AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

Clinical Thyroidology® for the Public

VOLUME 12 | ISSUE 10 | OCTOBER 2019

Although the death rate is much lower in patients with thyroid cancer than other cancers, recent studies have shown that the self-reported quality of life in these survivors is the same or worse than that reported in cancers with worse prognoses. Cancer survivors may experience changes in their physical or emotional state as a consequence of the diagnosis, treatment and monitoring of the cancer. This study obtained and analyzed patient-reported data to understand the illness from the patient's perspective, so that effective interventions can be developed aimed to improve health related quality of life.

Goswami S et al 2019. Clinical factors associated with worse quality-of-life scores in United States thyroid cancer survivors 2019 Surgery. Epub 2019 Mar 18. pii: S0039-6060(19)30066-2. PMID: 30898373.

Despite an overall excellent prognosis, patients with thyroid cancer face the burden of extended surveillance with neck ultrasounds, which are done to identify abnormal lymph nodes that would indicate cancer recurrence. Neck ultrasounds are usually performed every 6-12 months to monitor for cancer recurrence but it is unclear when these studies can stop, assuming they are negative. In this study, the authors investigated the need for annual ultrasound examinations in low and intermediate risk patients with papillary thyroid cancer.

Grani G et al 2019 Thyroid cancer patients with no evidence of disease: the need for repeat neck ultrasound. J Clin Endocrinol Metab Epub 2019 Jun 17. PMID: 31206157.

At present, the ATA recommends following small, low risk papillary thyroid cancers with ultrasound and clinical exam rather than surgery, which is known as active surveillance. The goal of this study was to evaluate how fast papillary thyroid cancers grow by measuring the cancer volume doubling time and to find clinical and ultrasound features that predict a rapid cancer growth.

Oh HS et al 2019 Tumor volume doubling time in active surveillance of papillary thyroid carcinoma. Thyroid 29:642–649. PMID 30864894.

In general, the tall-cell variant of papillary thyroid cancer has been shown to be more aggressive and have worse outcomes that the classical papillary thyroid cancer. There has been disagreement over what proportion of cells need be described as 'tall-cell' for patient outcomes to be worse. In this study, the authors reviewed all their cases of >1cm tall-cell papillary thyroid cancers over a 15 year and then compared outcomes of patients with <30% of cells that were tall-cell to patients with >30% of cells tall-cell.

Bongers PJ et al 2019 Papillary thyroid cancers with focal tall cell change are as aggressive as tall cell variants and should not be considered as low-risk disease Ann Surg Oncol. Epub 2019 May 21. PMID: 31115855.

There is some uncertainty about the clinical importance and treatment implications of having multifocal vs unifocal papillary thyroid cancer. In additional, there have been some conflicting reports examining whether multifocal papillary thyroid cancer is a risk factor for thyroid cancer recurrence. This study was performed to examine the independent risk of multifocal papillary thyroid cancer in predicting thyroid cancer outcomes, including cancer recurrence and death.

Geron Y et al 2019 Multifocality Is not an Independent Prognostic Factor in Papillary Thyroid Cancer: A Propensity Score–Matching Analysis Thyroid 29:513–522.

Positive TPOAb levels in the blood have been associated with difficulty getting pregnant (infertility) and pregnancy loss in some studies but not in others. Previous clinical trials did not show clear benefit of treatment with levothyroxine in women with positive TPOAb and history of infertility or pregnancy loss. This study was done to evaluate possible effect of positive TPOAb levels on live birth rate in women with history of current pregnancy losses.

Bliddal Set al. 2019 Thyroid peroxidase antibodies and prospective live birth rate – a cohort study of women with recurrent pregnancy loss. Thyroid. Epub 2019 Aug 13. PMID: 31407629.

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EDITOR'S COMMENTS

Welcome to another issue of *Clinical Thyroidology for the Public*. In this journal, we will bring to you the most up-to-date, cutting edge thyroid research. We also provide even faster updates of late-breaking thyroid news through Twitter at @thyroidfriends and on Facebook. Our goal is to provide patients with the tools to be the most informed thyroid patient in the waiting room. Also check out our friends in the **Alliance for Thyroid Patient Education**. The **Alliance** member groups consist of: the *American Thyroid Association, Bite Me Cancer, the Graves' Disease and Thyroid Foundation, the Light of Life Foundation, MCT8 – AHDS Foundation, ThyCa: Thyroid Cancer Survivors' Association, Thyroid Cancer Canada, Thyroid Cancer Alliance* and *Thyroid Federation International*.

The American Thyroid Association (ATA) extends its appreciation to all of the patients and their families that are part of the ATA community — our **Friends of the ATA**. It is for you that the ATA is dedicated to carrying out our mission of providing reliable thyroid information and resources, clinical practice guidelines for thyroid detection and treatments, resources for connecting you with other patients affected by thyroid conditions, and cutting edge thyroid research as we search for better diagnoses and treatment outcomes for thyroid disease and thyroid cancer.

October is Thyroid Nodules Awareness Month.

In this issue, the studies ask the following questions:

- Do thyroid cancer survivors have a worse quality of life than other cancer survivors?
- Do low and intermediate risk thyroid cancer patients still need regular neck ultrasounds?
- How fast do small thyroid cancers grow during active surveillance?
- Is there any difference in prognosis between focal tall-cell changes and tall-cell variants of papillary cancer?
- Is the prognosis for multifocal papillary cancer different than for unifocal cancers?
- Are TPO antibodies associated with worse pregnancy outcomes?

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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THYROID CANCER

What Factors Contribute to Worse Quality of Life in Thyroid Cancer Survivors?

BACKGROUND

In recent decades, there has been a significant increase in the number of patients diagnosed with thyroid cancer. It is estimated that at this time there are more than 760,000 thyroid cancer survivors living in the United States. Although the death rate is much lower than other cancers, recent studies have shown that the self-reported quality of life in these survivors is the same or worse than that reported in cancers with worse prognoses.

Cancer survivors may experience changes in their physical or emotional state as a consequence of the diagnosis, treatment and monitoring of the cancer. These changes can affect the individual in the short term or the long term. Examples of these changes include the presence of a scar, need for life-long thyroid hormone treatment, dry mouth, and the need to routinely evaluate for the presence of cancer recurrences or spread to other parts of the body.

More research on thyroid cancer survivors is necessary, in particular to evaluate the factors and complications of treatment that are more likely to impair quality of life. This study obtained and analyzed patient-reported data to understand the illness from the patient's perspective, so that effective interventions can be developed aimed to improve health related quality of life.

THE FULL ARTICLE TITLE

Goswami S et al 2019. Clinical factors associated with worse quality-of-life scores in United States thyroid cancer survivors 2019 Surgery. Epub 2019 Mar 18. pii: S0039-6060(19)30066-2. PMID: 30898373.

SUMMARY OF THE STUDY

In this study, the authors used a Patient-Reported Outcomes Measurement Information System (PROMIS). This is a 29-item profile measure that evaluates mental, physical and social health across 7 categories: depression, anxiety, pain interference, physical function, fatigue, sleep disturbance and ability to participate in social roles. It has been validated in the US population and in several cancer populations.

The survey was distributed in collaboration with the patient advocacy group Thyroid Cancer Survivors Association (ThyCa) using several online and social media sites from January to June 2017. Individuals who reported a diagnosis of thyroid cancer, who lived in the USA, and who were 18-89 years of age were eligible to take part. The survey was accessed by 3,174 individuals, of whom 1,743 reported living in the United States and completed the two parts of the survey. The data from this group was analyzed for this study.

The majority of the respondents were female (88%) and caucasian (95%). Although all types of thyroid cancer were included, the majority had been diagnosed with papillary type (85%). Approximately 30% of patients reported having had Stage 1 disease, 17% Stage 2, 14% Stage 3, 11% Stage 4 and 28% unknown stage. The overwhelming majority of patients (98%) had surgery for treatment and 78% also received radioactive iodine therapy. A much smaller percentage received external beam radiation (3.8%), chemotherapy (2.4%) and alternative therapies (3.2%).

The adverse effects reported depended on the type of treatment received, and included difficulty swallowing, difficulty with voice, concern with scar appearance, low blood calcium levels, dry mouth, dry eyes, change in taste and appetite.

Multiple factors were identified that had a statistically significant impact on health related quality of life. Younger patients (<45 years) had worse scores in the area of fatigue, depression and anxiety. People who reported infections in the surgical wound, difficulty swallowing and dry eyes after radioactive iodine therapy had worse scores related to pain. Patients who had treatment with chemotherapy, who developed infections of the surgical wound and lung scarring due to radioactive iodine therapy reported the worse physical functioning scores. Time since diagnosis was inversely associated with anxiety, depression, fatigue and sleep disturbance (the longer time since diagnosis, the less significant association noted).

THYROID CANCER, continued

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study is important because it is one of the first studies to describe the clinical factors associated with lower health related quality of life in thyroid cancer survivors using a validated measurement tool. Although it may not be fully representative of all thyroid cancer survivors, it used a large sample number and the results were consistent with prior reports found in the literature. The results are important because the doctors' perspectives in quality of life may not be the same as patients. Knowing the patients' perspective on their quality of life after treatment will be an extremely important factor to incorporate when developing guidelines to treat thyroid cancer in the future.

— Jessie Block-Galarza, MD

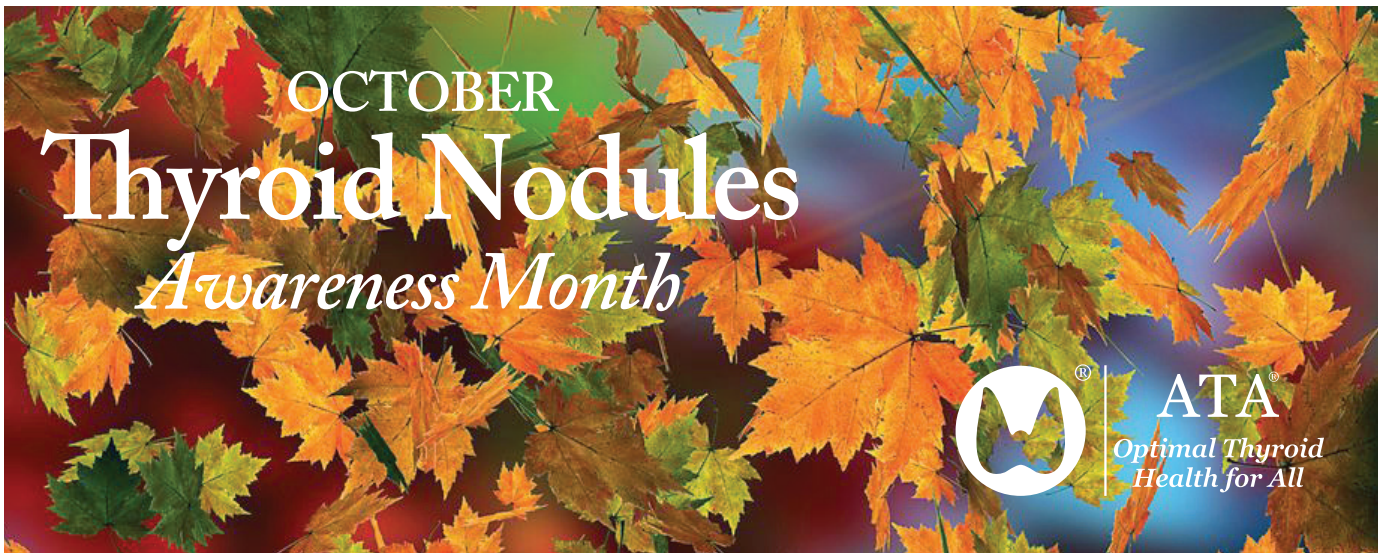
ATA THYROID BROCHURE LINKS

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

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).

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.



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VOLUME 12 | ISSUE 10 | OCTOBER 2019

THYROID CANCER

Do patients with low- and intermediate-risk thyroid cancer need continuing post-operative neck surveillance ultrasounds?

BACKGROUND

Thyroid cancer is the fastest rising cancer in the United States. The vast number of patients do well with an excellent prognosis. This is because of effective treatment with surgery and, when needed, radioactive iodine. Despite this overall excellent prognosis, patients with thyroid cancer face the burden of extended surveillance with neck ultrasounds, which are done to identify abnormal lymph nodes that would indicate cancer recurrence. This is because the lymph nodes in the neck are the most common place for thyroid cancer to recur. Neck ultrasounds are usually performed every 6-12 months to monitor for cancer recurrence but it is unclear when these studies can stop, assuming they are negative. In addition, neck ultrasounds have cost and not a large amount of evidence to support long-term annual tests.

The American Thyroid Association guidelines divide thyroid cancer into low, intermediate and high risk depending on the risk of cancer recurrence after the initial treatment. The vast majority of patients fall into the low and intermediate risk category. In this study, the authors investigated the need for annual ultrasound examinations in low and intermediate risk patients with papillary thyroid cancer.

THE FULL ARTICLE TITLE

Grani G et al 2019 Thyroid cancer patients with no evidence of disease: the need for repeat neck ultrasound. J Clin Endocrinol Metab Epub 2019 Jun 17. PMID: 31206157.

SUMMARY OF THE STUDY

The authors examined the medical records of patients at one medical center with low to intermediate risk papillary thyroid cancer treated with surgery (total thyroidectomy) and, if needed, radioactive iodine therapy. The patients were followed over a 7 year period with seral neck ultrasounds and blood tests to measure serum thyroglobulin levels as a cancer marker. The main study outcome was whether there were abnormal lymph nodes seen on a neck ultrasound by 3 years of follow up.

Patients were considered low or intermediate risk of cancer recurrence if their baseline thyroglobulin levels were <1 ng/ml. Out of 226 patients studied meeting this criteria, only 5 had lymph nodes that were considered to not be completely normal on ultrasound 3 years after thyroid cancer treatment. Over the study period, no patients underwent a second operation.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The study authors conclude that patients with low and intermediate risk thyroid cancer who had a total thyroidectomy only need blood tests for thyroglobulin after the first year if their levels are < 1 ng/mL. Therefore, the authors suggest that the yearly neck ultrasound can be avoided in these patients. While these results need to be confirmed with other long term studies, this study is important for patients because it may help them avoid unnecessary tests which helps them save money and minimizes the worry that is common during any thyroid cancer monitoring testing.

— Joshua Klopper, MD

ATA THYROID BROCHURE LINKS

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

THYROID CANCER, continued

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. Ultrasound is also frequently used to guide the needle into a nodule during a thyroid nodule biopsy.

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

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.

Total thyroidectomy: surgery to remove the entire thyroid gland.

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.

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).

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.

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THYROID CANCER

Cancer volume doubling time in the active surveillance of papillary thyroid carcinomas

BACKGROUND

Thyroid cancer is the fastest rising cancer in the United States and papillary thyroid cancer is the most common type of thyroid cancer. This is due, in part, to an increase of identifying small thyroid cancers on imaging tests done for other reasons. It is clear that many of these small cancers grow at very slow rates and never spread beyond the thyroid. Because of this, the traditional treatment thyroid surgery, possibly followed by radioactive iodine therapy, may not be indicated for these low risk, less aggressive, small thyroid cancers. At present, the American Thyroid Association recommends following these small low risk cancers with ultrasound and clinical exam rather than surgery, which is known as active surveillance. During active surveillance the patient is monitored closely and referred for thyroid surgery if there is evidence of cancer progression on follow-up tests.

It is important to identify early the patients with small cancers who are likely to progress rapidly and refer them for thyroid surgery as compared to patients with stable disease for a long time who do not require any intervention. The goal of this study was to evaluate how fast papillary thyroid cancers grow by measuring the cancer volume doubling time and to find clinical and ultrasound features that predict a rapid cancer growth.

THE FULL ARTICLE TITLE

Oh HS et al 2019 Tumor volume doubling time in active surveillance of papillary thyroid carcinoma. Thyroid 29:642–649. PMID 30864894.

SUMMARY OF THE STUDY

The study included 273 patients diagnosed with papillary thyroid cancer and followed using active surveillance for more than a year after diagnosis at a medical center in Korea between 2002 and 2016. Patients with an aggressive type of papillary thyroid cancer, cancer invasion outside the thyroid into other neck structures and spread to local lymph nodes and outside of the neck were excluded from the study. Patients had a physical exam and neck ultrasound performed every 6-12 months to measure the cancer volume and document the ultrasound appearance of the thyroid cancer. Thyroid surgery was recommended when the cancer size was greater than 1 cm or increased by 3 mm, the cancer volume increased by 50% from baseline, new local or distant metastases were detected or the cancer was growing towards other neck structures.

The average patient age at diagnosis was 51 years and 76% were women. The average initial maximal cancer diameter on ultrasound was 5.8 mm, while the average tumor volume was 62 mm3. Patients were classified into two groups based on the cancer volume doubling time: 1) a stable group with a cancer volume doubling time 5 years or longer, which included the majority (72%) of patients and 2) a rapid growing group with a cancer volume doubling time of less than 5 years (28% of patients). The maximum period of follow-up was 6 years for the rapid-growing group and 16 years for the stable group.

Most patients with a significant cancer growth were in the rapid growing group. There was a progressive and sustained cancer growth noted in this group, while there was minimal or no cancer growth in the stable group. Younger age of less than 50 years and the presence of macrocalcifications on neck ultrasound were associated with a faster cancer growth and cancer volume doubling time of less than 5 years. Gender, initial cancer size or other ultrasound features of the cancer were not associated with the tumor growth.

A total of 19% of patients, 60% being in the rapid growing group, stopped active surveillance and underwent thyroid surgery after an average time of 29 months of surveillance. At the time of thyroid surgery, almost 45% of patients had tumor extension outside the thyroid, one third had lymph node metastases in the neck and no patients had distant metastases. There were no significant differences in any of these parameters between the rapid-growing and stable groups. Two patients in the rapid-growing group and none in the stable group had lymph node metastases in the lateral neck.

THYROID CANCER, continued

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Cancer volume doubling time is a good indicator of the cancer growth rate and progression in patients with papillary thyroid cancer monitored by ultrasound during active surveillance. Indeed 2/3rds of patients have a relatively benign course with a cancer volume doubling time longer than 5 years. A younger age and cancer volume doubling time, macrocalcifications noted on ultrasound were associated with a faster growth and a shorter cancer volume doubling time. Cancer volume doubling time may be helpful to predict which cancers progress fast requiring early surgical referral and which cancers are stable for a long time. However, cancer volume doubling time may not predict other unfavorable prognostic factors, such as cancer extension outside the thyroid and lymph node metastases.

— Alina Gavrila, MD, MMSC

ATA THYROID BROCHURE LINKS

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

ABBREVIATIONS & DEFINITIONS

Active surveillance (AS): a treatment plan that involves closely watching a patient with low risk cancer without starting any treatment unless the condition is getting worse.

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

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

Thyroid Ultrasound (US): 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.

Macrocalcifications: Large flecks of calcium that can be seen either inside a thyroid nodule or in the periphery (so called egg-shell/rim calcifications), usually seen as large bright spots on ultrasonography.

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

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

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THYROID CANCER

All tall-cell variants of papillary thyroid cancer are created equal

BACKGROUND

Papillary thyroid cancer is the most common cause of thyroid cancer and most cases have excellent outcomes. However, some papillary thyroid cancer variants have been shown to be more aggressive, showing higher rates of spread to both lymph nodes and outside of the neck as well as having increased rates of cancer recurrence and decreased survival. One of these variants is tall-cell, which describes how the cells look under the microscope. There has been disagreement over what proportion of cells need be described as 'tall-cell' for patient outcomes to be worse. Current guidelines use 30% as a cutoff. Therefore, the authors reviewed all their cases of >1cm tall-cell papillary thyroid cancers over a 15 year period as well as a similar group of patients with classical papillary thyroid cancer as the control group. They had 2 separate pathologists re-review all of the slides and then compared outcomes of patients with <30% of cells that were tall-cell to patients with >30% of cells tall-cell.

THE FULL ARTICLE TITLE

Bongers PJ et al 2019 Papillary thyroid cancers with focal tall cell change are as aggressive as tall cell variants and should not be considered as low-risk disease Ann Surg Oncol. Epub 2019 May 21. PMID: 31115855.

SUMMARY OF THE STUDY

There were 131 patients with tall-cell papillary thyroid cancer (73% with <30% and 27% with >30% tall-cell cells) examined in this study and compared to 104 patients with classical papillary thyroid cancer. Compared to the group of patients with classical papillary thyroid cancer, both tall-cell groups had higher rates of "aggressive" features, ie vascular invasion, gross extension of the cancer outside of the thyroid and spread to the lymph nodes in the neck. Patients with classical papillary thyroid cancer had a higher 5-year disease-free survival rate (92.7%) as compared with those with focal tall-cell change (76.3%) and tall-cell variant (62.2%). After taking into account cancer size and other aggressive features, patients with <10% tall-cell features had significantly lower rates of persistent or recurrent disease compared to those with 10-30%, 20-30%, and >30% tall-cell features.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Almost all tall-cell featured papillary thyroid cancers are created equal. They all appear to behave the same and have worse outcomes than classical papillary thyroid cancer. A tall-cell proportion of <10% focal changes should be used as the cutoff for predicting outcomes, which can be used to help counsel patients on treatment and prognosis. Those patients with a tall-cell proportion >10% should be targeted for more aggressive therapy and closer monitoring.

— Melanie Goldfarb, MD

ATA THYROID BROCHURE LINKS

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

ABBREVIATIONS & DEFINITIONS

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

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

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THYROID CANCER

Do patients with multiple papillary thyroid cancers have a worse prognosis compared to those with a single cancer?

BACKGROUND

Papillary thyroid cancer is the most common cause of thyroid cancer. There is some uncertainty about the clinical importance and treatment implications of having multiple cancers in the thyroid (multifocal papillary thyroid cancer) as opposed to a single cancer (unifocal papillary thyroid cancer). In additional, there have been some conflicting reports examining whether multifocal papillary thyroid cancer is a risk factor for thyroid cancer recurrence (i.e. disease coming back after treatment).

This study was performed to examine the independent risk of multifocal papillary thyroid cancer in predicting thyroid cancer outcomes, including cancer recurrence and death. In order to account for potential differences in the characteristics of the patients that could also impact risk of disease outcomes, the authors performed a study in which statistical techniques were used to adjust for differences between groups.

THE FULL ARTICLE TITLE

Geron Y et al 2019 Multifocality Is not an Independent Prognostic Factor in Papillary Thyroid Cancer: A Propensity Score–Matching Analysis Thyroid 29:513–522.

SUMMARY OF THE STUDY

The authors reviewed the medical records of patients with classical or follicular variant papillary thyroid cancer who were treated at the Assaf Harofeh and Rabin Medical Centers in Israel and registered in a study database since 2005. About half of the patients were followed more than 10 years after thyroid cancer treatment. There were 1039 eligible patients identified, including 51% (534) with multifocal papillary thyroid cancer. There were 690 patients who were included in the statistical analysis who had sufficient data available on clinical features and outcomes. Relevant clinical features accounted for in the analysis included: age, sex, radiation exposure, family history of thyroid cancer, primary cancer size, stage of cancer, blood vessel invasion, American Thyroid Association risk of recurrence level, and the presence of extrathyroidal extension (the cancer invading outside the thyroid into adjacent tissues).

The authors reported that patients with multifocal papillary thyroid cancer were older, more frequently male, had a higher rate of extrathyroidal extension, more lymph node metastases, more advanced disease (stage III/IV), and a higher American Thyroid Association recurrence risk level, compared to those with unifocal papillary thyroid cancer. Furthermore, patients with multifocal papillary thyroid cancer received more aggressive treatment (higher rates of more extensive surgery, radioactive iodine use [and dose], and external beam radiation treatment). By the end of study follow-up, about 13% of patients in the entire study population died (from all causes) and 2% died from thyroid cancer. After the statistical analysis, the presence of multifocal papillary thyroid cancer did not significantly predict papillary thyroid cancer recurrence or death from all cause, but was associated with having persistent thyroid cancer at one year following treatment (detected on imaging or suspected on bloodwork).

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The authors concluded that the presence of multifocal papillary thyroid cancer is associated with other higher risk disease features at baseline, but is not necessarily a significant independent predictor of long-term thyroid cancer outcomes. Patients diagnosed with papillary thyroid cancer should discuss the features of their disease with their thyroid cancer specialist, to fully understand any potential implications for treatment decision-making.

— Anna M. Sawka, MD, PhD

THYROID CANCER, continued

ATA THYROID BROCHURE LINKS

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

ABBREVIATIONS & DEFINITIONS

Papillary thyroid cancer (PTC): 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).

Multifocal papillary thyroid cancer: having multiple papillary thyroid cancers in the thyroid

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

Radioactive iodine (RAI): this plays a valuable role in diagnosing and treating thyroid problems since it is taken up only by the thyroid gland. I-131 is the destructive form used to destroy thyroid tissue in the treatment of thyroid cancer and with an overactive thyroid. I-123 is the non-destructive form that does not damage the thyroid and is used in scans to take pictures of the thyroid (Thyroid Scan) or to take pictures of the whole body to look for thyroid cancer (Whole Body Scan).

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THYROID DISEASE AND PREGNANCY

Positive thyroid peroxidase antibody level is associated with a lower birth rate in women with recurrent pregnancy losses

BACKGROUND

Pregnancy loss or miscarriage is estimated to occur in 1 in 4 pregnancies. Recurrent pregnancy loss is defined as three or more early pregnancy losses (in the first trimester) or two or more pregnancy losses in the second trimester or later. The cause of pregnancy loss is not known in about 60% of cases. Autoimmune thyroid disease occurs when the body makes antibodies that attack the thyroid, turning it on (hyperthyroidism) or off (hypothyroidism). Increased levels of thyroid peroxidase antibody (TPOAb) in the blood is a marker for autoimmune thyroid disease. Positive thyroid peroxidase antibody (TPOAb) levels in the blood have also been associated with difficulty getting pregnant (infertility) and pregnancy loss in some studies but not in others. Previous clinical trials did not show clear benefit of treatment with levothyroxine in women with positive TPOAb and history of infertility or pregnancy loss. This study was done to evaluate possible effect of positive TPOAb levels on live birth rate in women with history of current pregnancy losses.

THE FULL ARTICLE TITLE

Bliddal Set al. 2019 Thyroid peroxidase antibodies and prospective live birth rate – a cohort study of women with recurrent pregnancy loss. Thyroid. Epub 2019 Aug 13. PMID: 31407629.

SUMMARY OF THE STUDY

A total of 825 women (average age 35 years old) with history of recurrent pregnancy losses (average number of previous pregnancy losses was 3) and without clear cause for these pregnancy losses were recruited from a university hospital in Denmark from 2011-2017. Blood TPOAb and thyroid stimulating hormone (TSH) levels were measured before pregnancy. Women were recommended to start levothyroxine if TPOAb was positive and TSH >2.5mIU/L or if TPOAb was negative and TSH >4mIU/L. The decision to start levothyroxine was made between patient and her doctor.

Of 825 women, 139 women (16.8%) were TPOAb positive. A total of 444 women had a pregnancy and were included in the analyses assessing possible association between TPOAb positivity and pregnancy, live birth, and pregnancy loss rates. Of these 444 women, 69 women were TPOAb positive (15.5%) and 52 women were treated with levothyroxine (75%).

Overall, 62.8% of these pregnancies were successful in carrying the baby to term (live birth rate). The live birth rate was significantly lower in TPOAb-positive women compared to TPOAb-negative women (51.3% vs. 65.2%). TSH levels was not significantly different between women with live births and women with pregnancy losses. TPOAb-positive women who were treated with levothyroxine had a higher birth rate compared to TPOAb-positive women who were not treated with levothyroxine (61.5% vs. 29.4%). TPOAb-negative women who were treated with levothyroxine also had a higher birth rate compared to TPOAb-negative women who were not treated with levothyroxine (85.7% vs. 64.3%), but the difference was not significant.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Among women with recurrent pregnancy losses, TPOAb-positive women had a lower birth rate compared to TPOAb-negative women. Treatment with levothyroxine improved birth rate in these women. Positive TPOAb titer may be an indicator for a problem with underlying immune system, interfering with developing baby. It may also be an indicator for mild abnormalities in thyroid function, increasing the risk of pregnancy losses. Previous clinical trials have not shown clear benefit of treatment with levothyroxine in women with positive TPOAb levels, normal thyroid function, and history of infertility or pregnancy loss. However, this study looked at women in a higher risk group, with history of recurrent pregnancy losses. Doses of levothyroxine used in this study were

THYROID DISEASE AND PREGNANCY, continued

also higher compared to doses of levothyroxine used in previous clinical trials.

Given the findings of this study, treatment with levothyroxine may decrease risk of further pregnancy loss in high-risk women with recurrent pregnancy losses.

However, treatment may not be generally necessary for pregnant women with positive TPOAb titer and normal thyroid function. More studies in high-risk women are needed to confirm the benefit of levothyroxine treatment in this group.

— Sun Lee, MD

ATA THYROID BROCHURE LINKS

Hyperthyroidism in Pregnancy: https://www.thyroid.org/hyperthyroidism-in-pregnancy/

ABBREVIATIONS & DEFINITIONS

Autoimmune thyroid disease: a group of disorders that are caused by antibodies that get confused and attack the thyroid. These antibodies can either turn on the thyroid (Graves' disease, hyperthyroidism) or turn it off (Hashimoto's thyroiditis, hypothyroidism).

Thyroid peroxidase (TPO) antibodies: these are antibodies that attack the thyroid instead of bacteria and viruses, they are a marker for autoimmune thyroid disease, which is the main underlying cause for hypothyroidism and hyperthyroidism in the United States.

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

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

Levothyroxine (LT_4): the major hormone produced by the thyroid gland and available in pill form as Synthroid™, Levoxyl™, Tyrosint™ and generic preparations.

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

Clinical Thyroidology® for the Public

VOLUME 12 | ISSUE 10 | OCTOBER 2019

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.

ATA® *Optimal Thyroid Health for All*

Graves' Disease & Thyroid Foundation

ThyCa: Thyroid Cancer Survivors' Association, Inc.℠ www.thyca.org

Light of Life Foundation checkyourneck.com

Bite Me Cancer

MCT8 - AHDS Foundation

Thyroid Cancer Alliance

Thyroid Cancer Canada / Cancer de la thyroïde Canada

Thyroid Federation International

American Thyroid Association
www.thyroid.org
ATA Patient Resources:
www.thyroid.org/thyroid-information/
Find a Thyroid Specialist: www.thyroid.org
(Toll-free): 1-800-THYROID
thyroid@thyroid.org

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Thyroid Cancer Alliance

Thyroid Cancer Canada
Cancer de la thyroïde Canada

Thyroid Federation International

Thyroid Disease and You...

Do you have any concerns about your thyroid function? Have you or a family member been diagnosed with thyroid disease or have you noticed a lump in your neck?

The American Thyroid Association and our Alliance Partners Invite Thyroid Patients and their Families to join us for the:

2019 ATA Alliance for Thyroid Patient Education Health Forum

Saturday, November 2, 2019
2:00 pm – 4:00 pm
Sheraton Grand Chicago, IL
301 E North Water Street - Michigan AB, Meeting Room Level 2
Chicago, IL 60611

ATA Physician Members and our ATA Alliance Partners are available to meet with thyroid patients and their families during the forum. This program is free and open to the public, please register to confirm your participation here: **https://www.eventbrite.com/e/ata-alliance-for-thyroid-patient-education-presents-the-2019-health-forum-tickets-70671956725**

Who should attend?

Please come if you have questions, symptoms, or concerns about a thyroid problem. We invite anyone who has had an overactive or underactive thyroid, thyroiditis, a thyroid nodule, thyroid cancer, or a family history of thyroid problems or related disorders, including rheumatoid arthritis, juvenile diabetes, or pernicious anemia. Free educational materials will be available for all.

Reservations requested. Walk-ins welcome.

E-mail **thyroid@thyroid.org** with any questions or requests for additional information.

American Thyroid Association | 6066 Leesburg Pike, Suite 550 | Falls Church, VA
www.thyroid.org | thyroid@thyroid.org

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FOUNDED 2005

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- Updates on the latest patient resources through the ATA website and elsewhere on the world wide web
- Special e-mail alerts about thyroid topics of special interest to you and your family

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JOIN US

"The ATA was a valuable resource for our family when my dad was diagnosed with Anaplastic Thyroid Cancer. When you're faced with a detrimental diagnosis where even a few days can make the difference in life or death, understanding your options quickly is critical. The ATA website offers a one-stop shop for patients and caregivers to find specialists, current clinical trials, general thyroid cancer information, and links to other patient support groups and information."

Mary Catherine Petermann
- Father who was diagnosed with Anaplastic Thyroid Cancer in 2006
- He was treated at Mayo Clinic
- He has clean scans as of October 2016

PLEASE JOIN OUR JOURNEY TO ADVANCED DISCOVERIES AND TREATMENT FOR THYROID DISEASE AND THYROID CANCER

As patients with thyroid disease navigate the challenges to their quality of life and researchers and physicians look for more effective directions, we at the ATA have our own destination– **funding for critical thyroid research, prevention, and treatment.** For 94 years, the ATA has led the way in thyroidology. It's a daily obstacle course to find new drugs, better treatments, advanced surgical methods, and more rapid diagnoses for the 20 million Americans who have some form of thyroid disease.

The ATA has paved the way with management guidelines for clinicians who diagnose and treat thyroid disease. For physicians treating pregnant women diagnosed with thyroid disease, our recent publication presents 97 evidence-based recommendations making sure that best practices are implemented with the latest, most effective treatment.

Through your generous support and donations, research takes the lead and hope is on the horizon. **Will you join us** in our campaign to raise **$1.5 million** for thyroid research, prevention, and treatment? Your compassionate, tax-deductible gift will provide funds for:

- Research grants that pave the way for 1,700 ATA physicians and scientists who have devoted their careers to understanding the biology of and caring for patients affected by thyroid disease.
- Patient education for individuals and families looking for life-changing clinical trials, the best thyroid specialists, and cutting edge treatment and drugs.
- Professional education that offers a wealth of knowledge and leading-edge research for trainees and practitioners.
- A website that is the go-to resource for thyroid information for patients and practitioners alike. In 2016 alone, there were more than 3,700,000 website views of ATA's library of online thyroid information patient brochures.

Donations **of all sizes** will change the future for thyroid patients. You will make a direct impact on patients like Mary Catherine's father as he deals with Anaplastic Thyroid Cancer. You will help scientists like ATA Associate Member Julia Rodiger, Ph.D., a scientist at the National Institutes of Health, as she analyzes thyroid hormones for intestinal stem cell development.

Thyroid Nodules

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 A THYROID NODULE?

The term thyroid nodule refers to an abnormal growth of thyroid cells that forms a lump within the thyroid gland. Although the vast majority of thyroid nodules are benign (noncancerous), a small proportion of thyroid nodules do contain thyroid cancer. In order to diagnose and treat thyroid cancer at the earliest stage, most thyroid nodules need some type of evaluation.

WHAT ARE THE SYMPTOMS OF A THYROID NODULE?

Most thyroid nodules do not cause symptoms. Often, thyroid nodules are discovered incidentally during a routine physical examination or on imaging tests like CT scans or neck ultrasound done for completely unrelated reasons. Occasionally, patients themselves find thyroid nodules by noticing a lump in their neck while looking in a mirror, buttoning their collar, or fastening a necklace. Abnormal thyroid function tests may occasionally be the reason a thyroid nodule is found. Thyroid nodules may produce excess amounts of thyroid hormone causing hyperthyroidism (see *Hyperthyroidism brochure*). However, most thyroid nodules, including those that cancerous, are actually non-functioning, meaning tests like TSH are normal. Rarely, patients with thyroid nodules may complain of pain in the neck, jaw, or ear. If a nodule is large enough to compress the windpipe or esophagus, it may cause difficulty with breathing, swallowing, or cause a "tickle in the throat". Even less commonly, hoarseness can be caused if the nodule invades the nerve that controls the vocal cords but this is usually related to thyroid cancer.

The important points to remember are the following:

- Thyroid nodules generally do not cause symptoms.
- Thyroid tests are most typically normal—even when cancer is present in a nodule.
- The best way to find a thyroid nodule is to make sure your doctor checks your neck!

WHAT CAUSES THYROID NODULES AND HOW COMMON ARE THEY?

We do not know what causes most thyroid nodules but they are extremely common. By age 60, about one-half of all people have a thyroid nodule that can be found either through examination or with imaging. Fortunately, over 90% of such nodules are benign. *Hashimoto's thyroiditis*, which is the most common cause of hypothyroidism (see *Hypothyroidism brochure*), is associated with an increased risk of thyroid nodules. Iodine deficiency, which is very uncommon in the United States, is also known to cause thyroid nodules.

HOW IS A THYROID NODULE EVALUATED AND DIAGNOSED?

Once the nodule is discovered, your doctor will try to determine whether the rest of your thyroid is healthy or whether the entire thyroid gland has been affected by a more general condition such as hyperthyroidism or hypothyroidism. Your physician will feel the thyroid to see whether the entire gland is enlarged and whether a single or multiple nodules are present. The initial laboratory tests may include measurement of thyroid hormone (thyroxine, or T4) and thyroid-stimulating hormone (TSH) in your blood to determine whether your thyroid is functioning normally.

Since it's usually not possible to determine whether a thyroid nodule is cancerous by physical examination and blood tests alone, the evaluation of the thyroid nodules often includes specialized tests such as thyroid ultrasonography and fine needle biopsy.

Thyroid Nodules

THYROID ULTRASOUND:

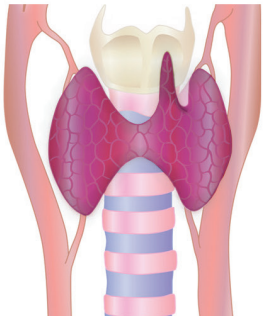
Thyroid ultrasound is a key tool for thyroid nodule evaluation. It uses high-frequency sound waves to obtain a picture of the thyroid. This very accurate test can easily determine if a nodule is solid or fluid filled (cystic), and it can determine the precise size of the nodule. Ultrasound can help identify suspicious nodules since some ultrasound characteristics of thyroid nodules are more frequent in thyroid cancer than in noncancerous nodules. Thyroid ultrasound can identify nodules that are too small to feel during a physical examination. Ultrasound can also be used to accurately guide a needle directly into a nodule when your doctor thinks a fine needle biopsy is needed. Once the initial evaluation is completed, thyroid ultrasound can be used to keep an eye on thyroid nodules that do not require surgery to determine if they are growing or shrinking over time. The ultrasound is a painless test which many doctors may be able to perform in their own office.

THYROID FINE NEEDLE ASPIRATION BIOPSY (FNA OR FNAB):

A fine needle biopsy of a thyroid nodule may sound frightening, but the needle used is very small and a local anesthetic may not even be necessary. This simple procedure is often done in the doctor's office. Sometimes, medications like blood thinners may need to be stopped for a few days before to the procedure. Otherwise, the biopsy does not usually require any other special preparation (no fasting). Patients typically return home or to work after the biopsy without even needing a bandaid! For a fine needle biopsy, your doctor will use a very thin needle to withdraw cells from the thyroid nodule. Ordinarily, several samples will be taken from different parts of the nodule to give your doctor the best chance of finding cancerous cells if they are present. The cells are then examined under a microscope by a pathologist.

The report of a thyroid fine needle biopsy will usually indicate one of the following findings:

1. The nodule is benign (noncancerous).
   - This result is obtained in up to 80% of biopsies. The risk of overlooking a cancer when the biopsy is benign is generally less than 3 in 100 tests or 3%. This is even lower when the biopsy is reviewed by an experienced pathologist at a major medical center. Generally, benign thyroid nodules do not need to be removed unless they are causing symptoms like choking or difficulty swallowing. Follow up ultrasound exams are important. Occasionally, another biopsy may be required in the future, especially if the nodule grows over time.
2. The nodule is malignant (cancerous) or suspicious for malignancy .
   - A malignant result is obtained in about 5% of biopsies and is most often due to papillary cancer, which is the most common type of thyroid cancer. A suspicious biopsy has a 50-75% risk of cancer in the nodule. These diagnoses require surgical removal of the thyroid after consultation with your endocrinologist and surgeon.
3. The nodule is indeterminate. This is actually a group of several diagnoses that may occur in up to 20% of cases. An Indeterminate finding means that even though an adequate number of cells was removed during the fine needle biopsy, examination with a microscope cannot reliably classify the result as benign or cancer.
   - The biopsy may be indeterminate because the nodule is described as a Follicular Lesion. These nodules are cancerous 20-30% of the time. However, the diagnosis can only be made by surgery. Since the odds that the nodule is not a cancer are much better here (70-80%), only the side of the thyroid with the nodule is usually removed. If a cancer is found, the remaining thyroid gland usually must be removed as well. If the surgery confirms that no cancer is present, no additional surgery to "complete" the thyroidectomy is necessary.
   - The biopsy may also be indeterminate because the cells from the nodule have features that cannot be placed in one of the other diagnostic categories. This diagnosis is called atypia, or a follicular lesion of undetermined significance. Diagnoses in this category will contain cancer rarely, so repeat evaluation with FNA or surgical biopsy to remove half of the thyroid containing the nodule is usually recommended.
4. The biopsy may also be nondiagnostic or inadequate. This result is obtained in less than 5% of cases when an ultrasound is used to guide the FNA. This result indicates that not enough cells were obtained to make a diagnosis but is a common result if the nodule is a cyst. These nodules may require reevaluation with second fine needle biopsy, or may need to be removed surgically depending on the clinical judgment of your doctor.



FURTHER INFORMATION

Further details on this and other thyroid-related topics are available in the patient thyroid information section on the American Thyroid Association® website at *www.thyroid.org*.

For information on thyroid patient support organizations, please visit the *Patient Support Links* section on the ATA website at *www.thyroid.org*

Thyroid Nodules

NUCLEAR THYROID SCANS:

Nuclear scanning of the thyroid was frequently done in the past to evaluate thyroid nodules. However, use of thyroid ultrasound and biopsy have proven so accurate and sensitive, nuclear scanning is no longer considered a first-line method of evaluation. Nuclear scanning still has an important role in the evaluation of rare nodules that cause hyperthyroidism. In this situation, the nuclear thyroid scan may suggest that no further evaluation or biopsy is needed. In most other situations, neck ultrasound and biopsy remain the best and most accurate way to evaluate all types of thyroid nodules.

MOLECULAR DIAGNOSTICS:

Can any other tests assist in evaluation of thyroid nodules?

Yes, new tests that examine the genes in the DNA of thyroid nodules are currently available and more are being developed. These tests can provide helpful information about whether cancer may be present or absent. These tests are particularly helpful when the specimen evaluated by the pathologist is indeterminate. These specialized tests are done on samples obtained during the normal biopsy process. There are also specialized blood tests that can assist in the evaluation of thyroid nodules. These are currently available only at highly specialized medical centers, however, their availability is increasing rapidly. Ask your doctor if these tests are available and might be helpful for evaluating your thyroid nodule.

HOW ARE THYROID NODULES TREATED?

All thyroid nodules that are found to contain a thyroid cancer, or that are highly suspicious of containing a cancer, should be removed surgically by an experienced thyroid surgeon. Most thyroid cancers are curable and rarely cause life-threatening problems (see *Thyroid Cancer brochure*). Thyroid nodules that are benign by FNA or too small to biopsy should still be watched closely with ultrasound examination every 6 to 12 months and annual physical examination by your doctor. Surgery may still be recommended even for a nodule that is benign by FNA if it continues to grow, or develops worrisome features on ultrasound over the course of follow up.

FURTHER INFORMATION

Further details on this and other thyroid-related topics are available in the patient thyroid information section on the American Thyroid Association® website at *www.thyroid.org*.

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