

# Thyroid, Papillary Carcinoma

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[Contributor Information and Disclosures](#)

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- **Overview**
- **Differential Diagnoses & Workup**
- **Treatment & Medication**
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## Background

Papillary carcinoma is a relatively common well-differentiated [thyroid cancer](#). Papillary/follicular carcinoma must be considered a variant of papillary thyroid carcinoma (mixed form). Despite its well-differentiated characteristics, papillary carcinoma may be overtly or minimally invasive. In fact, these tumors may spread easily to other organs. Papillary tumors have a propensity to invade lymphatics but are less likely to invade blood vessels. Papillary carcinoma appears as an irregular solid or cystic mass in a normal thyroid parenchyma.

Thyroid cancers are more often found in patients with a history of low- or high-dose external irradiation. Papillary tumors of the thyroid are the most common form of thyroid cancer to result from exposure to radiation. The life expectancy of patients with this cancer is related to their age. The prognosis is better for younger patients than for patients who are older than 45 years. Of patients with papillary cancers, about 11% present with metastases outside the neck and mediastinum. Some years ago, lymph node metastases in the cervical area were thought to be aberrant (supernumerary) thyroids because they contained well-differentiated papillary thyroid cancer.

## Pathophysiology

Papillary thyroid carcinoma seems closely related to the activation of *trk* and *ret* proto-oncogenes, both acting by amplifying and rearranging mechanisms. The *trk* proto-oncogene codes for tyrosine kinase receptors; the *ret* shows a paracentric inversion of chromosomes 10 and 11 in 30-35% of the cases. However, the *met* proto-oncogene is overexpressed and/or amplified in 3 of 4 patients.

In addition, evidence suggests that some molecules that physiologically regulate the growth of the thyrocytes, such as interleukin-1 and interleukin-8, or other cytokines (ie, insulinlike growth factor-1, transforming growth factor-beta, epidermal growth factor) could play a role in the pathogenesis of this cancer.

## Frequency

### United States

Approximately 74-80% of the thyroid cancers diagnosed each year in the United States are of the papillary type.

### International

Thyroid cancers are quite rare, accounting for only 1.5% of all cancers in adults and 3% of all cancers in children, but the rate of new cases is increasing in the last decades. The highest incidence of thyroid carcinomas in the world is found among female Chinese residents of Hawaii. During the last few years, the frequency of papillary cancer has increased, but this increase in frequency is related to an improvement in diagnostic techniques and the

information campaign about this carcinoma. Of all thyroid cancers, 74-80% of cases are papillary cancer. Follicular carcinoma incidences are higher in regions where incidence of endemic goiter is high.

### Mortality/Morbidity

In contrast to other cancers, thyroid cancer is almost always curable. Most thyroid cancers grow slowly and are associated with a very favorable prognosis. The mean survival rate after 10 years is higher than 90% and is 100% in very young patients with minimal nonmetastatic disease.

- Distant spread (ie, to lungs or bones) is very uncommon. Worldwide, autopsy reviews show a high incidence of microscopic foci of thyroid carcinoma.
- Differing from medullary thyroid carcinoma, papillary thyroid cancer is not a part of multiple endocrine neoplasia syndromes. Uncommon familial syndromes such as familial adenomatous polyposis, Gardner syndrome (Gardner's syndrome), and Cowden disease (Cowden's disease) may be associated with thyroid papillary tumors in about 5% of cases.
- The mean mortality rate is 1.5% for females and 1.4% for males.

### Race

This cancer occurs more frequently in whites than in blacks.

### Sex

The female-to-male ratio is near 3:1 and is related to the patient's age.

- In patients younger than 19 years, the female-to-male ratio is 3.2:1.
- In patients aged 20-45 years, the female-to-male ratio is 3.6:1.
- In patients older than 45 years, the female-to-male ratio is 2.8:1.

A useful and updated source for informations about the epidemiology of papillary carcinoma of the thyroid is American Cancer Society's [Cancer Facts and Figures](#).

### ACS Estimated New Thyroid Carcinoma Cases and Deaths by Sex, US, 2008

Open [table in new window](#)

Cases and Deaths	Total	Males	Females
Estimated new cases	37,340	8,930	28,410
Estimated deaths	1,590	680	910
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### Age

Thyroid carcinoma is common in persons of all ages, with a mean age of 49 years and an age range of 15-84 years. In the younger population, papillary thyroid carcinoma tends to occur more frequently

than follicular carcinoma, with a peak in patients aged 30-50 years.

## Clinical

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### History

Patients with papillary carcinoma, a relatively common well-differentiated [thyroid cancer](#), may present with the following history:

- Numerous cases of papillary thyroid cancer are subclinical.
- The most common presentation of thyroid cancer is an asymptomatic thyroid mass or a nodule that can be felt in the neck.
- Record a thorough medical history to identify any risk factors or symptoms.
- For any patient with a thyroid lump that has developed recently, obtain a history regarding every prior exposure to ionizing radiation and the lifetime duration of the radiation exposure.
- Consider a family history of thyroid cancer.
- Some patients have persistent cough, difficulty breathing, or difficulty swallowing.
- Pain is seldom an early warning sign of thyroid cancer.
- Other symptoms (eg, pain, stridor, vocal cord paralysis, hemoptysis, rapid enlargement) are rare. These symptoms can be caused by less serious problems.
- At the time of diagnosis, 10-15% of patients have distant metastases to the bones and lungs and, initially, are evaluated for pulmonary or osteoarticular symptoms (eg, pathologic fracture, spontaneous fracture).

### Physical

- Palpate the patient's neck to evaluate the size and firmness of the thyroid and to check for any thyroid nodules. The principal sign of thyroid carcinoma is a palpable, firm, and nontender nodule in the thyroid area. This mass is painless.
- Some patients have a tight or full feeling in the neck, hoarseness, or signs of tracheal or esophageal compression.
- With thyroid palpation, a usually solitary nodule that has a hard consistency, an average size of less than 5 cm, and ill-defined borders can be felt. This nodule is fixed in respect to surrounding tissues and moves with the trachea at swallowing.
- Usually, signs of [hyperthyroidism](#) or [hypothyroidism](#) are not observed.

See related CME at [Examining the Ears, Nose, and Oral Cavity in the Older Patient](#).

### Causes

- The thyroid is particularly sensitive to the effects of ionizing radiation. Exposure to ionizing radiation results in a 30% risk for thyroid cancer.
- A history of exposure of the head and neck to x-ray beams, especially during childhood, has been recognized as an important contributing factor for the development of thyroid cancer. For example, 7% of individuals exposed to the atomic bomb in Japan developed thyroid cancers.<sup>1</sup>
- From 1920-1960, therapeutic irradiation of body areas was used to treat tumors and benign conditions (eg, acne; excessive facial hair; tuberculosis in the neck; fungus diseases of the scalp; sore throats; chronic coughs; enlargement of the thymus, tonsils, and adenoids). Approximately 10% of individuals who were treated with irradiation developed thyroid cancer after a latency period of 30 years.
- Port et al report the "signature" of 7 genes (ie, *SFRP1*, *MMP1*, *ESM1*, *KRTAP2-1*, *COL13A1*, *BAALC*, *PAGE1*) in papillary thyroid cancers after the Chernobyl accident, demonstrating by PCR techniques their role in distinguishing such cases from sporadic forms.
- Patients who need radiotherapy for certain types of cancer of the head and neck area also may have an increased risk of developing thyroid cancer.
- Exposure to diagnostic x-ray beams does not increase the risk of developing thyroid cancers. Several reports have shown a relationship between [iodine deficiency](#) and the incidence of thyroid carcinomas.
- Many other conditions have been considered as predisposing to papillary thyroid cancer (oral contraceptive use, benign thyroid nodules, late menarche, late age at first birth).<sup>2,3</sup>
- Tobacco smoking seems to be associated with a decreased risk of thyroid cancer, but, obviously, it poses more health hazards than benefits.<sup>4</sup>

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## References

# Papillary Cancer

## The Most Common Thyroid Cancer

**This page includes more advanced information on a specific type of thyroid cancer. . . . Papillary Thyroid Cancer.** Please read our [Introduction to Thyroid Cancer](#) page first which gives a general overview of all types of thyroid cancer since it will make this page easier to understand.

**Papillary tumors are the most common of all thyroid cancers (>70%).** Papillary carcinoma typically arises as an irregular, solid or cystic mass that arises from otherwise normal thyroid tissue. This cancer has a high cure rate with ten year survival rates for all patients with papillary thyroid cancer estimated at 80-90%. Cervical metastasis (spread to lymph nodes in the neck) are present in 50% of small tumors and in over 75% of the larger thyroid cancers. The presence of lymph node metastasis in these cervical areas causes a higher recurrence rate but not a higher mortality rate. Distant metastasis (spread) is uncommon, but lung and bone are the most common sites. Tumors that invade or extend beyond the thyroid capsule have a worsened prognosis because of a high local recurrence rate.

## Characteristics of Papillary Thyroid Cancer

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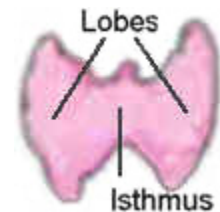
- Peak onset ages 30 through 50

- Females more common than males by 3 to 1 ratio
- Prognosis directly related to tumor size [less than 1.5 cm (1/2 inch) good prognosis]
- Accounts for 85% of thyroid cancers due to [radiation exposure](#)
- Spread to lymph nodes of the neck present in more than 50% of cases
- Distant spread (to lungs or bones) is very uncommon
- Overall cure rate very high (near 100% for small lesions in young patients)

## Management of Papillary Thyroid Cancer

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**Considerable controversy exists when discussing the management of well differentiated thyroid carcinomas** (papillary and even follicular). Some experts contend that if these tumors are small and not invading other tissues (the usual case) then simply removing the lobe of the thyroid which harbors the tumor (and the small central portion called the isthmus) will provide as good a chance of cure as removing the entire thyroid. These proponents of conservative surgical therapy relate the low rate of clinical tumor recurrence (5-20%) despite the fact that small amounts of tumor cells can be found in up to 88% of the opposite lobe thyroid tissues. They also cite some studies showing an increased risk of [hypoparathyroidism](#) and recurrent laryngeal nerve injury in patients undergoing total thyroidectomy (since there is an operation on both sides of the neck). Proponents of total thyroidectomy (more aggressive surgery) cite several large studies that show that in experienced hands the incidence of recurrent nerve injury and permanent hypoparathyroidism are quite low (about 2%). More importantly, these studies show that patients with total thyroidectomy followed by radioiodine therapy and thyroid suppression, have a significantly lower recurrence rate and lower mortality when tumors are greater than 1.5cm. One must remember that it is also desirable to reduce the amount of normal gland tissue that will take up radioiodine.



Based on these studies and the above natural history and epidemiology of papillary carcinoma, the following is a typical plan: Papillary carcinomas that are well circumscribed, isolated, and less than 1cm in a young patient (20-40) without a history of radiation exposure may be treated with hemithyroidectomy and isthmusctectomy. All others should probably be treated with total thyroidectomy and removal of any enlarged lymph nodes in the central or lateral neck areas. The surgical options are covered in greater detail (with drawings) on another "[surgical options](#)" page. Often other characteristics of the tumor that can be seen under the microscope will have an influence on whether the surgeon should take all the thyroid out--items such as vascular invasion, nerve invasion and capsule invasion.

## The Use of Radioactive Iodine Post-Operatively

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**Thyroid cells are unique in that they have the cellular mechanism to absorb iodine.** The iodine is used by thyroid cells to make thyroid hormone. No other cell in the body can absorb or concentrate iodine. Physicians can take advantage of this fact and give radioactive iodine to patients with thyroid cancer. There are several types of radioactive

iodine, with one type being toxic to cells. Papillary cancer cells absorb iodine and therefore they can be targeted for death by giving the toxic isotope (I-131). Once again, not everybody with papillary thyroid cancer needs this therapy, but those with larger tumors, spread to lymph nodes or other areas, tumors which appear aggressive microscopically, and older patients may benefit from this therapy. This is extremely individualized and no recommendations are being made here or elsewhere on this web site...too many variables are involved. But, this is an extremely effective type of "chemotherapy" with little or no potential down-sides (no hair loss, nausea, weight loss, etc.).

Uptake is enhanced by high TSH levels; thus patients should be off of thyroid replacement and on a low iodine diet for at least one to two weeks prior to therapy. It is usually given 6 weeks post surgery (this is variable) can be repeated every 6 months if necessary (within certain dose limits).

## What About Thyroid Hormone Pills After Thyroid Cancer Surgery?

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Regardless of whether a patient has just one thyroid lobe and the isthmus removed, or the entire thyroid gland removed, **most experts agree they should be placed on thyroid hormone for the rest of their lives.** This is to replace the hormone in those who have no thyroid left, and to suppress further growth of the gland in those with some tissue left in the neck. There is good evidence that papillary carcinoma responds to thyroid stimulating hormone (TSH) secreted by the [pituitary](#), therefore, exogenous thyroid hormone is given which results in decreased TSH levels and a lower impetus for any remaining cancer cells to grow. Recurrence and mortality rates have been shown to be lower in patients receiving suppression.

## What Kind of Long-Term Follow Up is Necessary?

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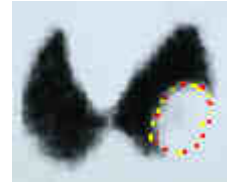
In addition to the usual cancer follow up, patients should receive a yearly chest x-ray as well as thyroglobulin levels. Thyroglobulin is not useful as a screen for initial diagnosis of thyroid cancer but is quite useful in follow up of well differentiated carcinoma (if a total thyroidectomy has been performed). A high serum thyroglobulin level that had previously been low following total thyroidectomy especially if gradually increased with TSH stimulation is virtually indicative of recurrence. A value of greater than 10 ng/ml is often associated with recurrence even if an iodine scan is negative.

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## Thyroid Cancer

There are about 20,000 new cases of thyroid cancer each year in the United States. Females are more likely to have thyroid cancer at a ratio of three to one. Thyroid cancer can occur in any age group, although it is most common after age 30 and its aggressiveness increases significantly in older patients. The majority of patients present with a nodule on their thyroid which typically does not cause symptoms. Remember, over 99% of thyroid nodules are not cancer! But,

when a thyroid cancer does begin to grow within a thyroid gland, it almost always does so within a discrete nodule within the thyroid.



**Symptoms of thyroid cancer:** Occasionally, symptoms such as hoarseness, neck pain, and enlarged lymph nodes do occur in people with thyroid cancer.. Although as much as 75 % of the population will have thyroid nodules, the vast majority are benign. That's right, most of us have nodule in our thyroid glands! Young people usually don't have thyroid nodules, but as we get older, more and more of us will develop a nodule. By the time we are 80, 90% of us will have at least one nodule. Far less than 1% of all thyroid nodules are malignant. A nodule which is cold on scan (shown in photo outlined in red and yellow) is more likely to be malignant, nevertheless, the majority of these are benign as well. A lot of information about thyroid nodules and the potential of these nodules to be malignant is contained on 3 pages about nodules:

1. [Introduction to thyroid nodules](#)
2. [The workup of thyroid nodules and the role of Fine Needle Aspiration Biopsy \(FNA\)](#)
3. [The role of thyroid ultrasound and what it means](#)

## Types of Thyroid Cancer

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### Thyroid Cancer Type and Incidence

- **Papillary and/or mixed papillary/follicular ~ 78%** [[Click here to see specifics](#)]
- **Follicular and/or Hurthle cell ~ 17%** [[Click here to see specifics](#)]
- **Medullary ~ 4%** [[click here to see specifics](#)]
- **Anaplastic ~ 1%** [[Click here to see specifics](#)]

**Note, Chief Justice William Rehnquist had anaplastic thyroid cancer.** After reading this overview page on thyroid cancer, [click here](#) to read more about Chief Justice William Rehnquist and his classic battle with the worst kind of thyroid cancer.

## What's the Prognosis?

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Most thyroid cancers are very curable. In fact, the most common types of thyroid cancer (papillary and follicular) are the most curable. In younger patients, both papillary and follicular cancers can be expected to have better than 97% cure rate if treated appropriately. Both papillary and follicular cancers are typically treated with complete removal of the lobe of the thyroid which harbors the cancer, PLUS, removal of most or all of the other side. The bottom line, most thyroid cancers are papillary thyroid cancer, and this is one of the most curable cancers of ALL cancers that humans get. As we

often tell our patients, if you must choose a type of cancer to have, papillary cancer would be your choice. Treat it correctly and the cure rate is extremely high!

Medullary cancer of the thyroid is significantly less common, but has a worse prognosis. Medullary cancers tend to spread to large numbers of lymph nodes very early on, and therefore requires a much more aggressive operation than does the more localized cancers such as papillary and follicular. This cancer requires complete thyroid removal PLUS a dissection to remove the lymph nodes of the front and sides of the neck.

The least common type of thyroid cancer is anaplastic which has a very poor prognosis. Anaplastic thyroid cancer tends to be found after it has spread and is not cured in most cases (it is very uncommon to survive anaplastic thyroid cancer). Often an operation cannot remove all the tumor. These patients often require a tracheostomy during the treatment, and treatment is much more aggressive than for other types of thyroid cancer--because this cancer is much more aggressive.

## What About Chemotherapy?

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Thyroid cancer is unique among cancers, in fact, thyroid cells are unique among all cells of the human body. They are the only cells which have the ability to absorb iodine. Iodine is required for thyroid cells to produce thyroid hormone, so they absorb it out of the bloodstream and concentrate it inside the cell. Most thyroid cancer cells retain this ability to absorb and concentrate iodine. This provides a perfect "chemotherapy" strategy. Radioactive iodine is given to the patient with thyroid cancer after their cancer has been removed. If there are any normal thyroid cells or thyroid cancer cells remain in the patient's body (and any thyroid cancer cells retaining this ability to absorb iodine) then these cells will absorb and concentrate the radioactive "poisonous" iodine. Since all other cells of our bodies cannot absorb the toxic iodine, they are unharmed. The thyroid cancer cells, however, will concentrate the poison within themselves and the radioactivity destroys the cell from within. No sickness. No hair loss. No nausea. No diarrhea. No pain. More about the use of radioactive iodine on the pages for each specific thyroid cancer type.

Most, but not all patients with thyroid cancer need radioactive iodine treatments after their surgery. This is important to know. Almost all, however, should have the iodine treatment if a cure is to be expected. Just who needs it and who doesn't is a bit more detailed than can be outlined here. Patients with medullary cancer of the thyroid usually do not need iodine therapy...because medullary cancers almost never absorb the radioactive iodine. Some small papillary cancers treated with a total thyroidectomy may not need iodine therapy as well, but for a different reason. These cancers are often cured with simple (complete) surgical therapy alone. Important!!! This varies from patient to patient and from cancer to cancer. Don't look for easy answers here. This decision will be made between the surgeon, the patient, and the referring endocrinologist or internist. Remember, radioactive iodine therapy is extremely safe. If you need it, take it. And, as we often tell our patients, radioactive iodine has a near zero complication rate, so if there is a chance that it will help... take it!

## Overview of Typical Thyroid Cancer Treatment

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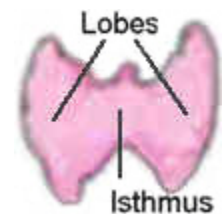
1. Usually diagnosed by sticking a needle into a thyroid nodule or removal of a worrisome thyroid nodule by a surgeon.
2. The removed thyroid nodule is looked at under a microscope by a pathologist who will then decide if the nodule is benign (95 - 99% of all nodules that are biopsied) or malignant (way less than 1% of all nodules, and about 1 - 5 % of nodules that are biopsied).
3. The pathologist decides which type of thyroid cancer it is: papillary, follicular, mixed papilofollicular, medullary, or anaplastic.
4. The entire thyroid is removed by a competent surgeon (sometimes this is done during the same operation where the biopsy takes place). He/she will assess the lymph nodes in the neck to see if they need to be removed also. In the case of anaplastic thyroid cancer, a decision will be made regarding the possibility of a tracheostomy.
5. About 4-6 weeks after the thyroid has been removed, the patient will undergo radioactive iodine treatment. This is very simple and consists of taking a single pill. The pill will contain the radioactive iodine in the dose that has been calculated for that individual. The patient goes home, avoids contact with other people for a couple of days (so they are not exposed to the radioactive materials), and that's it.
6. A week or two after the radioactive iodine treatment the patient is started on a thyroid hormone pill. You can't live without thyroid hormone and since you don't have a thyroid anymore, the patient will take one pill per day for the rest of their life. This is very simple and a very common medication (example of drug names are: Synthroid, Levoxyl, Armour Thyroid, etc).
7. Every 6 - 12 months the patient returns to his endocrinologist for blood tests to determine if the dose of daily thyroid hormone is correct and to make sure that the thyroid tumor is not coming back. The frequency of these follow up tests and which tests to get will vary greatly from patient to patient. Endocrinologists are typically quite good at this and will typically be the type of doctor that follows this patient long-term.

## Thyroid Operations

### Several Surgical Options for the Thyroid Gland Depending on the Problem

**Which operation is performed on a thyroid gland depends upon 2 major factors.** The first is the thyroid disease present which is necessitating the operation. The second is the anatomy of the thyroid gland itself as is illustrated below.

If a **dominant solitary nodule** is present in a single lobe, then removal of that lobe is the preferred operation (if an operation is even warranted). If a **massive goiter** is compressing the trachea and esophagus, the the goal of surgery will be to remove the mass and usually this means a sub-total or total thyroidectomy (occasionally a lobectomy will suffice). If a hot nodule is producing too much hormone resulting in **hyperthyroidism**, then removal of the lobe which harbors the hot nodule is all that is needed.



Most surgeons and **endocrinologists** recommend total or near total thyroidectomy in virtually all cases of **thyroid**

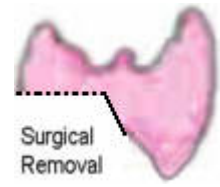
**carcinoma.** In some patients with papillary carcinomas of small size, a less aggressive approach may be taken (lobectomy with removal of the isthmus). A lymph node dissection within the anterior and lateral neck is indicated in patients with well differentiated (**papillary** or **follicular**) thyroid cancer if the lymph nodes can be palpated. This is a more extensive operation than is needed in the majority of thyroid cancer patients. All patients with **medullary** carcinoma of the thyroid require total thyroidectomy and aggressive lymph node dissection.

## Surgical Options

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### Partial Thyroid Lobectomy.

This operation is not performed very often because there are not many conditions which will allow this limited approach. Additionally, a benign lesion must be ideally located in the upper or lower portion of one lobe for this operation to be a choice. One example is shown on our [hyperthyroid treatments](#) page.



### Thyroid Lobectomy.

This is typically the "smallest" operation performed on the thyroid gland. It is performed for solitary dominant nodules which are worrisome for cancer or those which are indeterminate following **fine needle biopsy**. Also appropriate for follicular adenomas, solitary hot or cold nodules, or goiters which are isolated to one lobe (not common).



### Thyroid Lobectomy with Isthmusectomy.

This simply means removal of a thyroid lobe and the isthmus (the part that connects the two lobes). This removes more thyroid tissue than a simple lobectomy, and is used when a larger margin of tissue is needed to assure that the "problem" has been removed. Appropriate for those indications listed under thyroid lobectomy as well as for Hurthle cell tumors, and some very small and non-aggressive thyroid cancers.



### Subtotal Thyroidectomy.

Just as the name implies, this operation removes all the "problem" side of the gland as well as the isthmus and the majority of the opposite lobe. This operation is typical for small, non-aggressive thyroid cancers. Also a common operation for goiters which are causing problems in the neck or even those which extend into the chest (**substernal goiters**).



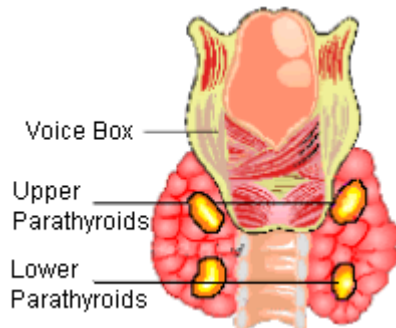
### Total Thyroidectomy.

This operation is designed to remove all of the thyroid gland. It is the operation of choice for all thyroid cancers which are not small and non-aggressive in young patients. Many (most?) surgeons prefer this complete removal of thyroid tissue for **all** thyroid cancers regardless of the type.

## Surgical Technique

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The standard neck incision is made typically measuring about 4-5 inches in length although many endocrine surgeons are now performing this operation through an incision as small as 3 inches in thin patients. This incision is made in the lower part of the central neck and usually heals **very** well. It is almost unheard of to have an infection or other problem with this wound. The surgeon will then typically remove the part of the thyroid which contains the "problem". As mentioned above, for thyroid cancer, this will usually entail all of the thyroid lobe which harbors the malignancy, the isthmus, and a variable amount of the opposite lobe (ranging from 0 to 100% depending on the size and aggressive nature of the cancer, the cancer type, and the experience of the surgeon). The surgeon must be careful of the recurrent laryngeal nerves which are very close to the back side of the thyroid and are responsible for movement of the vocal cords. Damage to this nerve will cause hoarseness of the voice which is usually temporary but can be permanent. This is an uncommon complication (about 1 to 2 percent), but it gets lots of press because it is serious. The surgeon must also be careful to identify the **parathyroid glands** so their blood supply can be maintained. Another potential complication of thyroid surgery (although VERY RARE) is **hypoparathyroidism** which is due to damage to all four parathyroid glands. Usually the only thyroid operations which have even a slight chance of this complication is the total or subtotal thyroidectomy. Although these complications can be serious, their risk should not be the sole determinant of whether or not to undergo surgery.



The relationship of the thyroid gland to the voice box and parathyroid glands can be seen here quite clearly. Remember that they share the same blood supply, so the surgeon must take care to preserve the parathyroid artery and vein while ligating the vessels to the thyroid gland itself. This is usually not a problem, but sometimes it is not possible to save them all. In this case, the surgeon will usually implant the parathyroid gland into a muscle in the neck. The parathyroid will grow there and function normally...its not a big deal, and you'll never know the difference.

Often formal surgery is not needed to determine if a thyroid mass is cancerous. Because these masses can often be felt, a physician can stick a small needle into it to sample cells for malignancy. This is called **Fine Needle Aspiration Biopsy (FNA)** and is covered in detail on another page which also covers the potential of thyroid masses to be malignant in much greater detail.

# Outcome after Treatment of High-Risk Papillary and Non-Hurthle-Cell Follicular Thyroid Carcinoma

▶ Terry Taylor, MD; Bonny Specker, PhD; Jacob Robbins, MD; Matthew Sperling; Mona Ho, MS; Kenneth Ain, MD; S. Thomas Bigos, MD; Jim Brierley, MB; David Cooper, MD; Bryan Haugen, MD; Ian Hay, MD; Vicki Hertzberg, PhD; Irwin Klein, MD; Herbert Klein, MD, PhD; Paul Ladenson, MD; Ronald Nishiyama, MD; Douglas Ross, MD; Steven Sherman, MD; and Harry R. Maxon, MD

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**Background:** Treatment of differentiated thyroid cancer has been studied for many years, but the benefits of extensive initial thyroid surgery and the addition of radioiodine therapy or external radiation therapy remain controversial.

**Objective:** To determine the relations among extent of surgery, radioiodine therapy, and external radiation therapy in the treatment of high-risk papillary and non-Hurthle-cell follicular thyroid carcinoma.

**Design:** Analysis of data from a multicenter study.

**Setting:** 14 institutions in the United States and Canada participating in the National Thyroid Cancer Treatment Cooperative Study Registry.

**Patients:** 385 patients with high-risk thyroid cancer (303 with papillary carcinoma and 82 with follicular carcinoma).

**Measurements:** Death, disease progression, and disease-free survival.

**Results:** Total or near-total thyroidectomy was done in 85.3% of patients with papillary carcinoma and 71.3% of patients with follicular cancer. Overall surgical complication rate was 14.3%. Total or near-total thyroidectomy improved overall survival (risk ratio [RR], 0.37 [95% CI, 0.18 to 0.75]) but not cancer-specific mortality, progression, or disease-free survival in patients with papillary cancer. No effect of extent of surgery was seen in patients with follicular thyroid cancer. Postoperative iodine-131 was given to 85.4% of patients with papillary cancer and 79.3% of patients with follicular cancer. In patients with papillary cancer, radioiodine therapy was associated with improvement in cancer-specific mortality (RR, 0.30 [CI, 0.09 to 0.93 by multivariate analysis only]) and progression (RR, 0.30 [CI, 0.13 to 0.72]). When tall-cell variants were excluded, the effect on outcome was not significant. After radioiodine therapy, patients with follicular thyroid cancer had improvement in overall mortality (RR, 0.17 [CI, 0.06 to 0.47]), cancer-specific mortality (RR, 0.12 [CI, 0.04 to 0.42]), progression (RR, 0.21 [CI, 0.08 to 0.56]), and disease-free survival (RR, 0.29 [CI, 0.08 to 1.01]). External radiation therapy to the neck was given to 18.5% of patients and was not associated with improved survival, lack of progression, or disease-free survival.

**Conclusions:** This study supports improvement in overall and cancer-specific mortality among patients with papillary and follicular thyroid cancer after postoperative iodine-131 therapy. Radioiodine therapy was also associated with improvement in progression in patients with papillary cancer and improvement in progression and disease-free survival in patients with follicular carcinoma.

# Hypothyroidism: Too little thyroid hormone

## Part 2: Diagnosis and Treatments of Hypothyroidism.



Since hypothyroidism is caused by too little thyroid hormone secreted by the thyroid, **the diagnosis of hypothyroidism is based almost exclusively upon measuring the amount of thyroid hormone in the blood.** There are normal ranges for all thyroid hormones which have been calculated by computers which measured these hormones in tens of thousands of people. If your thyroid hormone levels fall below the normal range,

that is consistent with hypothyroidism. These tests are very accurate and reliable and are so routine that they are available to everybody. [More about these tests on another page.](#) **NEW!** However, its not always so simple...keep reading.

### REMEMBER

**hypo = too little**

**thyroidism = disease of the thyroid**

**Thus, hypo-thyroidism = a disease of too little thyroid activity.**

**The idea is to measure blood levels of T4 and TSH.** In the typical person with an under-active thyroid gland, the blood level of T4 (the main thyroid hormone) will be low, while the TSH level will be high. This means that the thyroid is not making enough hormone and the pituitary recognizes it and is responding appropriately by making more Thyroid Stimulating Hormone (TSH) in an attempt to force more hormone production out of the thyroid. In the more rare case of hypothyroidism due to pituitary failure, the thyroid hormone T4 will be low, but the TSH level will also be low. The thyroid is behaving "appropriately" under these conditions because it can only make hormone in response to TSH signals from the pituitary. Since the pituitary is not making enough TSH, then the thyroid will never make enough T4. The real question in this situation is what is wrong with the pituitary? But in the typical and most common form of hypothyroidism, the main thyroid hormone T4 is low, and the TSH level is high.

The next question is: When is low too low, and when is high too high? Blood levels have "normal" ranges, but other factors need to be taken into account as well, such as the presence or absence of symptoms. You should discuss your levels with your doctor so you can interpret how they are helping (or not?) fix your problems.

**Oh, if only it were this simple all the time!** Although the majority of individuals with hypothyroidism will be easy to diagnose with these simple blood tests, many millions will have this disease in mild to moderate forms which are more difficult to diagnose. The solution for these people is more complex and this is due to several factors. First we must realize that not all patients with hypothyroidism are the same. There are many degrees of this disease from very severe to very mild. Additionally, and very importantly, we cannot always predict just how bad (or good) an individual patient will feel just by examining his/her thyroid hormone levels. In other words, some patients with very "mild" deviations in their thyroid laboratory test results will feel just fine while others will be quite symptomatic. The degree of thyroid hormone

abnormalities often, but NOT ALWAYS will correlate with the degree of symptoms. It is important for both you and your physician to keep this in mind since the goal is not necessarily to make the lab tests go into the normal range, but to make you feel better as well! We must also keep in mind that even the "normal" thyroid hormone levels in the blood have a fairly large range, so even if a patient is in the "normal" range, it may not be the normal level for them.

For the majority of patients with hypothyroidism, taking some form of thyroid hormone replacement (synthetic or natural, pill or liquid, etc) will make the "thyroid function tests" return to the normal range, AND, this is accompanied by a general improvement in symptoms making the patient feel better. This does not happen to all individuals, however, and for these patients it is very important to find an endocrinologist who will listen and be sympathetic. (We aim to help you find this type of doctor.) Because most patients will be improved (or made completely better) when sufficient thyroid hormone is provided on a daily basis to make the hormone levels in the blood come into the normal range, physicians will often will rely on test results to determine when a patient is on the appropriate dose and therefore doing well. Remember, these tests have a wide normal range. Find a doctor who helps make you FEEL better, not just make your labs better because once given this diagnosis, you are likely to carry it for a long, long time. There is more than one drug, there is more than one lab test, and there is a "just right" doctor for everybody.

## Treatment of Hypothyroidism

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**Hypothyroidism is usually quite easy to treat (for most people)!** The easiest and most effective treatment is simply taking a thyroid hormone pill (Levothyroxine) once a day, preferably in the morning. This medication is a pure synthetic form of T4 which is made in a laboratory to be an exact replacement for the T4 that the human thyroid gland normally secretes. It comes in multiple strengths, which means that an appropriate dosage can almost always be found for each patient. The dosage should be re-evaluated and possibly adjusted monthly until the proper level is established. The dose should then be re-evaluated at least annually. If you are on this medication, make sure your physician knows it so he/she can check the levels at least yearly. **Note:** Just like we discussed above, however, this simple approach does not hold true for everybody. Occasionally the correct dosage is a bit difficult to pin-point and therefore you may need an exam and blood tests more frequently. Also, some patients just don't do well on some thyroid medications and will be quite happy on another. For these reasons you should **not** be shy in discussing with your doctor your blood hormone tests, symptoms, how you feel, and the type of medicine you are taking. The goal is to make you feel better, make your body last longer, slow the risk of heart disease and osteoporosis...in addition to making your blood levels normal! Sometimes that's easy, when its not, you need a physician who is willing to spend the time with you that you deserve while you explore different dosages other types of medications (or alternative diagnoses).

Some patients will notice a slight reduction in symptoms within 1 to 2 weeks, but **the full metabolic response to thyroid hormone therapy is often delayed for a month or two** before the patient feels completely normal. It is important that the correct amount of thyroid hormone is used. Not enough and the patient may have continued fatigue or some of the other **symptoms of hypothyroidism**. Too high a dose could cause symptoms of nervousness, palpitations or insomnia typical of hyperthyroidism. Some recent studies have suggested that too much thyroid hormone may cause

increased calcium loss from bone increasing the patient's risk for [osteoporosis](#). For patients with heart conditions or diseases, an optimal thyroid dose is particularly important. Even a slight excess may increase the patient's risk for heart attack or worsen angina. Some physicians feel that more frequent dose checks and blood hormone levels are appropriate in these patients.

**After about one month of treatment, hormone levels are measured in the blood to establish whether the dose of thyroid hormone which the patient is taking is appropriate.** We don't want too much given or subtle symptoms of [hyperthyroidism](#) could ensue, and too little would not alleviate the symptoms completely. Often blood samples are also checked to see if there are antibodies against the thyroid, a sign of autoimmune thyroiditis. Remember, this is the most common cause of hypothyroidism. Once treatment for hypothyroidism has been started, it typically will continue for the patient's life. Therefore, it is of great importance that the diagnosis be firmly established and you have a good relationship with a physician you like and trust.

**Synthetic T4 can be safely taken with most other medications.** Patients taking cholestyramine (a compound used to lower blood cholesterol) or certain medications for seizures should check with their physician about potential interactions. Women taking T4 who become pregnant should feel confident that the medication is exactly what their own thyroid gland would otherwise make. However, they should check with their physician since the T4 dose may have to be adjusted during [pregnancy](#) (usually more hormone is needed to meet the increased demands of the mother's new increased metabolism). There are other potential problems with other drugs including iron-containing vitamins. Once again, pregnant women (and all women and men for that matter) taking iron supplements should discuss this with your physician. There are three brand name Levothyroxine tablets now available. You may want to consult with your physician or pharmacist on the most cost effective brand since recent studies suggest that none is better than the other.

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## Insomnia: How to Get a Good Night's Sleep

### What causes insomnia?

Insomnia is the body's way of saying that something isn't right. Things that may cause insomnia include stress, too much caffeine, depression, changes in work shifts, and pain from medical problems, such as arthritis.

Many people have insomnia. People who have insomnia may not be able to fall asleep. They may wake up during the night and not be able to fall back asleep, or they may wake up too early in the morning.

### Is insomnia a serious problem?

It's not really a serious problem for your health, but it can make you feel tired, depressed and irritable. It can also make it hard to concentrate during the day.

## **How much sleep do I need?**

Most adults need about 7 to 8 hours of sleep each night. You know you're getting enough sleep if you don't feel sleepy during the day. The amount of sleep you need stays about the same throughout adulthood. However, sleep patterns may change with age. For example, older people may sleep less at night and take naps during the day.

## **What can my doctor do to find out why I'm not sleeping?**

Your family doctor may ask you and your bed partner some questions about your sleep habits (such as when you go to bed and when you get up), any medicine you take, and the amount of caffeine and alcohol you drink. Your doctor may also ask if you smoke.

Other questions may include how long you've been having insomnia, if you have any pain (such as from arthritis), and if you snore while you sleep. Your doctor may also ask about events or problems in your life that may be upsetting you and making it hard for you to sleep.

## **What is a sleep diary?**

If the cause of your insomnia is not clear, your doctor may suggest that you fill out a sleep diary. The diary will help you keep track of when you go to bed, how long you lie in bed before falling asleep, how often you wake during the night, when you get up in the morning and how well you sleep. A sleep diary may help you and your doctor identify patterns and conditions that may be affecting your sleep.

## **How is insomnia treated?**

The treatment of insomnia can be simple. Often, once the problem that's causing the insomnia is taken care of, the insomnia goes away. The key is to find out what's causing the insomnia so that it can be dealt with directly. Simply making a few changes in their sleep habits helps many people.

## **What can I do to improve my sleep habits?**

Here are some things you can do to help you sleep better:

- Go to bed and wake up at the same time every day, including weekends, even if you didn't get enough sleep. This will help train your body to sleep at night.
- Develop a bedtime routine. Do the same thing every night before going to sleep. For example, take a warm bath and then read for 10 minutes every night before going to bed. Soon you'll connect these activities with sleeping, and doing them will help make you sleepy.
- Use the bedroom only for sleeping or having sex. Don't eat, talk on the phone or watch TV while you're in bed.
- Make sure your bedroom is quiet and dark. If noise is a problem, use a fan to mask the noise or use ear plugs. If you must sleep during the day, hang dark blinds over the windows or wear an eye mask.
- If you're still awake after trying to fall asleep for 30 minutes, get up and go to another room. Sit quietly for about 20 minutes before going back to bed. Do this as many times as you need to until you can fall asleep.



## Will sleeping pills help?

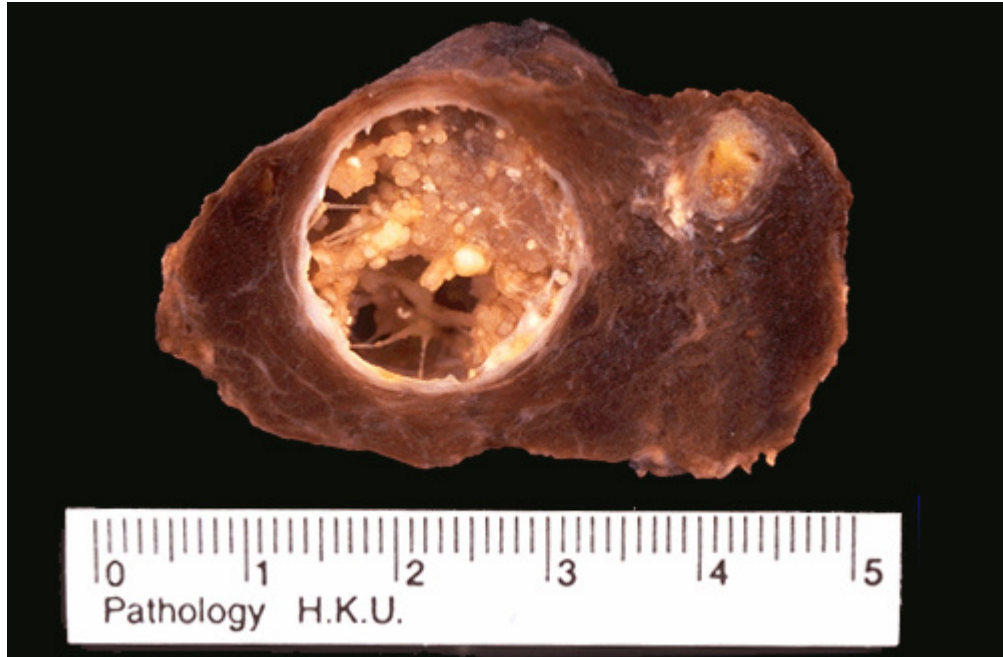
Sleeping pills can help in some cases, but they are not a cure for insomnia. They're only a temporary form of relief. They're best used for only a few days. Regular use can lead to rebound insomnia. This occurs when a person quits taking sleeping pills and his or her insomnia comes back.

Sleeping pills can be unsafe to use if you have certain health problems. Ask your doctor if sleeping pills would be helpful for you.

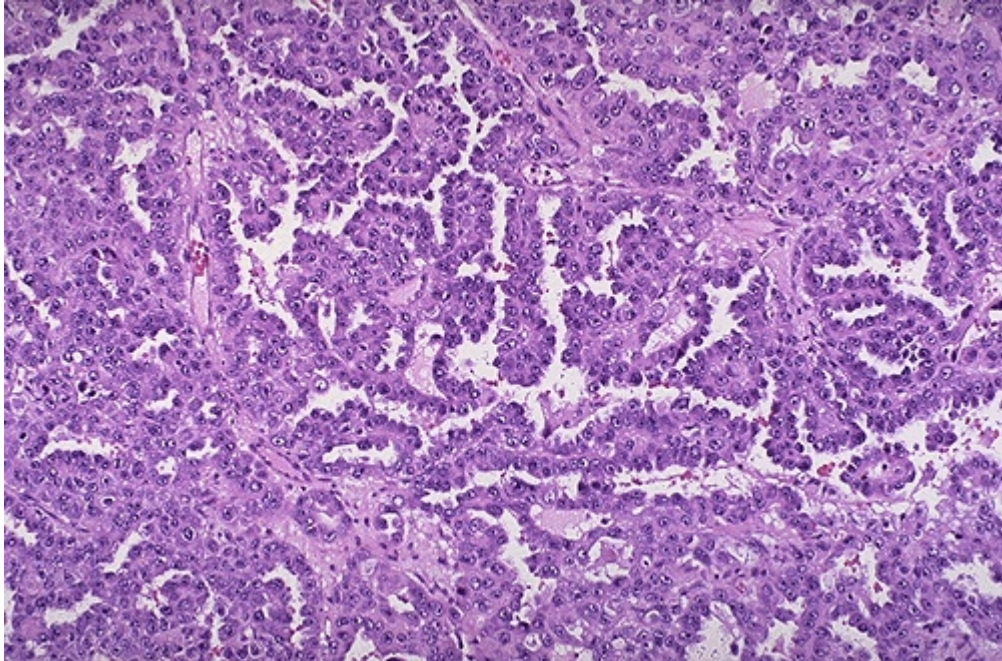
## Tips to help you sleep

- Avoid or limit your use of caffeine (coffee, tea, sodas, chocolate), decongestants, alcohol and tobacco.
- Exercise more often, but don't exercise within a few hours before going to bed.
- Learn to reduce or manage the stress in your life.
- Don't lie in bed worrying about things. Set aside another time just for worrying. For example, spend 30 minutes after dinner writing down what's worrying you and what you can do about it.
- Try eating a light snack before going to bed, but don't eat too much right before bedtime. A glass of warm milk or some cheese and crackers may be all you need.
- Don't nap during the day if naps seem to make your insomnia worse.

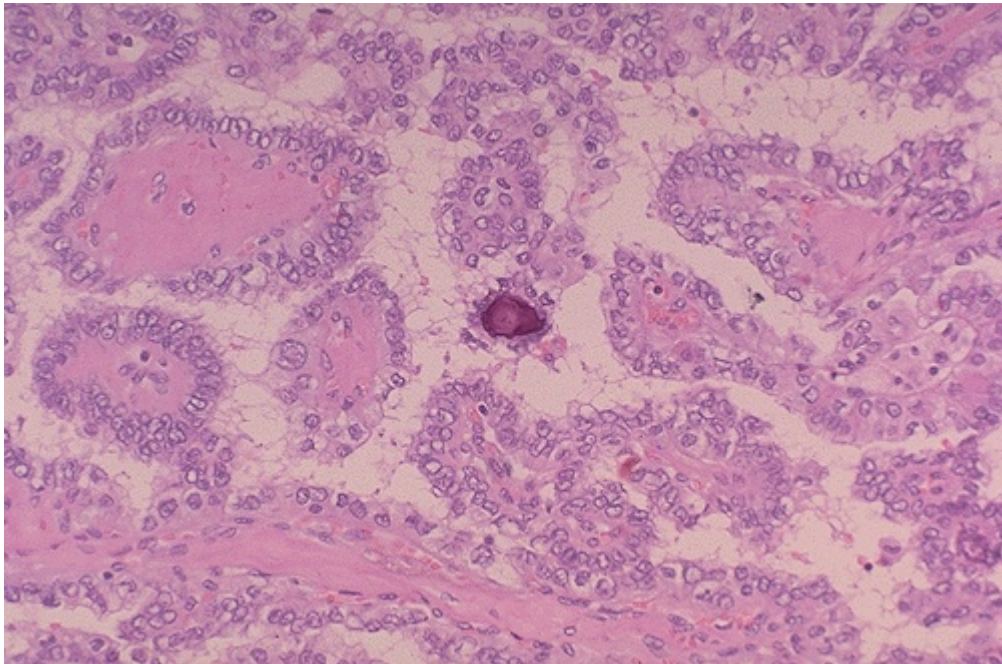
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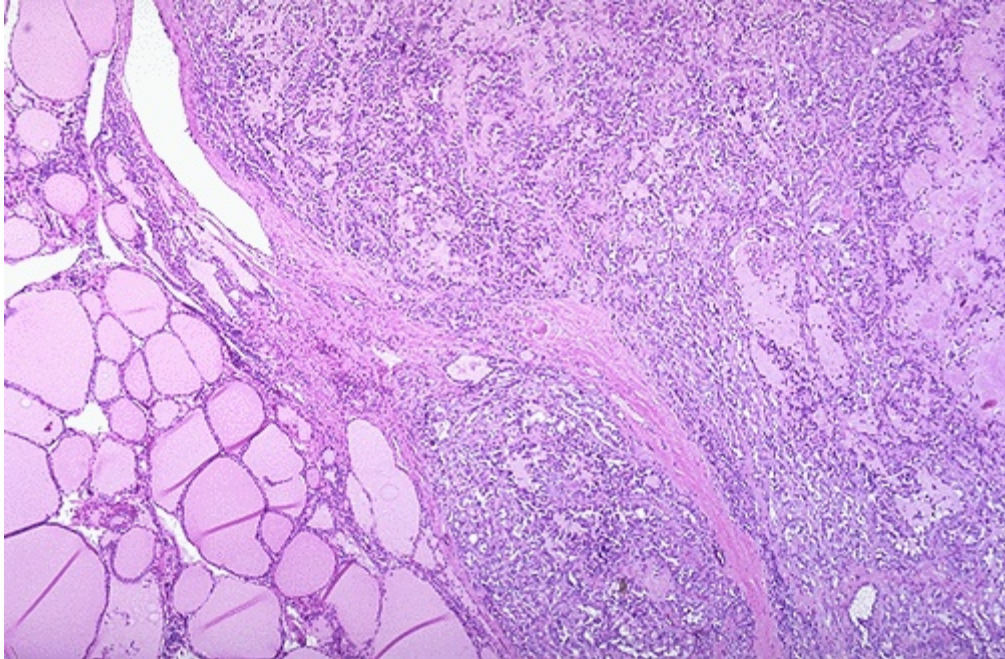
Sectioning through a lobe of excised thyroid gland reveals papillary carcinoma. This neoplasm can be multifocal, as seen here, because of the propensity to invade lymphatics within thyroid, and lymph node metastases are common. The larger mass is cystic and contains papillary excrescences. These tumors most often arise in middle-aged females.



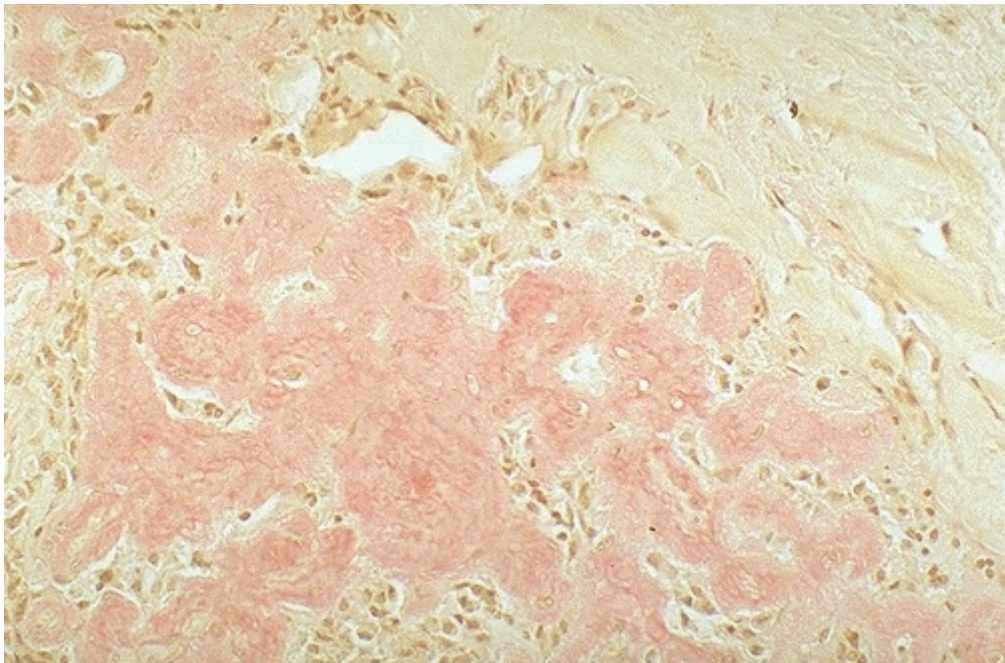
This is the microscopic appearance of a papillary carcinoma of the thyroid. The fronds of tissue have thin fibrovascular cores. The fronds have an overall papillary pattern. There is no such thing as a papillary adenoma, and all papillary neoplasms of the thyroid should be considered malignant.



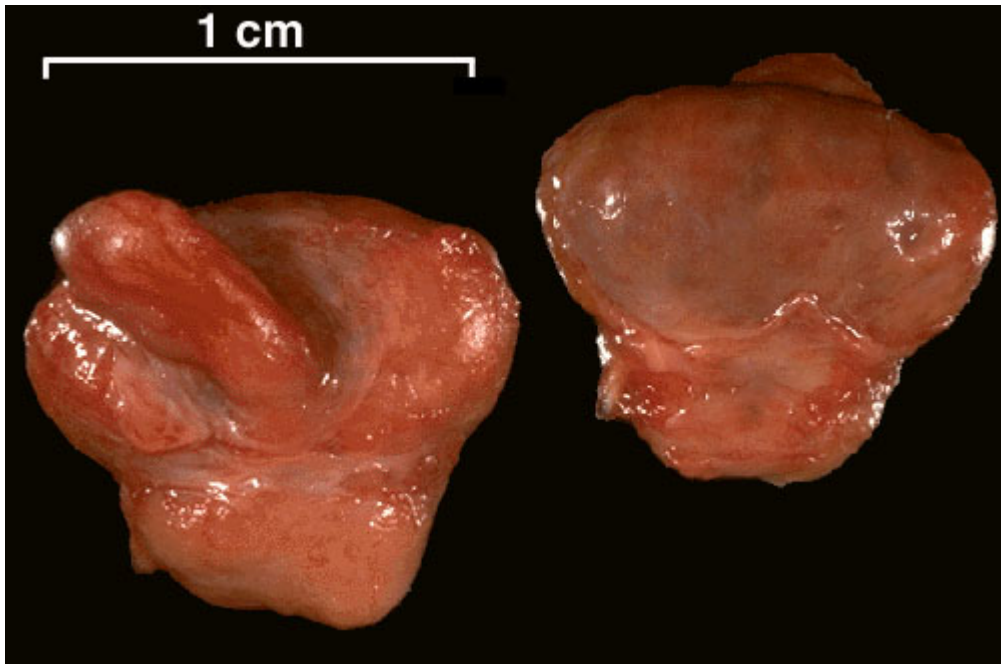
This is another papillary carcinoma of thyroid. Note the small psammoma body in the center. The cells of the neoplasm have clear nuclei. Papillary carcinomas are indolent tumors that have a long survival, even with metastases. The most favorite site of metastasis is to local lymph nodes in the neck. In fact, some papillary carcinomas may first present as nodal metastases.



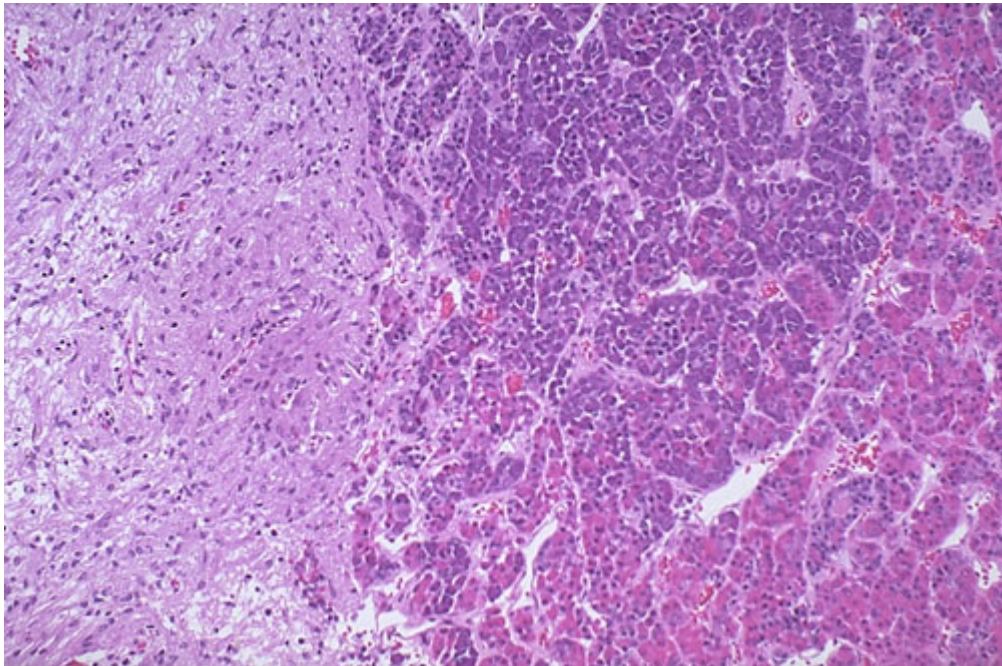
At the center and to the right is a medullary carcinoma of thyroid. At the far right is pink hyaline material with the appearance of amyloid. These neoplasms are derived from the thyroid "C" cells and, therefore, have neuroendocrine features such as secretion of calcitonin.



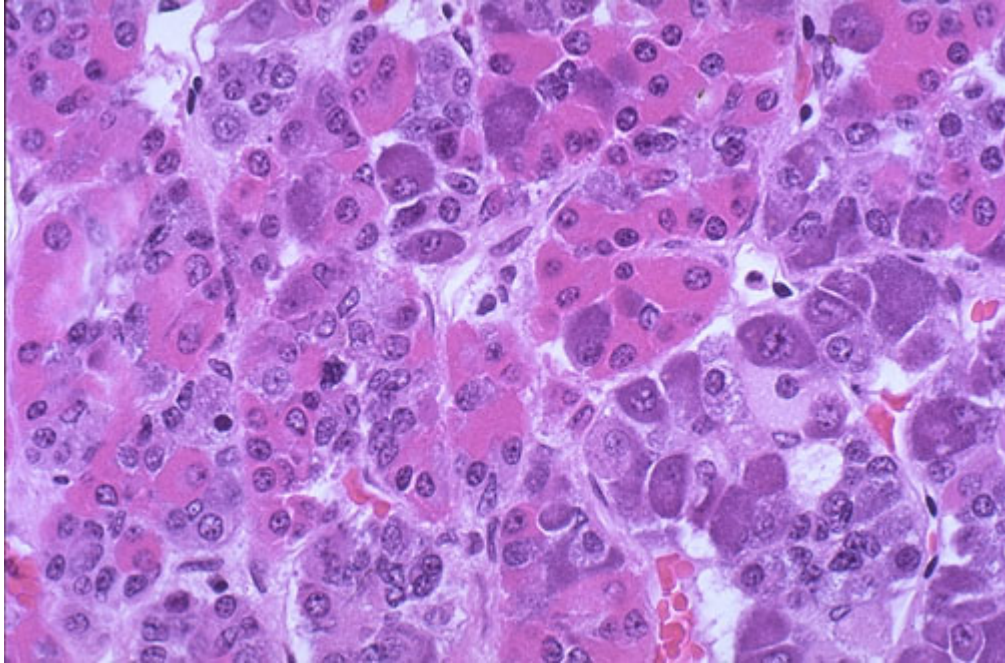
Here the amyloid stroma of the medullary thyroid carcinoma has been stained with Congo red. Medullary carcinomas can be sporadic or familial. The familial kind are associated with multiple endocrine neoplasia syndrome.



The normal gross appearance of the pituitary gland removed from the sella turcica is shown here. The larger porti (adenohypophysis), is toward the top. The image at the left shows the superior aspect of the pituitary with the stal hypothalamus entering it. The inferior aspect of the pituitary is shown at the right. The posterior pituitary (neurohy) portion at the bottom.



The normal microscopic appearance of the pituitary gland is shown here. The adenohypophysis is at the right and the neurohypophysis is at the left.

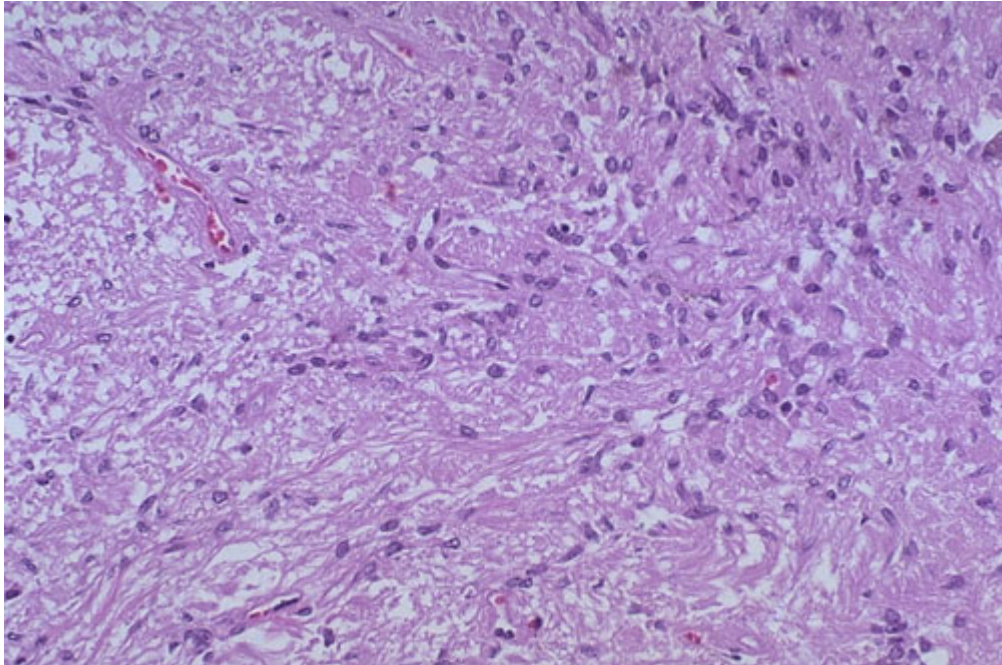


The normal microscopic appearance of the adenohypophysis is shown here. The adenohypophysis contains three major cell types: acidophils, basophils, and chromophobes. The staining is variable, and to properly identify specific hormone secretion, immunohistochemical staining is necessary. A simplistic classification is as follows:

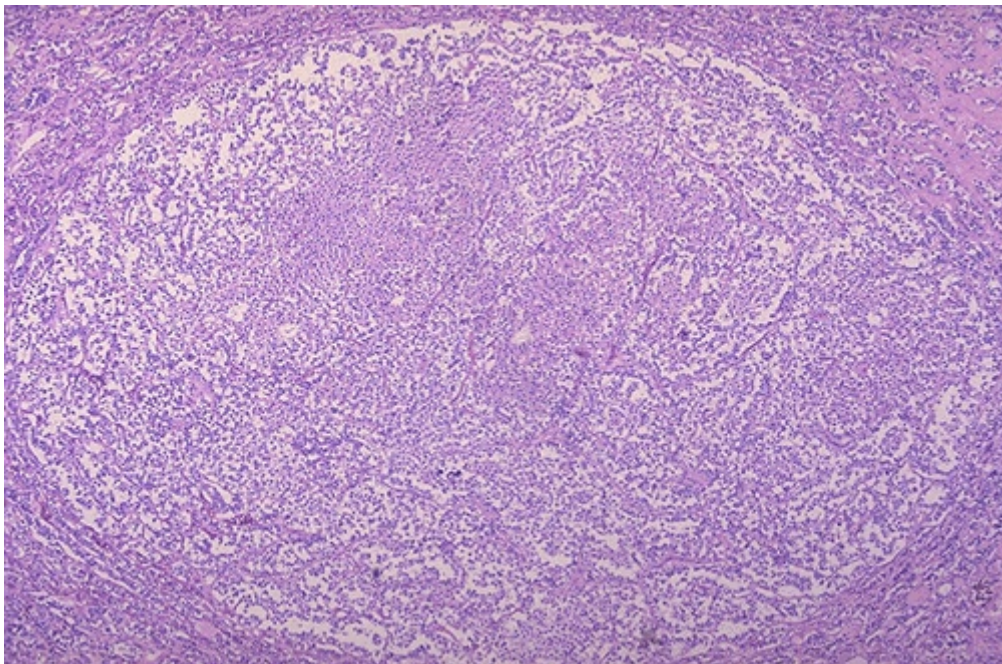
The pink acidophils secrete growth hormone (GH) and prolactin (PRL)

The dark purple basophils secrete corticotrophin (ACTH), thyroid stimulating hormone (TSH), and gonadotrophins follicle stimulating hormone-luteinizing hormone (FSH and LH)

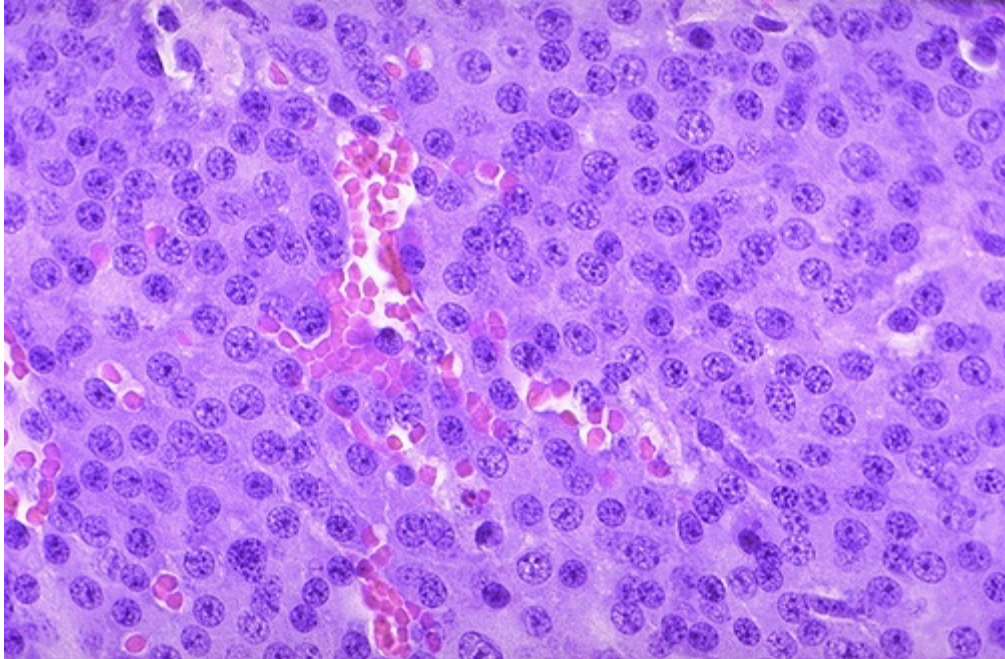
The pale staining chromophobes have few cytoplasmic granules, but may have secretory activity.



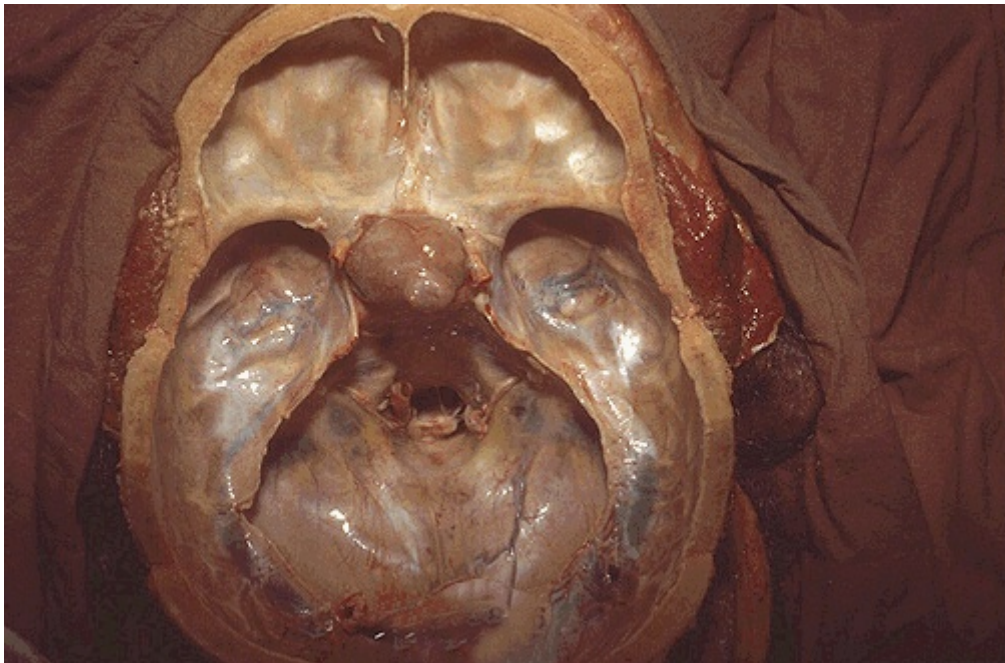
The neurohypophysis shown here resembles neural tissue, with glial cells, nerve fibers, nerve endings, and intra-axonal neurosecretory granules. The hormones vasopressin (antidiuretic hormone, or ADH) and oxytocin made in the hypothalamus (supraoptic and paraventricular nuclei) are transported into the intra-axonal neurosecretory granules where they are released.



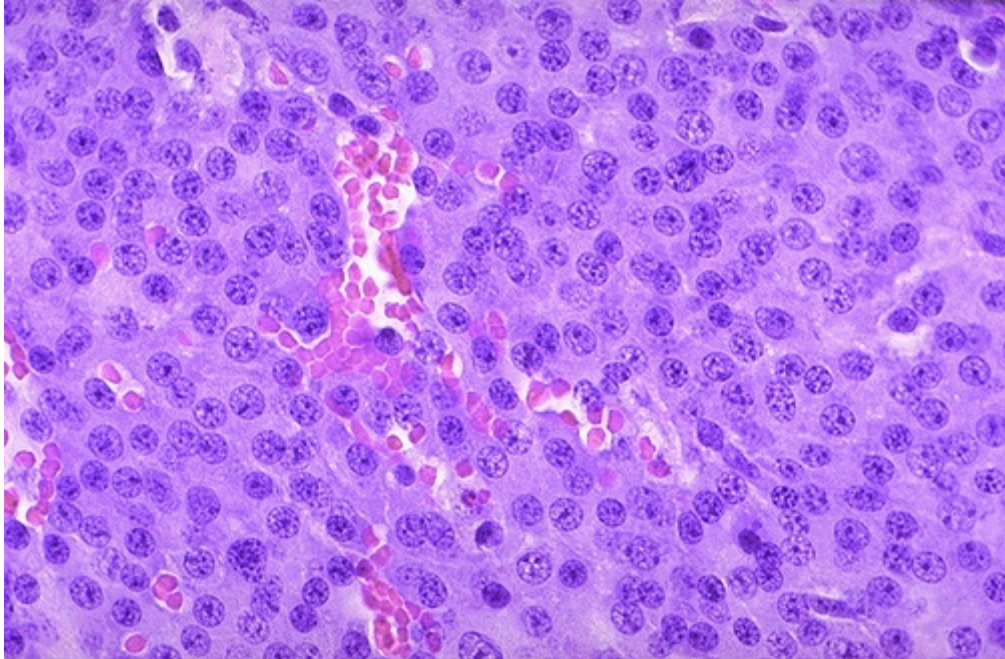
This is a microadenoma of the anterior pituitary. Such microadenomas may appear in 1 to 5% of adults. These microadenomas rarely have a significant hormonal output that leads to clinical disease.



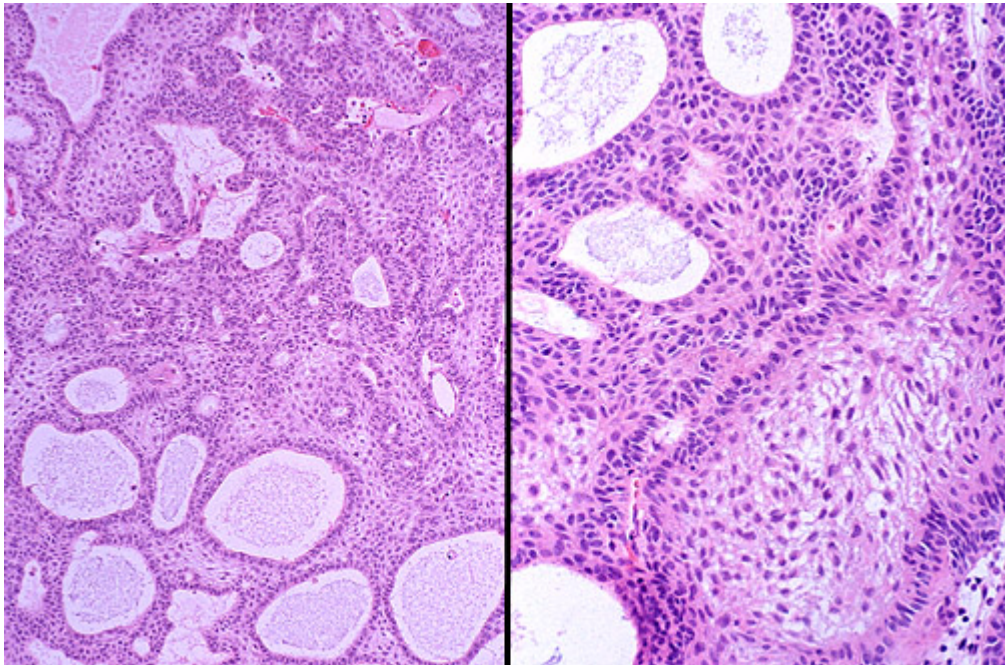
Here is a high power microscopic view of an adenohypophyseal adenoma. Endocrine neoplasms are composed of small round cells with small round nuclei and pink to blue cytoplasm. The cells may be arranged in nests or cords and endocrine tumors also have prominent vascularity.



The circumscribed mass lesion present here in the sella turcica is a pituitary adenoma. Though pituitary adenomas are benign, they can produce problems either from a mass effect (usually visual problems from pressing on the optic chiasm and/or headaches) or from production of hormones such as prolactin or ACTH.



The microscopic appearance of the pituitary adenoma is shown here. Note the monotonous appearance of these small round cells.



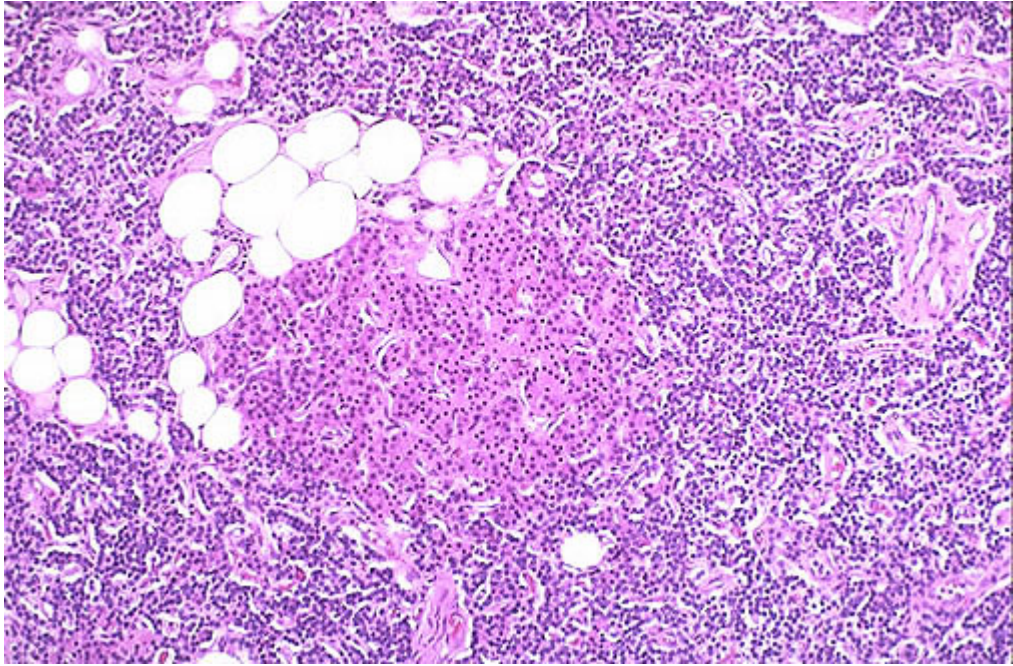
**CT**

A craniopharyngioma is seen here at medium and high power. It is derived from remnants of Rathke's pouch and forms an expanding mass arising in the sella turcica that erodes bone and infiltrates into surrounding structures. They are difficult to eradicate, even though they are composed of histologically appearing squamoid and columnar epithelium lining cystic spaces filled with oily fluid.

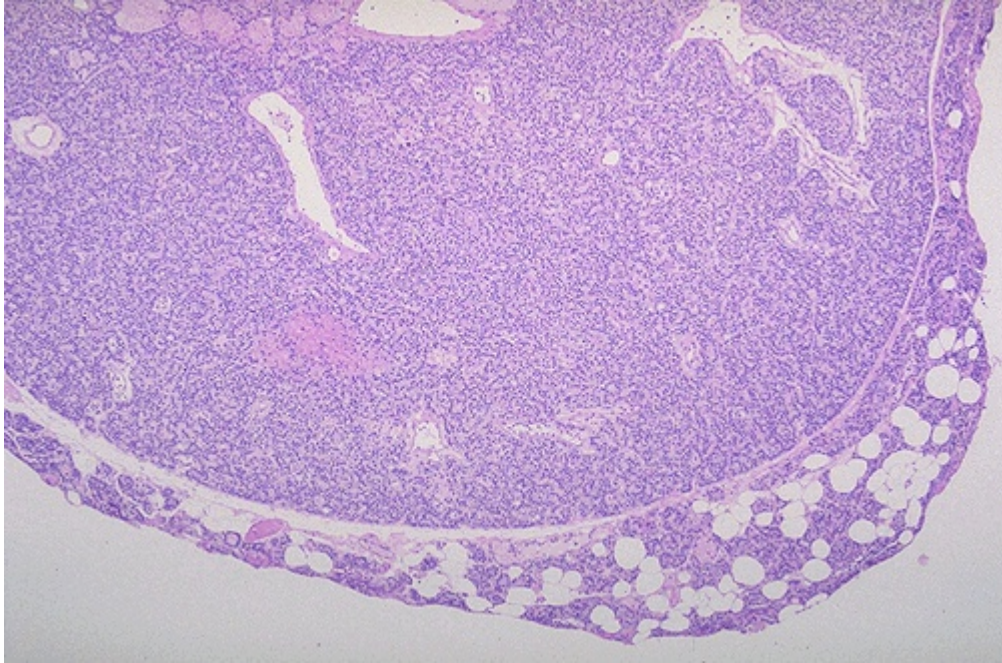




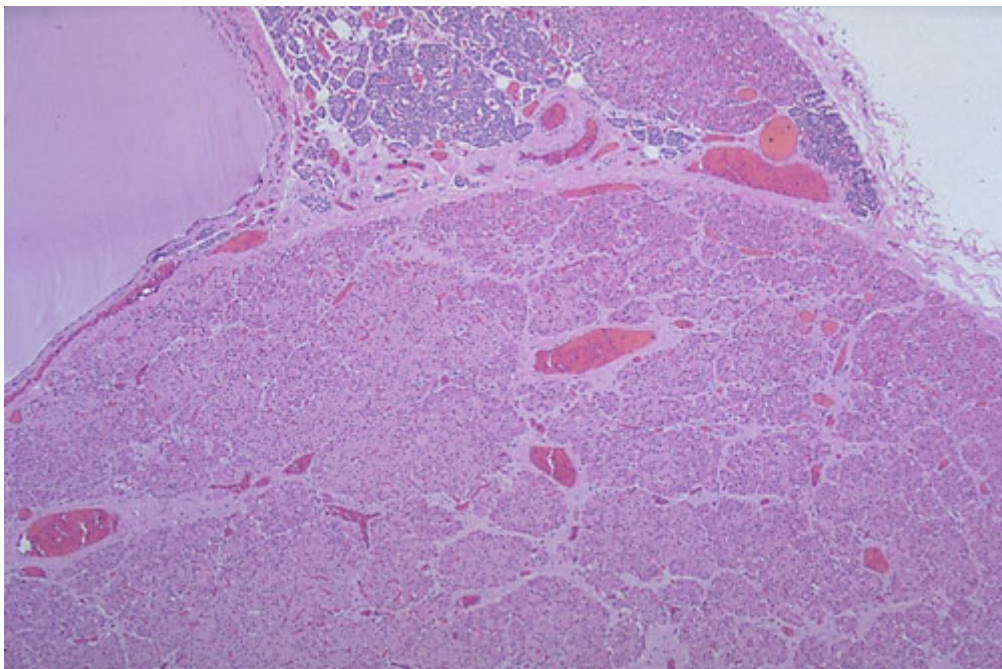
Parathyroid hyperplasia is shown here. Three and one-half glands have been removed (only half the gland at the lower left is present). Parathyroid hyperplasia is the second most common form of primary hyperparathyroidism, with parathyroid carcinoma the least common form.



In parathyroid hyperplasia, there is little or no adipose tissue, but any or all cell types normally found in parathyroid are present. Note the pink oxyphil cells here. This is actually "secondary hyperparathyroidism" with enlarged glands as a consequence of chronic renal failure with impaired phosphate excretion. The increased serum phosphate tends to drive serum calcium down, which in turn drives the parathyroids to secrete more parathormone.



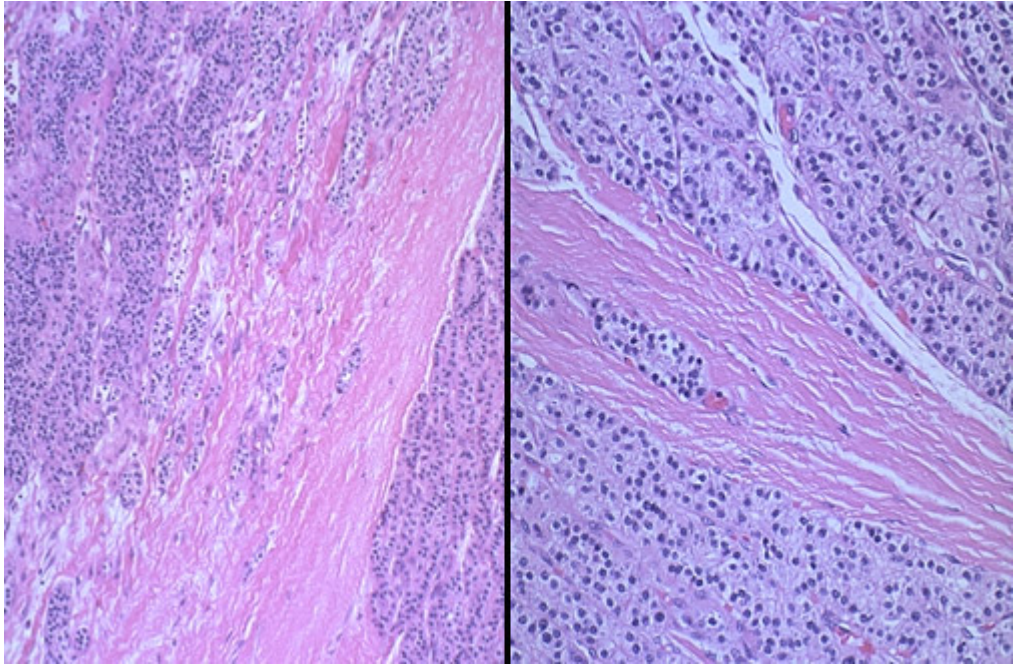
Here is a parathyroid adenoma, which is the most common cause for primary hyperparathyroidism. A rim of normal parathyroid tissue admixed with adipose tissue cells is seen compressed to the right and lower edge of the adenoma.



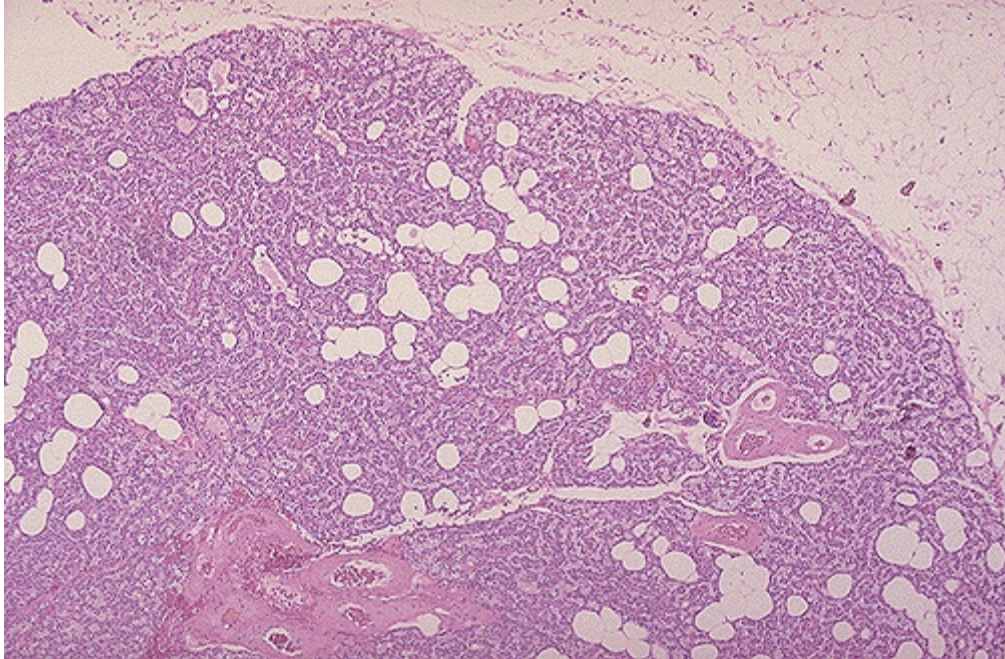
Adjacent to this parathyroid adenoma is a rim of normal parathyroid tissue (with a pink oxyphil cell nodule) at the upper right, and a small benign parathyroid cyst (an incidental finding) is at the upper left. Patients with this form of primary hyperparathyroidism are usually picked up with routine chemistry panels in which a high serum calcium is noted. A parathormone (PTH) assay reveals a high normal to elevated level of PTH.



This is the gross appearance of a parathyroid carcinoma. The serum calcium can be quite high. Note the large size and irregular cut surface. These carcinomas have a tendency to invade surrounding tissues in the neck, complicating their removal.

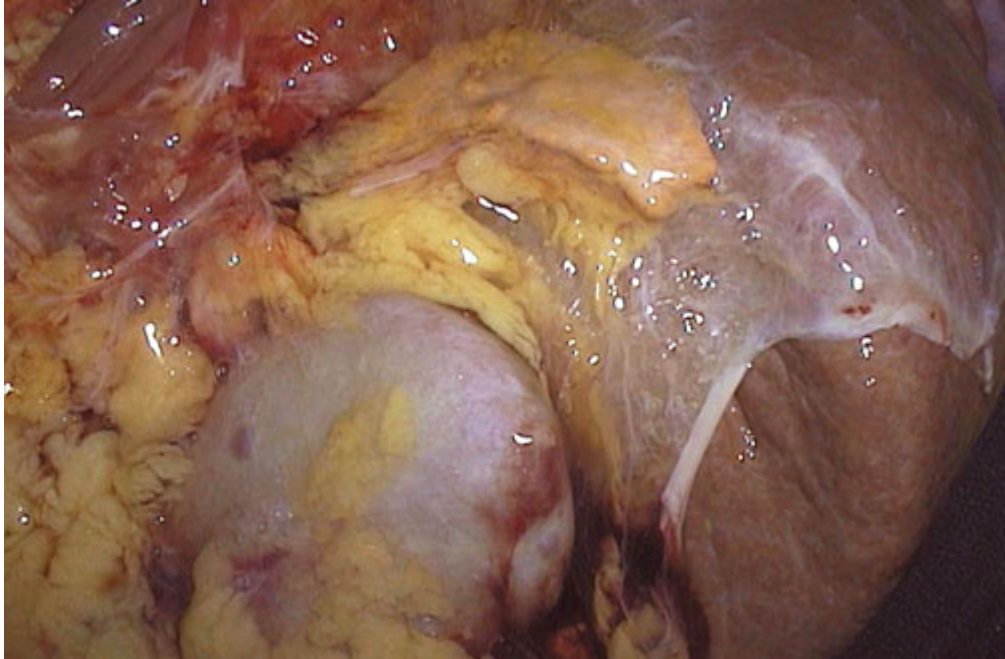


This is a parathyroid carcinoma seen at medium power on the left and higher power on the right. The nests of neoplastic cells that are not very pleomorphic. Note the bands of fibrous tissue between the nests. Parathyroid carcinomas infiltrate surrounding structures in the neck.



Here is a normal parathyroid gland for comparison. Adipose tissue cells are mixed with the parathyroid tissue. The amount of fat varies somewhat.

Identify the right adrenal and the right kidney by clicking in the image below:



A normal right adrenal gland is shown here positioned between the liver and the kidney in the retroperitoneum. Note the amount of adipose tissue, some of which has been reflected to reveal the upper pole of the kidney and the adrenal.

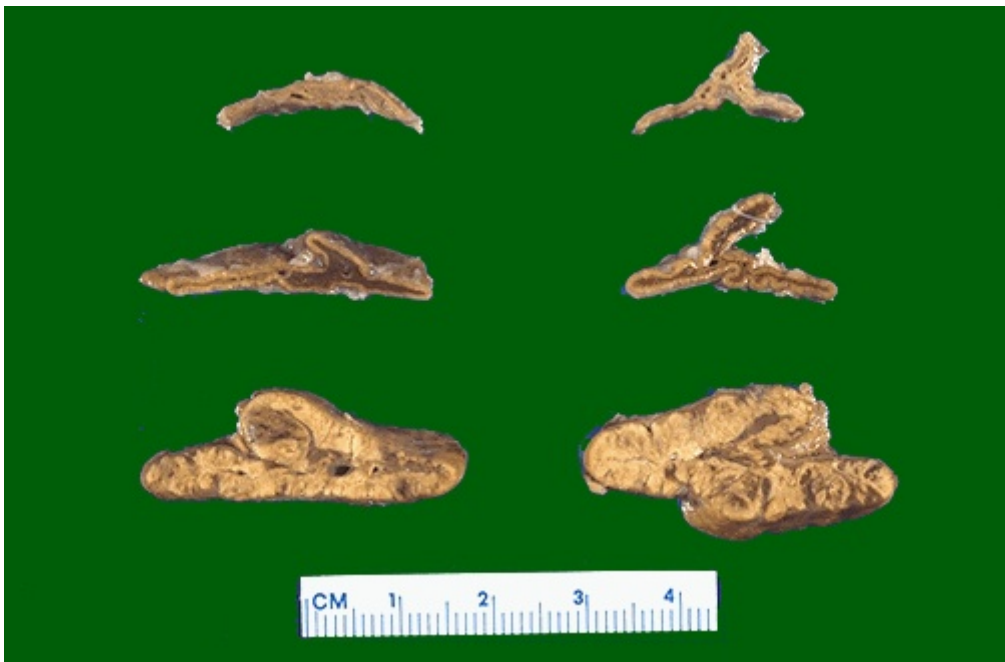
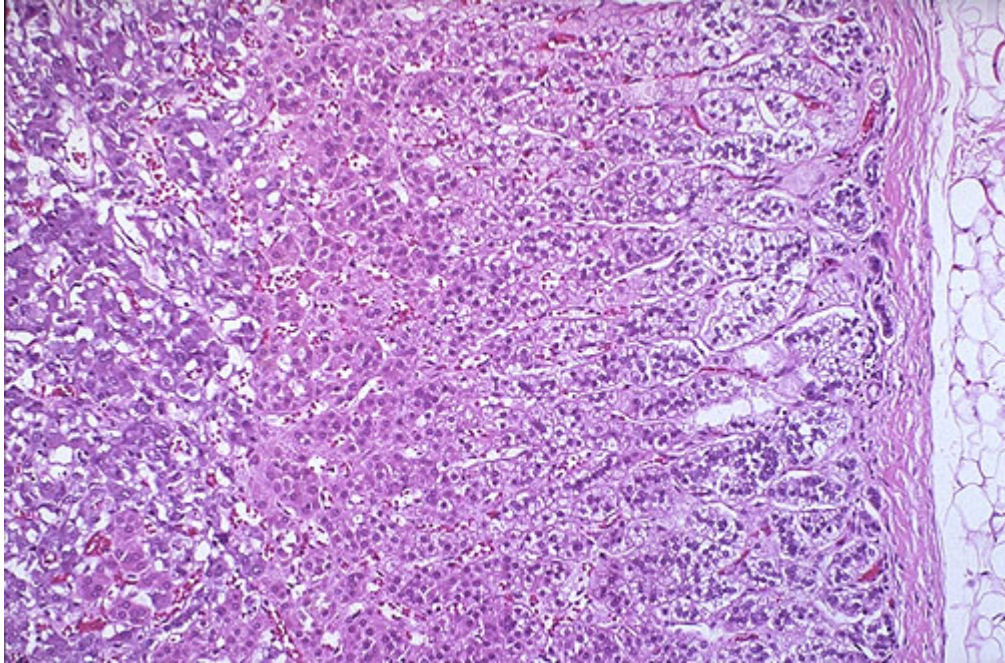


Here are normal adrenal glands. Each adult adrenal gland weighs from 4 to 6 grams.



Sectioning across the adrenals reveals a golden yellow outer cortex and an inner red to grey medulla.

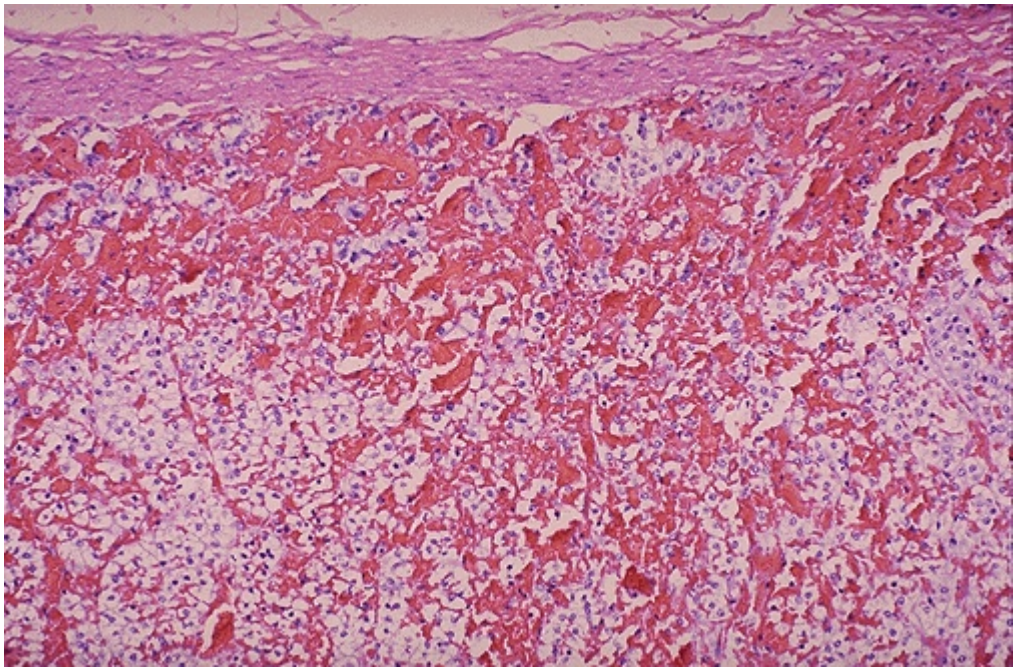
Identify the regions of the normal adrenal gland by clicking in the image below:



The pair of adrenals in the center are normal. Those at the top come from a patient with adrenal atrophy (with either Addison's disease or long-term corticosteroid therapy). The adrenals at the bottom represent bilateral cortical hyperplasia. This could be due to a pituitary adenoma secreting ACTH (Cushing's disease), or Cushing's syndrome from ectopic ACTH production, or idiopathic adrenal hyperplasia.



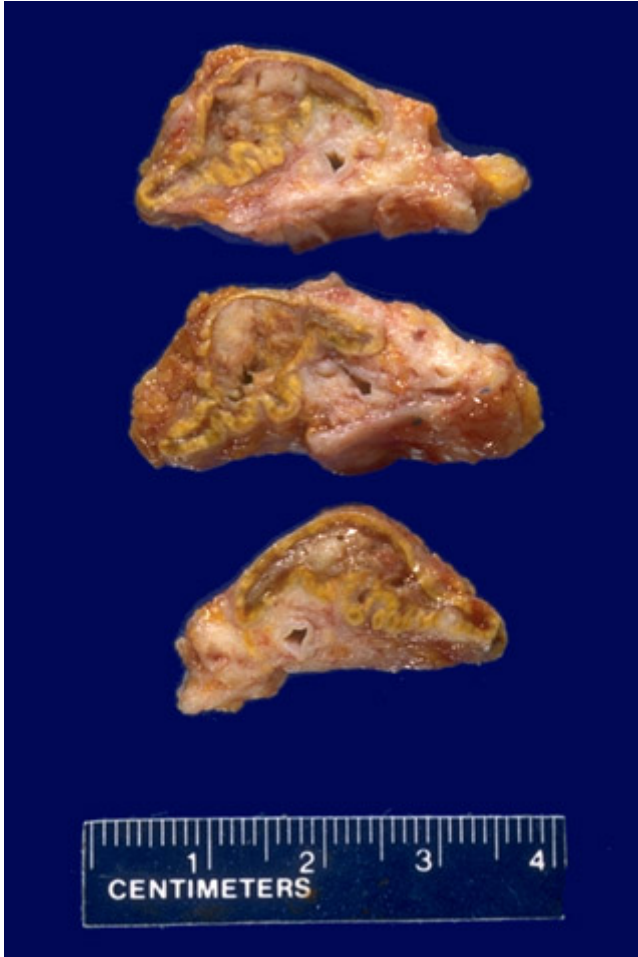
These adrenals are black-red from extensive hemorrhage in a patient with meningococemia. This produces the Waterhouse-Friderichsen syndrome.



This is the microscopic appearance of the adrenals with meningococemia. There is marked hemorrhagic necrosis with acute adrenal insufficiency.



The patient with Waterhouse-Friderichsen syndrome has sepsis with DIC and marked purpura.



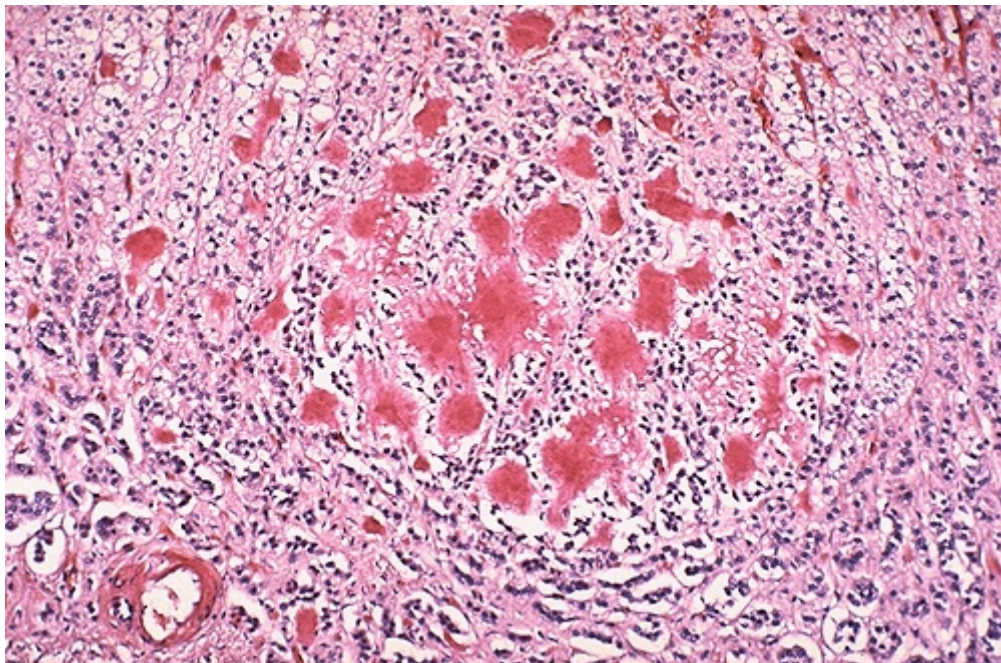
These sections through an enlarged adrenal gland demonstrate tan-white metastatic carcinoma infiltrating in and



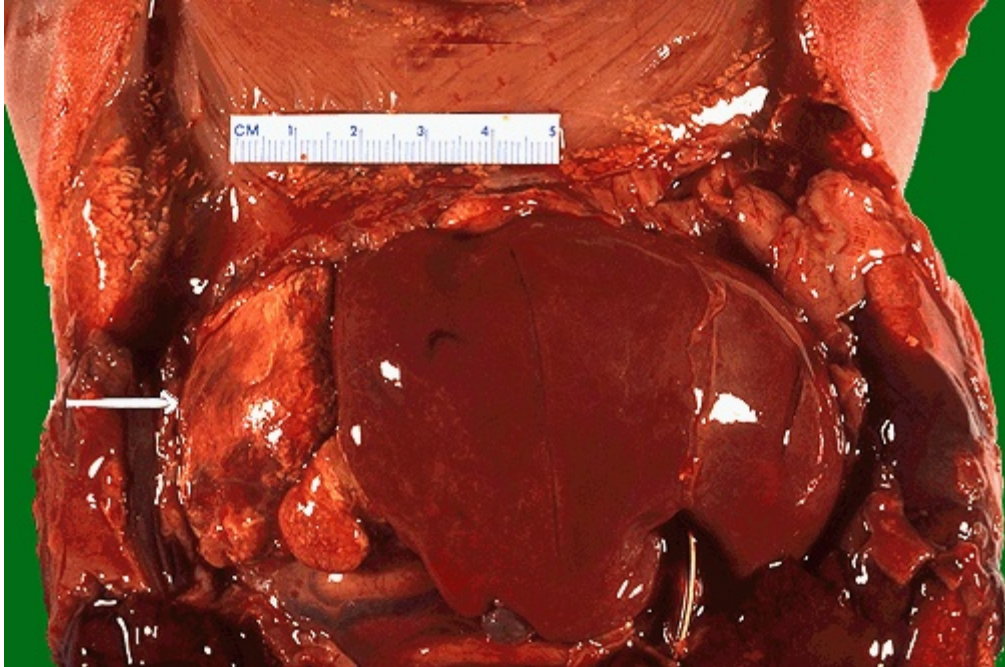
around the residual golden yellow cortex. The most common primary site for adrenal metastases is lung.



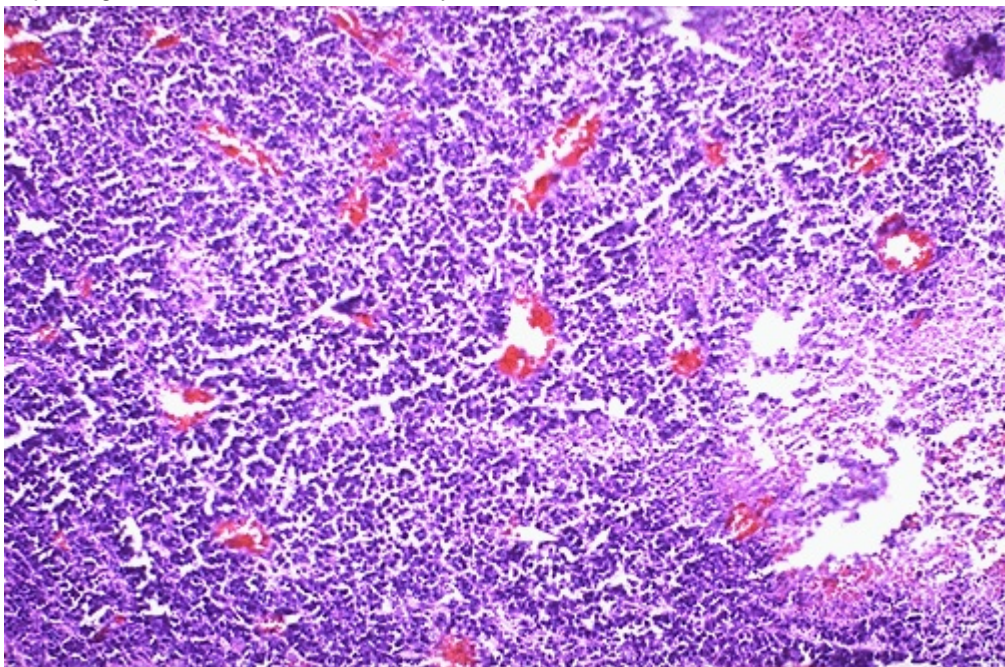
This is a caseating granuloma of tuberculosis in the adrenal gland. Tuberculosis used to be the most common cause of chronic adrenal insufficiency. Now, idiopathic (presumably autoimmune) Addison's disease is much more often the cause for chronic adrenal insufficiency.



Here are Congo red stained deposits of amyloid in the adrenal cortex. Amyloid may collect in adrenal as well as other organs.



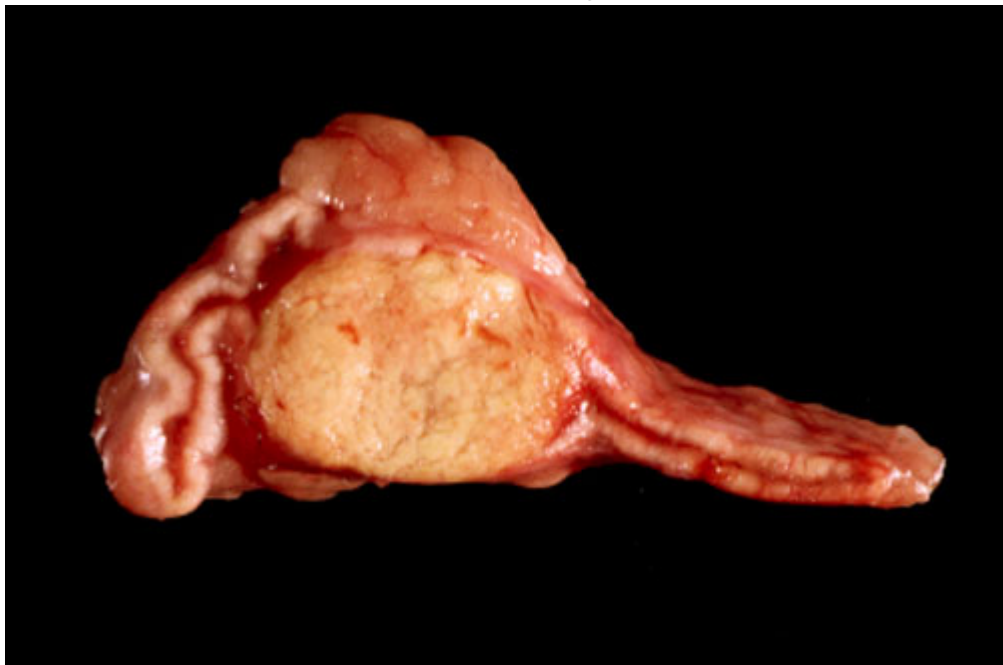
This neonate had a congenital neuroblastoma of the right adrenal. This neoplasm (marked by the white arrow) is displacing the liver to the left of the body.



This is a microscopic appearance of neuroblastoma, which is one of the "small round blue cell" tumors. These neoplasms can reach a large size in the retroperitoneum before detection. They often contain areas of necrosis and calcification.



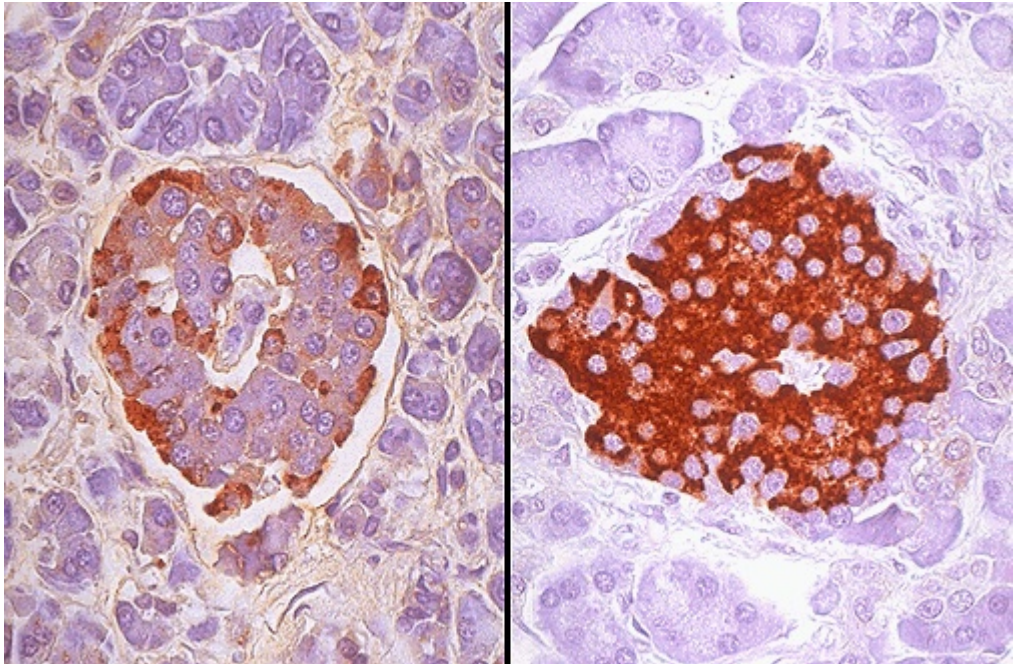
This adrenal gland removed surgically in a patient with Cushing's syndrome has been sectioned in half to reveal an adenoma. Some remaining atrophic adrenal is seen at the right. The adenoma is composed of yellow firm tissue just like adrenal cortex. This neoplasm is well-circumscribed. Histologically, it is composed of well-differentiated cells resembling cortical fasciculata zone. It is benign.



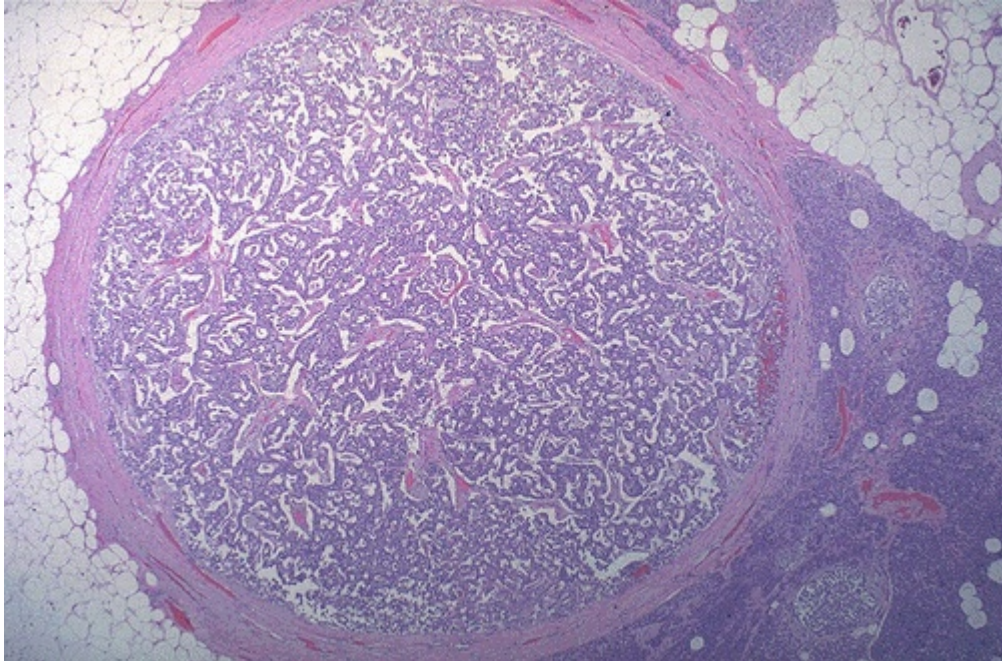
Here is a 1.3 cm left adrenal adenoma found in a patient with hypertension. She had hypokalemia on a routine chemistry panel. Further workup revealed a high serum aldosterone and a low serum renin, findings consistent with an aldosterone secreting adrenal adenoma (Conn's syndrome). This lesion accounts for about two-thirds of cases of primary hyperaldosteronism (PHA), while bilateral adrenal hyperplasia accounts for about 30% of PHA. Such adenomas are typically less than 2 cm in size and yellow on cut surface.



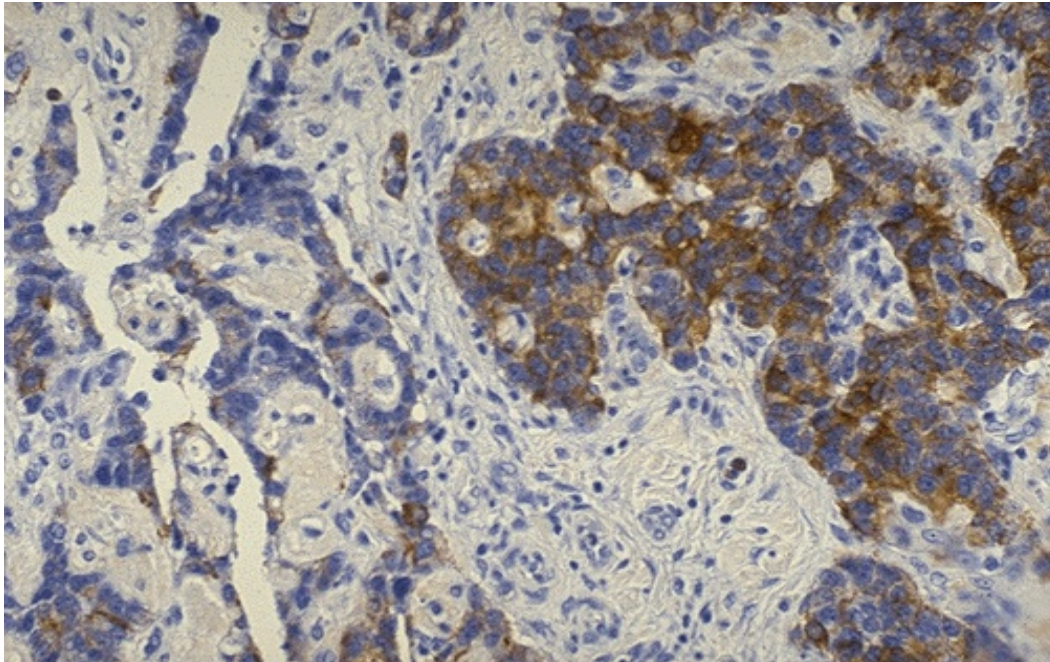
This pheochromocytoma demonstrates the chromaffin reaction. This neoplasm of the adrenal medulla contains catecholamines (epinephrine and norepinephrine). The section of tumor at the bottom has been placed into a dichromate fixative which turns the tissue brown as the catecholamines are oxidized. Compare to the section of pink to yellow tumor at the top which has not been placed in dichromate fixative.



Immunoperoxidase staining can help identify the nature of the cells present in the islets of Langerhans. On the right, antibody to insulin has been employed to identify the beta cells. On the left, antibody to glucagon identifies the alpha cells.



An islet cell adenoma is seen here, separated from the pancreas by a thin collagenous capsule. A few normal islets are seen in the pancreas at the right for comparison.



This is an immunohistochemical stain for insulin in the islet cell adenoma. Thus, it is an insulinoma.

<b>EPIDEMIOLOGY</b>	<b>CHARACTERIZATION</b>
<b>AGE</b>	
<b>Papillary Carcinoma of the Thyroid Gland of Childhood and</b>	<a href="#">Am J Surg Pathol. 2006 Nov;30(11):1420-1426 Abstract quote</a>

**Adolescence: Morphologic Subtypes, Biologic Behavior and Prognosis: A Clinicopathologic Study of 42 Sporadic Cases Treated at a Single Institution During a 30-Year Period.**

- [Collini P,](#)
- [Mattavelli F,](#)
- [Pellegrinelli A,](#)
- [Barisella M,](#)
- [Ferrari A,](#)
- [Massimino M.](#)

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Papillary thyroid carcinomas (PTCs) in pediatric age show an excellent outcome, independently of sex, size of relapse, and type of treatment.

Our aim was to study the biologic behavior and the impact on survival of PTC subtypes in childhood. From 1980 to 2009, 42 pediatric PTCs were subclassified into PTC, not otherwise specified and PTC variants. In all cases, sex, age, menarche, side, size, TNM/pTNM classification, neoplastic microfoci, vascular invasion, status of the node, and treatment (surgery and nonsurgical therapies) were registered. Follow-up was carried on up to March 2014. The solid variant was the most frequent subtype. Both extrathyroid local invasion (P<0.04) and distant metastases were significantly associated with PTC, not otherwise specified. After a median follow-up of 16 years, for the solid variant, overall survival and progression-free survival (PFS) rates were 100% and 77%, respectively. The solid/trabecular variant carried an increased risk of relapse (PFS 50%, P<0.01). The occurrence of poorly differentiated tall cell morphology was associated with a higher risk of relapse. Sensitivity to hormonal manipulation was maintained over time.

In conclusion, although overall survival was not influenced by PTC subtypes, the solid/trabecular variant carried a higher risk of relapse. At variance with adults, presence of the tall cell morphology did not carry a worse prognosis.

**RISK FACTOR**

**DESCRIPTION**

**IODINE**

Most common malignant tumor of the thyroid in countries with iodine-sufficient or iodine-excess diets

**EXTERNAL RADIATION**

Variable delay after exposure  
May show aggressive features

**Risk of thyroid carcinoma in a female population after radiotherapy for breast carcinoma.**

**Huang J, Walker R, Groome PG, Shelley W, Mackillop WJ.**

**The Radiation Oncology Research Unit, Department of Oncology, Queen's University, Kingston Regional Cancer Center, Kingston, Ontario, Canada.**

Cancer 2001 Sep 15;92(6):1411-1418 Abstract quote

**BACKGROUND:** There is increasing concern regarding the risk of developing a second primary tumor in the thyroid gland of scattered radiation among patients who have undergone radiotherapy (RT) for breast carcinoma. Previous studies have focused mainly on the possible increase in the incidence of contralateral breast carcinoma. To the authors' knowledge, the risk of thyroid carcinoma among these women has not been explored to date.

**METHODS:** In this population-based, retrospective cohort study, the authors identified 194,798 women with a history of invasive breast carcinoma (exclusive of those with distant metastasis) between 1973 and 1993, and ascertained the occurrence of thyroid carcinoma utilizing data from the Surveillance, Epidemiology, and End Results (SEER) program at the National Cancer Institute. Poisson regression was used to calculate the age-standardized incidence ratio (SIR) of thyroid carcinoma and the influence of RT on the relative risk (RR) between the RT cohort (48,495 women) and the non-RT cohort (146,303 women).

**RESULTS:** A total of 28 women in the RT cohort and 112 women in the non-RT cohort subsequently developed thyroid carcinoma. The distribution of thyroid carcinoma histologies in both the RT cohort and the non-RT cohort was similar to that of the general population. Overall, there was no significant increase in the risk of thyroid carcinoma in either the RT cohort compared with the general population; the SIR was 1.1 (95% confidence interval [95% CI], 0.8-1.4) for the RT cohort and 1.0 (95% CI, 1.0-1.4) for the non-RT cohort. When the RT cohort was compared with the non-RT cohort, the SIR was 1.0 (95% CI, 0.7-1.5).

	<p><b>CONCLUSIONS:</b> The risk of radiation-associated thyroid carcinoma after initial RT for breast carcinoma was undetectable in the current large population-based study. Continued monitoring of these women will be needed to confirm these findings are maintained with even longer follow-up periods. However, with 10,895 women having no thyroid carcinoma at the time of last follow-up in the current study, these findings should be reassuring to women considering breast radiation for breast carcinoma. Therefore, women who have received RT for breast carcinoma require no special surveillance. Furthermore, previous breast radiation need not be a factor in determining the optimal management of thyroid carcinoma in the women who received RT for breast carcinoma.</p>
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DISEASE ASSOCIATIONS	CHARACTERIZATION
<b>AUTOIMMUNE DISEASES</b>	Questionable association between Grave's disease and Hashimoto's thyroiditis
<b>GENETIC SYNDROMES</b>	Gardner's syndrome Cowden's syndrome
<b>THYROID/ PARATHYROID ADENOMAS</b>	Possible association

PATHOGENESIS	CHARACTERIZATION
<b>GENERAL</b>	
<p><b>Correlation Between Genetic Alterations and Microscopic Features, Clinical Manifestations, and Prognostic Characteristics of Thyroid Papillary Carcinomas.</b></p> <p><a href="#">Adeniran AJ, Zhu Z, Gandhi M, Steward DL, Fidler JP, Giordano TJ, Biddinger PW, Nikiforov YE.</a></p> <p>From the Departments of *Pathology and Laboratory Medicine, <del>dagger</del>Otolaryngology-Head and Neck Surgery, and <del>double dagger</del>Surgery, University of Cincinnati, Cincinnati, OH; and <del>section sign</del>Department of Pathology, University of Michigan Medical School and Comprehensive Cancer Center, University of Michigan, Ann Arbor,</p>	<p><a href="#">Am J Surg Pathol.</a> 2006 Feb;30(2):216-222. Abstract quote</p> <p>Papillary carcinoma is the most common type of thyroid malignancy. It has been recently shown that these tumors commonly have one of three genetic alterations: BRAF point mutations, RET/PTC rearrangements, or RAS point mutations.</p> <p>In this study, we analyze the relationship between these alterations and the microscopic features of papillary carcinomas, their clinical features, and prognostic characteristics. Ninety-seven papillary carcinomas were studied; in all cases, frozen tissue was available for nucleic acid extraction.</p> <p>Of 96 unselected cases, 42% were positive for BRAF, 18% for RET/PTC, and 15% for RAS mutations. Morphologic features were evaluated in detail in 61 cases and 6 characteristic nuclear features and 3 additional microscopic features were assessed quantitatively. At least 4 nuclear features were found in each tumor, with nuclear pseudoinclusions being the least frequent finding in all mutation groups. BRAF mutations were associated with older patient age, typical papillary appearance or the tall cell variant, a higher rate of extrathyroidal extension, and more advanced tumor stage at presentation. RET/PTC rearrangements presented at younger age and had predominantly typical papillary histology, frequent psammoma bodies, and a high rate of lymph node metastases.</p> <p>Tumors with RAS mutations were exclusively the follicular variant of papillary carcinoma and</p>

<p><b>MI.</b></p>	<p>correlated with significantly less prominent nuclear features and low rate of lymph node metastases. These findings demonstrate that BRAF, RET/PTC, and RAS mutations are associated with distinct microscopic, clinical, and biologic features of thyroid papillary carcinomas.</p>
<p><b>BRAF</b></p>	
<p><b>Mutational activation of BRAF is not a major event in sporadic childhood papillary thyroid carcinoma.</b></p> <p><a href="#">Rosenbaum E, Hosler G, Zahurak M, Cohen Y, Sidransky D, Westra WH.</a></p> <p><b>[1] 1Department of Oncology, The Johns Hopkins Medical Institutions, Baltimore, MD, USA [2] 2Department of Otolaryngology/Head and Neck Surgery (Division of Head and Neck Cancer Research), The Johns Hopkins Medical Institutions, Baltimore, MD, USA.</b></p>	<p>Mod Pathol. 2005 Jul;18(7):898-902. Abstract quote</p> <p>Papillary thyroid carcinoma may encompass a mixed group of neoplasms where divergence in clinical behavior may reflect distinct genetic alterations. For example, young patients with papillary thyroid carcinoma have a better prognosis than affected adults, and their carcinomas are much more likely to harbor chromosomal rearrangements involving the RET proto-oncogene. Mutational activation of the BRAF oncogene has recently been identified as the most common genetic alteration in papillary thyroid carcinoma, but little is known about its frequency as a function of patient age.</p> <p>We tested 20 papillary thyroid carcinomas from young patients ranging from 10 to 17 years of age for the thymine (T) --&gt; adenine (A) missense mutation at nucleotide 1796 in the BRAF gene using a newly developed assay that employs a novel primer extension method (Mutector((R)) assay). The prevalence of BRAF mutation was compared with a larger group of papillary thyroid carcinomas from previously tested adult patients (&gt;20 years). BRAF mutations were not common in papillary thyroid carcinomas from young patients compared to their counterparts in adults (20 vs 77%; OR=13.3, 95% confidence interval (CI)=3.4-56.5; P&lt;0.0001), but they become increasingly prevalent with advancing patient age (OR as a function of age at 10-year intervals=1.80 CI=1.33-2.44; P&lt;0.001). Unlike papillary thyroid carcinomas that arise in adults, mutational activation of BRAF is not a major genetic alteration in papillary thyroid carcinomas that arise in young patients.</p> <p>The increasing frequency of BRAF mutations as a function of age could help account for the well documented but poorly understood observation that age is a relevant prognostic indicator for patients with papillary thyroid carcinoma.</p>
<p><b>BRAF mutations in thyroid tumors are restricted to papillary carcinomas and anaplastic or poorly differentiated carcinomas arising from papillary carcinomas.</b></p> <p><a href="#">Nikiforova MN, Kimura ET, Gandhi M, Biddinger PW, Knauf JA, Basolo F, Zhu Z, Giannini R, Salvatore G, Fusco A, Santoro M, Fagin JA, Nikiforov YE.</a></p> <p><b>Department of Pathology and Laboratory Medicine, University of</b></p>	<p>J Clin Endocrinol Metab. 2003 Nov;88(11):5399-404. Abstract quote</p> <p>Activating point mutations of the BRAF gene have been recently reported in papillary thyroid carcinomas.</p> <p>In this study, we analyzed 320 thyroid tumors and six anaplastic carcinoma cell lines and detected BRAF mutations in 45 (38%) papillary carcinomas, two (13%) poorly-differentiated carcinomas, three (10%) anaplastic carcinomas, and five (83%) thyroid anaplastic carcinoma cell lines but not in follicular, Hurthle cell, and medullary carcinomas, follicular and Hurthle cell adenomas, or benign hyperplastic nodules. All mutations involved a T--&gt;A transversion at nucleotide 1796. In papillary carcinomas, BRAF mutations were associated with older age, classic papillary carcinoma or tall cell variant histology, extrathyroidal extension, and more frequent presentation at stages III and IV.</p> <p>All BRAF-positive poorly differentiated and anaplastic carcinomas contained areas of preexisting</p>



<p><b>Cincinnati, Cincinnati, Ohio 45267, USA.</b></p>	<p>papillary carcinoma, and mutation was present in both the well-differentiated and dedifferentiated components.</p> <p>These data indicate that BRAF mutations are restricted to papillary carcinomas and poorly differentiated and anaplastic carcinomas arising from papillary carcinomas. They are associated with distinct phenotypical and biological properties of papillary carcinomas and may participate in progression to poorly differentiated and anaplastic carcinomas.</p>
<p><b>EPSTEIN-BARR VIRUS</b></p>	
<p><b>Expression of Epstein-Barr virus in thyroid carcinoma correlates with tumor progression.</b></p> <p><b>Shimakage M, Kawahara K, Sasagawa T, Inoue H, Yutsudo M, Yoshida A, Yanoma S.</b></p> <p><b>Clinical Research Institute and Department of Pathology, Osaka National Hospital, Japan.</b></p>	<p>Hum Pathol. 2003 Nov;34(11):1170-7. Abstract quote</p> <p>There have been few studies regarding cancer progression from differentiated thyroid carcinoma to the undifferentiated one. To examine the possible involvement of Epstein-Barr virus (EBV) in this progression, 10 papillary carcinomas and 11 undifferentiated carcinomas were subjected to mRNA in situ hybridization, indirect immunofluorescence staining, polymerase chain reaction (PCR), and reverse-transcriptase PCR. mRNA in situ hybridization using a BamHIW probe revealed signals in all of the examined samples, although the signal strength was weaker in the papillary carcinomas than in the undifferentiated carcinomas. EBV nuclear antigen-2 (EBNA2) in situ hybridization produced almost the same results; however, the signals were detected less frequently in the papillary carcinomas. Indirect immunofluorescence using anti-EBNA2, anti-latent membrane protein-1 (LMP1), and anti-BZLF1 antibodies also showed positive results with high frequency and with more prominent fluorescence in undifferentiated carcinomas than in papillary carcinomas.</p> <p>An examination of thyroid carcinoma cell lines also confirmed these findings. EBV infected all of the thyroid carcinomas irrespective of the degree of pathological differentiation. The expression of EBV, especially of EBNA2 and LMP1 (both of which are oncogene products of EBV), was stronger in the undifferentiated carcinomas than in the papillary carcinomas.</p> <p>These results suggest that increased expression of EBV may be involved in the progression of thyroid papillary carcinoma to undifferentiated carcinoma.</p>
<p><b>PAX8-PPAR-GAMMA</b></p>	
<p><b>PAX8-PPAR? Rearrangement in Thyroid Tumors: RT-PCR and Immunohistochemical Analyses</b></p> <p><b>Marina N. Nikiforova, M.D.; Paul W. Biddinger, M.D.; Christy M. Caudill, B.S.; Todd G. Kroll, M.D., Ph.D.; Yuri E. Nikiforov, M.D., Ph.D.</b></p>	<p>Am J Surg Pathol 2002; 26(8):1016-1023 Abstract quote</p> <p>A PAX8-PPAR? rearrangement has been recently identified in follicular thyroid carcinomas, but not in follicular adenomas or other thyroid tumors.</p> <p>We report here the analyses of PAX8-PPAR? in a series of 118 thyroid tumors using a newly developed RT-PCR assay to detect this rearrangement in frozen and paraffin-embedded tissues and using immunostaining with a PPAR? antibody. PAX8-PPAR? was detected by RT-PCR in eight of 15 (53%) follicular carcinomas and two of 25 (8%) follicular adenomas but not in 35 papillary carcinomas (including 12 follicular variants), 12 Hurthle cell carcinomas, 12 Hurthle cell adenomas, two anaplastic carcinomas, one poorly differentiated carcinoma, or 16 hyperplastic nodules. The prevalence was higher in follicular carcinomas from patients with a history of radiation exposure (three of three).</p>

Strong, diffuse nuclear immunostaining with the PPAR $\gamma$  antibody correlated with the presence of PAX8-PPAR $\gamma$  detected by RT-PCR. Most sporadic follicular carcinomas positive for PAX8-PPAR $\gamma$  were overtly invasive, whereas tumors lacking the rearrangement were predominantly minimally invasive. The two follicular adenomas positive for PAX8-PPAR $\gamma$  had trabecular growth pattern and thick capsule, but no invasion, and thus may represent "pre-invasive" follicular carcinomas.

The absence of PAX8-PPAR $\gamma$  rearrangements in Hurthle cell tumors and papillary thyroid carcinomas highlights the differences in the molecular pathogenesis of these thyroid tumors.

**p53**

**Immunohistochemical detection of p53 homolog p63 in solid cell nests, papillary thyroid carcinoma, and hashimoto's thyroiditis: A stem cell hypothesis of papillary carcinoma oncogenesis.**

**Burstein DE, Nagi C, Wang BY, Unger P.**

**Ruttenberg Cancer Center, Mount Sinai School of Medicine, New York, New York, USA.**

Hum Pathol. 2004 Apr;35(4):465-73. Abstract quote

Most models suggest that the cell of origin of papillary carcinoma is the mature thyroid follicular epithelial cell. In a recent study, p63 was detected in papillary carcinoma, Hashimoto's thyroiditis, and in squamoid aggregates and solid cell nests (SCNs), embryonic remnants found sporadically in the fully developed thyroid.

In the present study, the relationship between solid cell nests and papillary carcinoma was investigated further. Four-micrometer sections from 88 routinely fixed and processed archival thyroidectomy specimens were pretreated with citric acid pH 6.0 for antigen retrieval, then incubated overnight with anti-p63 monoclonal antibody 4A4. Slides were stained with a streptavidin-biotin kit and diaminobenzidine as chromogen and were counterstained with hematoxylin. Squamoid aggregates or SCNs were noted in 21 specimens. Several morphologic variants of SCNs were found, all of which displayed p63 positivity. These included undifferentiated SCNs and those displaying commitment toward squamoid and ciliated glandular differentiation. Small, morphologically inconspicuous aggregates of p63-positive cells were commonly found in Hashimoto's thyroiditis.

Commitment of p63-positive undifferentiated cells toward thyroid follicular epithelial differentiation was occasionally noted. One SCN variant, also associated with Hashimoto's thyroiditis, was a floretlike arrangement of p63-positive cells with fusiform nuclei. p63 staining was strong and uniform in some SCNs, but in other SCNs it was compartmentalized and homologous to stem cell-staining patterns in normal squamous or bronchial epithelia. Stem cell-like staining, associated with compartmentalized p63 staining or p63-positive undifferentiated cells, was noted in 7 of 27 papillary carcinomas. p63 immunostaining is a highly sensitive means of detecting SCNs. p63 expression patterns in SCNs and a subset of papillary carcinomas are closely homologous to stem cell-associated p63 staining patterns that have been described elsewhere in squamous and bronchial epithelia.

We propose a stem-cell-associated model of papillary carcinoma oncogenesis that suggests that (1) p63-positive embryonic remnants rather than mature follicular cells are the cells of origin of a subset of papillary carcinomas; (2) these p63-positive cells are pluripotent and may stay undifferentiated or undergo benign squamoid or glandular maturation, may undergo thyroid follicular epithelial differentiation, may undergo oncogenic change leading to papillary carcinoma, or may trigger an immune reaction, resulting in lymphoid infiltration and Hashimoto's thyroiditis; and (3) Hashimoto's thyroiditis and papillary carcinoma may therefore be linked etiologically, because both disorders may

	be initiated by the same population of pluripotent p63-positive embryonal stem cell remnants.
<b>ras MUTATIONS</b>	
<p><b>Molecular Profile and Clinical-Pathologic Features of the Follicular Variant of Papillary Thyroid Carcinoma</b></p> <p><b>An Unusually High Prevalence of ras Mutations</b></p> <p><b>Zhaowen Zhu, MD, PhD, Manoj Gandhi, MD, Marina N. Nikiforova, MD, Andrew H. Fischer, MD, and Yuri E. Nikiforov, MD, PhD</b></p>	<p>Am J Clin Pathol 2003;120:71-77 Abstract quote</p> <p>The follicular variant (FV) of papillary thyroid carcinoma is characterized by a follicular growth pattern and cytologic features of papillary carcinoma. ret/PTC rearrangements are common in classic papillary thyroid carcinoma (PTC) and PAX8-PPARg and ras mutations in follicular thyroid carcinoma. Their prevalence in FV has not been established.</p> <p>We studied these genetic alterations and clinical-pathologic features in 30 FV cases and compared those with 46 non-FV papillary carcinomas. FV cases revealed 1 ret/PTC rearrangement (3%) and 13 ras mutations (43%). Non-FV cases harbored 13 ret/PTC (28%) (P = .006) and no ras mutations (P = .0002). No PAX8-PPARg was found in either group. FV cases demonstrated a significantly higher prevalence of tumor encapsulation, angiovascular invasion, and poorly differentiated areas and a lower rate of lymph node metastases.</p> <p>These data indicate that the FV of papillary carcinoma has a distinct set of molecular alterations and is characterized by a high frequency of ras point mutations.</p>

<b>RET/PTC</b>	
<p><b>Prevalence of RET/PTC Rearrangements in Hashimoto's Thyroiditis and Papillary Thyroid Carcinomas.</b></p> <p><b>Nikiforova MN, Caudill CM, Biddinger P, Nikiforov YE.</b></p> <p><b>Department of Pathology and Laboratory Medicine, University of Cincinnati, Cincinnati, OH, USA.</b></p>	<p>Int J Surg Pathol 2002 Jan;10(1):15-22 Abstract quote</p> <p>The relationship between Hashimoto's thyroiditis (HT) and follicular cell-derived thyroid cancer remains unclear. Recently, 2 studies reported a 95% prevalence of RET/PTC rearrangements in histologically benign tissue affected by HT, suggesting that multiple occult tumors exist in HT patients with high frequency.</p> <p>We tested the prevalence of RET/PTC rearrangements in 26 HT, in 6 papillary carcinomas arising in the background of HT, and in 27 papillary carcinomas not associated with HT. We detected no RET/PTC rearrangements in HT or papillary carcinomas arising in the background of HT, in contrast to a 33% prevalence among papillary carcinomas not associated with HT. However, the expression of wild-type RET was found in more than half of papillary carcinomas.</p> <p>These results suggest that, if the association between HT and thyroid cancer exists, its molecular basis is different from RET/PTC rearrangement.</p>

<b>CLINICAL AND GROSS VARIANTS</b>	<b>CHARACTERIZATION</b>
<b>GENERAL</b>	The tumor has a variable appearance on cut sections, usually averaging 2-3 cm. They are usually white with some calcifications and may resemble a scar. Other tumors may form cysts with
<b>VARIANTS</b>	

<b>THYROGLOSSAL DUCT CYST</b>	
<p><b>Papillary thyroid carcinoma of the thyroglossal duct cyst: comparative cytohistologic and immunochemical study of 2 new cases and review of the literature.</b></p> <p><b>Falconieri G, Della Libera D, Zanella M.</b></p> <p><b>Division of Anatomic Pathology, City Hospital, Conegliano TV, Italy.</b></p>	<p>Int J Surg Pathol 2001 Jan;9(1):65-71 Abstract quote</p> <p>We report a cytohistologic and immunohistochemical study of 2 cases of papillary thyroid carcinoma occurring in a thyroglossal duct cyst.</p> <p>The patients were a 21-year-old woman and a 48-year-old man. Needle aspiration cytology smears were consistent with papillary thyroid carcinoma. The Sistrunk procedure was done. Papillary carcinoma was found within a thyroglossal duct cyst. In 1 case, the tumor spread outside the cyst. Follow-up was uneventful in both patients (2 and 9 years, respectively).</p> <p>Our results would indicate that papillary carcinoma of thyroglossal duct cyst, though indistinguishable from its thyroid homologue, has a more indolent course and could therefore be singled out as a clinicopathologic entity. Needle aspiration cytology reliably assists in planning patient management.</p>

<b>HISTOLOGICAL TYPES</b>	<b>CHARACTERIZATION</b>
<b>GENERAL</b>	<p>Under the microscope, the tumor is composed papillae with a central fibrovascular core lined by oval nuclei, many of which have an optically clear nucleus, sometimes referred to as <i>Orphan Annie-eye nuclei</i>. Psammoma bodies, characterized by lamellated calcifications, are usually common. Nuclear grooves are also common. These tumors may invade the glandular lymphatics resulting in spread within the gland itself leading to multifocal tumors.</p>
<b>CYTOLOGY</b>	
<p><b>Cellular swirls in fine needle aspirates of papillary thyroid carcinoma: a new diagnostic criterion.</b></p> <ul style="list-style-type: none"> <li>• Szporn AH,</li> <li>• Yuan S,</li> <li>• Wu M,</li> <li>• Burstein DE.</li> </ul> <p><b>1Division of Cytopathology, Department of Pathology, Mount Sinai School of Medicine, New York, NY, USA.</b></p>	<p>Mod Pathol. 2006 Nov;19(11):1470-3. Epub 2006 Sep 1. Abstract quote</p> <p>No single cytologic feature is specifically diagnostic for papillary thyroid carcinoma. We report herein the presence of swirl-like cellular aggregates in fine needle aspirates of papillary thyroid carcinoma but not in other thyroid entities. Cellular swirls are defined as concentrically organized aggregates of tumor cells in which many of the most peripherally situated cells have ovoid rather than round nuclei that are oriented perpendicular to the radius of the swirl.</p> <p>One hundred Papanicolaou- and/or Diff-Quik-stained FNAs of the thyroid diagnosed as papillary carcinoma, including seven fine needle aspirates of cervical lymph nodes showing metastatic papillary carcinoma, with or without cell blocks, were reviewed for the presence of cellular swirls. An additional 100 thyroid FNAs, similarly stained and prepared, diagnosed as nodular goiter, Hashimoto's thyroiditis and follicular neoplasm were also reviewed for the presence of cellular swirls. Cellular swirls were easily observed at screening magnification and confirmed at high magnification.</p> <p>Seventeen of 100 FNAs (17%) of papillary carcinoma contained cellular swirls. No cases diagnosed as nodular goiter, Hashimoto's thyroiditis or follicular neoplasm contained these structures. Thirteen cases with swirls had histologic follow-up. These comprised seven papillary carcinomas with classical histopathology, two designated 'differentiated papillary carcinoma,' two with follicular variant histopathology; one with a minor component of follicular variant histopathology; one papillary</p>

	<p>carcinoma metastatic to a cervical lymph node with classic histopathology. Swirls occurred in cases with relatively little pleomorphism, or in well-differentiated regions of papillary carcinoma that also displayed less well-differentiated components.</p> <p>Cellular swirls are a finding that is highly specific to papillary thyroid carcinoma. They are easily seen at screening magnification. Their presence in a FNA specimen may be helpful in cases where classic criteria for papillary thyroid carcinoma are scarce, particularly in well-differentiated papillary thyroid carcinoma.</p> <p>While the size and scope of this study are insufficient to conclude that cellular swirls alone are diagnostic of papillary thyroid carcinoma in the absence of other criteria, we believe these structures should be added to the list of diagnostic criteria.</p>
<p><b>Fine-needle aspiration of papillary thyroid carcinoma: distinguishing between cases that performed well and those that performed poorly in the College of American Pathologists Nongynecologic Cytology Program.</b></p> <p><b>Renshaw AA, Wang E, Haja J, Wilbur D, Henry MR, Hughes JH; Cytopathology Committee, College of American Pathologists.</b></p> <p><b>Department of Pathology, Baptist Hospital of Miami, Miami, FL 33176-2197, USA.</b></p>	<p><a href="#">Arch Pathol Lab Med</a>. 2006 Apr;130(4):452-5. Abstract quote</p> <p>CONTEXT: Although the cytologic features of papillary thyroid carcinoma in fine-needle aspiration specimens are well known, the correlation of these features with the ability of cytologists to identify this tumor has not been well studied.</p> <p>OBJECTIVE: To compare the cytologic features of cases of papillary thyroid carcinoma that performed poorly with those of cases that performed well.</p> <p>DESIGN: The cytologic features of 13 cases of papillary thyroid carcinoma from the College of American Pathologists Nongynecologic Cytology Program that performed poorly were compared with those of 15 cases that performed well.</p> <p>RESULTS: Compared with cases that performed well, cases that performed poorly were significantly more likely to lack marked nuclear enlargement (38% vs 100%, <math>P &lt; .001</math>), lack pale chromatin (8% vs 47%, <math>P = .04</math>), and lack intranuclear inclusions (8% vs 53%, <math>P = .02</math>). The differences between the 2 groups in staining, type of preparation, nuclear grooves, nuclear crowding, colloid, cellularity, nuclear pleomorphism, and Hurthle cell change were not significant.</p> <p>CONCLUSIONS: Cases of papillary thyroid carcinoma that lack marked nuclear enlargement, pale chromatin, and intranuclear inclusions are significantly more difficult to recognize than cases that have these features. Increased awareness of these types of cases might improve the performance of thyroid fine-needle aspiration in clinical practice.</p>
<p><b>Focal Features of Papillary Carcinoma of the Thyroid in Fine-Needle Aspiration Material Are Strongly Associated With Papillary Carcinoma at Resection</b></p>	<p><a href="#">Am J Clin Pathol</a> 2002;118:208-210 Abstract quote</p> <p>The cytologic features of papillary carcinoma of the thyroid in fine-needle aspiration material have been well described. The significance of finding these features in only a small population of cells is not well characterized. I reviewed the results of 28 thyroid fine-needle aspirates processed as direct smears and cell blocks in which only a small population (&lt;20 cells) showed features of papillary carcinoma.</p>

<p><b>Andrew A. Renshaw, MD</b></p>	<p>Papillary carcinoma was considered in 142 (8.98%) of 1,581 aspirates, and in 28 cases (1.77%), 20 cells or fewer showed features of papillary carcinoma and follow-up was available. Papillary carcinomas greater than 1 cm were identified in 11 cases (39%; 3 follicular variants), papillary carcinomas less than 1 cm were identified in 4 cases (14%), and benign lesions in the remaining 13 cases (46%). The background material (either scant or abundant benign epithelium) did not correlate significantly with the result of resection.</p> <p>Identifying features of papillary carcinoma in a small population of cells in either a scant or an abundant thyroid aspirate are associated with a high rate of papillary carcinomas at resection, only a minority of which represent either the follicular variant or incidental tumors.</p>
<p><b>VARIANTS</b></p>	
<p><b>CLEAR CELL</b></p>	
<p><b>COLUMNAR CELL</b></p>	<p>Usually &gt;6 cm  Papillae lined by tall columnar cells with hyperchromatic nuclei and stippled chromatin  Mitoses common  Extrathyroidal extension and distant mets common  Poor prognosis with death within 5 years</p>
<p><b>CRIBRIFORM</b></p>	
<p><b>Somatic but Not Germline Mutation of the APC Gene in a Case of Cribriform-Morular Variant of Papillary Thyroid Carcinoma José Cameselle-Teijeiro, et al.</b></p>	<p>Am J Clin Pathol 2001;115:486-493 Abstract quote</p> <p>We report a case of cribriform-morular variant (C-MV) of papillary thyroid carcinoma (PTC) in a 27-year-old woman. In addition to conventional cytologic features of typical PTC, the fine-needle aspirate showed numerous epithelial cells with abundant, eosinophilic, very elongated cytoplasm.</p> <p>Microscopically, the tumor was encapsulated and highly cellular and exhibited a mixture of cribriform, follicular, papillary, trabecular, solid, and spindle cell patterns of growth, with morular foci showing peculiar nuclear clearing (biotin-rich nuclei). The cells were cuboidal or tall, with frequent nuclear pseudostratification and abundant eosinophilic cytoplasm. The nuclei were usually hyperchromatic, with grooving, pallor, and pseudoinclusions. Angioinvasion and foci of capsular invasion were observed. Immunohistochemically, the neoplastic cells showed reactivity for thyroglobulin, epithelial membrane antigen, low- and high-molecular-weight cytokeratins, vimentin, neuron-specific enolase, CD15, estrogen and progesterone receptors, and bcl-2 protein. Molecular genetic analysis of the APC gene revealed a mutation in exon 15 at codon 1309 in tumoral tissue but not in peripheral lymphocytes.</p> <p>These findings support a relationship between the morphologic pattern of the C-MV of PTC and the APC gene and the existence of this variant as a sporadic counterpart of familial adenomatous polyposis-associated thyroid carcinoma.</p>
<p><b>DIFFUSE SCLEROSIS</b></p>	<p>Common in children and young adults, may present with bilateral goiter  Frequent local recurrence  Frequent extrathyroidal extension with distant and nodal mets  More aggressive than usual papillary CA</p>

<b>ELASTOSIS</b>	
<p><b>Stromal elastosis in papillary thyroid carcinomas.</b></p> <p><b>Kondo T, Nakazawa T, Murata S, Katoh R.</b></p>	<p>Hum Pathol. 2005 May;36(5):474-9. Abstract quote</p> <p>Summary Stromal elastosis, defined as dense aggregations of elastic fibers, is found in some neoplastic tissues especially in malignant tumors of the breast and lung. Although also found in thyroid tissue, stromal elastosis in thyroid neoplasms have received little attention.</p> <p>To clarify the histopathological significance of stromal elastosis in the thyroid, we examined neoplastic (n = 223) and hyperplastic (n = 82) thyroid tissues in conjunction with cancer tissues (n =193) of various other organs. Stromal elastosis was observed as deposits of pale homogeneous material in hematoxylin and eosin stain, and distinctively highlighted by elastic-van Gieson's stain.</p> <p>On immunohistochemical examination, elastin and tropoelastin were confirmed in these deposits. Stromal elastosis was found in 66% of papillary thyroid carcinomas (PTCs), although it was not identified in other histological types of thyroid neoplasms. In PTCs, deposits of elastic fibers varied in size and shape, and were more frequently distributed in the periphery of the tumor tissue. The histological subtypes of PTC varied in prevalence of elastosis with the follicular variant's (9%) prevalence being significantly lower than that of the classical type (72%). The frequency of stromal elastosis in PTCs was very similar to the frequencies in breast and lung adenocarcinomas, and higher than the frequencies in carcinomas of other organs.</p> <p>In conclusion, our results suggest that stromal elastosis is a characteristic histological finding of PTCs, presumably associated with their growth pattern and/or histological architecture. It is, therefore, reasonable to propose that stromal elastosis is an ancillary feature in the histopathological diagnosis of PTCs.</p>
<b>FASCIITIS-LIKE STROMA</b>	
<b>FOLLICULAR VARIANT</b>	<p>Architectural growth pattern of a follicular tumor with cytologic features of papillary carcinoma, including psammoma bodies</p> <p>Same prognosis as ordinary variants but may have greater risk to metastasize outside of the neck and to have vascular invasion</p> <p>May be subdivided into a diffuse follicular variant which is aggressive with lymph node and distant mets and an encapsulated variant which has an excellent prognosis</p>
	<p>Total encapsulation of tumor</p> <p>Good prognosis</p>
<p><b>Observer Variation in the Diagnosis of Follicular Variant of Papillary Thyroid Carcinoma.</b></p> <p><b>Lloyd RV, Erickson LA, Casey MB,</b></p>	<p>Am J Surg Pathol. 2004 Oct;28(10):1336-1340. Abstract quote</p> <p>The histopathologic diagnosis of follicular variant of papillary thyroid carcinoma (FVPCA) can be difficult. Recent reports have suggested that this neoplasm may be frequently overdiagnosed by pathologists. We examined the observer variation in the diagnosis of FVPCA in 87 tumors by 10</p>

Lam KY, Lohse CM, Asa SL, Chan JK, DeLellis RA, Harach HR, Kakudo K, LiVolsi VA, Rosai J, Sebo TJ, Sobrinho-Simoes M, Wenig BM, Lae ME.

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experienced thyroid pathologists.

The criteria that the reviewers considered most helpful for making a diagnosis of FVPCA were also assessed. A concordant diagnosis of FVPCA was made by all 10 reviewers with a cumulative frequency of 39%. In this series, 24.1% of the patients had metastatic disease (n = 21). In the cases with metastatic disease, a diagnosis of FVPCA was made by all 10 reviewers with a cumulative frequency of 66.7%, and 7 of the reviewers made a diagnosis of FVPCA with a cumulative frequency of 100%. The most important criteria used to diagnose FVPCA included the presence of cytoplasmic invaginations into the nucleus (pseudo-inclusions), abundant nuclear grooves, and ground glass nuclei.

These results suggest that although the diagnosis of FVPCA is variable even among experienced thyroid pathologists, most reviewers agreed on this diagnosis for patients with metastatic disease. The use of well-defined histopathologic features should improve the consistency in diagnosing FVPCA. Since most cases with metastatic disease had obvious invasion, caution should be used in making a diagnosis of FVPCA in the absence of the major histopathologic features or clear-cut invasive growth.

**Macrofollicular variant of papillary carcinoma of the thyroid: a histologic, cytologic, and immunohistochemical study of 3**

Arch Pathol Lab Med. 2004 Jan;128(1):54-8. Abstract quote

CONTEXT: The macrofollicular variant of papillary carcinoma of the thyroid is a rare entity described by J. Albores-Saavedra and colleagues in 1991. It is characterized histologically by a predominance of



<p><b>cases and review of the literature.</b></p> <p><b>Lugli A, Terracciano LM, Oberholzer M, Bubendorf L, Tornillo L.</b></p>	<p>macrofollicles and clinically by a low incidence of metastasis. This entity may represent a source of diagnostic error, since it can be easily misinterpreted as a macrofollicular adenoma or nodular goiter.</p> <p>DESIGN: In this study, we describe 3 cases of papillary carcinoma of the thyroid with a macrofollicular growth pattern and review the literature.</p> <p>RESULTS: The fine-needle aspiration biopsies in 2 cases showed large cells with optically clear nuclei and nuclear grooves, suggestive of papillary carcinoma of the thyroid. In one case, the cytology showed no signs of malignancy. In all cases, the tumors showed a combination of the conventional follicular variant of papillary carcinoma of the thyroid and macrofollicles (diameter, &gt;250 microm) occupying more than 50% of the cross-sectional area. Cytologic features were large, cuboidal cells with optically clear, ground-glass nuclei with smooth outlines, a fine chromatin pattern, nuclear grooves, and pseudoinclusions. The colloid was dense and more eosinophilic than in adjacent normal follicles. In 2 cases, there was capsular or blood vessel infiltration, and one tumor had metastasized to a cervical lymph node. One tumor recurred 1 year later as an anaplastic carcinoma.</p> <p>Immunohistochemical staining showed a positivity of the tumor cells for cytokeratins 7, 17, and 19, thyroid transcription factor-1, and galectin-3 and a negativity for cytokeratin 20 and p53.</p> <p>CONCLUSIONS: Although it has been suggested that this tumor is a highly differentiated variant with a favorable prognosis, our study shows that its biologic behavior is not conclusive because metastases and recurrences with dedifferentiation may occur.</p>
	<p>Am J Clin Pathol 2002;117:16-18</p> <p>(1) Nuclei are ovoid rather than round  (2) Nuclei are crowded, often manifesting as lack of polarization in the cells that line a follicle  (3) Nuclei show a clear or pale chromatin pattern (nuclear clearing should not be confined to the central portion of the tumor, where artifactual bloating of the nuclei is common due to delayed fixation), or they exhibit prominent grooving  (4) Psammoma bodies are found.</p> <p>If 1 of these 4 features is lacking, 4 or more of the following subsidiary features have to be present for a diagnosis of encapsulated follicular variant PTC to be made: (1) presence of abortive papillae, (2) predominantly elongated or irregularly shaped follicles, (3) dark-staining colloid, (4) presence of rare nuclear pseudoinclusions, and (5) multinucleated histiocytes in lumens of follicles.</p>
<p><b>LIPOMATOUS STROMA</b></p>	
<p><b>MYXOID</b></p>	
<p><b>OXYPHILIC (HURTHLE CELL)</b></p>	
<p><b>PAPILLARY MICROCARCINOMA (Occult papillary carcinoma)</b></p>	<p>Measure 1-1.5 cm or less with majority measuring 4-7 mm.  Lymph node mets have been documented in tumors as small as 5 mm  May have prominent sclerosis</p>
<p><b>Microscopic papillary thyroid</b></p>	<p>Am J Surg Pathol 2003 Feb;27(2):159-66 Abstract quote</p>

<p><b>carcinoma compared with clinical carcinomas by loss of heterozygosity mutational profile.</b></p> <p><b>Hunt JL, LiVolsi VA, Baloch ZW, Barnes EL, Swalsky PA, Niehouse L, Finkelstein SD.</b></p>	<p>The clinical significance of microscopic papillary thyroid carcinoma (PTCa) is controversial. Many authors think that microscopic PTCa (&lt;1 cm) have the same pathogenetic origin as clinically sized papillary carcinomas (&gt;1 cm). Despite the fact that all clinical risk prognostication schemes have the size of the tumor as a primary category, small tumors do have malignant potential and can metastasize. There is growing evidence that small PTCa have the molecular translocations between the proto-oncogene RET and various activating partner genes that are characteristic of clinically sized PTCa.</p> <p>This study used a microdissection and genotyping assay to study the patterns of loss of heterozygosity of tumor suppressor genes in microscopic and clinically sized PTCa.</p> <p>Our results indicate that all PTCa harbor mutations with similar frequencies and distribution patterns, regardless of the size of the tumor. These data are further evidence that microscopic and clinically sized PTCa are pathogenetically related.</p>
<p><b>SARCOMATOID</b></p>	
<p><b>Spindle cell transformation of papillary carcinoma: an aggressive entity distinct from anaplastic thyroid carcinoma.</b></p> <p><b>Brandwein-Gensler MS, Wang BY, Urken ML.</b></p> <p><b>Department of Pathology, The Mount Sinai School of Medicine, The Mount Sinai New York University Medical Center, New York, NY 10029, USA.</b></p>	<p>Arch Pathol Lab Med. 2004 Jan;128(1):87-9. Abstract quote</p> <p>Spindle cells are not routinely encountered in the context of thyroid pathology and are most often present in anaplastic thyroid carcinoma, medullary thyroid carcinoma, and benign conditions such as Riedel struma or de Quervain granulomatous thyroiditis. Only a few publications have reported papillary thyroid carcinoma admixed with a prominent spindle cell component.</p> <p>While these tumors are clearly distinct from anaplastic thyroid carcinoma, prognostication as to their oncologic potential is not yet established. We describe a unique case of spindle cell transformation of papillary thyroid carcinoma. The blandness of the spindle cells was so impressive as to dissuade us from a malignant diagnosis on preoperative biopsies. However, this patient unfortunately died shortly after transformation of this papillary thyroid carcinoma.</p> <p>We conclude that this peculiar and rare spindle cell transformation should be regarded as a potentially lethal variant of papillary thyroid carcinoma.</p>
<p><b>SOLID</b></p>	<p>Common in children</p> <p>Solid areas must be &gt;50% of the tumor</p> <p>May be more aggressive</p>
<p><b>A new BRAF gene mutation detected in a case of a solid variant of papillary thyroid carcinoma.</b></p> <p><b>Trovisco V, Soares P, Soares R, Magalhaes J, Sa-Couto P, Sobrinho-Simoes M.</b></p>	<p>Hum Pathol. 2005 Jun;36(6):694-7. Abstract quote</p> <p>Summary BRAF gene mutations have been frequently detected in papillary thyroid carcinoma (PTC). Moreover, there is a close association between the type of mutation and the PTC histotype: BRAF V600E is associated with conventional PTC and with histological variants of PTC displaying a prominent papillary growth pattern, whereas BRAF K601E is associated with the follicular variant of PTC.</p> <p>We report the detection of a novel BRAF triplet deletion in a case of PTC displaying a predominantly solid growth pattern. The deletion leads to the replacement of a valine and a lysine by a glutamate in</p>

	<p>the BRAF activation segment (BRAF VK600-1E ), thus mimicking partially the 2 BRAF mutations previously described.</p> <p>Our study reinforces the existence of a close relationship between the occurrence of some types of BRAF mutation and some PTC histotypes. The genetic study of more cases of the solid variant of PTC is necessary to find whether there exists a significant association between the occurrence of BRAF VK600-1E and such PTC histotype.</p>
<p><b>Solid Variant of Papillary Thyroid Carcinoma Incidence, Clinical–Pathologic Characteristics, Molecular Analysis, and Biologic Behavior</b></p> <p><b>Yuri E. Nikiforov, M.D. , Ph.D. ; Lori A. Erickson, M.D. ; Marina N. Nikiforova, M.D. ; Christy M. Caudill, B.S. ; Ricardo V. Lloyd, M.D. , Ph.D.</b></p> <p><b>From the Department of Pathology and Laboratory Medicine (Y.E.N., M.N.N., C.M.C.), University of Cincinnati, Cincinnati, Ohio; and the Department of Laboratory Medicine and Pathology (L.A.E., R.V.L.), Mayo Clinic, Rochester, Minnesota, U.S.A.</b></p>	<p>Am J Surg Pathol 2001;25:1478-1484 Abstract quote</p> <p>Solid variant is a rare and poorly characterized variant of papillary thyroid carcinoma. In this study we analyzed 20 primary cases of the solid variant of papillary carcinoma found in a series of 756 papillary carcinomas operated at the Mayo Clinic between 1962 and 1989. The criteria for classification included predominantly (&gt;70%) solid growth pattern of primary tumor, retention of cytologic features typical of papillary carcinoma, and absence of tumor necrosis.</p> <p>For each case of the solid variant, a control case of classical papillary carcinoma matched by age, sex, tumor size, and length of follow-up was selected. The follow-up ranged from 6 to 32 years. Two patients with the solid variant of papillary carcinoma (10%) died from disease 7 and 10 years after initial surgery, while another two patients (10%) are alive with lung metastases. In contrast, the control group had no cases with distant metastases or death from disease. Molecular analyses showed a similar prevalence of RET /PTC rearrangements in both groups.</p> <p>In conclusion, the solid variant of papillary carcinoma is associated with a slightly higher frequency of distant metastases and less favorable prognosis than classical papillary carcinoma. However, it should be distinguished from poorly differentiated thyroid carcinoma, which has a reported lower survival rate compared with the solid variant of papillary carcinoma.</p>
<p><b>SPINDLE CELL METAPLASIA</b></p>	
<p><b>Spindle Cell Metaplasia of the Thyroid Arising in Association With Papillary Carcinoma and Follicular Adenoma</b></p> <p><b>JoAnne Vergilio, MD, Zubair W. Baloch, MD, PhD, and Virginia A. LiVolsi, MD</b></p>	<p>Am J Clin Pathol 2002;117:199-204 Abstract quote</p> <p>Spindle cell proliferations of the thyroid have been described in association with reactive processes and aggressive malignant neoplasms.</p> <p>We describe spindle cell proliferations in 10 patients arising in association with papillary carcinoma and follicular adenoma. The spindle proliferations were 0.3 to 3.0 cm in size, constituted from 1% to 95% of the primary neoplasm, and were either admixed with the neoplastic elements or peripherally located within the primary tumor.</p> <p>Cytologically, these proliferations showed bland-appearing spindle cells with fine chromatin and subtle nucleoli. Mitoses were rare, and inflammation was minimal. Immunostains showed reactivity with thyroglobulin, indicating their follicular origin. We believe it is important to recognize these metaplastic proliferations and distinguish them from aggressive malignant neoplasms.</p>
<p><b>TALL CELL</b></p>	<p>Usually &gt;6 cm with frequent extrathyroidal extension, increased mitotic figures, and vascular invasion</p> <p>More frequent in older patients</p> <p>Histology of cells which are twice as tall as it is wide, these cells should comprise &gt;30% of the tumor</p>

<p><b>Prevalence and prognostic significance of tall cell variant of papillary thyroid carcinoma.</b></p> <ul style="list-style-type: none"> <li>• <a href="#">Michels JJ</a>,</li> <li>• <a href="#">Jacques M</a>,</li> <li>• <a href="#">Henry-Amar M</a>,</li> <li>• <a href="#">Bardet S</a>.</li> </ul> <p><b>Department of Pathology, Centre Francois Baclesse, 14016 Caen Cedex 05, France.</b></p>	<p><a href="#">Hum Pathol</a>. 2007 Feb;38(2):212-9. Epub 2006 Nov 13. Abstract quote</p> <p>The aim of this study was to assess the prevalence, prognostic factors, and long-term outcome of tall cell variant (TCV) in comparison with the conventional forms of papillary thyroid carcinoma (PTC). A total of 945 patients with thyroid cancer were treated and followed up from 1960 to 1998.</p> <p>Pathologic review was performed in 778 patients (84%) of the cohort. Of these, 674 had PTC: 503 (74%) had conventional form (CF); 56 (8%), TCV; and 155 (17%), other variants of PTC. Tall cell variant was associated with tumors of larger size (<math>P &lt; .001</math>), bilaterality (<math>P &lt; .02</math>), multifocality (<math>P &lt; .04</math>), and extrathyroidal invasion (<math>P &lt; .001</math>). Treatment was similar in both groups, but neck dissection was performed more frequently in patients with TCV (<math>P &lt; .04</math>).</p> <p>The 10-year overall and event-free survival rates were, respectively, 90% and 85% in the CF versus 79% and 67% in the TCV group (<math>P &lt; .001</math>). Histologic subtype did not have an effect on clinical outcome after multivariate analysis, the most relevant factors being age, involved nodes, or the "Metastasis, Age, Completeness, Invasion, Size" classification after multivariate analysis.</p> <p>In this large cohort of patients, TCV represents 8.3% of PTC, and it is a more aggressive form of PTC than CF because of the higher stage and increased grade.</p>
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<b>SPECIAL STAINS/ IMMUNOPEROXIDASE</b>	<b>CHARACTERIZATION</b>
<b>CYTOKERATIN</b>	
<b>Cytokeratin 19 immunolocalization in cell block preparation of thyroid aspirates. An adjunct to fine-needle aspiration diagnosis of</b>	<p><a href="#">Arch Pathol Lab Med</a> 2003 May;127(5):579-83 Abstract quote</p> <p>CONTEXT: Immunohistochemical staining for cytokeratin 19 (CK-19) is a useful ancillary technique for diagnosing papillary thyroid carcinoma (papillary carcinoma) in histologic specimens. Although similar results have been obtained on aspirate smears, to our knowledge the utility of CK-19 immunolocalization in cell block preparations as an adjunct to fine-needle aspiration diagnosis of</p>

<p><b>papillary thyroid carcinoma.</b></p> <p><b>Khurana KK, Truong LD, LiVolsi VA, Baloch ZW.</b></p> <p><b>Department of Pathology, State University of New York Upstate Medical University Hospital, Syracuse 13210, USA.</b></p>	<p>papillary carcinoma has not been examined.</p> <p><b>OBJECTIVE:</b> The purpose of this study was to determine whether CK-19 immunostaining of cell block preparations of thyroid aspirates is a useful ancillary technique for diagnosing papillary carcinoma.</p> <p><b>MATERIALS AND METHODS:</b> Using a monoclonal antibody to CK-19 and a standard avidin-biotin complex technique, immunostaining was performed on paraffin-embedded cell blocks of 57 cases with the following cytologic diagnoses: (a) papillary carcinoma (20 cases); (b) atypical cytology, cannot exclude papillary carcinoma (19 cases); and (c) nonneoplastic thyroid (18 cases). The staining reaction in each case was graded on the basis of percentage of epithelial cells stained (1+, &lt;10%; 2+, &lt;10%-50%; 3+, &gt;50). Tissue follow-up was available in all cases.</p> <p><b>RESULTS:</b> Nineteen (95%) of 20 cases with an unequivocal diagnosis of papillary carcinoma were positive for CK-19 (3+). Tissue follow-up confirmed papillary carcinoma in all 20 cases. Of the 19 cases with a diagnosis of atypical cytology, cannot exclude papillary carcinoma, 7 (37%) cases displayed 3+ immunostaining and subsequent excision confirmed papillary carcinoma in all 7 cases. The remaining 12 cases with 1+ immunostaining included surgically confirmed goiter (6 cases), adenoma (2 cases), lymphocytic thyroiditis (3 cases), and papillary carcinoma (1 case). The follicular cells in 18 cases with a cytologic diagnosis of nonneoplastic thyroid showed 1+ immunostaining. Histologic follow-up of these cases confirmed the nonneoplastic cytologic diagnoses.</p> <p><b>CONCLUSIONS:</b> Cytokeratin 19 immunostaining of cell block preparations of thyroid aspirates serves as a useful tool for the diagnosis of papillary carcinoma. Strong immunostaining (3+) for CK-19 aids in accurate diagnosis of malignancy in cytomorphologically equivocal cases of papillary carcinoma.</p>
<p><b>Hyalinizing Trabecular Adenoma and Papillary Carcinoma of the Thyroid Gland Express Different Cytokeratin Patterns</b></p> <p><b>Mitsuyoshi Hirokawa, M.D., Ph.D.; J. Aidan Carney, M.D., Ph.D.; Yuji Ohtsuki, M.D., Ph.D.</b></p> <p><b>From the Department of Pathology, University of Tokushima School of Medicine, Tokushima, Japan (M.H.); Department of Laboratory Medicine and Pathology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, U.S.A. (J.A.C.); and Second Department of Pathology, Kochi Medical School, Kochi, Japan (Y.O.).</b></p>	<p>Am J Surg Pathol 2000;24:877-881 Abstract quote</p> <p>It has recently been suggested that hyalinizing trabecular adenoma of the thyroid is an encapsulated variant of papillary carcinoma because of certain similarities of their histology, the occasional occurrence of both tumors in the same gland, and their similar pattern of expression of cytokeratins, including staining for cytokeratin 19.</p> <p>To investigate this notion further, we examined immunocytochemically the expression of a series of cytokeratins in 12 hyalinizing trabecular adenomas and six papillary carcinomas. Hyalinizing trabecular adenoma showed no or minimal reactivity for cytokeratin 19, whereas papillary carcinoma was almost always strongly reactive. Also, hyalinizing trabecular adenoma showed no staining for high-molecular-weight (HMW) cytokeratin, whereas papillary carcinoma was strongly positive.</p> <p>Thus, there are different patterns of cytokeratin 19 and HMW cytokeratin expression in hyalinizing trabecular adenoma and papillary carcinoma. The findings do not support the suggestion that hyalinizing trabecular adenoma is an encapsulated variant of papillary carcinoma.</p>
<p><b>Immunohistochemical Diagnosis of Papillary Thyroid Carcinoma</b></p> <p><b>Carol C. Cheung, et al.</b></p>	<p>Mod Pathol 2001;14:338-342 Abstract quote</p> <p>In thyroid, the diagnosis of papillary carcinoma (PC) is based on nuclear features; however, identification of these features is inconsistent and controversial. Proposed markers of PC include HBME-1, specific cytokeratins (CK) such as CK19, and ret, the latter reflecting a ret/PTC</p>

	<p>rearrangement.</p> <p>We applied immunohistochemical stains to determine the diagnostic accuracy of these three markers. Formalin-fixed, paraffin-embedded tissue from 232 surgically resected thyroid nodules included 40 hyperplastic nodules (NH), 35 follicular adenomas (FA), 138 papillary carcinomas (PC; 54 classical papillary tumors and 84 follicular variant papillary carcinomas [FVPC]), 4 follicular carcinomas (FC), 6 insular carcinomas (IC), 7 Hürthle cell carcinomas (HCC), and 2 anaplastic carcinomas (AC). HBME-1 and ret were negative in all NH and FA; some of these exhibited focal CK19 reactivity in areas of degeneration. Half of the FC and AC exhibited HBME-1 staining but no positivity for CK19 or ret. In PC, 20% of cases stained for all three markers.</p> <p>Classical PC had the highest positivity with staining for HBME-1 in 70%, CK19 in 80%, and ret in 78%. FVPC were positive for HBME-1 in 45%, for CK19 in 57%, and for ret in 63%; only 7 FVPC were negative for all three markers. The six IC exhibited 67% staining for HBME-1 and 50% positivity for CK19 and ret. The seven HCC had 29% positivity for HBME-1 and CK19, and 57% positivity for ret.</p> <p>This panel of three immunohistochemical markers provides a useful means of diagnosing PC. Focal CK19 staining may be found in benign lesions, but diffuse positivity is characteristic of PC. HBME-1 positivity indicates malignancy but not papillary differentiation. Only rarely are all three markers negative in PC; this panel therefore provides an objective and reproducible tool for the analysis of difficult thyroid nodules.</p>
<p><b>Cytokeratin 19 Immunoreactivity in the Diagnosis of Papillary Thyroid Carcinoma A Note of Caution</b></p> <p><b>Sunati Sahoo, MD</b>  <b>Syed A. Hoda, MD</b>  <b>Juan Rosai, MD</b>  <b>Ronald A. DeLellis, MD</b></p>	<p>Am J Clin Pathol 2001;116:696-702 Abstract quote</p> <p>To evaluate the expression of cytokeratin (CK) 19, we stained sections obtained from formalin-fixed, paraffin tissue blocks of 35 thyroid tumors (follicular adenoma [FA], 20; papillary thyroid carcinoma [PTC], 10 follicular variant [FV] and 5 usual type) and scored the extent of staining as follows: 1+ (&lt;5% positively stained cells), 2+ (5%-25% positively stained cells), 3+ (25%-75% positively stained cells), and 4+ (&gt;75% positively stained cells).</p> <p>All 15 PTCs (including 10 FV-PTCs) were CK19 positive: 14 were 4+ and 1 (FV-PTC) was 2+. All 20 FAs also were CK19 positive: 15 were 1+, 1 was 2+, 4 were 3+, and none were 4+. In the FAs that were scored 1+, reactivity usually was confined to follicular cells lining cystically dilated atrophic follicles that lacked the typical nuclear features of PTC. The remaining FAs showed more diffuse reactivity, which was, however, less intense than that observed in the PTCs.</p> <p>Thus, immunoreactivity for CK19 is not specific for PTC, although we acknowledge that the extent and intensity of staining are considerably greater in this tumor than in FA. There were no significant differences in staining for CK19 between nonneoplastic follicles adjacent to PTCs and those adjacent to FAs.</p>
<p><b>p75 NEUROTROPHIN RECEPTOR</b></p>	
<p><b>The p75 neurotrophin receptor is widely expressed in conventional papillary thyroid carcinoma.</b></p> <p><b>Rocha AS, Risberg B, Magalhaes J, Trovisco V, de Castro IV, Lazarovici P, Soares P, Davidson B, Sobrinho-Simoes M.</b></p> <p><b>IPATIMUP-Institute of Molecular</b></p>	<p>Hum Pathol. 2006 May;37(5):562-8 Abstract quote.</p> <p>Papillary thyroid carcinomas (PTCs) are associated with alterations in several proto-oncogenes related with nervous system development and function, such as TrkA and RET, which are commonly rearranged in these carcinomas. The other oncogenic event recently identified in PTC is the BRAF V600E mutation.</p> <p>Because the role of TrkA was not completely elucidated in thyroid cancer etiopathogenesis, we decided to study the expression of active, phosphorylated TrkA and of its coreceptor p75</p>

<p><b>Pathology and Immunology, University of Porto, Porto, Portugal.</b></p>	<p>neurotrophin receptor (p75 NTR) in a series of 92 PTC (37 lesions of conventional PTC, 28 of follicular variant of PTC [FVPTC], and 27 of other variants of PTC) as well as in 21 samples of normal thyroid and nonneoplastic thyroid lesions used as a controls.</p> <p>We observed neoexpression of p75 NTR in PTC, particularly in conventional PTC and in other variants of PTC displaying a papillary growth pattern, rather than in FVPTC.</p> <p>No immunoexpression of p75 NTR was observed in normal thyroid nor in nonneoplastic thyroid lesions. The cellular localization of p75 NTR immunoexpression was also significantly associated with the growth pattern of PTC, being much more frequently detected in an apical localization in PTC with papillary architecture than in PTC with a follicular or solid growth pattern.</p> <p>This apical localization of p75 NTR was significantly associated with the presence of BRAF V600E. No significant differences were detected between normal thyroid, nonneoplastic lesions, and PTC (or any PTC variant) regarding expression/activation of TrkA, thus suggesting that by itself and in contrast to p75 NTR, TrkA is not altered during PTC development.</p>
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DIFFERENTIAL DIAGNOSIS	KEY DIFFERENTIATING FEATURES
<p><b>Benign conditions which may result in papillary hyperplasia, mimicking papillary carcinoma.</b></p>	<p>These changes are usually diffuse and preserve the glandular architecture with normal nuclei.</p>
<p><b>Rare lesions composed of circumscribed nodules with a microscopic appearance of papillary growth with edematous stalks containing follicles</b></p>	<p>These nodules show none of the cytologic features of papillary carcinoma and have been termed papillary hyperplasia in follicular nodules. Some investigators have also used the term papillary adenomas, a term that is in disfavor since it has also been applied to encapsulated papillary carcinomas which are malignant</p> <p>Untreated Grave's disease  Congenital errors of thyroid metabolism  Hyperfunctioning foci in goitrous glands</p>
<p><b>BREAST CANCER</b></p>	
<p><b>Breast tumor resembling the tall cell variant of papillary thyroid carcinoma: report of 5 cases.</b></p> <p><b>Eusebi V, Damiani S, Ellis IO, Azzopardi JG, Rosai J.</b></p>	<p>Am J Surg Pathol. 2003 Aug;27(8):1114-8. Abstract quote</p> <p>Five cases of a hitherto undescribed breast tumor having histologic features similar to those of the tall cell variant papillary thyroid carcinoma are described. They were composed of columnar mitochondrion-rich to oxyphilic cells arranged in nests, papillae, and follicle-like structures. In addition, the neoplastic cells showed numerous nuclear grooves and, in two cases, nuclear pseudo-inclusions.</p> <p>None of the patients had previous concomitant or subsequent evidence of a thyroid tumor. Immunohistochemistry further excluded a metastasis from the thyroid in the four cases tested, as they were consistently thyroglobulin and thyroid transcription factor 1 negative.</p>

TREATMENT AND PROGNOSIS	CHARACTERIZATION
PROGNOSIS	
GENERAL	
<p><b>Thyroid Carcinomas With Distant Metastases: A Review of 111 Cases With Emphasis on the Prognostic Significance of an Insular Component</b></p> <p><b>Myriam Decaussin, M.D.; Marie Hélène Bernard, M.D.; Patrice Adeleine, Ph.D.; Isabelle Treilleux, M.D., Ph.D.; Jean Louis Peix, M.D., F.R.C.S.; Michel Pugeat, M.D.; Jacques Tourniaire, M.D.; Nicole Berger, M.D.</b></p>	<p>Am J Surg Pathol 2002; 26(8):1007-1015 Abstract quote</p> <p>Distant metastases (DM) are rare in well-differentiated thyroid carcinomas and correlate with a poor survival. Among the histologic subtypes, insular carcinoma has an intermediate prognosis that lies between well and undifferentiated carcinomas. To assess the characteristics that could predict a worse prognosis, we reviewed the initial thyroid cancer slides from patients with DM. We achieved a comparative statistical analysis with a control group without DM. Among 1230 differentiated carcinomas treated from 1960 to 1999, 9% developed DM. In this group the mean age was 53 years, with a 73% rate of death. The histologic slides were available in 80 cases. The primary thyroid tumors were classified as papillary (51 cases), follicular (25), and pure insular carcinomas (4).</p> <p>Extrathyroidal extension was present in 47% of papillary carcinomas. The mean tumor size was above 5 cm for all the histologic subtypes, and at least a vascular invasion was found in 69%. Fifty-four percent of these tumors had an insular component compared with only 6.5% in the control group. The statistical analysis confirmed by univariate and multivariate logistic regression that the risk of DM was highly elevated in the presence of insular carcinoma.</p> <p>Our study indicates that elevated age, large tumor size, vascular invasion, and extrathyroidal extension are important prognostic factors in well-differentiated carcinomas. We also demonstrate that the presence of an insular component in an otherwise differentiated carcinoma is a strong independent poor prognostic factor.</p>
CYCLIN D1	
<p><b>Overexpression of cyclin D1 and underexpression of p27 predict lymph node metastases in papillary thyroid carcinoma.</b></p> <p><b>Khoo ML, Beasley NJ, Ezzat S, Freeman JL, Asa SL.</b></p> <p><b>Department of Pathology, University Health Network, Toronto, Ontario, Canada.</b></p>	<p>J Clin Endocrinol Metab 2002 Apr;87(4):1814-8 Abstract quote</p> <p>Lymph node metastasis in papillary thyroid carcinoma increases the morbidity of treatment and the risk of local regional relapse and may also affect cure rates and survival. Factors that predict lymph node metastasis are, however, unclear.</p> <p>We analyzed 125 patients with papillary thyroid carcinoma for factors that predict lymph node metastasis. On univariate analysis, age, extrathyroidal extension, tumor focality, overexpression of cyclin D1, and underexpression of p27 predicted lymph node metastasis, whereas patient gender and tumor size did not. On multivariate analysis, extrathyroidal extension, overexpression of cyclin D1, and underexpression of p27 proved to be strong independent predictors of lymph node metastasis.</p> <p>We suggest that immunohistochemistry for cyclin D1 and p27 will prove valuable in identifying papillary thyroid carcinomas with metastatic potential.</p>
METASTASES	
<p><b>Pattern of cervical lymph node metastases from papillary carcinoma of the</b></p>	<p>Br J Surg 2001 Sep;88(9):1241-4 Abstract quote</p> <p>INTRODUCTION: The management of cervical metastases from papillary thyroid carcinoma ranges from selective removal (berry picking) to a formal comprehensive neck dissection. Without a clear</p>



<p><b>thyroid.</b></p> <p><b>Sivanandan R, Soo KC.</b></p> <p><b>Department of Surgery, Singapore General Hospital, Singapore.</b></p>	<p>understanding of the distribution of nodes at risk, the formulation of strategies on how best to manage the clinically positive neck is difficult. This study reports on observations made in patients who underwent a therapeutic comprehensive neck dissection for metastatic papillary thyroid carcinoma by defining lymph node involvement with respect to neck level.</p> <p><b>METHODS:</b> The clinical records and pathological reports of 75 consecutive patients who underwent a neck dissection for cervical metastases from papillary thyroid carcinoma over a 10-year period were reviewed. All dissections were therapeutic in nature, being performed in patients with clinically positive neck nodes. Eighty neck dissection specimens were obtained and analyses were divided into three groups by virtue of the type of dissection performed: a bilateral comprehensive neck dissection, unilateral radical neck dissection and unilateral comprehensive neck dissection. The relative involvement of cervical nodes was analysed with reference to node levels I-V.</p> <p><b>RESULTS:</b> Patients in the anterolateral group (levels II, III and IV) were at greatest risk of metastatic disease, with level III nodes consistently the most frequently involved, across all treatment groups. Only three patients exhibited level I involvement, all of whom had extensive neck disease involving all or almost all neck levels.</p> <p><b>CONCLUSION:</b> The majority of patients present with multiple level node disease, with the anterolateral group at greatest risk. A comprehensive neck dissection is recommended for all patients with palpable cervical lymphadenopathy.</p>
<p><b>RECURRENCE</b></p>	
<p><b>Prognosis after lymph node recurrence in papillary thyroid carcinoma depends on age.</b></p> <p><b>Voutilainen PE, Multanen MM, Leppaniemi AK, Haglund CH, Haapiainen RK, Franssila KO.</b></p> <p><b>Department of Surgery, Helsinki University Central Hospital, Finland.</b></p>	<p>Thyroid 2001 Oct;11(10):953-7 Abstract quote</p> <p>Papillary thyroid carcinoma (PTC) is a malignancy that has good prognosis especially among patients up to 45 years of age; about half of the patients are female and of childbearing age. Lymph node recurrence (LNR) occurs in 10%-14% of patients but is considered to be associated with relatively good prognosis.</p> <p>The purpose of this study was to estimate the association between patient age at primary operation, and the behavior of the disease after LNR. Between 1967 and 1994, 495 patients underwent surgery for primary PTC at the Department of Surgery, Helsinki University Central Hospital. There were 391 (79.0%) women and 104 (21.0%) men with a mean age of 44.5 years (range, 10.8-85.4 years).</p> <p>Fifty-eight patients in whom LNR was the first clinical sign of persistent disease after complete clinical response to primary treatment were included in this series. At the time of primary operation, 37 (64.3%) of the 58 patients who developed LNR were younger than 45 years of age and 21 patients were older. The mean times to LNR in these groups were 42.0 months (range, 3.0-194.5 months) and 49.0 months (range, 3.6-209.0 months) respectively. Carcinoma-specific 5-year survival after LNR was 100% (95% confidence interval [CI] 88.8%-100.0%) in patients ages up to 45 years and 61.1% (40.5%-82.8%) in older patients; 10-year survival rates were 100%, and 41.3% (<math>p &lt; 0.0001</math>), respectively. Relative survival at 10 years was 98.6% for patients ages up to 45 years and 42.6% for older patients (<math>p = 0.0014</math>). Using the Cox model it was shown that development of LNR after primary treatment has an independent highly significant negative effect on survival (<math>p &lt; 0.001</math>) in patients over 45 years of age.</p> <p>Prognosis of PTC even after LNR on patients ages up to 45 years at the time of the primary operation is almost parallel to the normal reference population, but in patients over 45 years of age the prognosis is relatively poor.</p>
<p><b>RET PROTO-ONCOGENE</b></p>	

<p><b>Expression of the RET proto-oncogene in papillary thyroid carcinoma and its correlation with clinical outcome.</b></p> <p><b>Kjellman P, Learoyd DL, Messina M, Weber G, Hoog A, Wallin G, Larsson C, Robinson BG, Zedenius J.</b></p> <p><b>Department of Molecular Medicine, Endocrine Tumour Unit, Karolinska Hospital, Stockholm, Sweden</b></p>	<p>Br J Surg 2001 Apr;88(4):557-63 Abstract quote</p> <p>BACKGROUND: In papillary thyroid carcinoma (PTC), presence of the oncogenes RET/PTC has been described, but their correlation with prognosis is debated. The aim of this study was to investigate the expression of the RET proto-oncogene (RET) and correlate it with clinical outcome.</p> <p>METHODS: Sixty-one PTCs were analysed for expression of RET and the oncogenes RET/PTC1-4 by polymerase chain reaction of complementary DNA.</p> <p>RESULTS: Twenty-nine PTCs (48 per cent) expressed the RET tyrosine kinase domain (RET-TK). Twelve expressed wild-type RET (WT-RET). One tumour expressed RET/PTC3, one a variant of RET/PTC3, and one RET/PTC1 and WT-RET simultaneously. The remaining 14 expressed RET-TK only. WT-RET expression was detected more frequently in poorly differentiated PTCs (<math>P &lt; 0.05</math>) and in PTCs from patients with aggressive disease (<math>P &lt; 0.01</math>). WT-RET expression remained an independently significant risk factor for aggressive disease when analysed together with other recognized risk factors using a stepwise multiple logistic regression model.</p> <p>CONCLUSION: Almost half of the PTCs showed RET-TK expression; in only three was this explained by expression of a RET/PTC rearrangement. Instead, expression of WT-RET was detected in 45 per cent of the RET-TK-positive tumours and this expression was an independently significant risk factor for aggressive PTC.</p>
<p><b>VEGF-D</b></p>	
<p><b>VEGF-D expression and lymph vessels play an important role for lymph node metastasis in papillary thyroid carcinoma.</b></p> <p><b>Yasuoka H, Nakamura Y, Zuo H, Tang W, Takamura Y, Miyauchi A, Nakamura M, Mori I, Kakudo K.</b></p> <p><b>1Department of Pathology, Wakayama Medical University, Wakayama, Japan.</b></p>	<p>Mod Pathol. 2005 Aug;18(8):1127-33. Abstract quote</p> <p>Papillary thyroid carcinoma frequently metastasizes to regional lymph nodes, and lymph node metastasis increases the risk of local regional relapse. Recent evidence suggests that vascular endothelial growth factor-D (VEGF-D) promotes lymphangiogenesis, which in turn promotes lymphatic metastasis.</p> <p>Therefore, the role of VEGF-D messenger RNA transcript levels and VEGF-D immunoreactivity in lymph node metastasis in papillary thyroid carcinoma was investigated. In addition, the role of blood vascular vessel, lymph vessel, and Flt-4-positive vessel densities were studied in relation to their suspected association with lymph node metastasis, and with VEGF-D expression. VEGF-D messenger RNA transcript levels by quantitative real-time reverse transcription-polymerase chain reaction and VEGF-D immunoreactivity by immunohistochemistry in 49 papillary thyroid carcinomas were also studied. This was followed by quantitative immunohistochemical staining for CD34, podoplanin, and Flt-4. Lymph node metastasis was significantly correlated with VEGF-D messenger RNA transcript levels (<math>P=0.027</math>) and VEGF-D immunoreactivity (<math>P=0.019</math>). Increased lymph vessel density was also correlated with VEGF-D expression and lymph node metastasis.</p> <p>In conclusion, our findings indicate that VEGF-D expression and increased lymph vessel density may have an important role for lymph node metastasis in papillary thyroid carcinoma.</p>
<p><b>TREATMENT</b></p>	
<p><b>RADIATION</b></p>	

<p><b>Papillary thyroid carcinoma: prognostic factors and the role of radioiodine and external radiotherapy.</b></p> <p><b>Chow SM, Law SC, Mendenhall WM, Au SK, Chan PT, Leung TW, Tong CC, Wong IS, Lau WH.</b></p> <p><b>Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong, China.</b></p>	<p>Int J Radiat Oncol Biol Phys 2002 Mar 1;52(3):784-95 Abstract quote</p> <p><b>PURPOSE:</b> To evaluate the role of radioiodine and external radiotherapy treatment in papillary thyroid carcinoma (PTC).</p> <p><b>METHODS AND MATERIALS:</b> This is a retrospective study of 842 patients with the diagnosis of PTC registered from 1960 to 1997 at the Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong. The mean follow-up was 9.2 years. The stage distribution according to UICC/AJCC TNM staging was as follows: 58.6%, Stage I; 9.6%, Stage II; 26.1%, Stage III; 2.3%, Stage IV; and 3.4%, not stated.</p> <p><b>RESULTS:</b> The 10-year cause-specific survival (CSS) rates were as follows: Stage I, 99.8%; Stage II, 91.8%; Stage III, 77.4%; and Stage IV, 37.1%. Multivariate analysis showed that the statistically significant poor prognostic factors for CSS were as follows: age older than 45, postoperative gross locoregional (LR) residual disease, distant metastasis (DM) at presentation, and lack of radioactive iodine (RAI) treatment. In patients with no DM and no postoperative LR disease, adjuvant RAI ablation reduced both LR failure (RR [relative risk] = 0.29) and DM (RR = 0.2), although the CSS was not affected. In the subgroup of T1N0 M0 disease, no patient with RAI treatment had a relapse. External radiotherapy reduced the risk of LR failure to 0.35. Subgroup analysis revealed that external radiotherapy was particularly effective in increasing the probability of LR control of disease in patients with gross postoperative LR disease (RR = 0.36).</p> <p><b>CONCLUSIONS:</b> Both RAI and external radiotherapy were effective treatment in PTC. Total or near-total thyroidectomy followed by RAI treatment appears to result in the best outcome. External radiotherapy to improve LR control is indicated in patients with gross postoperative residual disease. Treatment should be individualized for patients with T1N0 M0 disease.</p>
<p><b>SURGERY</b></p>	
<p><b>The sentinel node procedure with Patent Blue V dye in the surgical treatment of papillary thyroid carcinoma.</b></p> <p><b>Pelizzo MR, Boschin IM, Toniato A, Bernante P, Piotto A, Rinaldo A, Ferlito A.</b></p> <p><b>Department of Medical and Surgical Science, 3rd Clinic of General Surgery, University of Padua, Italy.</b></p>	<p>Acta Otolaryngol 2001 Apr;121(3):421-4 Abstract quote</p> <p>How far to extend the surgical treatment of papillary thyroid carcinoma (PTC) is still an open question. A contribution may come from intra-operative lymphatic mapping because, in other malignancies, the procedure has become an important aid in defining lymph node status.</p> <p>To assess the feasibility of using the sentinel lymph node (SLN) technique with the intratumoral injection of Patent Blue V dye to guide nodal dissection in PTC, 29 patients with a preoperative diagnosis of PTC and no clinical or ultrasonographic evidence of nodal involvement underwent cervicotomy and exposure of the thyroid gland, followed by Patent Blue V dye injection into the thyroid nodule. Total thyroidectomy was subsequently performed, resecting the lymph nodes at levels III, IV, VI and VII. The thyroid, SLN and the other lymph nodes were snap-frozen and submitted for both intra-operative and subsequent definitive pathological evaluation. Intra-operative lymphatic mapping located the SLN in 22/29 patients (75.9%) and the SLN revealed neoplastic involvement in 4/22 (18.2%); other lymph nodes were also positive in 2 cases.</p> <p>In the 18 patients whose SLNs were not metastatic, the other nodes were also disease-free. The SLN technique thus seems helpful in avoiding unnecessary lymph node dissection in PTC without spread to the SLN.</p>
<p><b>Accuracy of sentinel lymph node in papillary thyroid carcinoma.</b></p> <p><b>Arch-Ferrer J, Velazquez D, Fajardo R, Gamboa-</b></p>	<p>Surgery 2001 Dec;130(6):907-13 Abstract quote</p> <p><b>BACKGROUND:</b> The sentinel lymph node has been used in several tumors. The aim of this study was to analyze the accuracy of the sentinel node in papillary thyroid carcinoma.</p> <p><b>METHODS:</b> A series of 22 patients with papillary thyroid carcinoma were included. Approximately 0.5 cc of isosulfan blue dye was injected at operation to trace the sentinel node. Lymph node</p>

<p><b>Dominguez A, Herrera MF.</b> <b>Department of Surgery,</b> <b>Instituto Nacional de</b> <b>Ciencias Medicas y</b> <b>Nutricion, Tlalpan, Mexico</b> <b>City, Mexico.</b></p>	<p>dissection of the ipsilateral central compartment and extensive sampling of the jugular compartment were performed in addition to sentinel node resection. Surgical specimens were stained with hematoxylin-eosin, and negative sentinel nodes were subsequently stained with immunohistochemistry for cytokeratin-7.</p> <p>RESULTS: Mean age was 37 +/- 14 years. Twenty patients were women, and 2 were men. Mean tumor size was 2.5 +/- 1 cm. A sentinel lymph node was found in 20 patients. With use of hematoxylin-eosin, metastases were identified in 12/20 sentinel nodes (60%). Eleven patients with positive sentinel nodes presented additional lymph node metastases: 9 in the central compartment, 1 in the jugular compartment, and 1 in both compartments. Two patients with negative sentinel nodes had lymph node metastases elsewhere. When sentinel nodes were processed by immunohistochemistry, accuracy increased to 100%.</p> <p>CONCLUSIONS: Sentinel node is highly accurate for diagnosing metastases in papillary thyroid carcinoma.</p>
<p><b>Sentinel lymph node biopsy</b> <b>in patients with papillary</b> <b>thyroid carcinoma.</b></p> <p><b>Fukui Y, Yamakawa T,</b> <b>Taniki T, Numoto S, Miki</b> <b>H, Monden Y.</b></p> <p><b>Department of Surgery,</b> <b>Kochi Municipal Hospital,</b> <b>Kochi, Japan.</b></p>	<p>Cancer 2001 Dec 1;92(11):2868-74 Abstract quote</p> <p>BACKGROUND: It remains controversial whether modified radical neck dissection (MRND) for patients with papillary thyroid carcinoma improves prognosis. However, it is highly probable that the incidence of local recurrence is reduced by lymph node dissection. Sentinel lymph node (SLN) biopsy (SLNB) for patients with melanoma and breast carcinoma has been validated as an accurate method for assessing lymph node status. The objective of this study was to determine the feasibility of SLNB for the evaluation of cervical lymph node status in patients with papillary thyroid carcinoma.</p> <p>METHODS: After injection of methylene blue around the tumor in 22 patients with papillary thyroid carcinoma, blue-stained lymph nodes were dissected as SLNs. After the SLNB, all patients also underwent subtotal thyroidectomy and MRND. SLNs and other lymph nodes were investigated with regard to their number, distribution, size, lymph node status, and ratio of metastatic area.</p> <p>RESULTS: There was concordance between the SLN findings and the regional lymph node status in 19 of 21 patients (90.5%; 7 patients had both positive SLN and regional lymph node results, and 12 patients had both negative SLN and regional lymph node results). Two patients had negative SLN results but, in the end, had positive nonsentinel lymph nodes (NSLNs). The overall reliability rate of SLNB was 86.3% (19 of 22 patients). The authors experienced no complications with the use of methylene blue for the detection of SLNs.</p> <p>CONCLUSIONS: SLNB using methylene blue is feasible technically and is safe, and the findings correlate with cervical lymph node status. Therefore, SLNB is a good technique for estimating the status of cervical lymph nodes in patients with papillary thyroid carcinoma.</p>