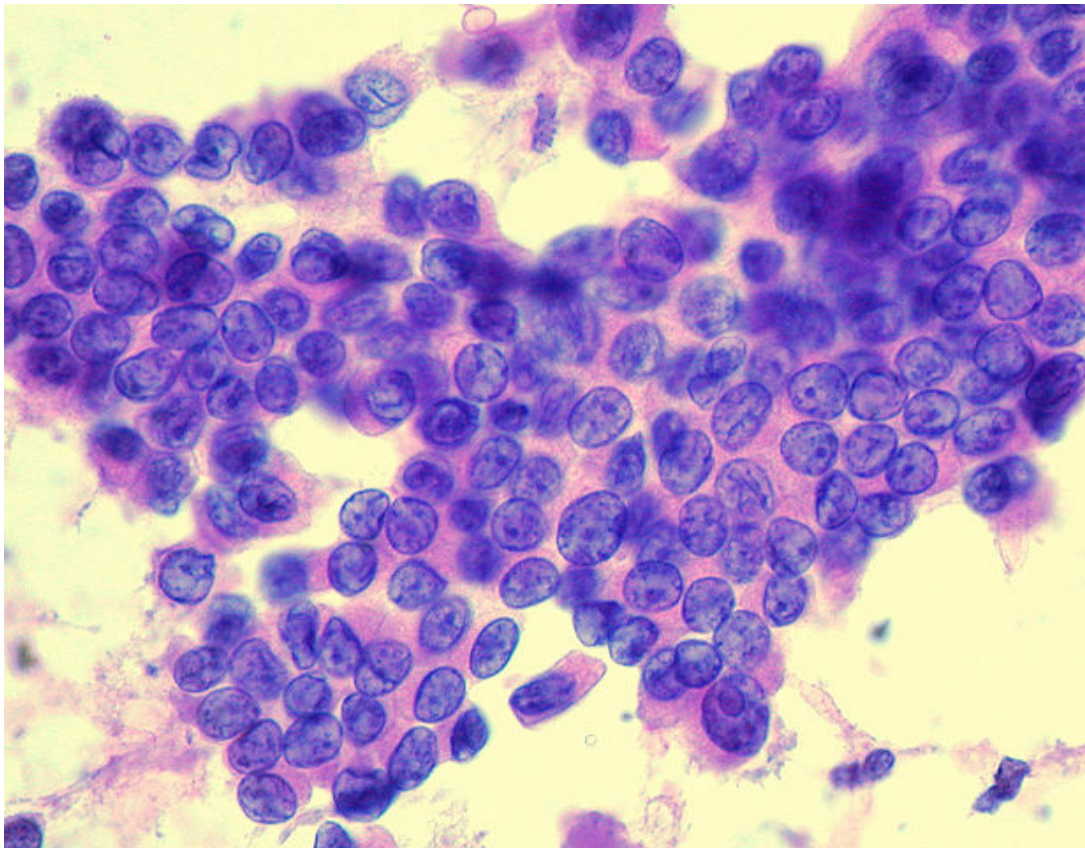


Thyroid Cancer — Classification and Treatment

[See online here](#)

Thyroid cancer is an uncommon cancer that can be managed well if detected early enough. It arises from follicular or parafollicular cells within the thyroid. There are subtypes of cancer depending on the cell involved and the mutations that occur. The most common cure for this cancer is surgical removal of the thyroid, along with chemotherapy or radiotherapy.



Definition and Background of Thyroid Cancer

General information on thyroid cancer

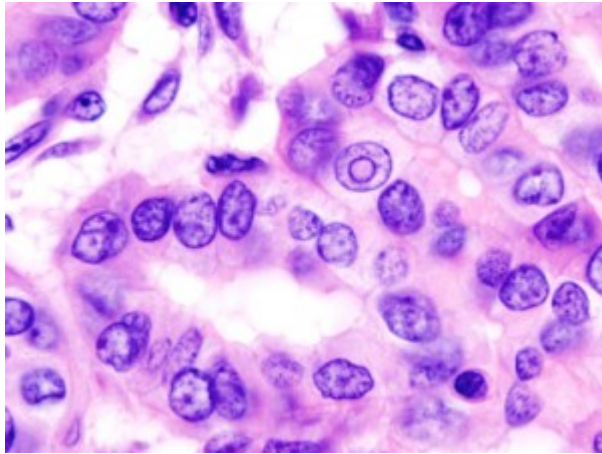


Image: "Histopathological image of papillary carcinoma of the thyroid gland obtained by a total thyroidectomy. Hematoxylin and eosin stain," by KGH. License: [CC BY—SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Thyroid cancer usually presents as a painless lump in the [neck](#). It is usually asymptomatic unless it's left for a significant amount of time. It may be felt by the patient or found on examination by the doctor. Biopsy-confirmed thyroid cancer is usually removed surgically to prevent any further progression and metastasis. If the cancer is confirmed to the thyroid, this is a curative operation. Once cancer spreads, treatment becomes more difficult, and the prognosis is worse.

Epidemiology of Thyroid Cancer

Most affected by thyroid cancer

Globally, 36,000 deaths were attributed to thyroid cancer in 2010. It only accounts for approximately 1 % of all cancers. There is a slight female predominance in younger adults who develop the disease, whereas cases in childhood and the elderly are of equal distribution between males and females.

Etiology of Thyroid Cancer

Origins of thyroid cancer

Genetic Causes

Multiple endocrine neoplasia types II increases the chance of developing thyroid cancer of, most likely, the medullary form.

[Genetic mutations](#) of various genes involved with the thyroid are another cause: MAP-kinase pathway genes / phosphatidylinositol-3-kinase (PI-3K) pathway.

Environmental Causes

- **Ionizing radiation:** It leads to [DNA](#) mutations, especially when exposure occurs within the first 2 decades of life. These may be due to previous cancer radiation treatments or to radiation disasters like Chernobyl which caused an Iodine-131 exposure; iodine is then taken up by the thyroid.
- **Disease:** Thyroiditis, amongst others, is thought to increase the risk of developing thyroid cancer.
- **Iodine Deficiency:** Associated with goiter, it leads to an increased chance of

follicular cancer of the thyroid.

Risk Factors

| Modifiable Risk Factors | Unmodifiable Risk Factors |
|-------------------------|--|
| Exposure to radiation | Exposure to background radiation |
| Possibly obesity | Exposure to radiation from previous cancer treatment |
| Iodine-deficient diet | Previous cancer (especially previous thyroid cancer) |
| | Exposure to artificial radiation (e.g., 131-iodine) |
| | Family history |
| | Cowden Syndrome (papillary / follicular) |
| | MEN 2 Syndrome (medullary) |
| | Familial adenomatous polyposis (papillary) |

Classification of Thyroid Cancer

Types of thyroid cancer

The classification of thyroid cancer depends on the [type of cell](#) cancer originates from. You cannot distinguish thyroid nodules by palpation on physical examination; hence, **ultrasound-guided biopsy** or **fine-needle aspiration** is performed to histologically confirm the cause of the thyroid nodule. Note: the swelling can be **benign**, e.g., benign nodular goiter, adenoma, etc.

| Type of thyroid cancer | Most commonly affects... | Prognosis and associations |
|---|---|---|
| Papillary carcinoma > 85 % of the cases (Differentiated thyroid cancer) | Often, young women | Prognosis is very good if detected relatively early. Associated with FAP (familial adenomatous polyposis) and Cowden syndrome (rare autosomal dominant inherited condition). Can spread via the lymphatic system to local cervical lymph nodes. |
| Follicular carcinoma 5–15% (Differentiated thyroid cancer) | Associated with Cowden syndrome | Hematogenous spread to the lungs or bones is common. Prognosis is generally good, if detected early enough. |
| Medullary carcinoma 5–8 % | 25 % of the cases occur in people with MEN 2 syndrome | An inherited mutated gene causes 25 % of these cancers. Prognosis is generally good, if detected early enough. |
| Anaplastic carcinoma (undifferentiated) < 5 % | Usually in people over 60 years of age. More common in women. | Generally faster growing. Extremely poor prognosis. |

Signs and Symptoms of Thyroid Cancer

How to detect thyroid cancer

The only clinical sign in early thyroid cancer is an **asymptomatic nodule in the neck**; this may be in the thyroid, or it could be a **cervical lymph node**. When the disease advances, it can present as a painful lump. Associated symptoms may include **trachea fixation**, recurrent **laryngeal nerve damage** (hoarseness), **cervical sympathetic nerve invasion**, **dysphagia** and **odynophagia**.

Patients are usually **euthyroid** but in advanced stages of the disease; **hypo-**

/hyperthyroid symptoms may be present.

Metastatic medullary thyroid cancers may present with symptoms that results from high levels of calcitonin: **diarrhea**, flushing, **pruritus**. This flushing is indistinguishable from the flushing in **carcinoid syndrome** (caused by elevated serotonin).

Papillary Carcinoma

This is the most common form of thyroid cancer, accounting for 85 % of the cases. Papillary carcinomas are associated with previous exposure to ionizing radiation that causes DNA mutations.

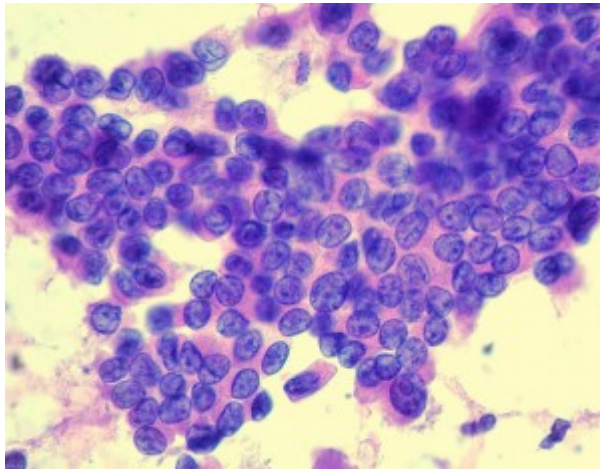


Image: "Papillary Carcinoma of the Thyroid. This illustrative cell group shows cardinal features of papillary carcinoma: nuclear grooves and pseudoinclusion. Scrape cytology from cut surface of tumor in thyroidectomy specimen, rapid H&E, 1000X," by Ed Uthman, MD. License: [CC BY-SA 2.0](#)

They can present as a **singular lesion or a multifocal lesion**. The lesions can have ill-defined borders or can be circumscribed. There may be areas of calcification and fibrosis and are commonly **cystic**. The nodule may appear **granular** when cut, and **papillary foci** may be visible. Metastatic spread to local cervical lymph nodes occurs in 50 % of the cases.

There are several variants of papillary carcinoma, but the most common consists mostly of follicles; follicular variant — associated with encapsulated nodules and lower rates of **lymph node spread** and extension beyond the thyroid.

Tg, thyroglobulin can be used as a tumor marker to monitor well-differentiated papillary thyroid cancer over time.

Pathophysiology

Activation of the MAP kinase pathway is a feature of most papillary thyroid cancers. This pathway becomes carcinogenic once mutated and leads to papillary carcinoma of the thyroid. It can occur in two ways:

- I. **Chromosomal translocations of RET** (proto-oncogene) (20 %) or NTRK1 (neurotrophic tyrosine kinase receptor 1) (5 - 10%) rearrangements. These encode

tyrosine kinase receptors in the membrane.

- II. **BRAF point mutation** (33 – 50 %): BRAF gene protein product is involved in the MAP kinase pathways (intermediate signaling component).

Diagnosis

Thyroid cancer can be routinely found on examination, often as a painless asymptomatic lump in the neck. The histopathology of a biopsy sample reveals the diagnosis. The histological diagnosis is based on nuclear features.

Pathology

The following features are noteworthy:

- Finely dispersed chromatin gives an optically clear appearance.
- Orphan Annie eye nuclear inclusions — uniform staining, ground glass / empty appearance.
- Psammoma body — round collection of calcium (microscopically) present within papillae.
- Cytoplasmic invaginations may appear like intranuclear inclusions, i.e., pseudoinclusions.
- Papillary architecture — dense fibrovascular cores.
- Commonly multifocal.
- Microcarcinomas = < 1 cm.
- Lymphatic spread is more likely than hematogenous spread.

Clinical Features

- Usually found as a painless mass in the neck — papillary carcinomas are non-functional tumors.
- Neck mass can be the primary thyroid carcinoma or an enlarged cervical lymph node from the metastatic spread.
- They are slow-growing carcinomas with a high survival rate post-operatively.

Follicular Carcinoma



Image: "This follicular adenoma of the thyroid is shown in a right lobectomy specimen, sectioned vertically and viewed from the posterior aspect to show a 2.7 cm tumor distending the lower pole," by Ed Uthman, MD. License: Public domain.

This type of thyroid cancer is rarer than papillary carcinoma, accounting for only 5 - 15 % of all cases. It more commonly occurs in women at a ratio of 3:1. It usually arises at an older age than papillary carcinomas, around the age of 40- 60 years old.

In areas where there is an iodine deficiency, this cancer accounts for 25 - 40 % of all cases of thyroid cancers.

Thyroglobulin can be used as a tumor marker for this type of thyroid cancer. Follicular cells in the thyroid are physiologically responsible for thyroid hormone production and secretion.

Pathophysiology

There are 2 separate molecular pathways that rarely occur together:

- I. 50 % have mutations in **RAS oncogenes**; e.g., KRAS. 33 - 50 % have PI-3K/AKT signaling pathway mutations. This causes continuous activation of this now carcinogenic pathway.
- II. 33 % of follicular cancers have **PAX8—PPARy1 fusion**.

Diagnosis

- **Tg, thyroglobulin** can be used as a tumor marker to monitor well-differentiated follicular thyroid cancer over time.
- Routinely found on examination, often as a painless asymptomatic lump in the neck.
- Histology is performed from a fine-needle aspiration preoperatively. However, it is impossible to recognize follicular adenoma from carcinoma purely on FNAC (fine-needle aspiration cytology).
- Diagnosis is confirmed post-operatively.

Pathology

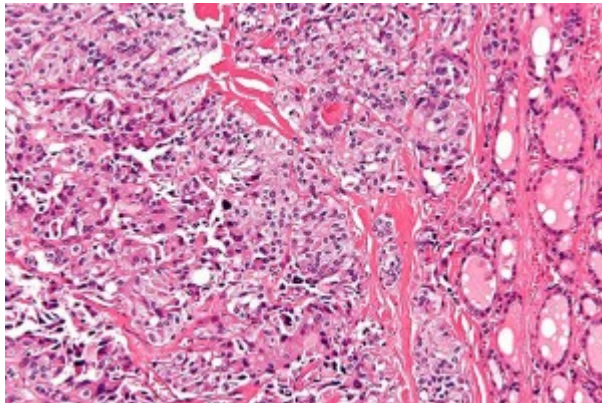
The following features are needed in order to diagnose follicular carcinoma:

- **Capsular invasion** (ensure no capsular rupture from the FNA procedure, a.k.a. WHAFFT—worrisome histologic alterations following FNA of the thyroid).
- **Capsular and vascular spread** can be determined by careful microscopic examination of the thyroid-capsule border to examine any invasion which may have occurred—confirming follicular carcinoma.
- Uniform cells form small follicles.
- Can be very invasive, spreading into **thyroid parenchyma** and soft tissue around the thyroid gland.
- Alternatively, can be minimally invasive.
- **Hurthle cell variant** — more likely to be bilateral, multifocal and more commonly spread to lymph nodes.
- It is possible to have nuclear features of papillary carcinoma; this is called a papillary variant of follicular carcinoma.

Clinical features

- Most are found as a solitary nodule.
- **Hematogenous metastases** occur more commonly than lymphatic spread — commonly to the lung and bone, unlike papillary carcinoma which commonly spreads to local cervical lymph nodes. Hematogenous spread shows widely invasive follicular carcinoma and is a poor prognostic sign.

Medullary Thyroid Cancer (MTC)



[Image](#): "High magnification micrograph of medullary thyroid carcinoma, abbreviated MTC. H&E stain," by Nephron. License: [CC BY—SA 3.0](#)

MTC is a cancer of the **parafollicular C-cells** within the thyroid. These are neuroendocrine cells that are responsible for producing **calcitonin**, a hormone that aims to reduce calcium blood levels (opposing parathyroid hormone). MTC is one of the rarest forms of thyroid cancers, making up only 5 - 8 % of all thyroid cancer cases.

Pathophysiology

30 % of MTCs occur as a result of a genetic mutation in the **RET proto-oncogene** (familial MTC). The other 70 % are termed **sporadic MTC**.

The 30 % of MTC that are due to genetic mutations are usually in the setting of **Multiple Endocrine Neoplasia syndrome** type 2A/2B = MTC + parathyroid gland tumor + tumor in the medullary part of the adrenal gland.

Common sites for metastases include local lymph nodes, mediastinal lymph nodes, [liver](#), [lung](#) and [bone](#).

Diagnosis

Patient may present with diarrhea, flushing and itching as a result of elevated levels of calcitonin or calcitonin gene-related peptide. These symptoms are present more noticeably when the MTC has metastasized (especially when it spreads to the liver).

Thyroid nodule or enlarged cervical lymph node.

Pathology

May be a solitary lesion or manifest as multiple lesions that can arise bilaterally. Familial cases are commonly multicentric — two or more foci in different segments of the thyroid.

Polygonal to spindle-shaped cells. These can form nests, trabeculae or follicles. Amyloid deposits may be present in the stroma.

Clinical features

Calcitonin can be used as a tumor marker as it is elevated in MTC. **CEA (carcinoembryonic antigen)** is also produced by MTC and can also be used as a tumor marker.

Sometimes, the tumor cells can also secrete other polypeptide hormones such as somatostatin, VIP (vasoactive intestinal peptide) and serotonin. The most common symptoms include diarrhea, flushing and itching due to elevated levels of calcitonin or calcitonin-gene related peptides.

Compression symptoms may be present, e.g., hoarseness from recurrent laryngeal nerve compression or dysphagia from esophageal compression. In familial cases, screening can be done to monitor calcitonin levels.

Anaplastic Thyroid Cancer

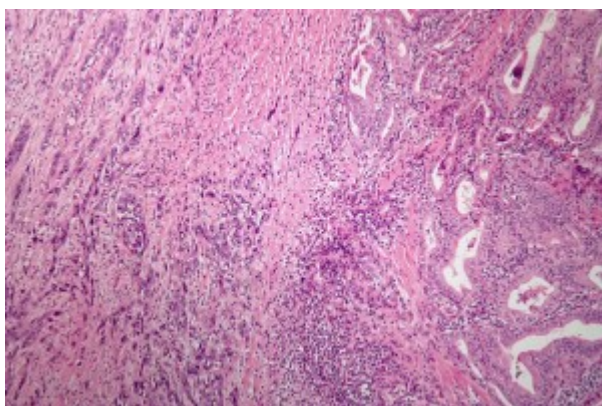


Image: "Low magnification micrograph of anaplastic thyroid carcinoma with a component of papillary thyroid carcinoma, tall

ATC is the rarest form of thyroid cancer and also has the worst prognosis because it is very aggressive and resistant to conventional treatments such as surgery and radioactive iodine. They have a relatively high mitotic rate and invade surrounding tissues via the lymphatic system and vasculature. They are thought to arise from dedifferentiation of more differentiated neoplasms.

ATC is always known as **stage IV cancer**. FNAC — vesicular appearance in older patients with regional lymphadenopathy supports a diagnosis of ATC.

Investigations

Methods for detecting thyroid cancer

The following investigations may reveal cases of thyroid cancer:

- **Fine-needle aspiration** — for preoperative diagnosis
- **Histopathology**
- **Ultrasound scan**
 - distinguish solid from cystic lesions;
 - identify calcifications;
 - find microcarcinomas;
 - guide fine-needle aspirations.
- **Thyroglobulin blood test** — tumor marker for some thyroid carcinomas (papillary, follicular, etc.).
- Metastases can be detected using **full body scintigraphy** with radioactive iodine—¹³¹I.
- **Chest X-ray**
- **MRI scan**
- **CT scan**
- **PET scan**
- TSH, Tg, T3/T4 **blood tests**.
- **Thyroid antibody tests** — determine if there is any autoimmune thyroid disease.
- **Calcitonin** — may indicate medullary thyroid cancer.

Treatment of Thyroid Cancer

Options for treating thyroid cancer

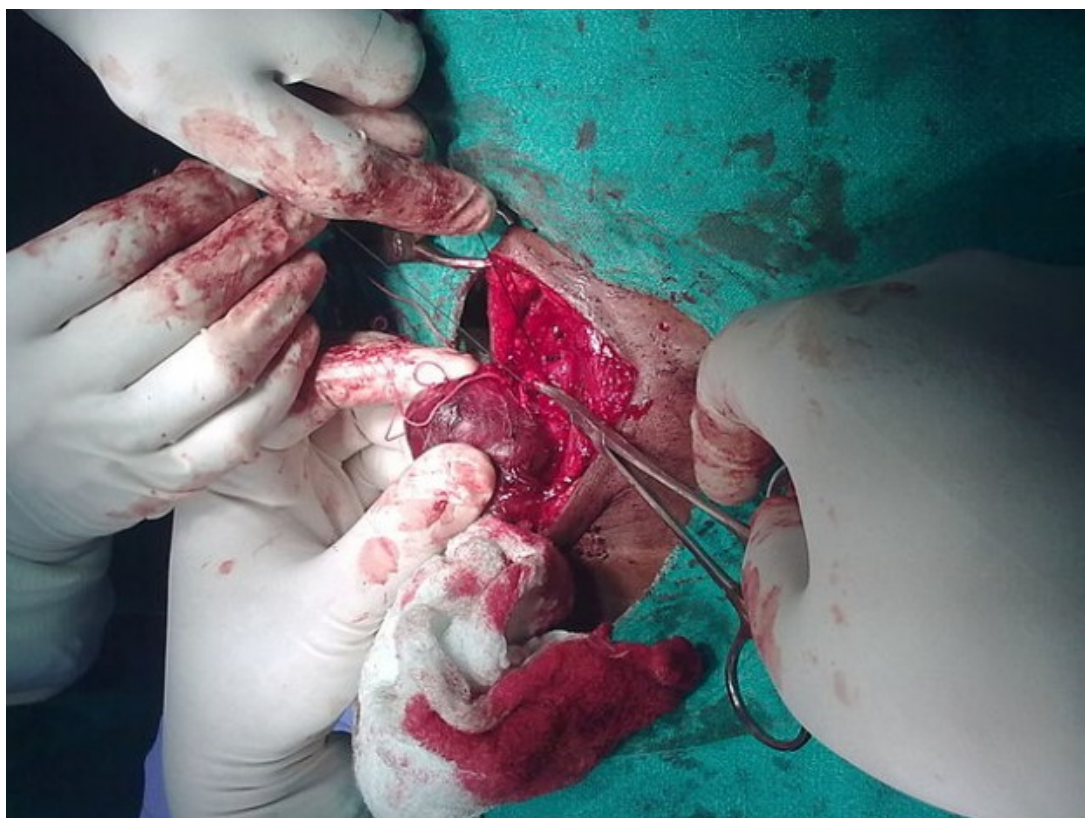


Image: "Thyroid Surgery," by n.raveender. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Thyroidectomy (hemi or total) is performed along with neck dissection. Neck dissection may include the sternocleidomastoid muscle, jugular vein and various nerves. If the patient is old or unsuitable for surgery, watchful waiting may be useful to prevent iatrogenic damage.

Radioactive iodine-131 treatment is only used in papillary and follicular thyroid carcinomas and is not effective in medullary, anaplastic and Hurthle cell cancers. The following alternative treatments are possible:

- **External radiotherapy** — may be useful when the cancer is inoperable or to relieve pain from bone metastases.
- **Chemotherapy** may be used in advanced disease.
- Some **kinase inhibitor drugs** are currently being tested for use in some types of thyroid cancer (e.g., sorafenib, sunitinib).
- **TSH-suppression therapy** is recommended for active/aggressive thyroid cancers that have been treated with surgery and radioactive iodine.
- **Levothyroxine** is given post-thyroidectomy to prevent hypothyroidism.

Papillary

Surgery — usually total thyroidectomy, but...

- ...if the disease is limited, hemithyroidectomy may be suitable.
- ...if a total thyroidectomy is performed, lifelong thyroid hormone replacement is required.
- ...postoperative radioactive iodine-131 therapy may be necessary.

Follicular

- **Initial** — hemithyroidectomy, followed by additional histology to confirm diagnosis. In case of confirmed follicular carcinoma, complete thyroidectomy with radioiodine ablation post-operatively.
- **Recurrence:** Use Thyroglobulin testing and ultrasound, or whole body scans using radioactive iodine (less effective), to find recurrent cancer.
- If a total thyroidectomy is performed, lifelong thyroid hormone replacement is required.

Medullary

- Total thyroidectomy with bilateral neck dissection.
- External radiotherapy is recommended in high-risk patients to reduce the risk of recurrence.
- Protein kinase inhibitors are currently being tested and may be effective by blocking abnormal kinase proteins (e.g., Vandetanib, Cabozantinib).

Anaplastic

- Very unlikely to be cured by surgery or any other form of treatment.
- Surgery is unlikely to cure as it is so invasive.
- Mostly managed with radiotherapy and chemotherapy with palliative intent.
- There are clinical trials which show some promise in increased prognosis.

Staging of Thyroid Cancer

There are many different staging systems used for various different types of thyroid cancer. The best staging system for general thyroid cancer is the **TNM system**.

Tumor — T1 Intrathyroidal <1 cm, T2 Intrathyroidal 1-4 cm, T3 Intrathyroidal >4 cm, T4 any size that extends beyond the thyroid capsule.

Nodes (lymph) — N0 no nodal spread, N1 regional nodes involved.

Metastases — M0 no metastases, M1 distant metastases.

Differential Diagnosis of Thyroid Cancer

Diseases with similar symptoms as thyroid cancer

| | |
|-------------------------------|--------------------------------------|
| Colloid nodule | Thyroid adenoma |
| Non-toxic multinodular goiter | Toxic adenoma |
| Lymphoma | Cyst |
| Thyroiditis | Graves' disease |
| Parathyroid carcinoma | Metastases from non-thyroidal cancer |

Prognosis of Thyroid Cancer

Survival rates for thyroid cancer

| Type of thyroid cancer | 5-year survival rate | 10-year survival rate |
|------------------------|----------------------|-----------------------|
| Papillary | 96 % | 93 % |
| Follicular | 91 % | 85 % |
| Medullary | 83 % | 75 % |
| Anaplastic | 7 % | — |

Papillary carcinoma: Metastases to an isolated cervical lymph node; does not affect prognosis. Sometimes, there can be hematogenous spread to the lung (most commonly), which can influence prognosis. Poor prognostic signs for papillary carcinoma are as follows: older, extrathyroidal spread, distant metastases (advanced stage).

Follicular carcinoma: Stages I and II have a good prognosis, but once advanced (e.g., stage IV), the prognosis falls to a 50% in a 5-year survival rate.

Thyroid Adenomas

- Discrete, solitary masses
- Variety of histologic patterns; however, the key feature is a well-circumscribed capsule with no invasion
- Gain-of-function of the TSH-R or α -subunit of Gs (GNAS)

Clinical features

- Must be differentiated from follicular carcinoma (ang-invasive > lympho-invasive)
- Present as a painless mass
- Usually non-functional
- Larger masses can produce local obstructive symptoms (dysphagia)

Thyroid Carcinoma

- Most cases occur in adults
- Subtypes
 - Papillary (75—85 %)
 - Follicular (10—20 %)
 - Medullary (5 %)
 - Anaplastic (< 5 %)
 - Lymphoma

Overview of thyroid carcinoma types

I. Differentiated

a. Papillary

- 70—80 % of thyroid cancer
- Male preponderance peak b/w 30—50
- Lymphatic spread
- Usually excellent prognosis
- High incidence in patients with Gardner's syndrome (Familial adenomatous polyposis coli)

b. Follicular

- 10—15 % of thyroid cancer

- Female preponderance peak b/w 40—60
- Slow growth painless nodules
- Cold nodules
- Invades capsule and vascular system
- Hematogenous spread
- Usually good-excellent prognosis

II. Medullary

- 10 % of thyroid cancer cases
- Aise from C cells, which produce calcitonin
- 20 % associated with Multiple Endocrine Neoplasia (MEN); RET proto-oncogene mutation
- Usually good prognosis

III. Anaplastic

- < 5 % of thyroid cancer
- Poor prognosis
- Often prior history of goiter or papillary thyroid cancer

IV. Lymphoma

- < 5 % of thyroid cancer
- Seen in association with Hashimoto's thyroiditis
- Usually good prognosis

References

Hu MI, Vassilopoulou-Sellin R, Lustig R, Lamont JP" [Thyroid and Parathyroid Cancers](#)" in Pazdur R, Wagman LD, Camphausen KA, Hoskins WJ (Eds) [Cancer Management: A Multidisciplinary Approach](#). 11 ed. 2008.

Kumar and Clark Clinical Medicine 8E

Robbins Basic Pathology 9E

Oxford Handbook of Clinical Medicine

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