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Overt hypothyroidism is associated with an increased incidence of infertility and miscarriage which can be improved with thyroid hormone treatment. Controversy exists whether the subtle abnormalities of thyroid function in subclinical hypothyroidism are truly associated with infertility and miscarriage and whether treatment with thyroid hormone reduces these events. In this study, the Practice Committee of the American Society for Reproductive Medicine developed guidelines for treating subclinical hypothyroidism in women with a history of infertility and miscarriage.

Practice Committee of the American Society for Reproductive Medicine. Subclinical hypothyroidism in the infertile female population: a guideline. *Fertil Steril* 2015;104:545-53.

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#### **Preoperative ultrasound can help predict recurrence risk in patients with papillary thyroid cancer**

The 10 year recurrence rate of papillary thyroid cancer is 14-26%. A recent study suggested that cancerous features on ultrasound prior to thyroid carried a worse prognosis. This study was done evaluate whether ultrasound characteristics of the thyroid nodule could predict cancer recurrence.

Kim SY et al. Association of preoperative US features and recurrence in patients with classic papillary thyroid carcinoma. *Radiology*. 2015;277(2):574-583.

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#### **Hürthle-Cell Nodules classified as suspicious by the Afirma gene expression classifier had a low cancer rate**

Thyroid biopsy is the most commonly used method to distinguish cancerous from non-cancerous thyroid nodules. However, 15-30% of biopsies are indeterminate zone where thyroid cancer cannot be excluded or confirmed. Afirma gene expression classifier (AGEC) examines possible mutations in 167 genes in the thyroid biopsy specimens to identify thyroid nodules with a low cancer risk. This study evaluates the performance of the AGEC in patients with indeterminate biopsies.

Brauner E et al. Performance of the Afirma gene expression classifier in Hürthle cell thyroid nodules differs from other indeterminate thyroid nodules. *Thyroid* 2015;25:789-96. Epub June 4, 2015.

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#### **Lenvatinib is effective in advanced medullary thyroid cancer**

Until recently, there was little therapy available to treat patients who have persistent or recurrent medullary thyroid cancer that cannot be removed by surgery. Lenvatinib is a new chemotherapy drug that can block multiple targets that cause cancers to grow and is helpful in treating other thyroid cancers. This report is a Phase 2 clinical trial to determine whether Lenvatinib is effective to treat metastatic medullary thyroid cancer.

Schlumberger M et al. A phase 2 trial of the multi-targeted tyrosine kinase inhibitor lenvatinib (E7080) in advanced medullary thyroid cancer (MTC). *Clin Cancer Res*. August 26, 2015 [Epub ahead of print].

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#### **Genetic influence on outcomes in thyroid cancer**

While the vast majority of patients with papillary thyroid cancer do well, 5-10% of patients have persistent or recurrent thyroid cancer and may die from their thyroid cancer. The use of genetic molecular marker analysis in thyroid biopsy specimens has been suggested to help predict the aggressiveness of thyroid cancers. The aim of this study was to correlate thyroid cancer genetic molecular marker analysis with pathologic findings at surgery and disease-free survival.

Yip L et al. Tumor genotype determines phenotype and disease-related outcomes in thyroid cancer: a study of 1510 patients. *Ann Surg* 2015;262:519-25.

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##### Clinical Thyroidology for the Public

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## CLINICAL **THYROIDOLOGY** FOR THE **PUBLIC**

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### EDITOR'S COMMENTS

Welcome to another issue of *Clinical Thyroidology for the Public*. In this journal, we will bring to you the most up-to-date, cutting edge thyroid research. We will be providing summaries of research studies that were discussed in a recent issue of *Clinical Thyroidology*, a publication of the American Thyroid Association for physicians. These summaries are presented in lay language to allow the rapid dissemination of thyroid research to the widest possible audience. This means that you are getting the latest information on thyroid research and treatment almost as soon as your physicians. As always, we are happy to entertain any suggestions to improve *Clinical Thyroidology for the Public* so let us know what you want to see.

We also provide even faster updates of late-breaking thyroid news through **Twitter** at [@thyroidfriends](https://twitter.com/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* and *Thyroid Federation International*.

November is [Hyperthyroidism Awareness Month](#).

#### In this issue, the studies ask the following questions:

1. Should infertile women with subclinical hypothyroidism be treated?
2. Do ultrasound features of cancerous thyroid nodules predict thyroid cancer recurrence?
3. How well does the Afirma gene expression classifier predict cancer in patients with indeterminate hürthle cell biopsies?
4. How effective is Levatinib in treating patients with metastatic medullary thyroid cancer?
5. Does molecular marker analysis of thyroid cancer biopsies correlate with recurrent or persistent cancer?

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

— Alan P. Farwell, MD, FACE



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**HYPOTHYROIDISM****Should women with subclinical hypothyroidism receive thyroid hormone replacement prior to and during pregnancy?****BACKGROUND**

Overt hypothyroidism occurs when the TSH level is increased and the free thyroxine level (FT<sub>4</sub>) is low. This can cause severe symptoms and is associated with an increased incidence of infertility, miscarriage and other adverse outcomes in those women who are trying to conceive or those who are already pregnant. It is clear that overt hypothyroidism should be treated with thyroid hormone replacement- usually levothyroxine. Subclinical hypothyroidism occurs when the TSH level is increased but the FT<sub>4</sub> level remains within the normal range. This is a milder form of the hypothyroidism and may not need to be treated in the absence of pregnancy. Controversy exists whether the subtle abnormalities of thyroid function in subclinical hypothyroidism are truly associated with infertility and miscarriage and whether treatment with thyroid hormone reduces these events. Additionally, the definition of subclinical hypothyroidism differs between the non-pregnant and pregnant state. The former is diagnosed when the TSH is above 4.5-5.0 mIU/L, whereas it is well accepted that a TSH greater than 2.5 mIU/L is diagnostic of subclinical hypothyroidism during the first trimester of pregnancy. In this study, the Practice Committee of the American Society for Reproductive Medicine reviewed the evidence and developed guidelines for treating subclinical hypothyroidism in women with a history of infertility and miscarriage.

**THE FULL ARTICLE TITLE**

Practice Committee of the American Society for Reproductive Medicine. Subclinical hypothyroidism in the infertile female population: a guideline. *Fertil Steril* 2015;104:545-53.

**SUMMARY OF THE STUDY**

In developing their recommendations, the authors performed a systematic literature search of English

language studies examining overt and subclinical hypothyroidism in pregnancy which were published between 1966-2014. The quality of each study was evaluated using standardized criteria. Based upon their review the authors concluded that there was insufficient evidence that subclinical hypothyroidism is associated with infertility when using a TSH in the range of 2.5-4.0 mIU/L; however, there was fair evidence that TSH levels greater than 4.0 mIU/L was associated with miscarriage. There was also fair evidence that treatment of subclinical hypothyroidism with thyroid hormone replacement when TSH levels are greater than 4.0 mIU/L is associated with improved pregnancy rates and decreased miscarriage rates. But there was limited evidence to support treatment with thyroid hormone when TSH levels prior to pregnancy are only between 2.5 and 4 mIU/L. In this setting, management options include either monitoring levels and treating when exceeds TSH >4 mIU/L, or treating with levothyroxine to maintain TSH <2.5 mIU/L.

**WHAT ARE THE IMPLICATIONS OF THIS STUDY?**

Despite the fact that there were very few published randomized controlled trials available for the authors to base their recommendations, this study may help guide physicians in treating their patients with subclinical hypothyroidism who are either attempting to become pregnant or are in the first trimester of pregnancy. These guidelines suggest thyroid hormone replacement in women with TSH levels >4 is associated with improved pregnancy rates and decreased miscarriage rates.

— Philip Segal, MD

**ATA THYROID BROCHURE LINKS**

Thyroid and Pregnancy: <http://www.thyroid.org/thyroid-disease-pregnancy/>

**ABBREVIATIONS & DEFINITIONS**

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

**Miscarriage:** this occurs when a baby dies in the first few months of a pregnancy, usually before 22 weeks of pregnancy.



## HYPOTHYROIDISM, continued

**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.

**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.

**Randomized Controlled Trial:** is a type of clinical study where the people being studied are randomly allocated one or other of the different treatments. This type of trial is considered the gold standard clinical studies.





**THYROID CANCER****Preoperative ultrasound can help predict recurrence risk in patients with papillary thyroid cancer****BACKGROUND**

Papillary thyroid cancer is increasing in incidence, and although it has a generally excellent prognosis, the 10 year recurrence rate is estimated to be 14-26%. The possibility of recurrence can cause anxiety in patients and physicians alike. A recent study suggested that cancerous features on ultrasound prior to thyroid surgery (at the time of diagnosis) carried a worse prognosis, but did not predict recurrence. This study was done to confirm the initial study and to evaluate whether ultrasound characteristics of the thyroid nodule could predict recurrence. If so, they suggest that the pre-operative ultrasound could be utilized to determine treatment and follow-up plans.

**THE FULL ARTICLE TITLE**

Kim SY et al Association of preoperative US features and recurrence in patients with classic papillary thyroid carcinoma. *Radiology*. 2015;277(2):574-583.

**SUMMARY OF THE STUDY**

The records of 2111 patients having thyroid surgery between January 2003 and February 2006 at Yonsei University in Seoul, Korea were reviewed. A total of 515 patients who had classical papillary thyroid cancer measuring 1 cm or larger were included. Small cancers (micropapillary, <1 cm) cancers were excluded, as were other types of lesions or other reasons for surgery. The 515 patients had an average age of 45.8 years (432 women and 83 men). The size of the primary cancer was approximately 2 cm and 70.5% of the patients had extension of the cancer outside of the thyroid. Also, 62.3 % of the patients had spread of the cancer to the lymph nodes. All patients had a central lymph node dissection at the time of total thyroidectomy. Approximately 22% of the patients also had a lateral neck compartment dissection due to pre-operative identification of abnormal lymph nodes. Further, 84.9% of the patients were treated with radioactive iodine therapy (420 with 30 mCi, 17 patients received 50-200mCi doses). Radioactive iodine therapy was used in this group of patients if there was spread to the lymph node metastases or if there was extension outside of the thyroid. They were followed on average for 93 months (range 12-137 months) with the usual methods of follow-up, including ultrasound, thyroid

function testing, thyroglobulin levels with thyroglobulin antibody testing radioactive iodine whole body scans when indicated.

The authors reviewed the pre-operative ultrasound for cancerous findings (darkness, abnormal margins of the nodule, microcalcifications, taller-than-wide shape) and these were compared with the characteristics of the patients, the pathology of the cancer at surgery and the risk of persistent and recurrent cancer. This was done in three different models, taking into account various ways of reviewing the information (pre-operative information, post-operative information, or a combined model).

A total of 56 of the 515 (10.9%) patients had a recurrence. A total of 32 had lateral lymph node recurrence, 7 with thyroid bed recurrence and 5 had both. A total of 8 patients had spread of the cancer outside the neck (3 lung, adrenal gland, brain, liver) and 4 had both local and distant metastatic recurrences. A total of 11 of the patients had persistent cancer (defined by elevated thyroglobulin or whole body scan findings).

Malignant-appearing papillary thyroid cancer on pre-operative ultrasound is significantly associated with higher cancer staging in this study. The more worrisome ultrasound appearance is associated with recurrence in the pre-operative and combined model of analysis in this study. In the pre-operative analysis, the ultrasound findings associated with risk were nodule size, microcalcifications, and taller-than-wide shape.

**WHAT ARE THE IMPLICATIONS OF THIS STUDY?**

This study suggests that the findings on pre-operative ultrasound can help predict recurrence rates in addition to the known factors that predict recurrence (extrathyroidal extension, lymph node metastasis, age at diagnosis, pathologic diagnosis or type of cancer, radioactive iodine therapy). This may allow early decision-making regarding risk of recurrence and the level of aggressive treatment. One benefit may be avoiding use of radioactive iodine in patients without cancerous appearance on ultrasound. Another benefit may be identifying the rare patient

**THYROID CANCER**, continued

who requires even more aggressive therapies and closer follow-up. A careful pre-operative ultrasound may help avoid unnecessary treatment with radioiodine in a patient whose nodule has no worrisome features.

— Julie Hallanger Johnson, MD

**ATA THYROID BROCHURE  
LINKS**

Thyroid cancer: <http://www.thyroid.org/cancer-of-the-thyroid/>

**ABBREVIATIONS & DEFINITIONS**

**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

**Microcalcifications:** Small flecks of calcium within a thyroid nodule, usually seen as small bright spots on ultrasonography. These are frequently seen in nodules containing papillary thyroid cancer.

**Taller-than-wide shape:** larger measurement in the anteroposterior measurements than the transverse measurement

**Papillary thyroid cancer:** the most common type of thyroid cancer.

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

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

**Central neck compartment:** the central portion of the neck between the hyoid bone above, and the sternum and collar bones below and laterally limited by the carotid arteries.



**THYROID NODULES****Hürthle-Cell Nodules classified as suspicious by the Afirma gene expression classifier had a low cancer rate****BACKGROUND**

Thyroid nodules are common and may be found in up to 50% of people. While most nodules are benign (non-cancerous), up to 8% of nodules are cancers. Thyroid biopsy is the most commonly used method to distinguish cancerous from non-cancerous thyroid nodules. Although most thyroid biopsy results are either non-cancerous or cancerous, 15-30% of these results are in the gray indeterminate zone, when thyroid cancer cannot be excluded or confirmed. For example, Hurthle cell nodules yield indeterminate biopsy results. While surgery is recommended to remove thyroid nodules with indeterminate results, most of the excised nodules are found to be non-cancerous. Molecular genetic tests are currently available to further evaluate thyroid nodules with indeterminate biopsy results. The Afirma gene expression classifier (AGEC) examines possible mutations in 167 genes in the thyroid biopsy specimens to identify thyroid nodules with a low cancer risk. This test classifies thyroid nodules as “benign” with a cancer risk of less than 6% or “suspicious” with a cancer risk of 44%. A few prior small studies have showed an increased rate of suspicious AGEC results in Hurthle cell nodules, while most of these nodules proved to be non-cancerous after surgical removal. This is the largest study reported to date that evaluates the performance of the AGEC in patients with Hurthle cell nodules.

**THE FULL ARTICLE TITLE:**

Brauner E et al. Performance of the Afirma gene expression classifier in Hürthle cell thyroid nodules differs from other indeterminate thyroid nodules. *Thyroid* 2015;25:789-96. Epub June 4, 2015.

**SUMMARY OF THE STUDY**

The study included patients followed at three tertiary care centers who had HCNs with indeterminate biopsy results reported as suspicious for a Hürthle-cell nodule or with a predominance of Hürthle cells. The study included 62 patients with Hurthle cell nodules diagnosed during the 1-year period before the use of AGEC; among

the 50 patients who underwent surgery, 17 (27%) had cancerous nodules. The study also included 169 patients with Hurthle cell nodules who underwent repeat thyroid biopsy with AGEC after the initial biopsy showed indeterminate cytology. Among these patients, 97 were treated based on clinical and ultrasound features without using the AGEC result; 78 patients (80%) underwent surgery and 23 (29%) had cancerous thyroid nodules, the cancer rate being similar to the patients with HCNs treated prior to the use of AGEC. A total of 72 out of the 169 patients who had the AGEC were treated based on this test results; among these patients, 45 (63%) had suspicious AGEC results, 26 (36%) had benign results and one was non-diagnostic. Only 6 out of the 43 patients (14%) with suspicious AGEC results who underwent surgery had cancerous nodules. A total of 23 out of the 26 patients with benign AGEC results (88%) were followed clinically; only 3 patients had surgery and all 3 nodules were non-cancerous.

**WHAT ARE THE IMPLICATIONS OF THIS STUDY?**

This study shows a low AGEC performance for identifying Hurthle cell cancer. Although a large proportion of Hurthle cell nodules are classified as suspicious by the AGEC, only 14% of these nodules are cancerous. Further, only 32% of patients with Hurthle cell nodules avoided surgery based on a benign AGEC result. This study suggests that clinical judgment appears to better identify Hurthle cell cancer than the AGEC.

—Alina Gavrilă, MD, MMSC

**ATA THYROID BROCHURE LINKS**

Thyroid Nodules: <http://www.thyroid.org/thyroid-nodules/>

Thyroid cancer: <http://www.thyroid.org/cancer-of-the-thyroid/>

Thyroid Surgery: <http://www.thyroid.org/thyroid-surgery/>

**THYROID NODULES, 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), 5-10% are cancerous (malignant).

**Hürthle cell nodule:** thyroid nodule made of Hurthle cells, which are normal cells found in the thyroid together with the follicular cells. Hurthle cells have a distinctive appearance under the microscope.

**Thyroid fine needle aspiration biopsy (FNAB):** a simple procedure that is done in the doctor's office to determine if a thyroid nodule is benign (non-cancerous) or cancerous. 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 usually when the diagnosis is a follicular or Hurthle cell lesion. Follicular and Hurthle cells are normal cells found in the thyroid. Current analysis of thyroid biopsy results cannot differentiate between follicular or Hurthle cell cancer from non-cancerous nodules. This occurs in

15-20% of biopsies and often results in the need for surgery to remove the nodule.

**Non-diagnostic thyroid biopsy:** this happens when not enough cells are obtained during the biopsy to provide a diagnosis. This occurs in 5-10% of biopsies. It often results in the need to repeat the biopsy.

**Molecular genetic tests:** tests that analyze genes and microRNAs expressed in benign or cancerous cells. Molecular tests can be used in thyroid biopsy specimens to either diagnose cancer or to determine that the nodule is benign.

**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.

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



**THYROID CANCER****Lenvatinib is effective in advanced medullary thyroid cancer****BACKGROUND**

Medullary thyroid cancer is a relatively rare type of thyroid cancer that often runs in families. Unlike the more common papillary and follicular thyroid cancers, surgery is the only initial therapy as radioactive iodine therapy is ineffective because the cells do not take up the radioactive iodine. Until recently, there was little therapy available to treat patients who have persistent or recurrent medullary thyroid cancer that cannot be removed by surgery. Lenvatinib is a new chemotherapy drug that can block multiple targets that cause cancers to grow. These drugs typically are not curative, but can delay the time to progression of the cancer. In an international multicenter clinical trial, Lenvatinib showed improved progression-free survival (PFS) for patients with metastatic papillary and follicular cancers unable to be treated with the usual therapies such as surgery or radioactive iodine therapy. Lenvatinib has since been approved by the FDA for use in papillary and follicular thyroid cancer. This report is a Phase 2 clinical trial to determine whether Lenvatinib is effective to treat metastatic medullary thyroid cancer.

**THE FULL ARTICLE TITLE**

Schlumberger M et al. A phase 2 trial of the multi-targeted tyrosine kinase inhibitor lenvatinib (E7080) in advanced medullary thyroid cancer (MTC). Clin Cancer Res. August 26, 2015 [Epub ahead of print].

**SUMMARY OF THE STUDY**

A total of 59 patients with unresectable or metastatic medullary thyroid cancer were included in the trial. A total

of 44% of patients enrolled had been treated with another drug prior to enrolling in the trial. Lenvatinib was given starting at 24 mg daily dose for 8 cycles, each for 28-days. The dose was decreased for side effects or toxicities.

Of the patients who completed 8 cycles of Lenvatinib, 44% showed a 36% objective response to the study drug within 3.5 months of starting the drug. Calcitonin and CEA, cancer markers for medullary thyroid cancer, decreased in all subjects. The median time to progression of medullary thyroid cancer was 9 months. A total of 60% of patients required lower doses of Lenvatinib due to toxicity or side effects and 24% of patients had to stop the drug for severe side effects.

**WHAT ARE THE IMPLICATIONS OF THIS STUDY?**

The study showed that Lenvatinib can be an effective drug in patients with metastatic or unresectable medullary thyroid cancer, including those patients who had already been treated ineffectively with another chemotherapy drug. More studies need to be done to figure out which patients will best respond to Lenvatinib but this study is hopeful for the treatment of metastatic medullary thyroid cancer since there is not yet a cure.

—Wendy Sacks, MD

**ATA THYROID BROCHURE LINKS**

Thyroid cancer: <http://www.thyroid.org/cancer-of-the-thyroid/>

**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.

**Clinical trials:** when a new drug is developed, it must undergo an extensive series of steps, called phases, to prove that it is more effective in patients than the drugs that are currently available to treat the condition. A Phase I trial tests a new drug or treatment in a small

group of people for the first time to evaluate its safety, determine a safe dosage range and identify side effects. A Phase II trial gives the drug to a larger group of people to see if it is effective and to further evaluate its safety. A Phase III trial gives the drug to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments and collect information that will allow the drug or treatment to be used safely.

**THYROID CANCER**, continued

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

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

## 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 November is [Hyperthyroidism Awareness Month](#) and a bracelet is available through the [ATA Marketplace](#) to support thyroid cancer awareness and education related to thyroid disease.



**THYROID CANCER****Genetic influence on outcomes in thyroid cancer****BACKGROUND**

Papillary thyroid cancer is increasing in frequency, especially in women. Fortunately, the vast majority of patients with papillary thyroid cancer do well. However, 5-10% of patients have persistent or recurrent thyroid cancer and some may die from their thyroid cancer. An improved method to determine the risk of recurrence and death for patients with thyroid cancer could help determine the extent of surgery, the use of additional treatment, and need for follow-up. This could potentially reduce the cost of treating thyroid cancer while maintaining or improving the effectiveness of treatment. The use of genetic molecular marker analysis in thyroid biopsy specimens has been suggested to help predict the aggressiveness of thyroid cancers. The aim of this study was to correlate thyroid cancer genetic molecular marker analysis with pathologic findings at surgery and disease-free survival.

**THE FULL ARTICLE TITLE:**

Yip L et al. Tumor genotype determines phenotype and disease-related outcomes in thyroid cancer: a study of 1510 patients. *Ann Surg* 2015;262:519-25.

**SUMMARY OF THE STUDY**

The authors examined a series of 1510 consecutive surgical patients diagnosed with thyroid cancer and treated at one medical center. Patients underwent preoperative ultrasound-guided needle biopsy. Genetic molecular marker analysis of the primary cancer was performed for genetic mutations. Total thyroidectomy was performed for all patients with abnormal lymph node removal as needed. The average follow-up was 33 months. More than 6 months of follow-up was available for 1349 patients.

Of 1510 tumors, 1039 (69%) had a genetic mutation identified. No tumor had more than one mutation.

Compared with cancers with mutations in the RAS-, PAX8/PPARG-, or BRAF K601E genes, those with mutations in the BRAF V600E or RET/PTC genes were more advanced and had a greater risk of early recurrence. The 5-year disease-free survival for patients with RAS-, PAX8/PPARG-, and BRAF K601E-positive cancers was 96%, 100%, and 100%, as compared with BRAF V600E- and RET/PTC-positive papillary thyroid cancer (80% and 77%). RET/PTC-positive papillary thyroid cancer had a high incidence of lateral neck lymph-node spread (35%) and distant spread (8%) at presentation. Recurrences were more frequent in patients with BRAF V600E (9.7%) or RET/PTC (9.4%). Overall survival was not affected by the mutation identified.

**WHAT ARE THE IMPLICATIONS OF THIS STUDY?**

Specific genetic mutations or rearrangements are predictive of aggressiveness and a higher risk of distant spread and early recurrence for patients with papillary thyroid cancer. Determining genetic mutations prior to surgery could provide information to help determine the extent of surgery, the need for radioiodine treatment and the intensity of follow-up. More studies are needed to make specific and actionable recommendations.

— Ronald B. Kuppersmith, MD, FACS

**ATA THYROID BROCHURE LINKS**

Thyroid cancer: <http://www.thyroid.org/cancer-of-the-thyroid/>

Radioactive Iodine Therapy: <http://www.thyroid.org/radioactive-iodine/>

Thyroid Surgery: <http://www.thyroid.org/thyroid-surgery/>

**ABBREVIATIONS & DEFINITIONS**

**Thyroid fine needle aspiration biopsy (FNAB):** 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.

**THYROID CANCER**, continued

**Mutation:** A permanent change in one of the genes.

**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.

**Molecular markers:** genes 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. Common thyroid cancer-associated genes include RAS, PAX8/PPARG, RET and BRAF

**Papillary thyroid cancer:** the most common type of thyroid cancer.

**Thyroidectomy:** surgery to remove the entire thyroid gland. When the entire thyroid is removed it is termed a total thyroidectomy. When less is removed, such as in removal of a lobe, it is termed a partial thyroidectomy.

**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 towards the improvement of thyroid education and resources for patients.

**WHO WE ARE** (in alphabetical order)

- **American Thyroid Association**
- **Bite Me Cancer**
- **Graves' Disease and Thyroid Foundation**
- **Light of Life Foundation**
- **ThyCa: Thyroid Cancer Survivors' Association, Inc.**
- **Thyroid Cancer Canada**
- **Thyroid Federation International**

**AMERICAN THYROID ASSOCIATION**

[www.thyroid.org](http://www.thyroid.org)

ATA Patient Resources: <http://www.thyroid.org/patients/>

Find a Thyroid Specialist: [www.thyroid.org](http://www.thyroid.org)

Phone (toll-free): 1-800-THYROID

e-mail: [thyroid@thyroid.org](mailto:thyroid@thyroid.org)

**ATA Mission:** The ATA leads in promoting thyroid health and understanding thyroid biology.

**ATA Vision:** The ATA is the leading organization focused on thyroid biology and the prevention and treatment of thyroid disorders through excellence and innovation in research, clinical care, education, and public health.

**ATA Values:** The ATA values scientific inquiry, clinical excellence, public service, education, collaboration, and collegiality.

To further our mission, vision and values the ATA sponsors "Friends of the ATA" online to advance the information provided to patients and the public such as this publication, *Clinical Thyroidology for the Public*. We welcome your support.

*continued on next page*



AMERICAN  
THYROID  
ASSOCIATION  
FOUNDED 1923



ThyCa: Thyroid Cancer  
Survivors' Association, Inc.<sup>SM</sup>  
[www.thyca.org](http://www.thyca.org)





**ATA Alliance for Thyroid Patient Education****Continued...****BITE ME CANCER**<http://www.bitemecancer.org>

Bite Me Cancer was formed as a nonprofit foundation in September, 2010, by Nikki Ferraro, who was 17-years old at the time. Nikki was diagnosed with a rare form of thyroid cancer in April 2010 when she was a junior at Chantilly HS in Virginia. Nikki was determined to lead a Relay for Life team just two weeks after her diagnosis. She named the team Bite Me Cancer and experienced immediate success. When Nikki decided to create a foundation a few months later, she wanted to continue the legacy of her team name and thus her foundation became the Bite Me Cancer Foundation.

e-mail: [info@bitemecancer.org](mailto:info@bitemecancer.org)**GRAVES' DISEASE AND THYROID FOUNDATION**[www.gdatf.org](http://www.gdatf.org)

Phone (toll-free): 1-877-NGDF-123 or 643-3123

e-mail: [Gravesdiseasefd@gmail.com](mailto:Gravesdiseasefd@gmail.com)

Founded in 1990, the Graves' Disease Foundation offers support and resources to Graves' disease patients, their families, and health care professionals. Their mission is to find the cause of and the cure for Graves' thyroid disease through research, to improve the quality of life for persons with Graves' disease and their caregivers and to educate persons with Graves' disease, their caregivers, healthcare professionals, and the general public about Graves' disease and its treatment. The web site features a monitored bulletin board.

**LIGHT OF LIFE FOUNDATION**[www.checkyourneck.com](http://www.checkyourneck.com)email: [info@checkyourneck.com](mailto:info@checkyourneck.com)

The Light of Life Foundation, founded in 1997, is a nonprofit organization that strives to improve the quality of life for thyroid cancer patients, educate the public and professionals about thyroid cancer, and promote research and development to improve thyroid cancer care.

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**ATA Alliance for Thyroid Patient Education****Continued...****THYCA: THYROID CANCER SURVIVORS' ASSOCIATION, INC.**[www.thyca.org](http://www.thyca.org)

Phone (toll-free): 877 588-7904

e-mail: [thyca@thyca.org](mailto:thyca@thyca.org)

ThyCa: Thyroid Cancer Survivors' Association, Inc., founded in 1995, is an international nonprofit organization, guided by a medical advisory council of renowned thyroid cancer specialists, offering support and information to thyroid cancer survivors, families, and health care professionals worldwide.

**THYROID CANCER CANADA**[www.thyroidcancercanada.org](http://www.thyroidcancercanada.org)

Phone: 416-487-8267

Fax: 416-487-0601

e-mail: [info@thyroidcancercanada.org](mailto:info@thyroidcancercanada.org)

Thyroid Cancer Canada is a non-profit organization founded in 2000. The organization works towards creating an environment in which people who are dealing with thyroid cancer, especially the newly diagnosed, are met with support and information. Their goals & objectives include facilitating communication among thyroid cancer patients, providing credible information about the disease, providing emotional support, and assisting thyroid cancer patients with voicing their needs to health care professionals and those who are responsible for health care policy.

**THYROID FEDERATION INTERNATIONAL**<http://www.thyroid-fed.org/>e-mail: [tfi@thyroid-fed.org](mailto:tfi@thyroid-fed.org)

Thyroid Federation International (TFI) was established in Toronto in 1995. Thyroid Federation International aims to work for the benefit of those affected by thyroid disorders throughout the world by providing a network of patient support organizations.

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# Hyperthyroidism

## 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 IS HYPERTHYROIDISM?

The term *hyperthyroidism* refers to any condition in which there is too much thyroid hormone produced in the body. In other words, the thyroid gland is overactive. Another term that you might hear for this problem is *thyrotoxicosis*, which refers to high thyroid hormone levels in the blood stream, irrespective of their source.

## WHAT ARE THE SYMPTOMS OF HYPERTHYROIDISM?

Thyroid hormone plays a significant role in the pace of many processes in the body. These processes are called your *metabolism*. If there is too much thyroid hormone, every function of the body tends to speed up. It is not surprising then that some of the symptoms of hyperthyroidism are nervousness, irritability, increased perspiration, heart racing, hand tremors, anxiety, difficulty sleeping, thinning of your skin, fine brittle hair and weakness in your muscles—especially in the upper arms and thighs. You may have more frequent bowel movements, but diarrhea is uncommon. You may lose weight despite a good appetite and, for women, menstrual flow may lighten and menstrual periods may occur less often. Since hyperthyroidism increases your metabolism, many individuals initially have a lot of energy. However, as the hyperthyroidism continues, the body tends to break down, so being tired is very common.

Hyperthyroidism usually begins slowly but in some young patients these changes can be very abrupt. At first, the symptoms may be mistaken for simple nervousness due to stress. If you have been trying to lose weight by dieting, you may be pleased with your success until the hyperthyroidism, which has quickened the weight loss, causes other problems.

In Graves' disease, which is the most common form of hyperthyroidism, the eyes may look enlarged because the upper lids are elevated. Sometimes, one or both eyes may bulge. Some patients have swelling of the front of the neck from an enlarged thyroid gland (a goiter).

## WHAT CAUSES HYPERTHYROIDISM?

The most common cause (in more than 70% of people) is overproduction of thyroid hormone by the entire thyroid gland. This condition is also known as Graves' disease (see the *Graves' Disease* brochure for details). Graves' disease is caused by antibodies in the blood that turn on the thyroid and cause it to grow and secrete too much thyroid hormone. This type of hyperthyroidism tends to run in families and it occurs more often in young women. Little is known about why specific individuals get this disease. Another type of hyperthyroidism is characterized by one or more nodules or lumps in the thyroid that may gradually grow and increase their activity so that the total output of thyroid hormone into the blood is greater than normal. This condition is known as toxic nodular or *multinodular goiter*. Also, people may temporarily have symptoms of hyperthyroidism if they have a condition called *thyroiditis*. This condition is caused by a problem with the immune system or a viral infection that causes the gland to leak stored thyroid hormone. The same symptoms can also be caused by taking too much thyroid hormone in tablet form. These last two forms of excess thyroid hormone are only called thyrotoxicosis, since the thyroid is not overactive.



# Hyperthyroidism

## HOW IS HYPERTHYROIDISM DIAGNOSED?

If your physician suspects that you have hyperthyroidism, diagnosis is usually a simple matter. A physical examination usually detects an enlarged thyroid gland and a rapid pulse. The physician will also look for moist, smooth skin and a tremor of your fingertips. Your reflexes are likely to be fast, and your eyes may have some abnormalities if you have Graves' disease.

The diagnosis of hyperthyroidism will be confirmed by laboratory tests that measure the amount of thyroid hormones—thyroxine (T4) and triiodothyronine (T3)—and thyroid-stimulating hormone (TSH) in your blood. A high level of thyroid hormone in the blood plus a low level of TSH is common with an overactive thyroid gland. If blood tests show that your thyroid is overactive, your doctor may want to obtain a picture of your thyroid (a *thyroid scan*). The scan will find out if your entire thyroid gland is overactive or whether you have a toxic nodular goiter or thyroiditis (thyroid inflammation). A test that measures the ability of the gland to collect iodine (a *thyroid uptake*) may be done at the same time.

## HOW IS HYPERTHYROIDISM TREATED?

No single treatment is best for all patients with hyperthyroidism. The appropriate choice of treatment will be influenced by your age, the type of hyperthyroidism that you have, the severity of your hyperthyroidism, other medical conditions that may be affecting your health, and your own preference. It may be a good idea to consult with an endocrinologist who is experienced in the treatment of hyperthyroid patients. If you are unconvinced or unclear about any thyroid treatment plan, a second opinion is a good idea.

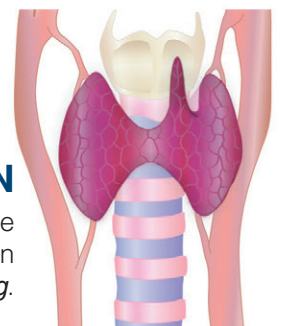
## ANTITHYROID DRUGS

Drugs known as *antithyroid agents*—methimazole (Tapazole®) or in rare instances propylthiouracil (PTU)—may be prescribed if your doctor chooses to treat the hyperthyroidism by blocking the thyroid gland's ability to make new thyroid hormone. Methimazole is presently the preferred one due to less severe side-effects. These drugs work well to control the overactive thyroid, bring quick control of hyperthyroidism and do not cause permanent damage to the thyroid gland. In about 20% to 30% of patients with Graves' disease, treatment with antithyroid drugs for a period of 12 to 18 months will result in prolonged remission of the disease. For patients with toxic nodular or multinodular goiter, antithyroid drugs are sometimes used in preparation for either radioiodine treatment or surgery.

Antithyroid drugs cause allergic reactions in about 5% of patients who take them. Common minor reactions are red skin rashes, hives, and occasionally fever and joint pains. A rarer (occurring in 1 of 500 patients), but more serious side effect is a decrease in the number of white blood cells. Such a decrease can lower your resistance to infection. Very rarely, these white blood cells disappear completely, producing a condition known as *agranulocytosis*, a potentially fatal problem if a serious infection occurs. If you are taking one of these drugs and get an infection such as a fever or sore throat, you should stop the drug immediately and have a white blood cell count that day. Even if the drug has lowered your white blood cell count, the count will return to normal if the drug is stopped immediately. But if you continue to take one of these drugs in spite of a low white blood cell count, there is a risk of a more serious, even life-threatening infection. Liver damage is another very rare side effect. A very serious liver problem can occur with PTU use which is why this medication should not generally be prescribed. You should stop either methimazole or PTU and call your doctor if you develop yellow eyes, dark urine, severe fatigue, or abdominal pain.

## FURTHER INFORMATION

Further details on this and other thyroid-related topics are available in the patient information section on the American Thyroid Association® website at [www.thyroid.org](http://www.thyroid.org).







# Hyperthyroidism

## RADIOACTIVE IODINE

Another way to treat hyperthyroidism is to damage or destroy the thyroid cells that make thyroid hormone. Because these cells need iodine to make thyroid hormone, they will take up any form of iodine in your blood stream, whether it is radioactive or not. The radioactive iodine used in this treatment is administered by mouth, usually in a small capsule that is taken just once. Once swallowed, the radioactive iodine gets into your blood stream and quickly is taken up by the overactive thyroid cells. The radioactive iodine that is not taken up by the thyroid cells disappears from the body within days. Over a period of several weeks to several months (during which time drug treatment may be used to control hyperthyroid symptoms), radioactive iodine destroys the cells that have taken it up. The result is that the thyroid or thyroid nodules shrink in size, and the level of thyroid hormone in the blood returns to normal. Sometimes patients will remain hyperthyroid, but usually to a lesser degree than before. For them, a second radioiodine treatment can be given if needed. More often, *hypothyroidism* (an underactive thyroid) occurs after a few months and lasts lifelong, requiring treatment. In fact, when patients have Graves' disease, a dose of radioactive iodine is chosen with the goal of making the patient hypothyroid so that the hyperthyroidism does not return in the future. Hypothyroidism can easily be treated with a thyroid hormone supplement taken once a day (see *Hypothyroidism* brochure).

Radioactive iodine has been used to treat patients for hyperthyroidism for over 60 years and has been shown to be generally safe. Importantly, there has been no clear increase in cancer in hyperthyroid patients that have been treated with radioactive iodine. As a result, in the United States more than 70% of adults who develop hyperthyroidism are treated with radioactive iodine. More and more children over the age of 5 are also being safely treated with radioiodine.

## SURGERY

Your hyperthyroidism can be permanently cured by surgical removal of most of your thyroid gland. This procedure is best performed by a surgeon who has much experience in thyroid surgery. An operation could be risky unless your hyperthyroidism is first controlled by

an antithyroid drug (see above) or a beta-blocking drug (see below). Usually for some days before surgery, your surgeon may want you to take drops of nonradioactive iodine—either Lugol's iodine or supersaturated potassium iodide (SSKI). This extra iodine reduces the blood supply to the thyroid gland and thus makes the surgery easier and safer. Although any surgery is risky, major complications of thyroid surgery occur in less than 1% of patients operated on by an experienced thyroid surgeon. These complications include damage to the parathyroid glands that surround the thyroid and control your body's calcium levels (causing problems with low calcium levels) and damage to the nerves that control your vocal cords (causing you to have a hoarse voice).

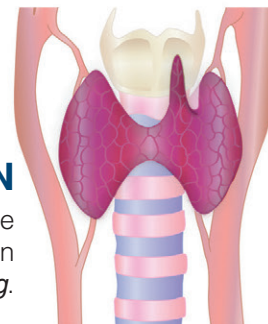
After your thyroid gland is removed, the source of your hyperthyroidism is gone and you will likely become hypothyroid. As with hypothyroidism that develops after radioiodine treatment, your thyroid hormone levels can be restored to normal by treatment once a day with a thyroid hormone supplement.

## BETA-BLOCKERS

No matter which of these three methods of treatment are used for your hyperthyroidism, your physician may prescribe a class of drugs known as the *beta adrenergic blocking agents* that block the action of thyroid hormone on your body. They usually make you feel better within hours to days, even though they do not change the high levels of thyroid hormone in your blood. These drugs may be extremely helpful in slowing down your heart rate and reducing the symptoms of palpitations, shakes, and nervousness until one of the other forms of treatment has a chance to take effect. Propranolol (Inderal®) was the first of these drugs to be developed. Some physicians now prefer related, but longer-acting beta-blocking drugs such as atenolol (Tenormin®), metoprolol (Lopressor®), nadolol (Corgard®), and Inderal-LA® because of their more convenient once- or twice-a-day dosage.

## OTHER FAMILY MEMBERS AT RISK

Because hyperthyroidism, especially Graves' disease, may run in families, examinations of the members of your family may reveal other individuals with thyroid problems.



## FURTHER INFORMATION

Further details on this and other thyroid-related topics are available in the patient information section on the American Thyroid Association® website at [www.thyroid.org](http://www.thyroid.org).