

# Clinical Thyroidology<sup>®</sup> for the Public



AMERICAN THYROID ASSOCIATION  
Optimal Thyroid Health for All



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Sawka AM et al for the Canadian Thyroid Cancer Active Surveillance Study Group (Greater Toronto Area) 2023 Gender differences in fears related to low-risk papillary thyroid cancer and its treatment. JAMA Otolaryngol Head Neck Surg. Epub 2023 Sep 1. PMID: 37410454.

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Chiosea S et al. 2023 Molecular profiling of 50,734 Bethesda III-VI thyroid nodules by ThyroSeq v3: Implications for personalized management. J Clin Endocrinol Metab. Epub 2023 Apr 18. PMID: 37071871.

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determine the planned management.

Schumm MA et al 2023 Prognostic value of preoperative molecular testing and implications for initial surgical management in thyroid nodules harboring suspected (Bethesda V) or known (Bethesda VI) papillary thyroid cancer. JAMA Otolaryngol Head Neck Surg 149:735–742. PMID: 37382944.

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**The importance of evaluating the lateral neck in patients with papillary thyroid microcarcinomas**

Most papillary thyroid microcarcinomas are considered low risk as they are very slow growing. However, a subgroup of papillary thyroid microcarcinomas are higher risk and can spread outside the neck. The aim of this study was to evaluate the association between the spread of cancer to the lymph nodes in the neck in patients with papillary thyroid microcarcinomas and future risk of cancer recurrence.

Ruan J et al 2023 Lateral lymph node metastasis in papillary thyroid microcarcinoma: A study of 5241 follow-up patients. Endocrine. Epub 2023 Aug 7. PMID: 37596455.

### THYROID CANCER.....12

**Is more radioactive iodine the answer for increased thyroglobulin levels alone?**

Our current American Thyroid Association 2015 guidelines categorize patient's thyroid cancer in terms of how likely it is to recur in a neck lymph node in the next ten years. Thyroglobulin levels that are rising or remain elevated and no evidence of cancer is noted on imaging are termed "biochemically incomplete or indeterminate response to therapy." The goal of this study is to better understand if additional doses of radioactive iodine therapy is beneficial when the thyroid cancer is not responding to therapy in the "biochemically indeterminate or incomplete" category.

Gambale C et al 2023 Usefulness of second <sup>131</sup>I treatment in biochemical persistent differentiated thyroid cancer patients. Eur Thyroid J. Epub 2023 Sep 1. PMID: 37768697.

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**Medical therapy for thyroid eye disease**

Graves' disease can be associated with inflammation of the muscles that control eye movements, known as thyroid eye disease (TED). In recent years, agents that modify the immune system have been studied as alternative treatments to steroids and surgery. The aim of this study was to report real world experience with these new medical therapies in the treatment of TED at a single medical center in the US.

Toro-Tobon et al. 2023 Medical therapy in patients with moderate to severe, steroid-resistant, thyroid eye disease.



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

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## Editor's Comments

Welcome to another issue of *Clinical Thyroidology for the Public*! In keeping with the celebration of the American Thyroid Association's Centennial year, the accompanying editorial provides a history of this publication — this is our 176th issue since beginning in 2008! In this journal, we will bring to you the most up-to-date, cutting edge thyroid research. We also provide even faster updates of late-breaking thyroid news through X (previously known as Twitter) at [@thyroidfriends](https://twitter.com/thyroidfriends) and on [Facebook](https://www.facebook.com/thyroidfriends). Our goal is to provide patients with the tools to be the most informed thyroid patient in the waiting room. Also check out our friends in the [Alliance for Thyroid Patient Education](#). The [Alliance](#) member groups consist of: the *American Thyroid Association*®, *Bite Me Cancer*, *the Graves' Disease and Thyroid Foundation*, *the Light of Life Foundation*, *MCT8 – AHDS Foundation*, *ThyCa: Thyroid Cancer Survivors' Association*, *Thyroid Cancer Canada*, *Thyroid Cancer Alliance* and *Thyroid Federation International*.

We invite all of you to join our [Friends of the ATA](#) community. It is for you that the American Thyroid Association® (ATA®) is dedicated to carrying out our mission of providing reliable thyroid information and resources, clinical practice guidelines for thyroid detection and treatments, resources for connecting you with other patients affected by thyroid conditions, and cutting edge thyroid research as we search for better diagnoses and treatment outcomes for thyroid disease and thyroid cancer. We thank all of the *Friends of the ATA* who support our mission and work throughout the year to support us. We invite you to help keep the ATA® mission strong by choosing to make a donation that suits you — it takes just one moment to give online at: [www.thyroid.org/donate](http://www.thyroid.org/donate) and all donations are put to good work. The ATA® is a 501(c)3 nonprofit organization and your gift is tax deductible.

December is [Thyroid and Development Awareness Month](#).

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

- What are the fears that patient experience when diagnosed with thyroid cancer?
- Can molecular markers lead to personalized treatment of thyroid cancer?
- Can molecular markers prior to surgery help determine the initial surgery?
- What factors predict cancer recurrence in patients with papillary thyroid microcarcinomas?
- Is more radioactive iodine the answer for increased thyroglobulin levels alone?
- How effective are the new drugs for treating thyroid eye disease?

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

— Alan P. Farwell, MD



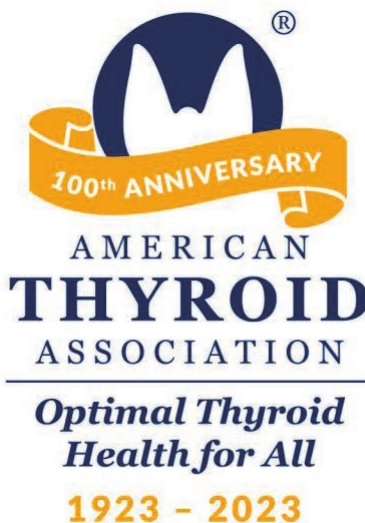
## AMERICAN THYROID ASSOCIATION CENTENNIAL

### Clinical Thyroidology for the Public – A Historical Celebration!

The Centennial celebration of the American Thyroid Association has been a time to reflect and recount many of the historical milestones over the past 100 years. *CTFP* is much younger than that, being about 16 years old. *CTFP* was the idea of Dr. Ernest Mazzaferri, who thought it would be a great opportunity to better inform patients by summarizing the latest research into thyroid diseases in language that would be understandable by the lay public. As we note in the Editor’s comments in every issue: “In this journal, we will bring to you the most up-to-date, cutting edge thyroid research... Our goal is to provide patients with the tools to be the most informed thyroid patient in the waiting room.”

The most current thyroid research is summarized for physicians in the monthly on-line journal *Clinical Thyroidology*. Dr. Mazzaferri suggested that we use the summaries in *Clinical Thyroidology* as the basis for this new journal and, in August and December 2008, *Clinical Thyroidology for the Patient* (the original name for *CTFP*) was born with Dr. Mazzaferri serving as the first Editor in Chief. *CTFP* became the 1st patient-focused journal to provide this detail of breaking clinical research to the lay public.

I took over as Editor in Chief of *CTFP* with Volume 2 in 2009 and started publishing issues every other month. Starting in 2010 with Volume 3, *CTFP* became a monthly on-line journal, summarizing the research that was presented to physicians the prior month in *Clinical Thyroidology*. Realizing that not just patients were interested in thyroid research, *CTFP* was re-named *Clinical Thyroidology for the Public* in 2014. This current issue (Volume 16, Issue 12) is our 176th issue. In



2017, *CTFP* was honored with the “Outstanding Achievement Award, NonProfit” by Interactive Media Awards. Access to *CTFP* has always been open to all without cost and will remain so for the foreseeable future.

*CTFP* has succeeded in developing widespread and world-wide interest. In 2016, there were more than 800,000 page views/downloads from 156 countries. In 2023, this had grown to around 2.5 million page views/downloads from 208 countries. The top 10 countries accessing *CTFP* in 2023 are the United States, the United Kingdom, India, Canada, Australia, the Philippines, Ireland, Singapore, Malaysia and the United

Arab Emirates. Users from 99 countries downloaded complete PDFs of this journal in 2023, with the top 10 being the United States, Canada, India, the Philippines, the United Kingdom, Indonesia, Thailand, Mexico, Egypt and Australia.

*CTFP* would not be the journal that it is today without the participation of our excellent and dedicated editorial board, who are responsible for writing the summaries for *CTFP*. A total of 42 ATA members have served on the *CTFP* board since 2008, with the longest serving member being Dr. Whitney Woodmansee, who was part of my inaugural editorial board in 2009. Finally, essential to the success of *CTFP* is the tireless work of Sharleene Cano, ATA Director of Publications and Membership; Karen Durland, *CTFP* designer; Jane Arrington, Website designer; Bobbi Smith, our prior CEO; and Amanda Perl, our current CEO. I hope you all have enjoyed reading *CTFP* and find it interesting and informative.

— Alan P. Farwell, MD  
Editor-in-Chief



## THYROID CANCER

# Fears experienced by women and men diagnosed with low-risk papillary thyroid cancer

### BACKGROUND

Many patients experience emotions such as shock, fear, and anxiety when they get diagnosed with thyroid cancer. In addition, patients may express concerns related to the uncertainty of having cancer, and the potential risks associated with cancer treatment. In studies involving cancer patients, gender has been found to be important in influencing the level of distress that patients experience. Therefore, information about how men and women experience fears related to thyroid cancer diagnosis and treatment are needed to inform strategies on how we can best support patients with thyroid cancer.

This study aimed to examine the association between gender and age with fears related to thyroid cancer progression or potential surgical treatment.

### THE FULL ARTICLE TITLE

Sawka AM et al for the Canadian Thyroid Cancer Active Surveillance Study Group (Greater Toronto Area) 2023 Gender differences in fears related to low-risk papillary thyroid cancer and its treatment. *JAMA Otolaryngol Head Neck Surg*. Epub 2023 Sep 1. PMID: 37410454.

### SUMMARY OF THE STUDY

The authors surveyed 200 Canadian patients (153 women and 47 men) with low-risk papillary thyroid cancer who were offered the choice of active surveillance (monitoring with ultrasound rather than proceeding with immediate

surgery) or immediate thyroid surgery for treatment of their thyroid cancer. Overall, 78% (155 total patients: 120 women and 35 men) of the study participants chose to undergo active surveillance.

In terms of gender, men and women reported similar levels of fear of thyroid cancer progression, but women reported a higher level of fear of surgery and its potential negative consequences. Specifically, women reported more fear than men in response to questions on fears about surgery, anesthesia, pain, deteriorating health due to the operation, and the recovery period. Women also reported experiencing more fear about potential thyroid surgery-related complications such as voice changes, low calcium levels, and the appearance of the scar. Furthermore, the authors found that younger age was associated with greater report of fear of thyroid cancer progression and fear of surgery.

### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The study findings suggest that men and women with papillary thyroid cancer may benefit from different approaches when receiving cancer-related education and support from their healthcare team. In addition, both men and women diagnosed with a low risk thyroid cancer are willing to follow with active surveillance rather than moving to immediate surgery.

— Debbie Chen, MD

### ATA RESOURCES

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

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



## THYROID CANCER, continued

### ABBREVIATIONS & DEFINITIONS

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

**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*.

**Active surveillance:** the practice of monitoring a small, low risk thyroid cancer with ultrasound rather than proceeding with immediate surgery.





## THYROID NODULES

# Molecular profiling of thyroid nodules: the road towards personalized treatment

### BACKGROUND:

Thyroid nodules are common, being seen on ultrasound in more than 50% of individuals over the age of 60. However, only 5 to 10% of these nodules are cancerous. Thyroid nodule biopsy can help to determine whether the nodule is benign or a cancer in 70-80% of cases. The remaining 20-30% of thyroid nodules are called indeterminate, meaning the cells are neither entirely normal nor abnormal, so a clear diagnosis cannot be made based on these results. Based on the Bethesda scoring system for thyroid nodules, indeterminate nodules are scored as Bethesda 3 or 4, where the cancer risk ranges from 13-34%. Further, Bethesda 5 nodules, which are suspicious for cancer, carry a cancer risk up to 83%.

More recently, molecular marker tests of the biopsy samples have been developed to further identify the cancer risk of thyroid nodules scored Bethesda 3, 4 or 5. If a molecular marker is negative, the nodule is considered to be benign. Certain molecular markers can also predict an aggressive cancer behavior and help choose the best surgical management. In addition, personalized treatment options for advanced thyroid cancer have been developed that target specific molecular markers. The aim of this study was to evaluate the molecular profile of thyroid nodules classified as Bethesda 3-5 by using comprehensive molecular marker testing.

### THE FULL ARTICLE TITLE:

Chiose S et al. 2023 Molecular profiling of 50,734 Bethesda III-VI thyroid nodules by ThyroSeq v3: Implications for personalized management. *J Clin Endocrinol Metab.* Epub 2023 Apr 18. PMID: 37071871.

### SUMMARY OF THE STUDY:

This is a study of 50,734 thyroid biopsy samples with cytology in the Bethesda 3-5 categories which were further analyzed using the ThyroSeq v3 assay at the University of Pittsburgh Medical Center from January 2018 to May 2021. The samples were collected from 1102 different

practice sites as part of routine clinical care. The average patient age was 58 years, 75% of the patients being women. The ThyroSeq v3 assay evaluates 112 molecular markers. The positive samples, which have a higher probability of being cancer, were then further divided into three groups based on their risk of aggressive behavior using the ThyroSeq Cancer Risk Classifier: low risk, intermediate risk and high risk.

Among the 50,734 samples, 65% were negative for molecular markers, 0.2% were positive for medullary thyroid cancer, 0.6% were positive for parathyroid cells, and 34% were positive for follicular thyroid cancer. Thus, based on the molecular markers, 71% of the Bethesda class 3 and 52% of the Bethesda class 4 biopsies were benign. Of the 32% of biopsies that were positive for molecular markers, Bethesda classes 3 and 4 biopsies showed predominantly low risk, *RAS*-like alterations which can be seen in benign nodules, while Bethesda class 5 biopsies showed mainly the cancer marker *BRAF* V600E-like alterations and fusions. A total of 70% of the positive samples had a low-risk profile, while 6% had a high-risk profile for aggressive behavior, more frequently seen in the Bethesda 5 biopsies.

### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

In this large group, 2/3 of the Bethesda class 3 and 4 thyroid nodule biopsies showed no molecular alterations when using the ThyroSeq v3 molecular test. This is clinically important, since the patients with a negative molecular test can avoid undergoing surgery for cancer diagnosis. Specific cancer markers, including *BRAF* and *TERT* mutations, were detected in the majority of Bethesda 5 biopsies, while low risk mutations were mainly seen in the Bethesda 3 and 4 biopsies. This information can be used to evaluate the cancer aggressiveness and prescribe personalized treatment in advanced thyroid cancer that targets specific genetic alterations.

— Alina Gavrilă, MD, MMSC



## THYROID NODULES, continued

### ATA RESOURCES

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

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

### ABBREVIATIONS & DEFINITIONS

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

**Thyroid nodule 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 when a few abnormal/atypical cells are seen but not enough to be abnormal/diagnose cancer (atypia of unknown significance/AUS) or when the diagnosis is a follicular or oncocytic lesion. Follicular and oncocytic cells are normal cells found in the thyroid. Current analysis of thyroid biopsy results cannot differentiate between a follicular or oncocytic cancer from non-cancerous adenomas. This occurs in 15-20% of biopsies.

**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*.

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

**Follicular cells:** thyroid cells that play the key role in the thyroid hormone synthesis and release into the blood.



## THYROID CANCER

# Obtaining molecular markers on thyroid biopsies prior to surgery may affect initial surgery and intensity of postoperative follow-up

### BACKGROUND

Thyroid nodules are very common. When a biopsy is indicated for a patient with a thyroid nodule, the results are evaluated according to the risk of cancer (called the “Bethesda system”). Low risk patients (Bethesda 2) are often just monitored. For Bethesda 3 and 4 thyroid nodules, molecular marker testing is recommended and has led to increased accuracy for diagnosing thyroid cancers, allowing for more individualized treatment plans. Since the risk for cancer in Bethesda 5 and 6 nodules is greater than 50%, molecular marker testing is usually not done as most often patients are recommended to proceed to surgery. The surgery may be removal of the lobe containing the cancer (lobectomy) or removal of the whole thyroid (total thyroidectomy). After surgery, radioactive iodine therapy may be recommended. However, even in these cancers, some can be aggressive and others may be slow growing, progressing slowly and not posing an immediate threat.

Molecular marker testing can identify high risk thyroid cancers with increased likelihood of aggressive features, cancer recurrence after initial therapy, and spread outside of the thyroid. This study was performed to see if molecular marker testing for Bethesda 5 and 6 nodules could aid in prediction of the aggressiveness of the thyroid cancer and even help to determine the planned management.

### THE FULL ARTICLE TITLE

Schumm MA et al 2023 Prognostic value of preoperative molecular testing and implications for initial surgical management in thyroid nodules harboring suspected (Bethesda V) or known (Bethesda VI) papillary thyroid cancer. *JAMA Otolaryngol Head Neck Surg* **149**:735–742. PMID: 37382944.

### SUMMARY OF THE STUDY

This is a study of patients from a single institution who had Bethesda 5 or 6 thyroid nodules and thyroid cancer confirmed after surgery. They were classified into risk of cancer recurrence based on 2014 American Thyroid Association guidelines. Samples of the nodules were analyzed using ThyroSeq molecular testing and stratified into Cancer Risk Classifier molecular risk groups, which are based on the probability of cancer aggressiveness. These groups include (i) negative (no detectable genetic alteration); (ii) low-risk (*RAS* and *RAS*-like alterations); (iii) intermediate risk (*BRAF* V600E or other *BRAF*-like alterations); and (iv) high risk (combination *BRAF/RAS* plus *TERT* or other high-risk alterations). Molecular testing results were then correlated with available clinical follow-up data. Outcomes included cancer persistence or recurrence, spread of the cancer outside of the thyroid and cancer recurrence-free survival.

There were 105 patients identified, all of whom had papillary thyroid cancer and were followed for an average of 3.8 years. The average age was 44 and 68% were female. Molecular markers were identified in 100 (95%) of these samples, of which 6 (6%) were low disease risk, 88 (88%) intermediate disease risk, and 6 (6%) high disease risk.

When no molecular markers were identified (n=5) or there was low risk cancer (n=6), there was no recurrence or spread of the cancer outside of the thyroid identified in follow up. In the 88 patients with intermediate disease risk, 6 (7%) experienced recurrence of the cancer, including 1 patient who also developed spread of the cancer outside of the thyroid. Those with high disease risk (n=6), all of whom demonstrated *BRAF* V600E plus *TERT* mutations, underwent total thyroidectomy





## THYROID CANCER, continued

followed by radioactive iodine therapy. Of these 6 high-disease-risk patients, 4 (67%) developed recurrence of the cancer, 3 of whom also developed spread of the cancer outside of the thyroid.

### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study shows that when patients were found to have high risk molecular markers, they were more likely to have

persistent or recurrent cancer and spread of the cancer outside of the thyroid than patients with intermediate or low risk molecular markers. In contrast, 100% of those with low risk molecular markers had 36-month cancer recurrence-free survival. This study suggests the possibility of considering less surgery or avoiding radioactive iodine therapy in patients with low and intermediate risk molecular markers despite having Bethesda 5 or 6 nodules.

— Marjorie Safran, MD

### ATA RESOURCES

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

### 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.

**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™ Gene Expression Classifier 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.

**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 gene that codes for a protein that is involved in a signaling pathway and is important for cell growth. Mutations in the *BRAF* gene in adults appear to cause cancer.

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



## THYROID CANCER

### The importance of evaluating the lateral neck in patients with papillary thyroid microcarcinomas

#### BACKGROUND

Papillary thyroid cancer is the most common thyroid cancer. Many of these cancers are small (<1 cm) and are referred to as microcarcinomas. Papillary thyroid microcarcinomas are common, particularly with increasing age. Most papillary thyroid microcarcinomas are considered low risk as they are very slow growing. Because of this, papillary thyroid microcarcinomas are usually managed with either active surveillance (following the cancers by ultrasound rather than immediate surgery) or with removal of the lobe containing the cancer (lobectomy). Oftentimes, these microcarcinomas are considered “cured” after lobectomy. However, a subgroup of papillary thyroid microcarcinomas are higher risk and can spread outside the neck. Additionally, these cancers can recur after surgery. Identification of such patients at diagnosis may identify those that would benefit from more intensive management.

The aim of this study was to evaluate the association between the spread of cancer to the lymph nodes in the neck in patients with papillary thyroid microcarcinomas and future risk of cancer recurrence.

#### THE FULL ARTICLE TITLE

Ruan J et al 2023 Lateral lymph node metastasis in papillary thyroid microcarcinoma: A study of 5241 follow-up patients. *Endocrine*. Epub 2023 Aug 7. PMID: 37596455.

#### SUMMARY OF THE STUDY

This is a study of 5241 patients with papillary thyroid microcarcinoma from China between 1997 and 2016. Aggressive subtypes of papillary thyroid cancer and patients with less than 1 year of follow-up were excluded from the study. Patients were monitored for cancer recurrence using serum thyroglobulin levels and neck ultrasonography. Spread of the cancer to the lymph nodes were confirmed either after surgical removal or by a positive radioactive iodine whole-body scan. The patients were predominantly female (76%) and young (79% were

less than 55 years of age), and the average cancer size was 0.6 cm. Cancer was found in lymph nodes in the central neck in 26% cases and in the lateral neck in 2.5% of cases. Average postoperative follow-up was 60 months.

During follow-up, cancer recurrence occurred in 114 of 5241 (2.2%) patients. Sites of recurrence were the thyroid bed (41), lymph nodes (69) and distant sites (3). There were 24 patients who died but only 1 of these deaths was associated with their thyroid cancer (0.05%). The 5-year cancer-free survival was 98.9% if there was no cancer in the lymph nodes at the time of initial surgery, 96% if there was cancer in the lymph nodes in the central neck at the time of initial surgery and 87% if there was cancer in the lymph nodes in the lateral neck at the time of initial surgery. Thus, the presence of cancer in the lymph nodes at the time of initial surgery was the only significant predictor of cancer recurrence. There was a 3-fold increase risk of cancer recurrence if there was cancer in the lymph nodes in the central neck at the time of initial surgery and ~11-fold increase risk of cancer recurrence if there was cancer in the lymph nodes in the lateral neck at the time of initial surgery.

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

This study shows that the majority of patients with papillary thyroid microcarcinoma have a very low risk of cancer recurrence (2.2%) and the vast majority of patients with cancer recurrence (94%) had cancer identified in lymph nodes at the time of initial surgery. The presence of cancer in the lateral neck nodes at diagnosis was the strongest predictor of future recurrence. This study suggests that patients with papillary thyroid microcarcinoma without lymph node involvement can be followed less intensely while those with any lymph node involvement should continue to be followed closely. This study also suggests that all patients with papillary cancer should have a lateral neck node survey by ultrasound prior to surgery to better direct the surgery and to plan for future care.

— Alan P. Farwell, MD



## THYROID CANCER, continued

### ATA RESOURCES

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

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

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

### ABBREVIATIONS & DEFINITIONS

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

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

**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.



## THYROID CANCER

### Is more radioactive iodine the answer for increased thyroglobulin levels alone?

#### BACKGROUND

Thyroid cancer is almost always treated with surgery initially. If the cancer is high risk and the entire thyroid was removed, radioactive iodine can be used to destroy and remaining thyroid cancer cells. After the initial therapy, our current American Thyroid Association 2015 guidelines categorize patient's thyroid cancer in terms of how likely it is to recur in a neck lymph node in the next ten years. We use ultrasound imaging to identify any cancer remaining in the thyroid bed or in the lymph nodes in the neck (structural response to therapy) and measurement of thyroglobulin levels as thyroid cancer markers (biochemical response to therapy). The best-case scenario (low to undetectable thyroglobulin levels) is called "biochemically excellent response to therapy," while the worst-case scenario (spread of the cancer to lymph nodes or other organs found on ultrasound) is called "structurally incomplete response to therapy." In between is when thyroglobulin levels are rising or remain elevated and no evidence of cancer is noted on imaging (biochemically incomplete or indeterminate response to therapy).

This study was done because it is unclear whether patients who received radioactive iodine therapy right after their initial surgery will further benefit from more radioactive iodine if they are in either the "biochemically incomplete or biochemically indeterminate response to therapy" categories. The goal of this study is to better understand if additional doses of radioactive iodine therapy is beneficial when the thyroid cancer is not responding to therapy in the "biochemically indeterminate or incomplete" category.

#### THE FULL ARTICLE TITLE

Gambale C et al 2023 Usefulness of second 131I treatment in biochemical persistent differentiated thyroid cancer patients. Eur Thyroid J. Epub 2023 Sep 1. PMID: 37768697.

#### SUMMARY OF THE STUDY

A total of 153 patients from the University of Pisa were studied from 2009 to 2012 who had surgery and a first dose of radioactive iodine for their thyroid cancer. Of these 153 patients, 37% had a thyroid cancer that was a low risk of recurrence based on their surgical pathology. About half had a "biochemical incomplete response to therapy" and half had a "biochemical indeterminate response to therapy" on average 7.5 months after their first radioactive iodine dose (range of 30-100 millicurie, mCi) based on the 2009 ATA guidelines. In other words, the ranges of the thyroid cancer marker, thyroglobulin, were 1.3 and 3.7 µg/L and between 2.6 and 8.6 µg/L for the stimulated thyroglobulin level. These patients then received a second radioactive iodine dose of 100 mCi about 20 months after the first radioactive iodine dose. Patient were reassessed for response of therapy 8 months after the second radioactive iodine dose then followed for another 7.7 years.

A majority 71% of the patients remained in the "biochemically indeterminate or incomplete" response to therapy even after the second dose of radioactive iodine was given. Only 12% of the patients were reclassified into the desirable "biochemically excellent response to therapy" after the second dose. In fact, 17% of the patients were found to have spread of the cancer outside of the neck. In the long term 7 year follow up, 9 more people were found to have spread of the cancer outside of the neck. Over the 7 year period, 10 more people qualified for the "excellent" response to therapy after a third dose of radioactive iodine and 9 more did so with no additional radioactive iodine treatment.

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

This study shows that most of the patients in the "biochemical incomplete or indeterminate response to therapy" category stayed in the same category despite



## THYROID CANCER, continued

receiving a 2nd dose of radioactive iodine therapy. Overall, about 23% will develop a spread of the cancer outside of the neck that was not identified after the 2nd dose, usually within the first three years. Thus, these data suggest that a

2nd dose of radioactive iodine in patients with increased thyroglobulin levels but no evidence of cancer on a neck ultrasound is not very effective and can be deferred.

— Pinar Smith, MD

### ATA RESOURCES

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

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

### ABBREVIATIONS & DEFINITIONS

**Thyroglobulin:** a protein made only by thyroid cells, both normal and cancerous. When all normal thyroid tissue is destroyed after radioactive iodine therapy in patients with thyroid cancer, thyroglobulin can be used as a thyroid cancer marker in patients that do not have thyroglobulin antibodies.

**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).

**Post-Radioactive iodine Whole Body Scan:** the scan done after radioactive iodine treatment that identifies what was treated and if there is any evidence of metastatic thyroid cancer.

**Stimulated thyroglobulin testing:** this test is used to measure whether there is any cancer present in a patient that has previously been treated with surgery and radioactive iodine. TSH levels are increased, either by withdrawing the patient from thyroid hormone or treating the patient with recombinant human TSH, then levels of thyroglobulin are measured. Sometimes this test is combined with a whole body iodine scan.

**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.



## THYROID EYE DISEASE

### Medical therapy for thyroid eye disease

#### BACKGROUND

Graves' disease is a common cause of hyperthyroidism. It is an autoimmune disease in which the person makes antibodies that attack the thyroid gland (TSI or TRAb) and turns on the thyroid, causing an overactive thyroid. This condition can be associated with inflammation of the muscles that control eye movements. This can cause eye bulging (proptosis) and difficulty with eye movements leading to pain, eye irritation, double vision and even loss of vision. These symptoms are known as thyroid eye disease (TED). Moderate to severe cases of TED are typically treated with high doses of glucocorticoids (steroids) and some patients may require surgery to correct the eye changes. In recent years, agents that modify the immune system have been studied as alternative treatments to steroids and surgery. One drug, Teprotumumab, was approved by the FDA in 2020 for the treatment of TED. Patients treated with this medication showed significant improvement in TED symptoms. A second drug, Tocilizumab, has been studied and used off label (not FDA-approved) for TED. This drug works by inhibiting an important immune system mediator known as interleukin-6 and is FDA-approved for other immune mediated disorders. The aim of this study was to report real world experience with these new medical therapies in the treatment of TED at a single medical center in the US.

#### THE FULL ARTICLE TITLE:

Toro-Tobon et al. 2023 Medical therapy in patients with moderate to severe, steroid-resistant, thyroid eye disease. Thyroid. Epub 2023 Jul 29. PMID: 37515425.

#### SUMMARY OF THE STUDY:

This study examines the real-world experience of patients treated with medical therapy for TED at a large, multi-center health system in the US. Patients were identified by screening the electronic medical record database of the Mayo Clinic health system and records reviewed in detail. Adult subjects with TED treated with either teprotumumab (10–20 mg/kg every 3 weeks for a total of eight intravenous infusions) or tocilizumab (4 mg/kg for the

first infusion, followed by 8 mg/kg every month, for a total of four intravenous infusions) between 2018-2022 were identified. Prior treatment with steroids was recorded and it was documented whether patients had progression of TED on steroids (steroid resistant). Overall, 37 patients were identified with moderate to severe TED that had been treated with either teprotumumab (31 patients, 13 steroid resistant and 18 who had not previously received steroids) or tocilizumab (6 patients all with steroid resistance). Eye symptoms were evaluated at baseline, 12, 24, and 52 weeks after medication infusion.

Patients treated with either teprotumumab or tocilizumab reported improved eye symptoms including proptosis and double vision at week 24. Both medications showed a tendency for worsening symptoms at further time points following completion of the therapy. Patients with and without steroid resistance prior teprotumumab therapy demonstrated benefits. Teprotumumab therapy was associated with side effects of ear issues (including hearing loss and ear ringing) and high blood glucose levels. There were no side effects reported in the tocilizumab group, but this group included very few patients (6). The authors concluded that both medications showed promise in improving TED and further studies are needed to better understand their long term benefits and safety, especially in steroid resistant patients.

#### WHAT ARE THE IMPLICATIONS OF THE STUDY?

Medical therapy may be a good option for TED and importantly may become an alternative treatment to high dose steroids or surgery. Although a small study, both agents, teprotumumab and tocilizumab, were associated with a reduction in TED symptoms. Currently, only Teprotumumab is FDA-approved for the treatment of TED. More studies in larger groups of patients are needed to fully understand the safety and efficacy of these newer medications in the treatment of TED.

— Whitney W. Woodmansee MD



## THYROID EYE DISEASE, continued

### ATA RESOURCES

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

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

Thyroid Eye Disease: <https://www.thyroid.org/thyroid-eye-disease/>

### ABBREVIATIONS & DEFINITIONS: FROM ACTIVE LIST

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

**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.



# Clinical Thyroidology® for the Public

## 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.



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



MCT8 - AHDS Foundation



### American Thyroid Association®

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

ATA® Patient Resources:

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

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

(Toll-free): 1-800-THYROID

[thyroid@thyroid.org](mailto:thyroid@thyroid.org)

### Bite Me Cancer

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

[info@bitemecancer.org](mailto:info@bitemecancer.org)

### Graves' Disease and Thyroid Foundation

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

(Toll-free): 877-643-3123

[info@ngdf.org](mailto:info@ngdf.org)

### Light of Life Foundation

[www.checkyourneck.com](http://www.checkyourneck.com)

[info@checkyourneck.com](mailto:info@checkyourneck.com)

### MCT8 – AHDS Foundation

[mct8.info](http://mct8.info)

[Contact@mct8.info](mailto:Contact@mct8.info)

### Thyca: Thyroid Cancer Survivors' Association, Inc.

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

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[thyca@thyca.org](mailto:thyca@thyca.org)

### Thyroid Cancer Alliance

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

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

Rotterdam, The Netherlands

### Thyroid Cancer Canada

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

416-487-8267

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### Thyroid Federation International

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

[tfi@thyroid-fed.org](mailto:tfi@thyroid-fed.org)



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