribute to the risk of developing thyroid cancer. Obesity is one aspect of metabolic health, which also includes blood sugar, lipids and blood pressure. Healthy metabolic health is described as having ideal levels of blood sugar, lipids, blood pressure and ideal weight without using medications. Unhealthy metabolic health would include those individuals with abnormalities in these areas, or requiring medication to control any of these areas. This study examined the effect of obesity on the incidence of thyroid cancer according to metabolic health status.

THE FULL ARTICLE TITLE

Kwon H et al 2019 Metabolic Obesity Phenotypes and Thyroid Cancer Risk: A Cohort Study. Thyroid 29:349-358.

SUMMARY OF THE STUDY

The study included 255,051 eligible participants from the Kangbuk Samsung Health Study who had a health maintenance examination between 2002-2014. Participants were 18 years and older, had at least one follow-up visit and were thyroid cancer-free at baseline. Information on socioeconomic status, lifestyle factors such as physical activity, smoking and alcohol use, medical and medication history was taken from self-administered questionnaires. Weight, height, waist circumference and blood pressure were evaluated by trained nurses. Blood was also obtained to test levels of glucose, lipids, insulin, and thyroid hormones. Additionally, self-reported information on thyroid cancer and age at diagnosis was obtained from the participants at baseline and at each follow-up visit. Thyroid cancer incidence was then estimated by body mass index (BMI) category and waist circumference in metabolically healthy and unhealthy men and women.

Overall, 57% of the participants were men. A total of 63.8% of men and 36.8% of women were metabolically unhealthy. Patients were followed-up for an average of 5.3 years. Overall, 1037 men and 1890 women developed thyroid cancer. The authors showed that a higher BMI was associated with an increased risk of developing thyroid cancer in metabolically healthy and unhealthy men and in metabolically unhealthy women. Additionally, increased waist circumference was associated with increased risk of thyroid cancer in metabolically unhealthy men and women.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study showed that higher BMI and increased waist circumference were associated with an increased risk of thyroid cancer in metabolically unhealthy men and women, as well as metabolically healthy men. This may suggest that obesity, especially if associated with metabolic abnormalities, such as high blood pressure, diabetes mellitus and high cholesterol, could be linked to the increased thyroid cancer incidence observed in the past few years. This has implications as obesity and its metabolic abnormalities are potentially risk factors that can be modified, for example, by lifestyle changes. Further research is needed to better understand the relationship between obesity and thyroid cancer, and whether weight loss may modify the risk for thyroid cancer.

— Maria Papaleontiou, MD

ATA THYROID BROCHURE LINKS

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

THYROID CANCER, continued

ABBREVIATIONS & DEFINITIONS

Incidence: occurrence of a given medical condition in a population within a specified period of time.

Body-mass index (BMI): a standardized measure of obesity calculated by dividing the weight in kilograms by the square of the height. A normal BMI is 18.5-24.9, overweight is 25-30 and obese is >30.

Metabolic health: assessment includes levels of blood sugar, lipids, blood pressure and ideal weight. Healthy metabolic health is described as having ideal levels of blood sugar, lipids, blood pressure and ideal weight without using medications. Unhealthy metabolic health would include those individuals with abnormalities in these areas, or requiring medication to control any of these areas.

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HYPOTHYROIDISM

Levothyroxine dose may change after weight loss surgery in patients with hypothyroidism

BACKGROUND

Obesity is a major health problem in the United States and is getting worse. Further, the number of patients that are severely obese (BMC >35) is steadily increasing. These individuals are at high risk for significant weight-related complications. Bariatric, or weight loss, surgery is becoming more common and is the most effective treatment for severely obese individuals. The goal of bariatric surgery is to markedly decrease stomach volume so patients must eat less and, therefore, lose weight. Among different procedures used for bariatric surgery, sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) are mostly frequently used. In SG, stomach is cut to create a sleeve to the small intestines, decreasing the size of the stomach while keeping it intact. In RYGB, stomach is cut leaving only a small pouch, and the front portion of the remaining stomach is connected directly to the small intestines. Both procedures also decrease stomach acid content. In RYGB, the small intestines are also shortened. Since levothyroxine is absorbed in the small intestine, the amount of levothyroxine required may change after bariatric surgery in patients who have hypothyroidism. This study was done to compare changes in levothyroxine dose in the first 2 years after SG and RYGB bariatric surgery.

THE FULL ARTICLE TITLE

Julià H et al. 2019 Changes in Thyroid Replacement Therapy after Bariatric Surgery: Differences between Laparoscopic Roux-en-Y Gastric Bypass and laparoscopic Sleeve Gastrectomy. Obes Surg doi. 10.1007/s11695-019-03890-9 [Epub ahead of print]

SUMMARY OF THE STUDY

A total of 35 patients (91.4% women) with hypothyroidism who underwent bariatric surgery in Spain between January 2004 and December 2015 were included in the study. A total of 13 patients had SG and 22 patients had RYGB. All patient had blood thyroid stimulating hormone (TSH) levels measured before surgery and at 3, 6, 12, 18, and 24 months after bariatric surgery, and levothyroxine dose was changed as needed. At each visit, the levothyroxine dose was recorded as 1) total dose per day and 2) total dose/body weight (weight-based dose) per day.

At 24 months after bariatric surgery, the average total daily levothyroxine dose was significantly less in patients who had SG (133.7 mcg/day before surgery as compared to 104 mcg/day after surgery) while the average weight-based daily levothyroxine dose was unchanged (1.15 mcg/kg/day before surgery and 1.11 mcg/kg/day after surgery). In contrast, the average total daily levothyroxine dose was unchanged in the RYGB group after surgery (129.5 mcg/day before surgery and 125.2 mcg/day after surgery). While the dose of the group as a whole did not change, there was a marked variability in changes in total daily levothyroxine dose among the patients who underwent RYGB, with 41% requiring a decrease in dose, 41% no change, and 18% an increase in dose. However, the average weight-based daily levothyroxine dose increased in RYGB group (1.11 mcg/kg/day before surgery and 1.57 mcg/kg/day after surgery).

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study shows that the levothyroxine requirements in patients with hypothyroidism change after bariatric surgery. Interestingly, while the total daily dose is more affected after SG than RYGB, the dose/body weight changed to a greater degree after RYGB than SG. Given the variability in changes in levothyroxine dose and potential need to decrease the levothyroxine dose after bariatric surgery, thyroid hormone levels should be closely monitored in patients with hypothyroidism for at least 24 months after bariatric surgery.

— Sun Lee, MD

HYPOTHYROIDISM, continued

ATA THYROID BROCHURE LINKS

Hypothyroidism (Underactive): https://www.thyroid.org/hypothyroidism/
Thyroid Hormone Treatment: https://www.thyroid.org/thyroid-hormone-treatment/
Thyroid and Weight: https://www.thyroid.org/thyroid-and-weight/

ABBREVIATIONS & DEFINITIONS

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

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

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

Bariatric surgery: surgery where the stomach volume is decreased to assist in weight loss. Two general types are Roux-en-Y gastric bypass, where part of the stomach is removed and gastric sleeve surgery, where the stomach is constricted but remains intact.

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THYROID CANCER

Calcitonin normalizes within 1 week after surgery in most patients with node-negative medullary thyroid cancer

BACKGROUND

Medullary thyroid cancer is a relatively rare type of thyroid cancer that often runs in families. In contrast to papillary and follicular thyroid cancer, which arise from the thyroid follicular cells, medullary thyroid cancer arises from the parafollicular cells (commonly known as C-cells) in the thyroid. The C-cells produce the hormone calcitonin, which has a minor effect on blood calcium levels. Calcitonin levels are also increased in patients with medullary thyroid cancer. Calcitonin can be measured as a blood test to help diagnose medullary thyroid cancer and its level can indicate the amount of medullary thyroid cancer present before thyroid surgery. After surgery, calcitonin can be used as a cancer marker to help determine if any cancer cells are remaining. If calcitonin levels normalize after surgery, it suggests that the cancer has not spread outside of the thyroid. Typically, calcitonin is measured about 3 months after thyroid surgery for medullary thyroid cancer. This study was designed to check how long it takes calcitonin to normalize after successful medullary thyroid cancer surgery.

THE FULL ARTICLE TITLE

Machens A et al 2019 Time to calcitonin normalization after surgery for node-negative and node-positive medullary thyroid cancer. Br J Surg 106:412-418. Epub 2019 Feb 6. PMID: 30725475.

SUMMARY OF THE STUDY

The medical records of patients who had surgery for medullary thyroid cancer at a University teaching hospital in Germany between 1994 and 2018 were studied. Only those patients who did not need a second surgery had their information included in the study. Calcitonin levels were measured before surgery and at the time of discharge from the hospital which was 3-6 days after the operation. A little over 6 out of 10 patients had normal calcitonin levels on the day of discharge from the hospital, which was 4 days after surgery on average. The other patients had more aggressive cancer, bigger surgeries and were in the hospital a little over 6 days on average. The patients with normalized calcitonin levels were more often women, had lower calcitonin levels before surgery (545 vs 9513 pg/mL), had smaller cancers (about 1 cm compared to about 2.5cm) and had fewer lymph nodes with medullary thyroid cancer in them (1 vs 17). The more lymph nodes removed with medullary thyroid cancer in them was associated with a longer time to calcitonin normalization after the surgery (as long as 50+ days on average if more than 10 lymph nodes had disease).

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Patients who do not have lymph node involvement with medullary thyroid cancer often have normal calcitonin levels by 5 days after surgery. The more lymph nodes containing medullary thyroid cancer there are, the longer time it takes for the calcitonin to normalize, even if all of the disease is removed. These findings are important to patients as they may be reassured within a week after surgery for medullary thyroid cancer with negative calcitonin measurements. Patients may not have to wait 3 months to gain information on the presence or absence of medullary thyroid cancer after surgery. It is important that patients understand that even if the calcitonin is detectable early after medullary thyroid cancer surgery, it may normalize over time.

— Joshua Klopper, MD

ATA THYROID BROCHURE LINKS

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

THYROID CANCER, continued

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.

Calcitonin: a hormone that is produced in humans by the parafollicular cells (commonly known as C-cells) of the thyroid gland. Calcitonin has a minor effect on blood calcium levels. Calcitonin levels are increased in patients with medullary thyroid cancer.

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

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www.thyroid.org/donate/

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THYROID CANCER

Thyroid cancer that no longer responds to radioactive iodine may become sensitive after starting anti-cancer drugs

BACKGROUND

The usual treatment for thyroid cancer is surgery to remove the thyroid gland. If the patient is at increased risk for thyroid cancer recurrence, surgery is followed by radioactive iodine therapy to destroy any remaining thyroid cancer cells. Most patients with thyroid cancer that require radioactive iodine therapy respond to the initial treatment. Those rare patients with either high risk thyroid cancers or those that continue to have recurrence or persistence of the thyroid cancer often receive additional radioactive iodine treatments. However, thyroid cancer cells can lose their capacity to take up iodine from the circulation and, therefore, they can become resistant to radioactive iodine therapy. Certain gene mutations in the thyroid cancer cells, especially BRAF mutations, can affect the thyroid cells ability to take up iodine. A few, small clinical studies have showed that targeted therapy with drugs that inhibit BRAF and MEK, another gene mutation in thyroid cancer cells, may restore the ability of the thyroid cancer cells to take up radioactive iodine. This study performed at the University of Texas MD Anderson Cancer Center evaluated whether the radioactive iodine sensitivity is restored in 13 patients with advanced, radioactive iodine resistant thyroid cancer treated with either a single drug or a combination of BRAF and/or MEC inhibitors.

THE FULL ARTICLE TITLE

Jaber T et al 2018 Targeted therapy in advanced thyroid cancer to resensitize tumors to radioactive iodine. J Clin Endocrinol Metab 103:3698–3705. PMID: 30032208.

SUMMARY OF THE STUDY

This is a study of 13 patients with advanced, radioactive iodine resistant thyroid cancer who underwent a radioactive iodine whole-body scan (WBS) while being treated with BRAF and/ or MEK inhibitor drugs. The average age was 55.6 years. A total of 10 patients (77%) had classic or follicular variant of papillary thyroid cancer, 2 patients (15%) had poorly differentiated thyroid cancer and 1 patient (8%) had follicular thyroid cancer. The 9 patients with thyroid cancer with a BRAF mutation were treated with a BRAF inhibitor (7 with dabrafenib, 1 with vemurafenib, and 1 with a combination dabrafenib and trametinib). The 3 patients with thyroid cancer with a RAS mutation were treated with a MEK inhibitor (2 with trametinib, 1 with an investigational drug). One patient who had no identified mutations was treated with a MEK inhibitor (trametinib). The average duration of drug therapy before the radioactive iodine scanning was 14 months.

A total of 8 of the 13 patients (62%) showed radioactive iodine uptake on the whole-body scan and received and additional radioactive iodine treatment. One additional patient received radioactive iodine treatment despite of having a negative radioiodine scan. Of note, all 3 patients with RAS mutations showed uptake on the scan and received radioactive iodine treatment. The average I-131 dose was 204 mCi. The cancer drug was discontinued 2 days after the radioactive iodine treatment. During an average follow-up period of 14 months after the radioactive iodine treatment, all nine patients remained off the cancer drugs.

Among the 9 patients who received radioactive iodine therapy, 8 had stable disease and 1 had progressive disease on drug therapy prior to the radioactive iodine treatment. After the radioactive iodine therapy, 3 patients had a partial response, while 5 patients had stable disease. The patient with progressive disease prior to the radioactive iodine therapy had 88% shrinkage of the metastatic cancer lesions after the radioactive iodine therapy. When comparing the responses in the 9 patients on drug therapy prior to the radioactive iodine treatment, 5 patients showed greater responses after the radioactive iodine therapy than with the prior drug therapy.

With regard to adverse effects, 2 patients had an inflammation of the lungs and 1 patient had severe inflammation of the salivary glands after the radioactive iodine therapy. The symptoms of all 3 patients resolved within three months.

THYROID CANCER, continued

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Targeted therapy with BRAF or MEK inhibitor drugs in patients with advanced thyroid cancer with BRAF and/or RAS mutations can re-sensitize the cancers to radioactive iodine and subsequent radioactive iodine therapy can result in a positive clinical response. This provides hope for the rare patients with advanced, progressive thyroid cancers. Additional studies are needed to identify the patients who are most likely to benefit from this treatment, and to evaluate the magnitude and duration of the clinical response and its impact on survival.

— Alina Gavrila, MD, MMSC

ATA THYROID BROCHURE LINKS

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

ABBREVIATIONS & DEFINITIONS

Differentiated thyroid cancer (DTC): includes papillary and follicular thyroid cancer.

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

Iodine: an element found naturally in various foods that is important for making thyroid hormones and for normal thyroid function. Common foods high in iodine include iodized salt, dairy products, seafood and some breads.

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).

Radioactive iodine uptake (RAIU): this is a measurement of thyroid tissue activity, either normal or cancerous, and is reported as the percent of a dose of radioactive iodine that is retained in the thyroid tissue 24 h after the dose is given.

Targeted therapy (TTx): drugs that specifically attack the cancer cells without damaging the normal cells, thus resulting in fewer side effects.

Mutation: A permanent change in one of the genes.

Cancer-associated genes: these are genes that are normally expressed in cells. Cancer cells frequently have mutations in these genes. It is unclear whether mutations in these genes cause the cancer or are just associated with the cancer cells. The cancer-associated genes important in thyroid cancer are BRAF, RET/PTC, TERT and RAS.

BRAF gene: this is a gene that codes for a protein that is part of a chain of molecules working together to signal the cells when to grow and divide. Mutations in the BRAF gene in adults appear to cause cancer. Dabrafenib and vemurafenib are anticancer drugs that target the mutated BRAF proteins within the cancer cells, thus slowing down the cancer growth.

MEK 1 and 2: are proteins located further down the chain of molecules in the BRAF pathway. Trametinib is an anticancer drug that targets these proteins, thus affecting the cancer growth.

Sialadenitis: inflammation of salivary gland.

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THYROID CANCER

An evaluation of the molecular marker tests for thyroid cancer

BACKGROUND

Thyroid nodules are very common, occurring in up to 50% of the population. The main concern about a thyroid nodule is whether it is a cancer. Fortunately, ~95% of thyroid nodules are benign (non-cancer). Thyroid biopsy is the best test outside of surgery in determining whether thyroid nodule is cancerous or not. However, 15-20% of thyroid biopsies are indeterminate, meaning a diagnosis between cancer and benign cannot be made by simply looking at the cells. In the most recent cytology classification system, indeterminate biopsies fall into Bethesda category III (atypia of unknown significance (AUS) or follicular lesion of unknown significance (FLUS) and Bethesda category IV (follicular or hurthle cell lesion). In the past, most of the patients with indeterminate thyroid biopsies were referred to surgery, resulting in a lot of surgeries for benign disease.

Measuring molecular markers, which are gene mutations that are seen in cancer, allows the identification of indeterminate biopsies as benign and, thus, to avoid surgery.

There are 3 such companies offering measurement of molecular markers in thyroid biopsy specimens:

- Thyroseq™ — a gene sequencing test that evaluates 5 classes of genetic alterations in 112 genes,
- Afirma GEC or GSC™ — a gene-expression classifier that identifies biopsies as "benign" or "suspicious," and
- mir-THYtype™ — an mRNA-based classifier test.

These 3 papers report the performance of these assays in evaluating Bethesda III and IV indeterminate biopsies.

SUMMARY OF THE STUDIES

Thyroseq™

Steward DL et al Performance of a multigene genomic classifier in thyroid nodules with indeterminate cytology: a prospective blinded multicenter study. JAMA Oncol. Epub 2018 Nov 8. PMID: 30419129.

This study was performed across 10 institutions (9 in the United States and 1 in Singapore) from January 2015 to December 2016. Patients who underwent biopsies of thyroid nodules that were indeterminate and who subsequently underwent surgery were included. A total of 256 subjects with 286 indeterminate nodules were included in the analysis. Of these biopsies, 59% of nodules had a negative Thyroseq v3 result (i.e., no high-risk mutations). Five (3%) samples were reported as negative that turned out to be low-risk cancers. Thyroseq v3 identified 13 of 34 (38%) of benign Hürthle-cell adenomas as positive for cancer, but correctly identified 10 of 10 Hürthle-cell cancers.

Afirma™

Harrell RM et al 2018 Statistical comparison of Afirma GSC and Afirma GEC outcomes in a community endocrine surgical practice: early findings. Endocr Pract. E-pub 2018 Nov 1. PMID: 30383497.

This study reviewed nodules tested with the original Afirma GEC (collected January 2011 to June 2017) or the Afirma GSC (collected August 2017 to June 2018). A total of 481 GEC-tested nodules were compared to 139 GSC-tested nodules. Benign results were obtained in 85 of 139 (61.2%) in the GSC group and 200 of 481 (41.6%) in the GEC group, resulting in a concomitant decrease in surgery. The largest increase in identifying benign results was in those with Hurtle cell cytology, as 17.3% of GEC-tested nodules were reported as benign as compared to 64.7% of GSC-tested samples. The percentage of suspicious nodules using Afirma that were proved to be cancer was 120 of 209 (57.4%) in the GEC group and 28 of 37 (75.7%) in the GSC group.

mir-THYtype™

Santos MTD et al 2018 Molecular classification of thyroid nodules with indeterminate cytology: development and validation of a highly sensitive and specific new miRNA-based classifier test using fine-needle aspiration smear slides. Thyroid. Epub 2018 Nov 22. PMID: 30319072.

THYROID CANCER, continued

An analysis was performed to identify patients with thyroid nodules who underwent thyroid biopsy between January 2013 and July 2017 that resulted in indeterminate cytology (Bethesda classes III to V) and who underwent total or partial thyroidectomy. Overall, the mir-THYpe test was able to correctly classify 153 of 173 samples. Of the 76 cancer samples, 70 were correctly classified while 83 of the 97 benign samples were correctly classified.

WHAT ARE THE IMPLICATIONS OF THESE STUDIES?

These 3 molecular marker tests use different techniques to evaluate indeterminate biopsy sample and all perform well to identify benign nodules which do not have to proceed to surgery. Two of these tests are currently being used commercially (Thyroseq™ and Afirma GSC™) while the mir-THYtype™ is a new test that does not require a separate biopsy sample for analysis. These tests are a major step forward in the analysis of thyroid nodules and present a much great opportunity to decrease the number of surgeries done for benign thyroid nodules.

— Alan P. Farwell, MD, FACE

ATA THYROID BROCHURE LINKS

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

ABBREVIATIONS & DEFINITIONS

Thyroid biopsy: a simple procedure that is done in the doctor's office to determine if a thyroid nodule is benign (non-cancerous) or cancer. The doctor uses a very thin needle to withdraw cells from the thyroid nodule. Patients usually return home or to work after the biopsy without any ill effects.

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) – Bethesda category III) or when the diagnosis is a follicular or hurthle cell lesion (Bethesda category IV). 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.

Molecular markers: genes and microRNAs that are expressed in benign or cancerous cells. Molecular markers can be used in thyroid biopsy specimens to either to diagnose cancer or to determine that the nodule is benign. The two most common molecular marker tests are the Afirma GSC™ and Thyroseq™.

Genes: a molecular unit of heredity of a living organism. Living beings depend on genes, as they code for all proteins and RNA chains that have functions in a cell. Genes hold the information to build and maintain an organism's cells and pass genetic traits to offspring.

Mutation: A permanent change in one of the genes.

microRNA: a short RNA molecule that has specific actions within a cell to affect the expression of certain genes.

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Clinical Thyroidology® for the Public

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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
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

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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"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.

Hyperthyroidism in Pregnancy

WHAT IS THE THYROID GLAND?

The thyroid gland is a butterfly-shaped endocrine gland that is normally located in the lower front of the neck. The thyroid's job is to make thyroid hormones, which are secreted into the blood and then carried to every tissue in the body. Thyroid hormone helps the body use energy, stay warm and keep the brain, heart, muscles, and other organs working as they should.

WHAT ARE THE NORMAL CHANGES IN THYROID FUNCTION ASSOCIATED WITH PREGNANCY?

HORMONE CHANGES. A normal pregnancy results in a number of important physiological and hormonal changes that alter thyroid function. These changes mean that laboratory tests of thyroid function must be interpreted with caution during pregnancy. Thyroid function tests change during pregnancy due to the influence of two main hormones: human chorionic gonadotropin (hCG), the hormone that is measured in the pregnancy test and estrogen, the main female hormone. HCG can weakly turn on the thyroid and the high circulating hCG levels in the first trimester may result in a slightly low TSH. When this occurs, the TSH will be slightly decreased in the first trimester and then return to normal throughout the duration of pregnancy. Estrogen increases the amount of thyroid hormone binding proteins in the serum which increases the total thyroid hormone levels in the blood since >99% of the thyroid hormones in the blood are bound to these proteins. However, measurements of "Free" hormone (that are not bound to protein, representing the active form of the hormone) usually remain normal. The thyroid is functioning normally if the TSH and Free T4 remain in the trimester-specific normal ranges throughout pregnancy.

SIZE CHANGES. The thyroid gland can increase in size during pregnancy (enlarged thyroid = goiter). However, pregnancy-associated goiters occur much more frequently in iodine-deficient areas of the world. It is relatively uncommon in the United States. If very sensitive imaging techniques (ultrasound) are used, it is possible to detect an increase in thyroid volume in some women. This is usually only a 10-15% increase in size and is not typically apparent on physical examination by the physician. However, sometimes a significant goiter may develop and prompt the doctor to measure tests of thyroid function.

WHAT IS THE INTERACTION BETWEEN THE THYROID FUNCTION OF THE MOTHER AND THE BABY?

For the first 18-20 weeks of pregnancy, the baby is completely dependent on the mother for the production of thyroid hormone. By mid-pregnancy, the baby's thyroid begins to produce thyroid hormone on its own. The baby, however, remains dependent on the mother for ingestion of adequate amounts of iodine, which is essential to make the thyroid hormones. The World Health Organization recommends iodine intake of 250 micrograms/day during pregnancy to maintain adequate thyroid hormone production. Because iodine intakes in pregnancy are currently low in the United States, the ATA recommends that US women who are planning pregnancy, pregnant, or breastfeeding should take a daily supplement containing 150 mcg of iodine.

HYPERTHYROIDISM & PREGNANCY

WHAT ARE THE MOST COMMON CAUSES OF HYPERTHYROIDISM DURING PREGNANCY?

Overall, the most common cause of hyperthyroidism in women of childbearing age is Graves' disease (see *Graves' Disease brochure*), which occurs in 0.2% of pregnant patients. In addition to other usual causes of hyperthyroidism (see *Hyperthyroidism brochure*), very high levels of hCG, seen in severe forms of morning sickness (hyperemesis gravidarum), may cause transient hyperthyroidism in early pregnancy. The correct diagnosis is based on a careful review of history, physical exam and laboratory testing.

WHAT ARE THE RISKS OF GRAVES' DISEASE/ HYPERTHYROIDISM TO THE MOTHER?

Graves' disease may present initially during the first trimester or may be exacerbated during this time in a woman known to have the disorder. In addition to the classic symptoms associated with hyperthyroidism, inadequately treated maternal hyperthyroidism can result in early labor and a serious complication known as pre-eclampsia. Additionally, women with active Graves' disease during pregnancy are at higher risk of developing very severe hyperthyroidism known as thyroid storm. Graves' disease often improves during the third trimester of pregnancy and may worsen during the post partum period.

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Hyperthyroidism in Pregnancy

WHAT ARE THE RISKS OF GRAVES' DISEASE/ HYPERTHYROIDISM TO THE BABY?

The risks to the baby from Graves' disease are due to one of three possible mechanisms:

1)UNCONTROLLED MATERNAL HYPERTHYROIDISM: Uncontrolled maternal hyperthyroidism has been associated with fetal tachycardia (fast heart rate), small for gestational age babies, prematurity, stillbirths and congenital malformations (birth defects). This is another reason why it is important to treat hyperthyroidism in the mother.

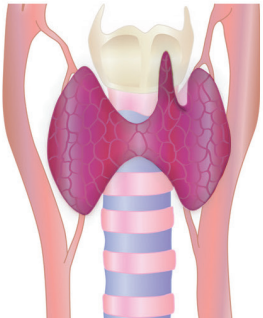
2)EXTREMELY HIGH LEVELS OF THYROID STIMULATING IMMUNOGLOBLULINS (TSI): Graves' disease is an autoimmune disorder caused by the production of antibodies that stimulate the thyroid gland referred to as thyroid stimulating immunoglobulins (TSI). These antibodies do cross the placenta and can interact with the baby's thyroid. High levels of maternal TSI's have been known to cause fetal or neonatal hyperthyroidism, but this is uncommon (only 1-5% of women with Graves' disease during pregnancy). Fortunately, this typically only occurs when the mother's TSI levels are very high (many times above normal). Measuring TSI in the mother with Graves' disease is recommended in early pregnancy and, if initially elevated, again around weeks 18-22.

When a mother with Graves' disease requires antithyroid drug therapy during pregnancy, fetal hyperthyroidism is rare because antithyroid drugs also cross the placenta and can prevent the fetal thyroid from becoming overactive. Of potentially more concern to the baby is when the mother has been treated for Graves' disease (for example radioactive iodine or surgery) and no longer requires antithyroid drugs. It is very important to tell your doctor if you have been treated for Graves' Disease in the past so proper monitoring can be done to ensure the baby remains healthy during the pregnancy.

3)ANTI-THYROID DRUG THERAPY (ATD). Methimazole (Tapazole) or propylthiouracil (PTU) are the ATDs available in the United States for the treatment of hyperthyroidism (see *Hyperthyroidism brochure*). Both of these drugs cross the placenta and can potentially impair the baby's thyroid function and cause fetal goiter. Use of either drug in the first trimester of pregnancy has been associated with birth defects, although the defects associated with PTU are less frequent and less severe. Definitive therapy (thyroid surgery or radioactive iodine treatment) may be considered prior to pregnancy in order to avoid the need to use PTU or methimazole in pregnancy. When ATDs are required, PTU is preferred until week 16 of pregnancy. It is recommended that the lowest possible dose of ATD be used to control maternal hyperthyroidism in order to minimize the development of hypothyroidism in the baby. Overall, the benefits to the baby of treating a mother with hyperthyroidism during pregnancy outweigh the risks if therapy is carefully monitored.

WHAT ARE THE TREATMENT OPTIONS FOR A PREGNANT WOMAN WITH GRAVES' DISEASE/ HYPERTHYROIDISM?

Mild hyperthyroidism (slightly elevated thyroid hormone levels, minimal symptoms) often is monitored closely without therapy as long as both the mother and the baby are doing well. When hyperthyroidism is severe enough to require therapy, anti-thyroid medications are the treatment of choice, with PTU being preferred in the first trimester. The goal of therapy is to keep the mother's free T4 in the high-normal to mildly elevated range on the lowest dose of antithyroid medication. Addition of levothyroxine to ATDs ("block-and-replace") is not recommended. Targeting this range of free hormone levels will minimize the risk to the baby of developing *hypothyroidism* or *goiter*. Maternal hypothyroidism should be avoided. Therapy should be closely monitored during pregnancy. This is typically done by following thyroid function tests (TSH and thyroid hormone levels) monthly.



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*

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Hyperthyroidism in Pregnancy

In patients who cannot be adequately treated with anti-thyroid medications (i.e. those who develop an allergic reaction to the drugs), surgery is an acceptable alternative. Surgical removal of the thyroid gland is safest in the second trimester.

Radioiodine is contraindicated to treat hyperthyroidism during pregnancy since it readily crosses the placenta and is taken up by the baby's thyroid gland. This can cause destruction of the gland and result in permanent hypothyroidism.

Beta-blockers can be used during pregnancy to help treat significant palpitations and tremor due to hyperthyroidism. They should be used sparingly due to reports of impaired fetal growth associated with long-term use of these medications. Typically, these drugs are only required until the hyperthyroidism is controlled with anti-thyroid medications.

WHAT IS THE NATURAL HISTORY OF GRAVES' DISEASE AFTER DELIVERY?

Graves' disease typically worsens in the postpartum period or may occur then for the first time. When new hyperthyroidism occurs in the first months after delivery, the cause may be either Graves' disease or postpartum thyroiditis and testing with careful follow-up is needed to distinguish between the two. Higher doses of anti-thyroid medications may be required during this time. As usual, close monitoring of thyroid function tests is necessary.

CAN THE MOTHER WITH GRAVES' DISEASE, WHO IS BEING TREATED WITH ANTI-THYROID DRUGS, BREASTFEED HER INFANT?

Yes. Although very small quantities of both PTU and methimazole are transferred into breast milk, total daily doses of up to 20mg methimazole or 450mg PTU are considered safe and monitoring of the breastfed infants' thyroid status is not required.

FURTHER INFORMATION

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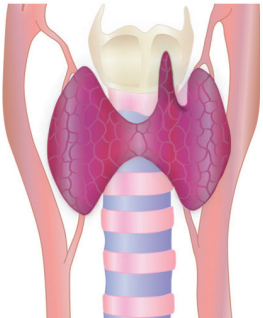

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