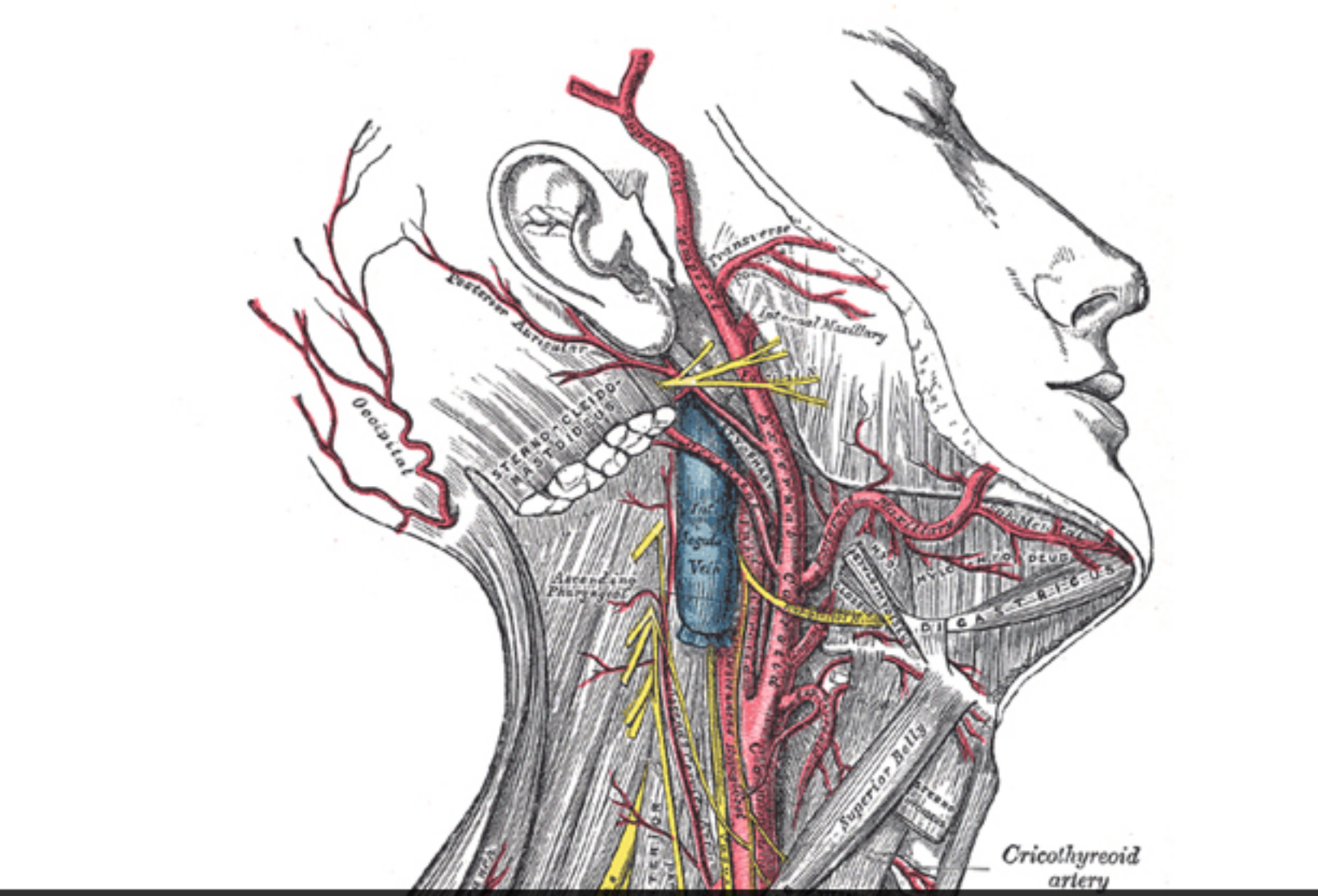

Thyroid, Head and Neck Cancers

Shawanna Hatch

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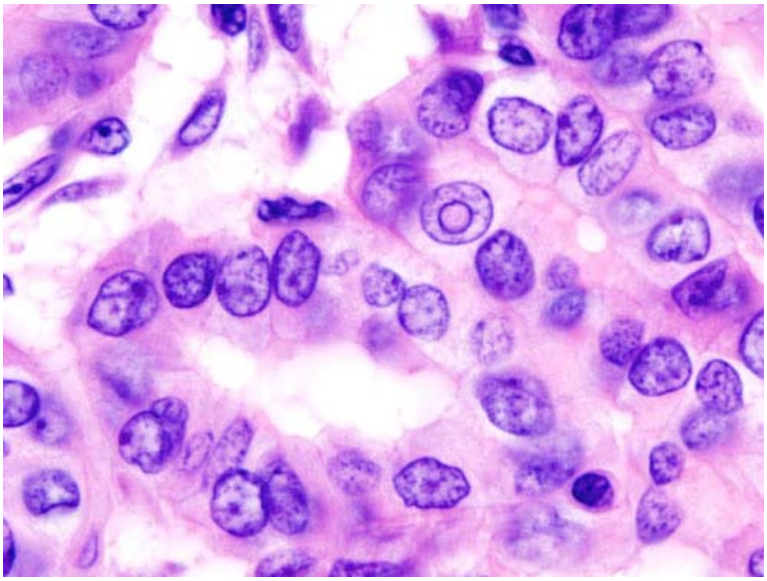
Thyroid Cancer

Thyroid cancer

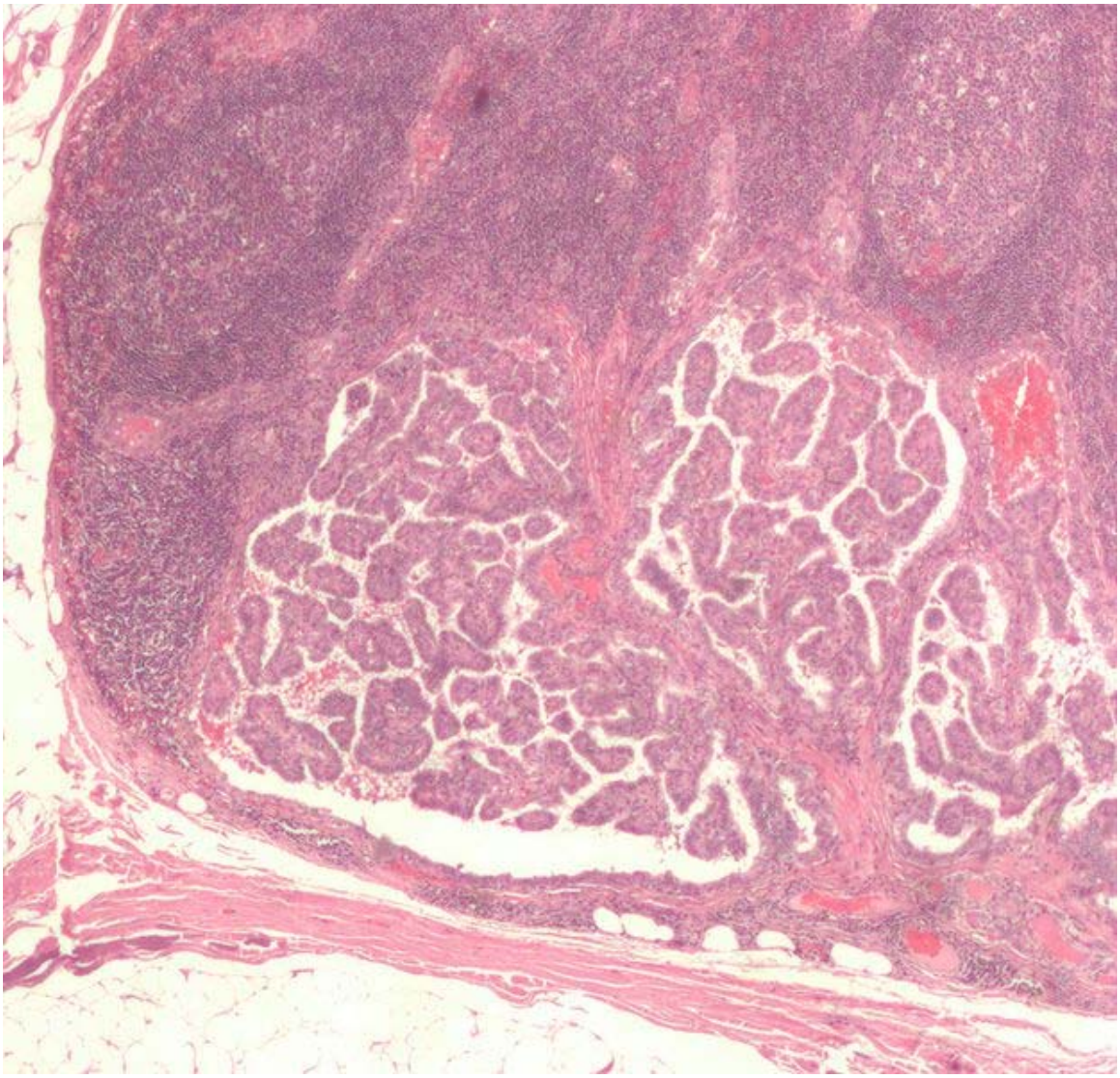


Micrograph (high power view) of papillary thyroid carcinoma demonstrating diagnostic features (nuclear clearing and overlapping nuclei). H&E stain.

ICD-10	C73.
ICD-9	193
eMedicine	ent/646
MeSH	D013964

Thyroid cancer is a thyroid neoplasm that is malignant. It can be treated with radioactive iodine or surgical resection of the thyroid gland. Chemotherapy or radiotherapy may also be used.

Symptoms



Micrograph of a lymph node with papillary thyroid carcinoma.

Most often the first symptom of thyroid cancer is a nodule in the thyroid region of the neck. However, many adults have small nodules in their thyroids, but typically under 5% of these nodules are found to be malignant. Sometimes the first sign is an enlarged lymph node. Later symptoms that can be present are pain in the anterior region of the neck and changes in voice.

Thyroid cancer is usually found in a euthyroid patient, but symptoms of hyperthyroidism or hypothyroidism may be associated with a large or metastatic well-differentiated tumor.

Thyroid nodules are of particular concern when they are found in those under the age of 20. The presentation of benign nodules at this age is less likely, and thus the potential for malignancy is far greater.

Diagnosis

After a thyroid nodule is found during a physical examination, a referral to an endocrinologist, a thyroidologist or otolaryngologist may occur. Most commonly an ultrasound is performed to confirm the presence of a nodule, and assess the status of the whole gland. Measurement of thyroid stimulating hormone and anti-thyroid antibodies will help decide if there is a functional thyroid disease such as Hashimoto's thyroiditis present, a known cause of a benign nodular goiter.

Classification

Thyroid cancers can be classified according to their histopathological characteristics. The following variants can be distinguished (distribution over various subtypes may show regional variation):

- Papillary thyroid cancer (75% to 85% of cases) - often in young females - excellent prognosis
- Follicular thyroid cancer (10% to 20% of cases)
- Medullary thyroid cancer (5% to 8% of cases)- cancer of the parafollicular cells, part of MEN-2.
- Anaplastic thyroid cancer (Less than 5%). It is not responsive to treatment and can cause pressure symptoms.
- Others
    - Lymphoma
    - Squamous cell carcinoma, sarcoma

The follicular and papillary types together can be classified as "differentiated thyroid cancer". These types have a more favorable prognosis than the medullary and undifferentiated types.

- Papillary microcarcinoma is a subset of papillary thyroid cancer defined as measuring less than or equal to 1 cm. The highest incidence of papillary thyroid microcarcinoma in autopsy series was reported by Harach et al. in 1985, who found 36 of 101 consecutive autopsies were found to have an incidental microcarcinoma. Michael Pakdaman et al. report the highest incidence in a retrospective surgical series at 49.9% of 860 cases. Management strategies for incidental papillary microcarcinoma on ultrasound (and confirmed on FNAB) range from total thyroidectomy with radioactive iodine ablation to observation alone. Harach et al. suggest using the term "occult papillary tumor" to avoid giving patients distress over having cancer.It was Woolner et al. who first arbitrarily coined the term "occult papillary carcinoma" in 1960, to describe papillary carcinomas ≤ 1.5 cm in diameter.

Etiology

From the 1940s to 1960s, external, low-dose radiation to the head and neck during infancy and childhood was used to treat many benign diseases. This type of therapy has been shown to predispose persons to thyroid cancer. The younger the patient was at time of exposure, the higher the risk of developing cancer.

Another cause may be due to high-dose irradiation to the head and neck. Patients with Hodgkin lymphoma treated with mantlefield irradiation have an increased risk of developing thyroid cancer, although hypothyroidism is more likely.

Treatment

Thyroid cancer may require surgery. Common surgeries include thyroidectomy, lobectomy, and tracheostomy.

Radioactive Iodine-131 is used in patients with papillary or follicular thyroid cancer for ablation of residual thyroid tissue after surgery and for the treatment of thyroid cancer. Patients with medullary, anaplastic, and most Hurthle cell cancers do not benefit from this therapy.

External irradiation may be used when the cancer is unresectable, when it recurs after resection, or to relieve pain from bone metastasis.

Sorafenib and sunitinib, approved for other indications show promise for thyroid cancer and are being used for some patients who do not qualify for clinical trials. Numerous agents are in phase II clinical trials and XL184 has started a phase III trial.

Prognosis

The prognosis of thyroid cancer is among the best of all cancers.

By European statistics, the overall relative 5-year survival rate for thyroid cancer is 85% for females and 74% for males.

Prognosis is better in younger people than older ones.

Prognosis depends mainly on the type of cancer and cancer stage.

Thyroid cancer type	5-year survival					10-year survival
	Stage I	Stage II	Stage III	Stage IV	Overall	Overall
Papillary	100%	100%	93%	51%	96% or 97%	93%
Follicular	100%	100%	71%	50%	91%	85%

Medullary	100%	98%	81%	28%	80%, 83% or 86%	75%
Anaplastic	(always stage IV)			7%	7% or 14%	

Chapter 2

Thyroid Nodule

Thyroid nodule	
ICD-9	241.0
DiseasesDB	5332
eMedicine	med/3224
MeSH	D016606

Thyroid nodules are lumps which commonly arise within an otherwise normal thyroid gland. They indicate a thyroid neoplasm, but only a small percentage of these are thyroid cancers.

Presentation

Often these abnormal growths of thyroid tissue are located at the edge of the thyroid gland so they can be felt as a lump in the throat. When they are large or when they occur in very thin individuals, they can even sometimes be seen as a lump in the front of the neck.

Diagnosis

After a nodule is found during a physical examination, a referral to an endocrinologist, a thyroidologist or otolaryngologist may occur. Most commonly an ultrasound is performed to confirm the presence of a nodule, and assess the status of the whole gland. Measurement of thyroid stimulating hormone and anti-thyroid antibodies will help decide if there is a functional thyroid disease such as Hashimoto's thyroiditis present, a known cause of a benign nodular goiter. Fine needle biopsy for histopathology is also used.

Thyroid nodules are extremely common in young adults and children. Almost 50% of people have had one, but they are usually only detected by a GP during the course of a health examination, or through a different affliction.

Fine needle biopsy

One approach used to determine whether the nodule is malignant is the fine needle biopsy (FNB), which some have described as the most cost-effective, sensitive and accurate test.

FNB or ultrasound-guided FNA usually yields sufficient thyroid cells to assess the risk of malignancy, although in some cases, the suspected nodule may need to be removed surgically for pathological examination.

Rarely, a biopsy is done using a large cutting needle, so that a piece of nodule capsule can be obtained.

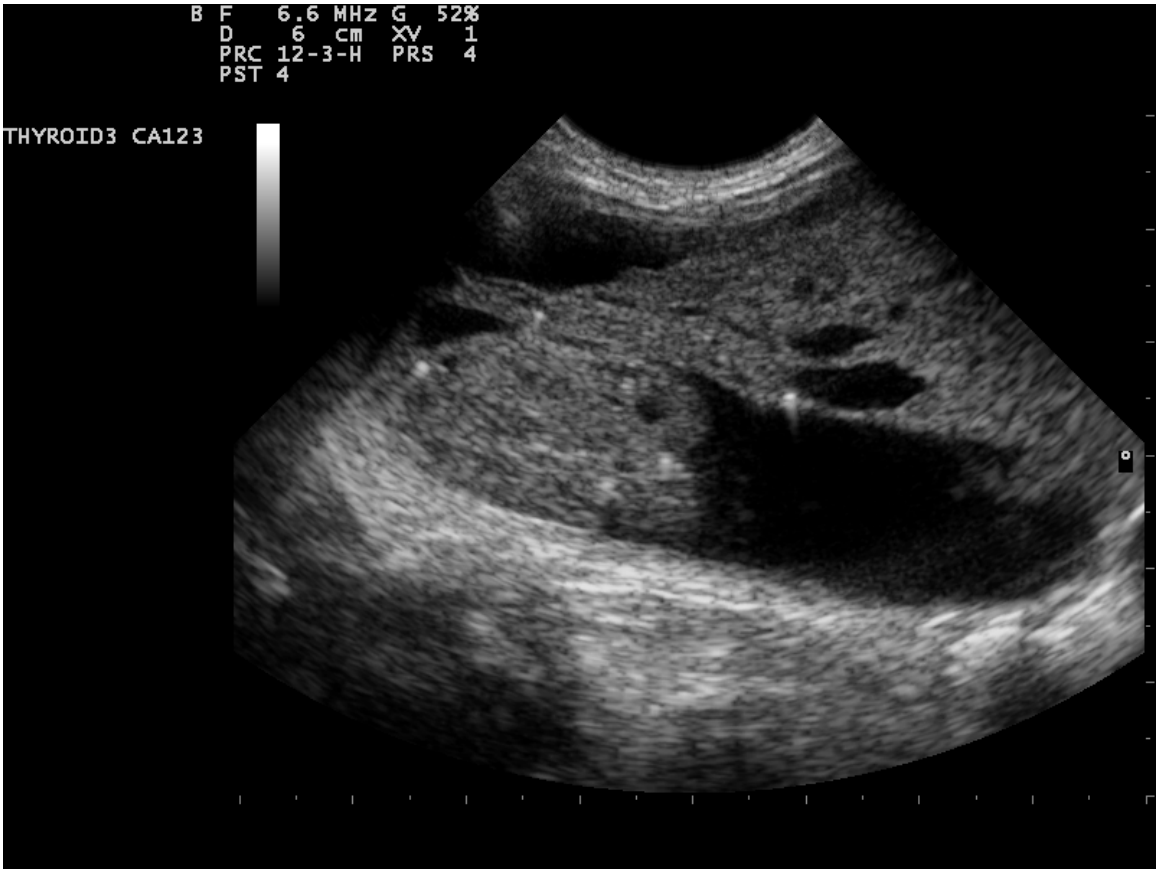
Blood tests

Blood or imaging tests may be done prior to or in lieu of a biopsy. The possibility of a nodule which secretes thyroid hormone (which is less likely to be cancer) or hypothyroidism is investigated by measuring thyroid stimulating hormone (TSH), and the thyroid hormones thyroxine (T4) and triiodothyronine (T3).

Tests for serum thyroid autoantibodies are sometimes done as these may indicate autoimmune thyroid disease (which can mimic nodular disease).

Imaging

The blood assays may be accompanied by ultrasound imaging of the nodule to determine the position, size and texture, and to assess whether the nodule may be cystic (fluid filled). Also suspicious findings in a nodule are hypoechoic, irregular borders, microcalcifications, or very high levels of blood flow within the nodule. Less suspicious findings in benign nodules include, hyperechoic, comet tail artifacts from colloid, no blood flow in the nodule and a halo, or smooth border.



Comet tail artifacts from colloid.

Some clinicians will also request technetium (Tc) or radioactive iodine (I) imaging of the thyroid. An ^{123}I scan showing a hot nodule, accompanied by a lower than normal TSH, is strong evidence that the nodule is not cancerous.

Malignancy

Only a small percentage of lumps in the neck are malignant, and most thyroid nodules are benign.

There are many factors to consider when diagnosing a malignant lump.

If the patient is a smoker, the chances of malignancy are considerably higher. When coupled with difficulty swallowing or breathing, this may be a symptom of a serious condition and requires speedy medical attention.

Solitary thyroid nodule

Risks for cancer

Solitary thyroid nodules are more common in females yet more worrisome in males. Other associations with neoplastic nodules are family history of thyroid cancer and prior radiation to the head and neck.

Radiation exposure to the head and neck may be for historic indications such as tonsillar and adenoid hypertrophy, "enlarged thymus", acne vulgaris, or current indications such as Hodgkin's lymphoma. Children living near the Chernobyl nuclear power plant during the catastrophe of 1986 have experienced a 60-fold increase in the incidence of thyroid cancer. Thyroid cancer arising in the background of radiation is often multifocal with a high incidence of lymph node metastasis and has a poor prognosis.

Signs and symptoms

Worrisome sign and symptoms include voice hoarseness, rapid increase in size, compressive symptoms (such as dyspnoea or dysphagia) and appearance of lymphadenopathy.

Investigations

- TSH - A thyroid-stimulating hormone level should be obtained first. If it is suppressed, then the nodule is likely a hyperfunctioning (or "hot") nodule. These are rarely malignant.
- FNAC - fine needle aspiration cytology is the investigation of choice given a non-suppressed TSH. Repeat the FNAC in 6 months if the nodule enlarges.
- Imaging - Ultrasound and radioiodine scanning.

Thyroid Scan

Cold - 85% of nodules are cold. Of these, up to 25% are malignant.
Hot - 5% of nodules are hot. Among these, 1% are malignant.

Surgery

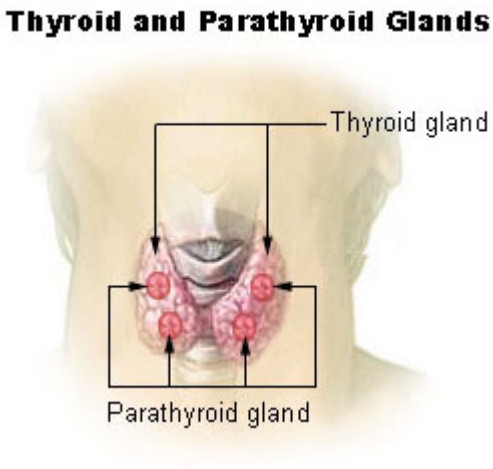
Surgery should be performed in the following instances

- Reaccumulation of the nodule despite 3-4 repeated FNACs
- Size in excess of 4 cm in some cases
- Compressive symptoms
- Signs of malignancy (vocal cord dysfunction, lympadenopathy)

Chapter 3

Thyroid

thyroid



Thyroid and parathyroid.

Latin	*glandula thyroidea*
System	Endocrine system
Precursor	Thyroid diverticulum (an extension of endoderm into 2nd Branchial arch)
MeSH	*Thyroid+Gland*
Dorlands/Elsevier	*Thyroid gland*

In vertebrate anatomy, the **thyroid gland** or simply, the **thyroid**, is one of the largest endocrine glands in the body, and is not to be confused with the parathyroid glands. The thyroid gland is found in the neck, inferior to (below) the thyroid cartilage (also known as the Adam's Apple) and at approximately the same level as the cricoid cartilage. The

thyroid controls how quickly the body uses energy, makes proteins, and controls how sensitive the body should be to other hormones.

The thyroid gland participates in these processes by producing thyroid hormones, the principal ones being triiodothyronine (T_3) and thyroxine (T_4). These hormones regulate the rate of metabolism and affect the growth and rate of function of many other systems in the body. T_3 and T_4 are synthesized utilizing both iodine and tyrosine. The thyroid gland also produces calcitonin, which plays a role in calcium homeostasis.

The thyroid gland is controlled by thyroid-stimulating hormone (TSH) produced by the pituitary (to be specific, the anterior pituitary) and thyrotropin-releasing hormone (TRH) produced by the hypothalamus. The thyroid gland gets its name from the Greek word for "shield", after the shape of the related thyroid cartilage. The most common problems of the thyroid gland consist of an overactive thyroid gland, referred to as hyperthyroidism, and an underactive thyroid gland, referred to as hypothyroidism.

Anatomy

The thyroid gland is a butterfly-shaped organ and is composed of two cone-like lobes or wings, *lobus dexter* (right lobe) and *lobus sinister* (left lobe), connected via the isthmus. The organ is situated on the anterior side of the neck, lying against and around the larynx and trachea, reaching posteriorly the oesophagus and carotid sheath. It starts cranially at the oblique line on the thyroid cartilage (just below the laryngeal prominence, or 'Adam's Apple'), and extends inferiorly to approximately the fifth or sixth tracheal ring. It is difficult to demarcate the gland's upper and lower border with vertebral levels because it moves position in relation to these during swallowing.

The thyroid gland is covered by a fibrous sheath, the *capsula glandulae thyroidea*, composed of an internal and external layer. The external layer is anteriorly continuous with the *lamina pretrachealis fasciae cervicalis* and posteriorolaterally continuous with the carotid sheath. The gland is covered anteriorly with infrahyoid muscles and laterally with the sternocleidomastoid muscle also known as sternomastoid muscle. On the posterior side, the gland is fixed to the cricoid and tracheal cartilage and cricopharyngeus muscle by a thickening of the fascia to form the posterior suspensory ligament of Berry. The thyroid gland's firm attachment to the underlying trachea is the reason behind its movement with swallowing. In variable extent, Lalouette's Pyramid, a pyramidal extension of the thyroid lobe, is present at the most anterior side of the lobe. In this region, the recurrent laryngeal nerve and the inferior thyroid artery pass next to or in the ligament and tubercle.

Between the two layers of the capsule and on the posterior side of the lobes, there are on each side two parathyroid glands.

The thyroid isthmus is variable in presence and size, and can encompass a cranially extending pyramid lobe (*lobus pyramidalis* or *processus pyramidalis*), remnant of the

thyroglossal duct. The thyroid is one of the larger endocrine glands, weighing 2-3 grams in neonates and 18-60 grams in adults, and is increased in pregnancy.

The thyroid is supplied with arterial blood from the superior thyroid artery, a branch of the external carotid artery, and the inferior thyroid artery, a branch of the thyrocervical trunk, and sometimes by the thyroid ima artery, branching directly from the brachiocephalic trunk. The venous blood is drained via superior thyroid veins, draining in the internal jugular vein, and via inferior thyroid veins, draining via the *plexus thyroideus impar* in the left brachiocephalic vein.

Lymphatic drainage passes frequently the lateral deep cervical lymph nodes and the pre- and parathracheal lymph nodes. The gland is supplied by parasympathetic nerve input from the superior laryngeal nerve and the recurrent laryngeal nerve.

Evolution

Thyroid cells phylogenetically derived from primitive iodide-concentrating gastroenteric cells (endostyle) which, during evolution, migrated and specialized in uptake and storage of iodine in follicular cellular structures, also in order to adapt the organisms from iodine-rich sea to iodine-deficient land. Venturi et al. suggested that iodide has an ancestral antioxidant function in all iodide-concentrating cells from primitive algae to more recent vertebrates. In 2008, this ancestral antioxidant action of iodides has been experimentally confirmed by Küpper et al. Since 700 million years ago thyroxine is present in fibrous exoskeletal scleroproteins of the lowest invertebrates (Porifera and Anthozoa), without showing any hormonal action. When some primitive marine chordates started to emerge from the iodine-rich sea and transferred to iodine-deficient fresh water and finally land, their diet became iodine deficient. Therefore, during progressive slow adaptation to terrestrial life, the primitive vertebrates learned to use the primitive thyroxine in order to transport antioxidant iodide into the cells. Therefore, the remaining triiodothyronine (T_3), the real active hormone, became active in the metamorphosis and thermogenesis for a better adaptation of the organisms to terrestrial environment (fresh water, atmosphere, gravity, temperature and diet). In fact, the U.S. Food and Nutrition Board and Institute of Medicine recommended daily allowance of iodine ranges from 150 micrograms /day for adult humans to 290 micrograms /day for lactating mothers. However, the thyroid gland needs no more than 70 micrograms /day to synthesize the requisite daily amounts of T_4 and T_3. These higher recommended daily allowance levels of iodine seem necessary for optimal function of a number of body systems, including lactating breast, gastric mucosa, salivary glands, oral mucosa, thymus, epidermis, choroid plexus and brain, etc.

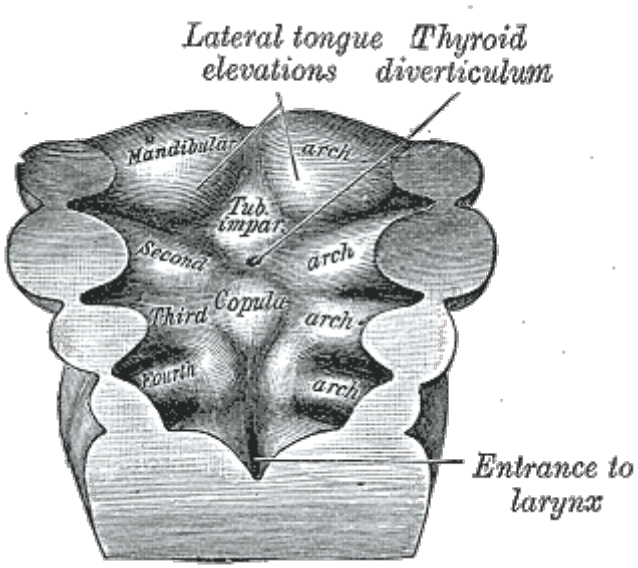
Embryological development

In the fetus, at 3–4 weeks of gestation, the thyroid gland appears as an epithelial proliferation in the floor of the pharynx at the base of the tongue between the tuberculum impar and the copula linguae at a point latter indicated by the foramen cecum. The thyroid then descends in front of the pharyngeal gut as a bilobed diverticulum through the thyroglossal duct. Over the next few weeks, it migrates to the base of the neck. During

migration, the thyroid remains connected to the tongue by a narrow canal, the thyroglossal duct.

Thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) start being secreted from the fetal hypothalamus and pituitary at 18-20 weeks of gestation, and fetal production of thyroxine (T_4) reach a clinically significant level at 18–20 weeks. Fetal triiodothyronine (T_3) remains low (less than 15 ng/dL) until 30 weeks of gestation, and increases to 50 ng/dL at term. Fetal self-sufficiency of thyroid hormones protects the fetus against e.g. brain development abnormalities caused by maternal hypothyroidism. However, preterm births can suffer neurodevelopmental disorders due to lack of maternal thyroid hormones due their own thyroid being insufficiently developed to meet their postnatal needs.

The portion of the thyroid containing the parafollicular C cells, those responsible for the production of calcitonin, are derived from the neural crest. This is first seen as the ultimobranchial body, which joins the primordial thyroid gland during its descent to its final location in the anterior neck.



Histology

At the microscopic level, there are three primary features of the thyroid:

Feature	Description
Follicles	The thyroid is composed of spherical follicles that selectively absorb iodine (as iodide ions, I^-) from the blood for production of thyroid hormones, but also for storage of iodine in thyroglobulin, in fact iodine is necessary for other important iodine-concentrating organs as breast, stomach, salivary glands, thymus etc. Twenty-five percent of all the body's iodide ions are in the thyroid gland. Inside the follicles, colloid serves as a reservoir of materials for thyroid hormone production and, to a lesser extent, acts as a reservoir for the hormones themselves. Colloid is rich in a protein called thyroglobulin.
Thyroid epithelial cells (or "follicular cells")	The follicles are surrounded by a single layer of thyroid epithelial cells, which secrete T_3 and T_4. When the gland is not secreting T_3/T_4 (inactive), the epithelial cells range from low columnar to cuboidal cells. When active, the epithelial cells become tall columnar cells.
Parafollicular cells (or "C cells")	Scattered among follicular cells and in spaces between the spherical follicles are another type of thyroid cell, parafollicular cells, which secrete calcitonin.

Disorders

Disorders of the thyroid gland fall into the following categories:

Hyperthyroidism

Hyperthyroidism, or overactive thyroid, is the overproduction of the thyroid hormones T_3 and T_4, and is most commonly caused by the development of Graves' disease, an autoimmune disease in which antibodies are produced which stimulate the thyroid to secrete excessive quantities of thyroid hormones. The disease can result in the formation of a toxic goiter as a result of thyroid growth in response to a lack of negative feedback mechanisms. It presents with symptoms such as a thyroid goiter, protruding eyes (exopthalmos), palpitations, excess sweating, diarrhea, weight loss, muscle weakness and unusual sensitivity to heat.

Beta blockers are used to decrease symptoms of hyperthyroidism such as increased heart rate, tremors, anxiety and heart palpitations, and anti-thyroid drugs are used to decrease the production of thyroid hormones, in particular, in the case of Graves' disease. These medications take several months to take full effect and have side-effects such as skin rash

or a drop in white blood cell count, which decreases the ability of the body to fight off infections. These drugs involve frequent dosing (often one pill every 8 hours) and often require frequent doctor visits and blood tests to monitor the treatment, and may sometimes lose effectiveness over time. Due to the side-effects and inconvenience of such drug regimens, some patients choose to undergo radioactive iodine-131 treatment. Radioactive iodine is administered in order to destroy a proportion of or the entire thyroid gland, since the radioactive iodine is selectively taken up by the gland and gradually destroys the cells of the gland. Alternatively, the gland may be partially or entirely removed surgically, though iodine treatment is usually preferred since the surgery is invasive and carries a risk of damage to the parathyroid glands or the nerves controlling the vocal cords. If the entire thyroid gland is removed, hypothyroidism results.

Hypothyroidism

Hypothyroidism is the underproduction of the thyroid hormones T_3 and T_4. Hypothyroid disorders may occur as a result of congenital thyroid abnormalities, autoimmune disorders such as Hashimoto's thyroiditis, iodine deficiency, especially in poorer countries, or the removal of the thyroid following surgery to treat severe hyperthyroidism. Typical symptoms are abnormal weight gain, tiredness, baldness, cold intolerance, and bradycardia. Hypothyroidism is treated with hormone replacement therapy, such as levothyroxine, which is typically required for the rest of the patient's life. Thyroid hormone treatment is given under the care of a physician and may take a few weeks to become effective.

Negative feedback mechanisms result in growth of the thyroid gland when thyroid hormones are being produced in sufficiently low quantities as a means of increasing the thyroid output; however, where the hypothyroidism is caused by iodine insufficiency, the thyroid is unable to produce T_3 and T_4 and as a result, the thyroid may continue to grow to form a non-toxic goiter. It is termed non-toxic as it does not produce toxic quantities of thyroid hormones, despite its size.

Initial hyperthyroidism followed by hypothyroidism

This is the overproduction of T_3 and T_4 followed by the underproduction of T_3 and T_4. There are two types: Hashimoto's thyroiditis and postpartum thyroiditis.

Hashimoto's thyroiditis is an autoimmune disorder whereby the body's own immune system reacts with the thyroid tissues. At the beginning, the gland is overactive, and then becomes underactive as the gland is destroyed resulting in too little thyroid hormone production or hypothyroidism. Hashimoto's is most common in middle-age females and tends to run in families. Also more common in individuals with hashimoto's thyroiditis are type 1 diabetes and celiac disease.

Postpartum thyroiditis occurs in some females following delivery. The gland becomes inflamed and the condition initially presents with overactivity of the gland followed by underactivity. In some cases, the gland does recover with time and resume its functions.

Cancers

Cancers do occur in the thyroid gland and are more common in females. In most cases, the thyroid cancer presents as a painless mass in the neck. It is very unusual for the thyroid cancers to present with symptoms, unless it has been neglected. One may be able to feel a hard nodule in the neck. Diagnosis is made using a needle biopsy and various radiological studies.

Non-cancerous nodules

Many individuals may find the presence of small masses (nodules) in the neck. The majority of these thyroid nodules are benign (non cancerous). The presence of a thyroid nodule does not mean that one has thyroid disease. Most thyroid nodules do not cause any symptoms, and most are discovered on an incidental examination. Doctors usually perform a needle aspiration biopsy of the thyroid to determine the status of the nodules. If the nodule is found to be non-cancerous, no other treatment is required. If the nodule is suspicious then surgery is recommended.

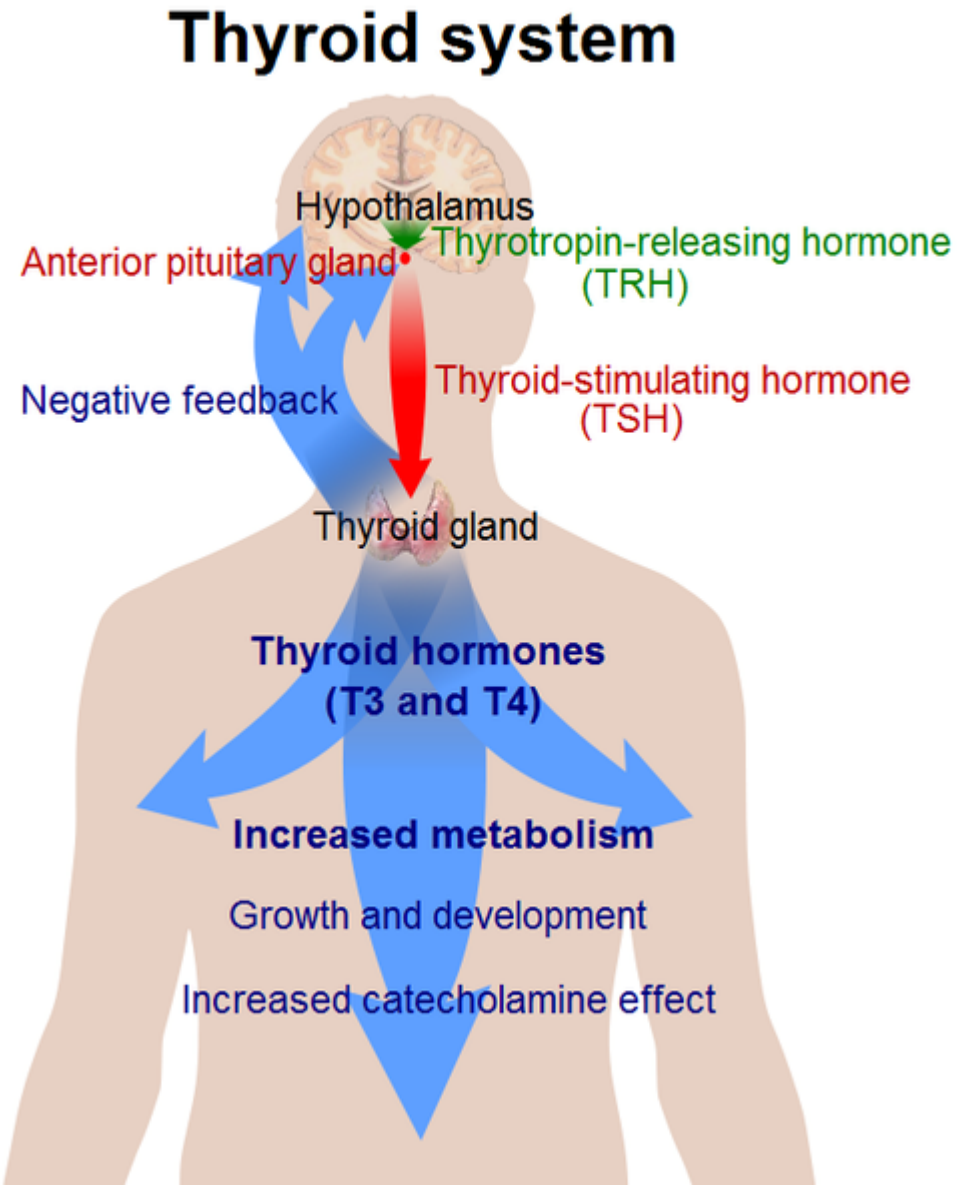
Seasonal Aggravation

Limited research shows that seasonal allergies may trigger episodes of hypo- or hyperthyroidism.

Physiology

The primary function of the thyroid is production of the hormones triiodothyronine (T_3), thyroxine (T_4), and calcitonin. Up to 80% of the T_4 is converted to T_3 by peripheral organs such as the liver, kidney and spleen. T_3 is several times more powerful than T_4, which is largely a prohormone, perhaps four or even ten times more active.

T_3 and T_4 production and action



The system of the thyroid hormones T_3 and T_4.

Thyroxine (T_4) is synthesised by the follicular cells from free tyrosine and on the tyrosine residues of the protein called thyroglobulin (Tg). Iodine is captured with the "iodine trap" by the hydrogen peroxide generated by the enzyme thyroid peroxidase (TPO) and linked to the 3' and 5' sites of the benzene ring of the tyrosine residues on Tg, and on free tyrosine. Upon stimulation by the thyroid-stimulating hormone (TSH), the follicular cells reabsorb Tg and cleave the iodinated tyrosines from Tg in lysosomes, forming T_4 and T_3 (in T_3, one iodine atom is absent compared to T_4), and releasing them into the blood. Deiodinase enzymes convert T_4 to T_3. Thyroid hormone secreted from the gland is about 80-90% T_4 and about 10-20% T_3.

Cells of the developing brain are a major target for the thyroid hormones T_3 and T_4. Thyroid hormones play a particularly crucial role in brain maturation during fetal development. A transport protein that seems to be important for T_4 transport across the blood-brain barrier (OATP1C1) has been identified. A second transport protein (MCT8) is important for T_3 transport across brain cell membranes.

Non-genomic actions of T_4 are those that are not initiated by liganding of the hormone to intranuclear thyroid receptor. These may begin at the plasma membrane or within cytoplasm. Plasma membrane-initiated actions begin at a receptor on the integrin alphaV beta3 that activates ERK1/2. This binding culminates in local membrane actions on ion transport systems such as the Na(+)/H(+) exchanger or complex cellular events including cell proliferation. These integrins are concentrated on cells of the vasculature and on some types of tumor cells, which in part explains the proangiogenic effects of iodothyronines and proliferative actions of thyroid hormone on some cancers including gliomas. T_4 also acts on the mitochondrial genome via imported isoforms of nuclear thyroid receptors to affect several mitochondrial transcription factors. Regulation of actin polymerization by T_4 is critical to cell migration in neurons and glial cells and is important to brain development.

T_3 can activate phosphatidylinositol 3-kinase by a mechanism that may be cytoplasmic in origin or may begin at integrin alpha V beta3.

In the blood, T_4 and T_3 are partially bound to thyroxine-binding globulin (TBG), transthyretin, and albumin. Only a very small fraction of the circulating hormone is free (unbound) - T_4 0.03% and T_3 0.3%. Only the free fraction has hormonal activity. As with the steroid hormones and retinoic acid, thyroid hormones cross the cell membrane and bind to intracellular receptors (α_1, α_2, β_1 and β_2), which act alone, in pairs or together with the retinoid X-receptor as transcription factors to modulate DNA transcription.

T_3 and T_4 regulation

The production of thyroxine and triiodothyronine is regulated by thyroid-stimulating hormone (TSH), released by the anterior pituitary. The thyroid and thyrotropes form a negative feedback loop: TSH production is suppressed when the T_4 levels are high. The TSH production itself is modulated by thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus and secreted at an increased rate in situations such as cold exposure (to stimulate thermogenesis). TSH production is blunted by somatostatin (SRIH), rising levels of glucocorticoids and sex hormones (estrogen and testosterone), and excessively high blood iodide concentration.

An additional hormone produced by the thyroid contributes to the regulation of blood calcium levels. Parafollicular cells produce calcitonin in response to hypercalcemia. Calcitonin stimulates movement of calcium into bone, in opposition to the effects of parathyroid hormone (PTH). However, calcitonin seems far less essential than PTH, as calcium metabolism remains clinically normal after removal of the thyroid (thyroidectomy), but not the parathyroids.

Thyroid function tests

Test	Abbreviation	Normal ranges
Serum thyrotropin/thyroid-stimulating hormone	**TSH**	**0.3–3.0 μU/ml**
Free thyroxine	**FT_4**	**7–18 ng/l = 0.7–1.8 ng/dl**
Serum triiodothyronine	**T_3**	**0.8–1.8 μg/l = 80–180 ng/dl**
Radioactive iodine-123 uptake	**RAIU**	**10–30%**
Radioiodine scan (gamma camera)	N/A	N/A - thyroid contrasted images
Free thyroxine fraction	FT4F	0.03–0.005%
Serum thyroxine	T_4	46–120 μg/l = 4.6–12.0 μg/dl
Thyroid hormone binding ratio	THBR	0.9–1.1
Free thyroxine index	FT4I	4–11
Free triiodothyronine l	FT_3	230–619 pg/d
Free T3 Index	FT3I	80–180
Thyroxine-binding globulin	TBG	12–20 ug/dl T4 +1.8 μg
TRH stimulation test	Peak TSH	9–30 μIU/ml at 20–30 min.
Serum thyroglobulin l	Tg	0-30 ng/m
Thyroid microsomal antibody titer	TMAb	Varies with method
Thyroglobulin antibody titer	TgAb	Varies with method

- μU/ml = mU/l, microunit per milliliter
- ng/dl, nanograms per deciliter
- μg, micrograms
- pg/d, picograms per day
- μIU/ml = mIU/l, micro-international unit per milliliter

Significance of iodine

In areas of the world where iodine is lacking in the diet the thyroid gland can become considerably enlarged, a condition called endemic goiter. Pregnant women on a diet that is severely deficient of iodine can give birth to infants who can present with thyroid hormone deficiency (congenital hypothyroidism), manifesting in problems of physical growth and development as well as brain development (a condition referred to as endemic cretinism). In many developed countries, newborns are routinely tested for congenital hypothyroidism as part of newborn screening. Children with congenital hypothyroidism are treated supplementally with levothyroxine, which facilitates normal growth and development.

Thyroxine is critical to the regulation of metabolism and growth throughout the animal kingdom. Among amphibians, for example, administering a thyroid-blocking agent such as propylthiouracil (PTU) can prevent tadpoles from metamorphosing into frogs; in contrast, administering thyroxine will trigger metamorphosis.

Because the thyroid concentrates this element, it also concentrates various radioactive isotopes of iodine produced by nuclear fission. In the event of large accidental releases of such material into the environment, the uptake of radioactive iodine isotopes by the thyroid can, in theory, be blocked by saturating the uptake mechanism with a large surplus of non-radioactive iodine, taken in the form of potassium iodide tablets. One consequence of the Chernobyl disaster was an increase in thyroid cancers in children in the years following the accident.

The use of iodised salt is an efficient way to add iodine to the diet. It has eliminated endemic cretinism in most developed countries, and some governments have made the iodination of flour, cooking oil, and salt mandatory. Potassium iodide and sodium iodide are typically used forms of supplemental iodine.

As with most substances, either too much or too little can cause problems. Recent studies on some populations are showing that excess iodine intake could cause an inceased prevelence of autoimmune thyroid disease, resulting in permanent hypothyroidism.

History

There are several findings that evidence a great interest for thyroid disorders just in the Medieval Medical School of Salerno (12th century). Rogerius Salernitanus, the Salernitan surgeon and author of "Post mundi fabricam" (around 1180) was considered at that time the surgical text par excellence all over Europe. In the chapter "De bocio" of his magnum opus, he describes several pharmacological and surgical cures, some of which nowadays are reappraised quite scientifically effective.

In modern times, the thyroid was first identified by the anatomist Thomas Wharton (whose name is also eponymised in Wharton's duct of the submandibular gland) in 1656.

Thyroxine was identified only in the 19th century.

In other animals

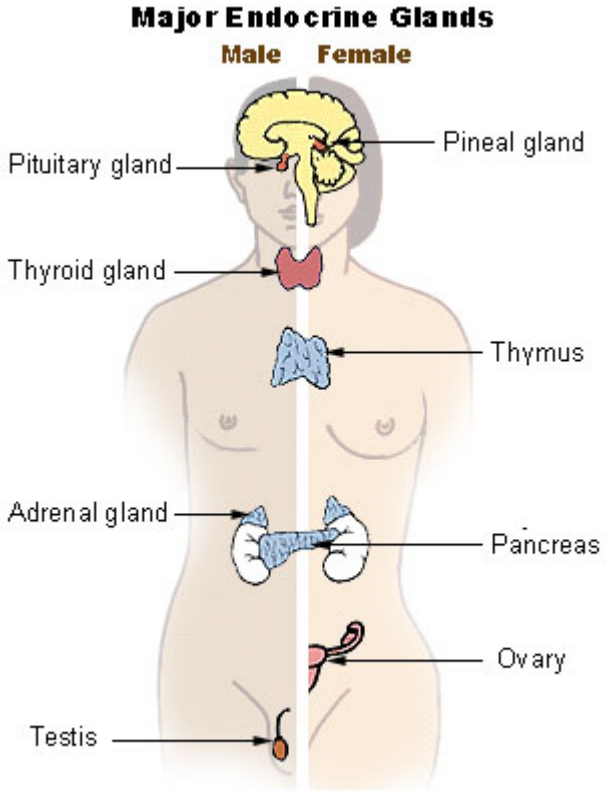
The thyroid gland is found in all vertebrates. In fish, it is, in general, located below the gills and is not always divided into distinct lobes. However, in some teleosts, patches of thyroid tissue are found elsewhere in the body, associated with the kidneys, spleen, heart, or eyes.

In tetrapods, the thyroid is always found somewhere in the neck region. In most tetrapod species, there are two paired thyroid glands - that is, the right and left lobes are not joined

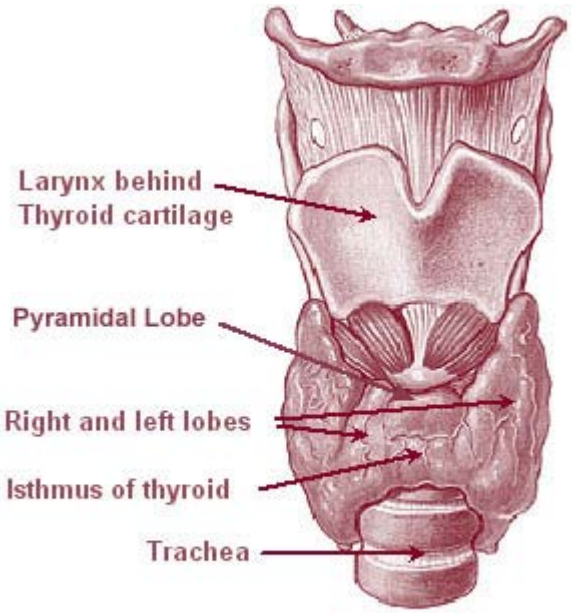
together. However, there is only ever a single thyroid gland in most mammals, and the shape found in humans is common to many other species.

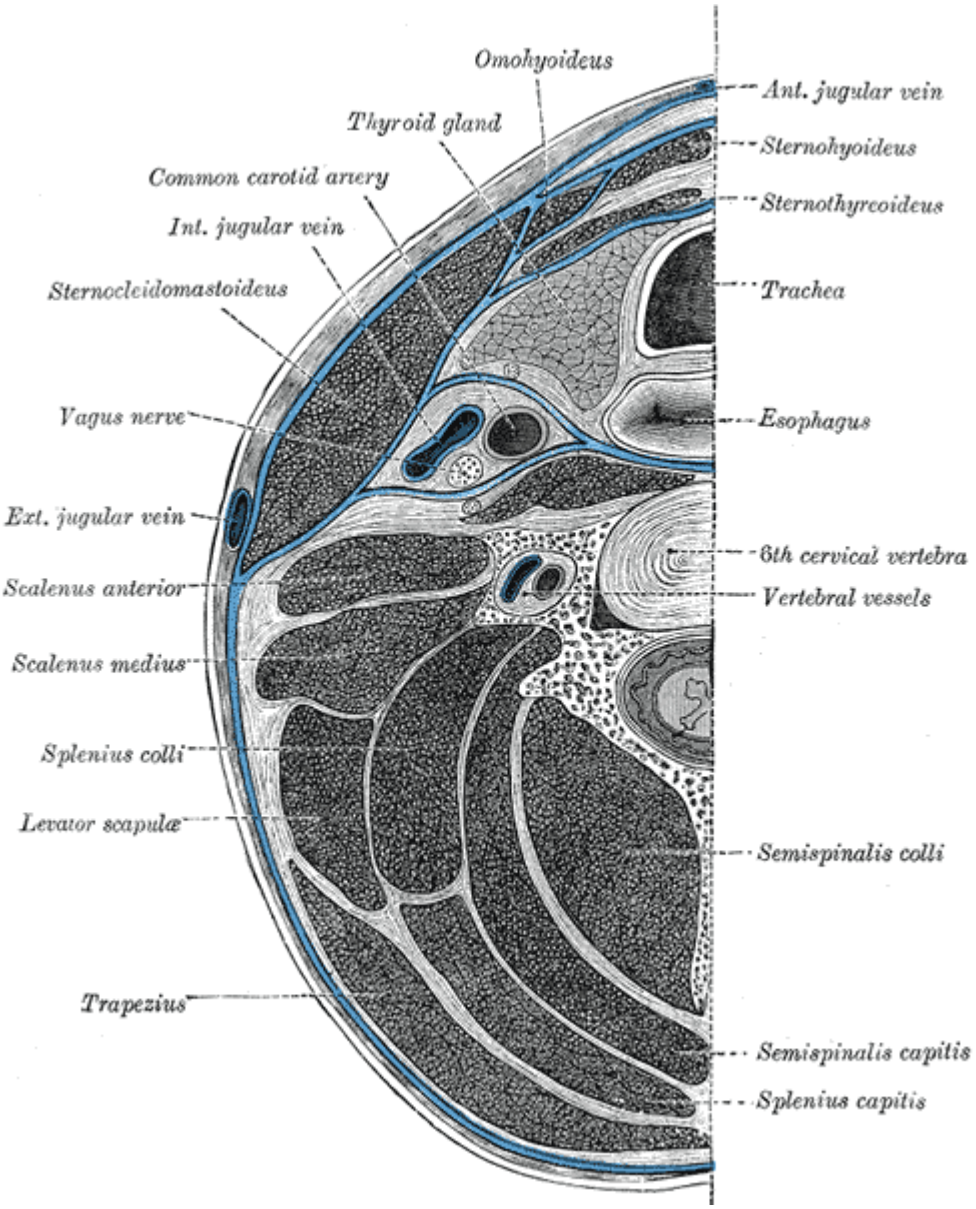
In larval lampreys, the thyroid originates as an exocrine gland, secreting its hormones into the gut, and associated with the larva's filter-feeding apparatus. In the adult lamprey, the gland separates from the gut, and becomes endocrine, but this path of development may reflect the evolutionary origin of the thyroid. For instance, the closest living relatives of vertebrates, the tunicates and *Amphioxus*, have a structure very similar to that of larval lampreys, and this also secretes iodine-containing compounds (albeit not thyroxine).

Additional images

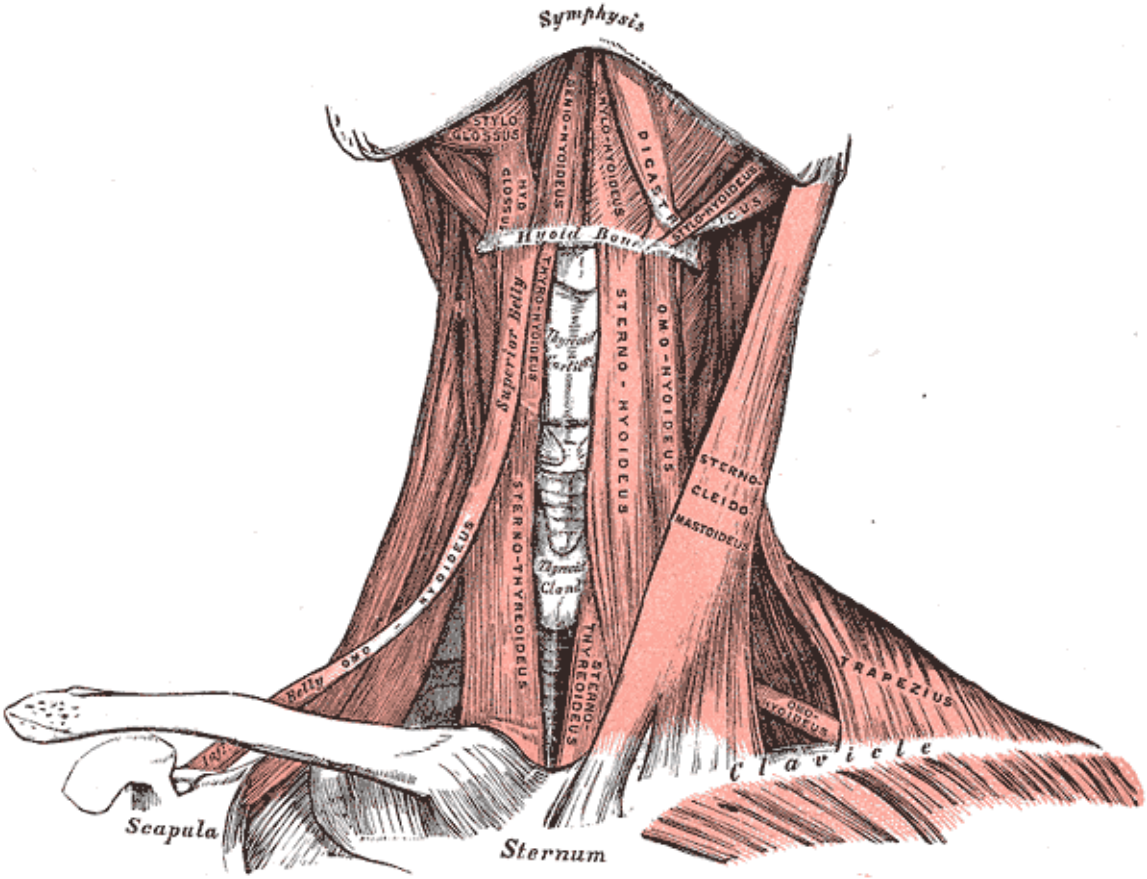


Position of the Thyroid in Males and Females

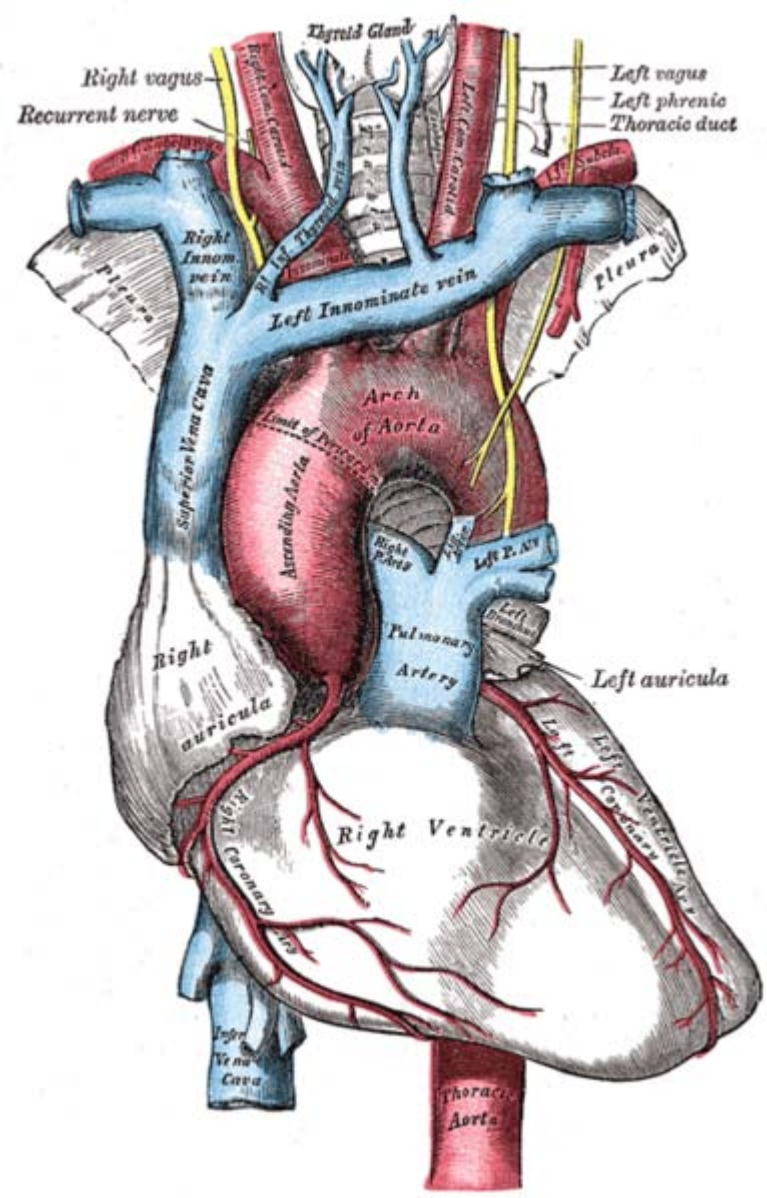

Larynx behind
Thyroid cartilage
Pyramidal Lobe
Right and left lobes
Isthmus of thyroid
Trachea



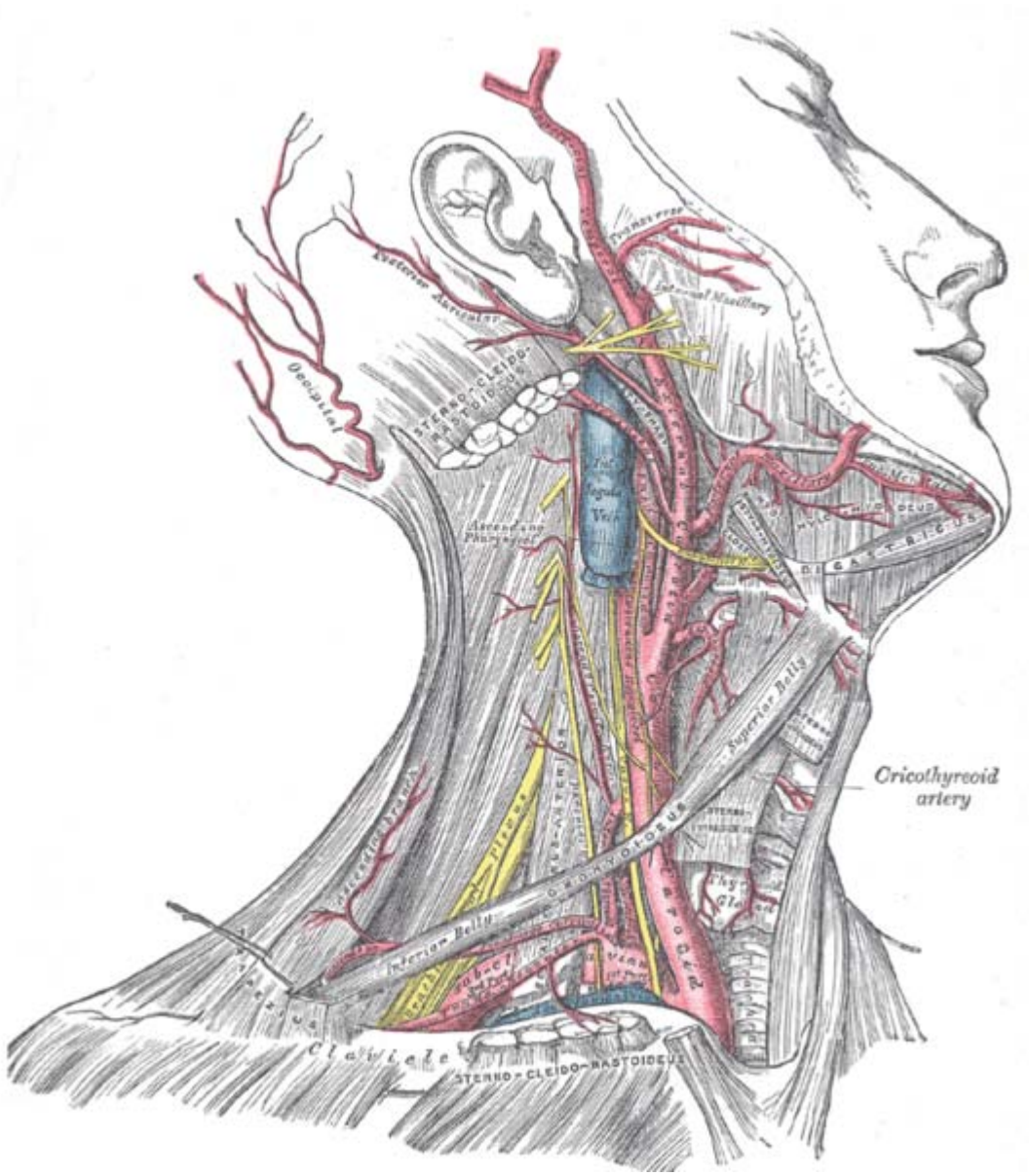
Section of the neck at about the level of the sixth cervical vertebra.



Muscles of the neck. Anterior view.



The arch of the aorta, and its branches.



Superficial dissection of the right side of the neck, showing the carotid and subclavian arteries.

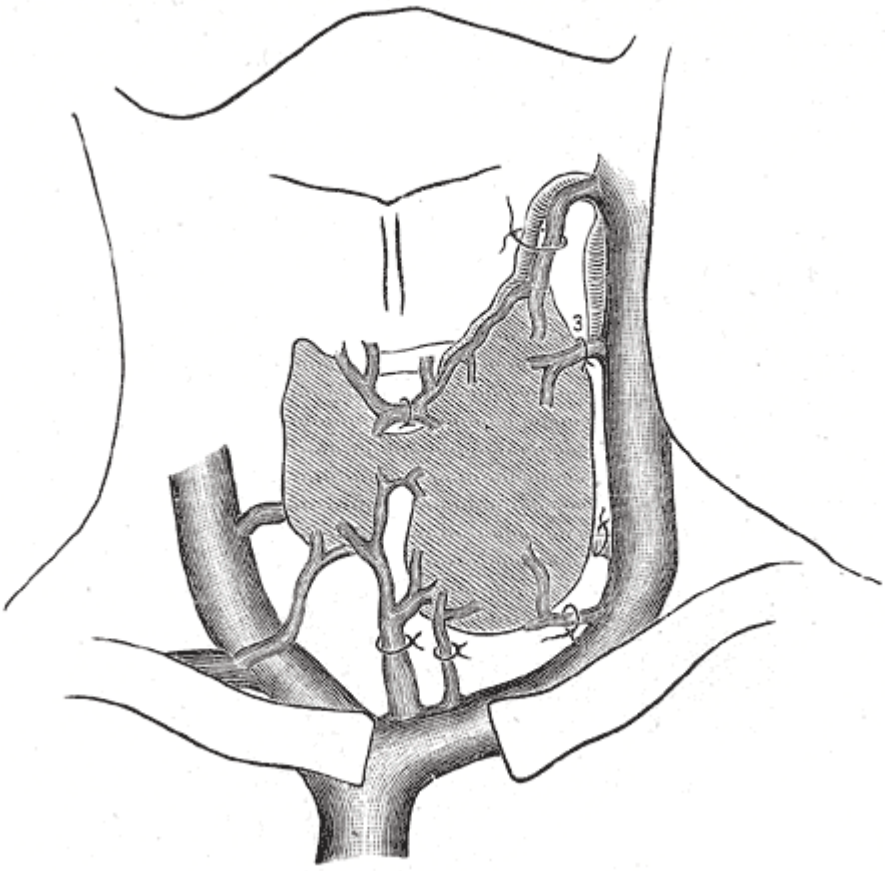
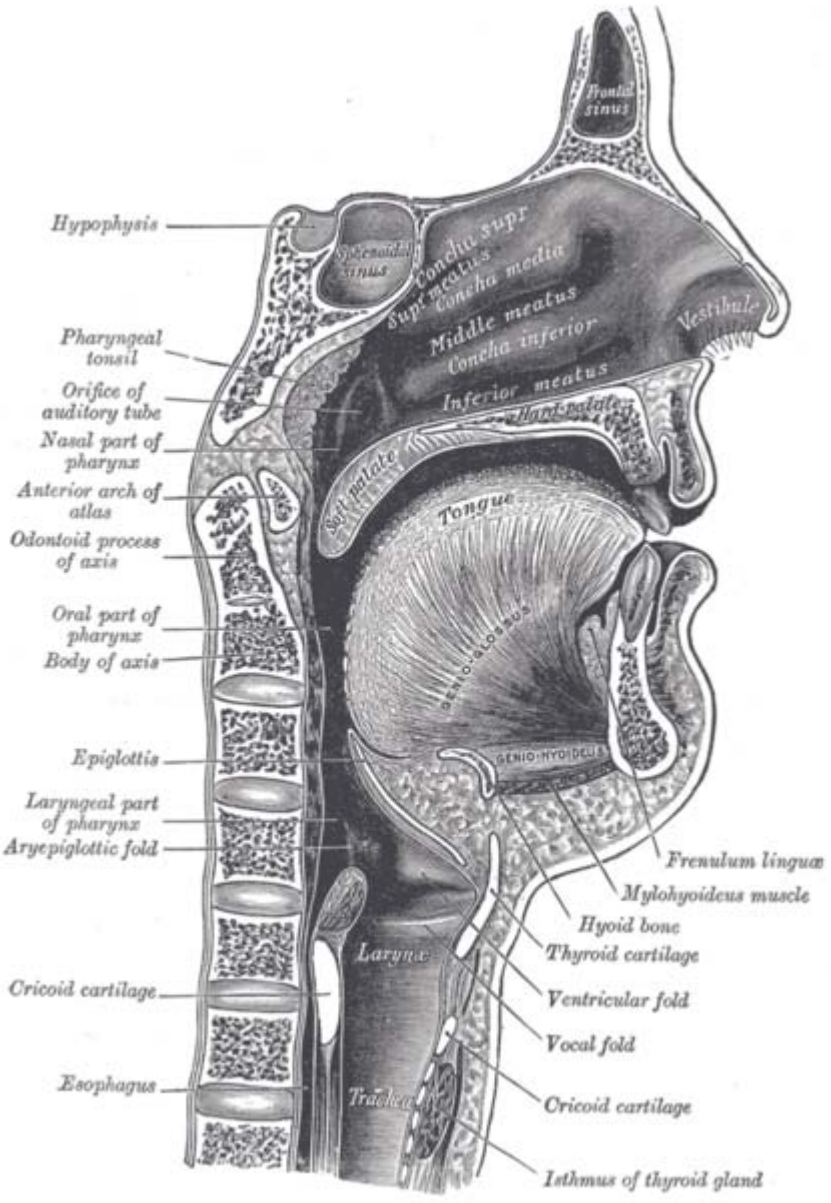
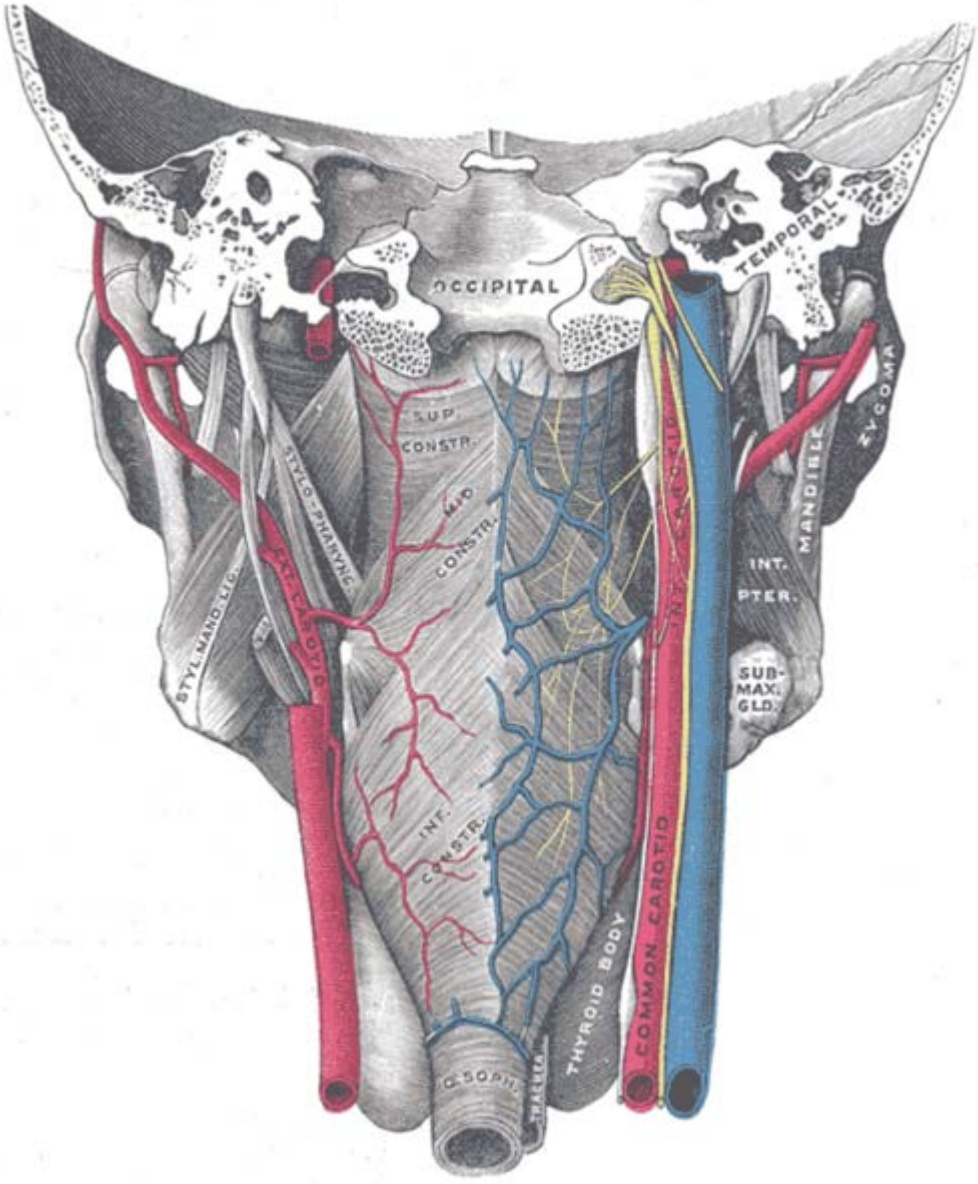


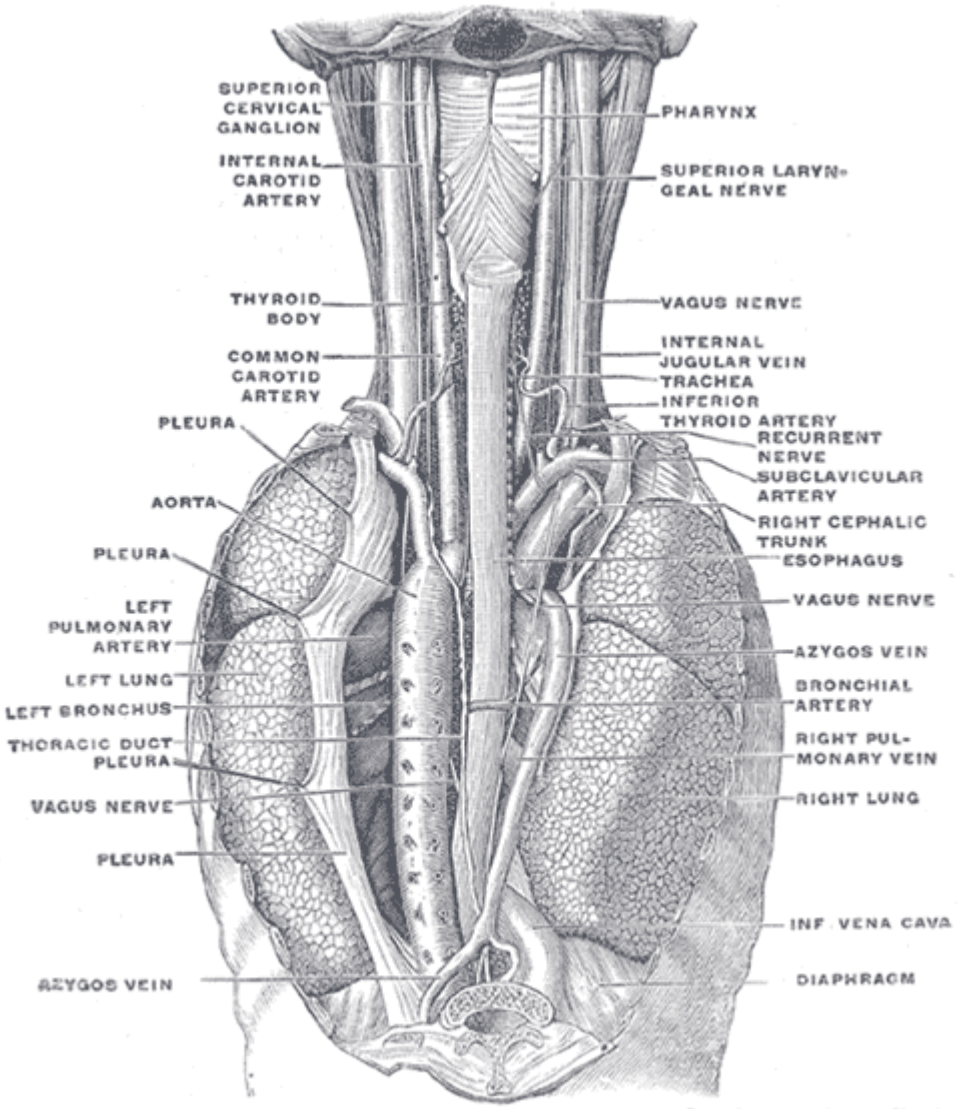
Diagram showing common arrangement of thyroid veins.



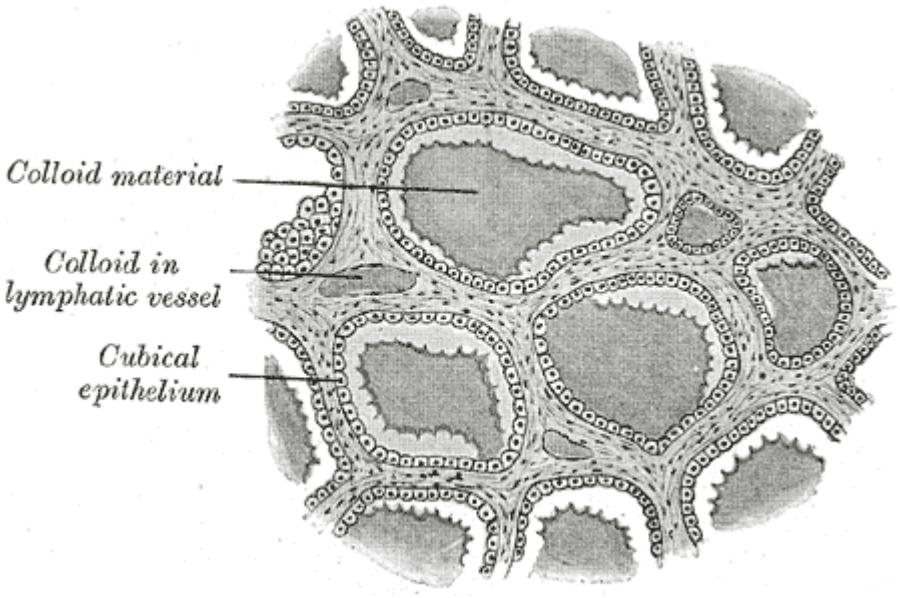
Sagittal section of nose mouth, pharynx, and larynx.



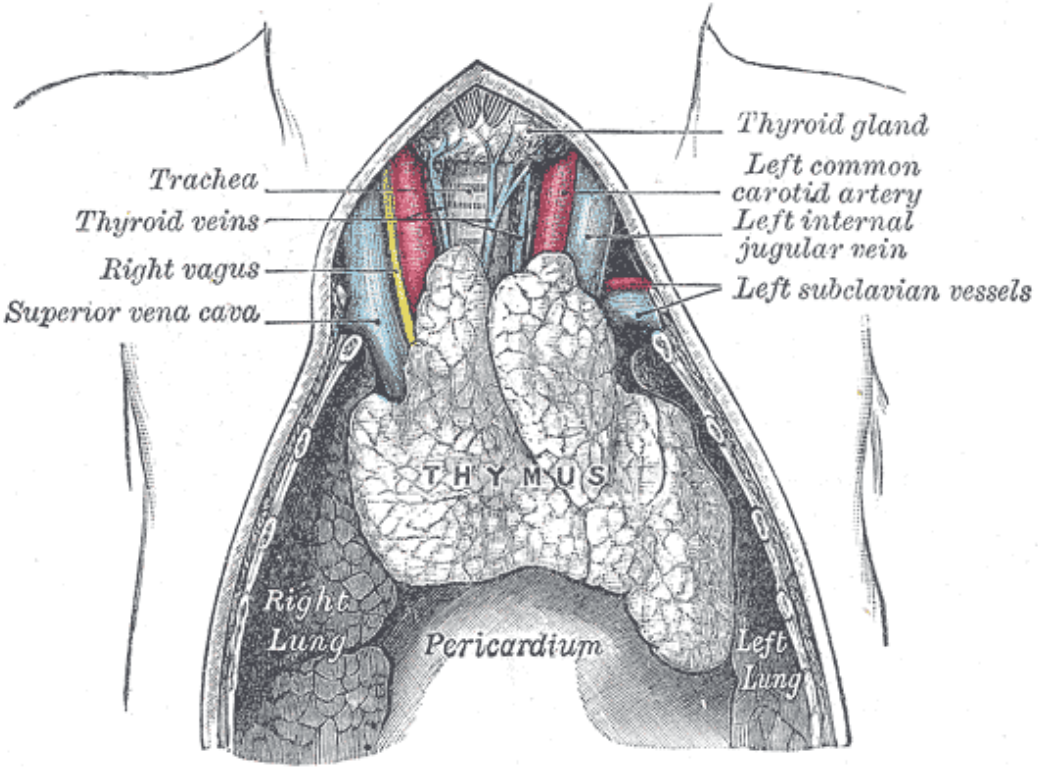
Muscles of the pharynx, viewed from behind, together with the associated vessels and nerves.



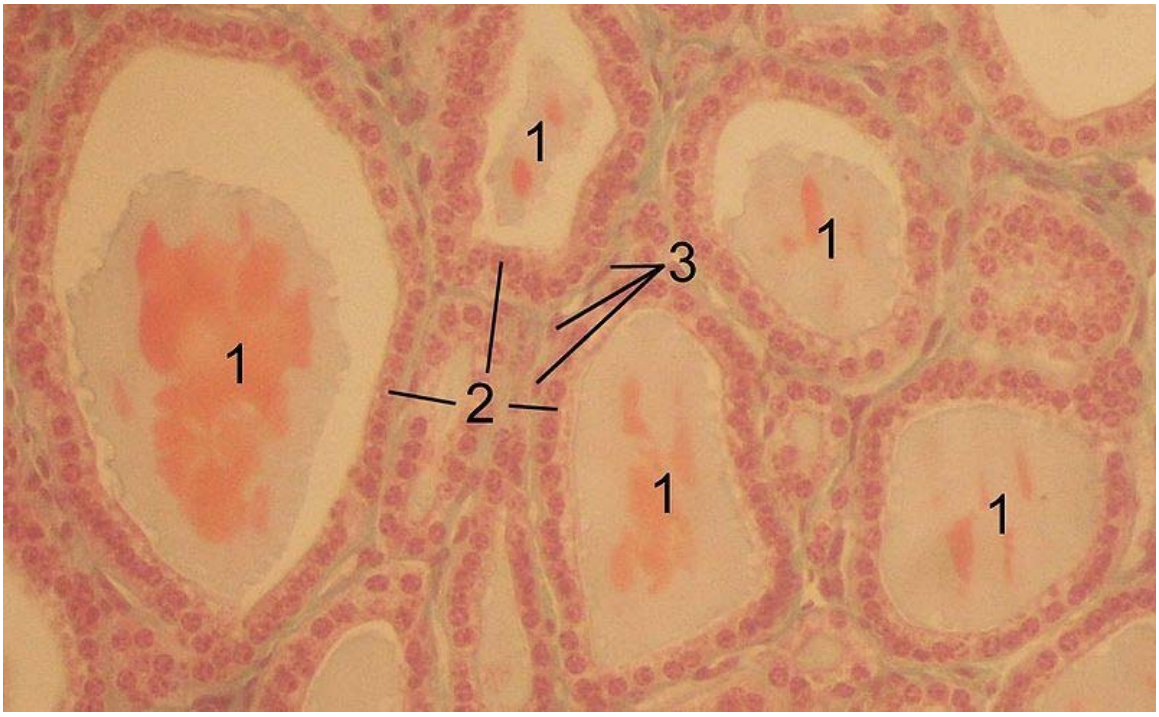
The position and relation of the esophagus in the cervical region and in the posterior mediastinum. Seen from behind.



Section of thyroid gland of sheep.



The thymus of a full-term fetus, exposed in situ.

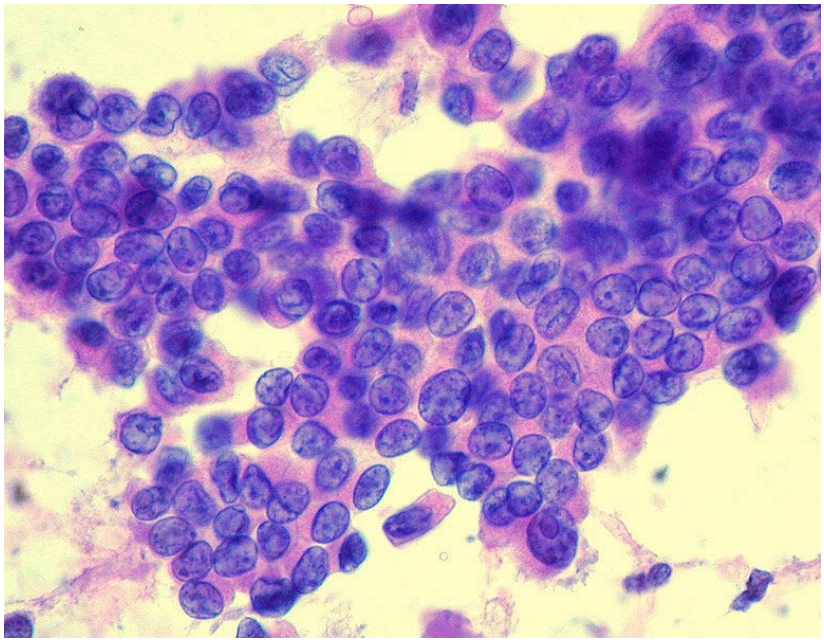


Thyoid histology

Chapter 4

Papillary Thyroid Cancer

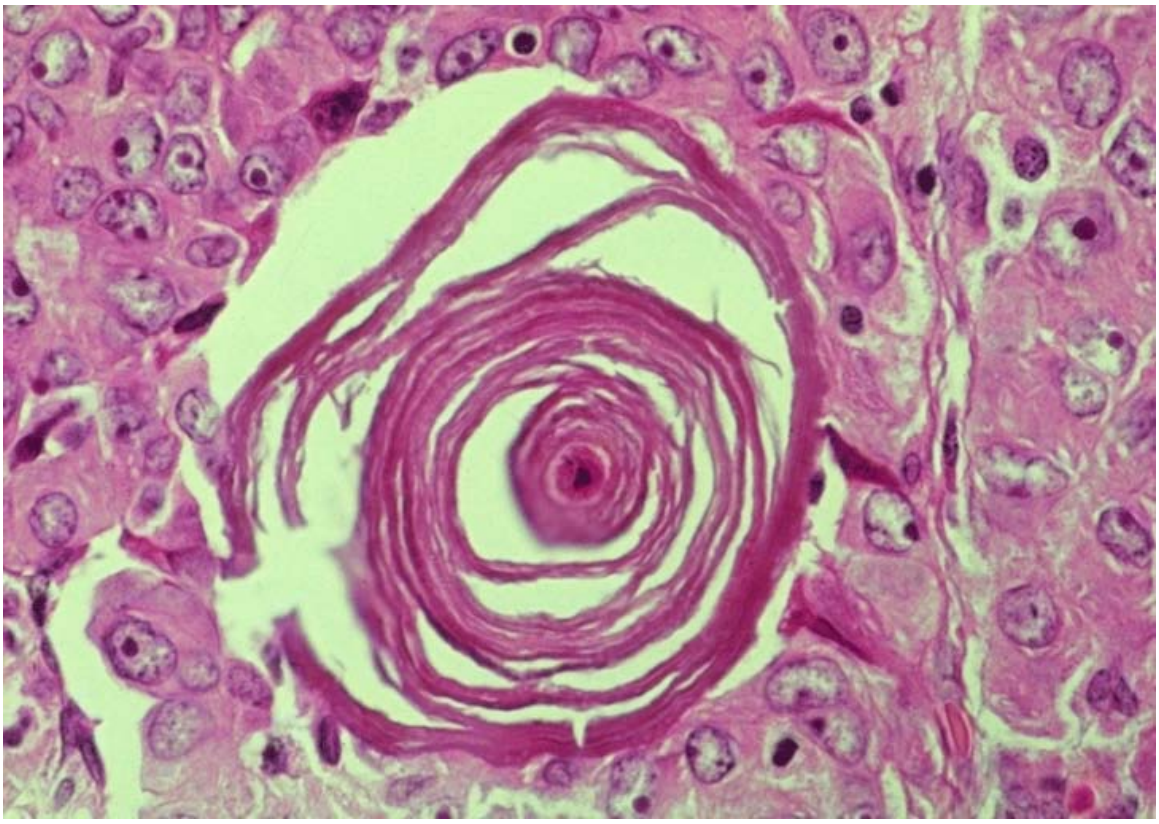
Papillary thyroid cancer



Papillary thyroid carcinoma.

ICD-10	C73.
ICD-9	193
OMIM	603744
eMedicine	med/2464

MeSH D013964



A psammoma body in papillary carcinoma of the thyroid.

Papillary thyroid cancer or **papillary thyroid carcinoma** is the most common type of thyroid cancer, representing 75% to 85% of all thyroid cancer cases. It occurs more frequently in women and presents in the 30-40 year age group. It is also the predominant cancer type in children with thyroid cancer, and in patients with thyroid cancer who have had previous radiation to the head and neck.

Markers

Thyroglobulin can be used as a tumor marker for well-differentiated papillary thyroid cancer. HBME-1 staining may be useful for differentiating papillary carcinomas from follicular carcinomas; in papillary lesions it tends to be positive.

Pathology

- Characteristic Orphan Annie eye nuclear inclusions (nuclei with uniform staining, which appear empty) and psammoma bodies on light microscopy. The former is useful in identifying the follicular variant of papillary thyroid carcinomas.

- Lymphatic spread is more common than hematogenous spread
- Multifocality is common
- The so-called Lateral Aberrant Thyroid is actually a lymph node metastasis from papillary thyroid carcinoma.
- Papillary microcarcinoma is a subset of papillary thyroid cancer defined as measuring less than or equal to 1 cm. The highest incidence of papillary thyroid microcarcinoma in autopsy series was reported by Harach et al. in 1985, who found 36 of 101 consecutive autopsies were found to have an incidental microcarcinoma. Michael Pakdaman et al. report the highest incidence in a retrospective surgical series at 49.9% of 860 cases. Management strategies for incidental papillary microcarcinoma on ultrasound (and confirmed on FNAB) range from total thyroidectomy with radioactive iodine ablation to observation alone. Harach et al. suggest using the term "occult papillary tumor" to avoid giving patients distress over having cancer.It was Woolner et al. who first arbitrarily coined the term "occult papillary carcinoma" in 1960, to describe papillary carcinomas ≤ 1.5 cm in diameter.

Although papillary carcinoma has a propensity to invade lymphatics, it is less likely to invade blood vessels. This kind of tumors are most commonly unencapsulated, and they have a high tendency to metastasize locally to lymph nodes, which may produce cystic structures near the thyroid that are difficult to diagnose because of the paucity of malignant tissue. Furthermore, papillary tumors may metastasize to the lungs and produce a few nodules or the lung fields may exhibit a snowflake appearance throughout.

Other characteristics of the papillary carcinoma is that E.M. shows increased mitochondria, increased RER, as well as increased apical microvilli. Moreover, papillary carcinomas have an indolent growth, and 40% of cases spread out of the capsule.

Associated mutations

Mutations associated with papillary thyroid cancer are mainly two forms of chromosomal translocation and one form of point mutation. These alterations lead to activation of a common carcinogenic pathway - the MAPK/ERK pathway.

Chromosomal translocations involving the RET proto-oncogene (encoding a tyrosine kinase receptor that plays essential roles in the development of neuroendocrine cells) located on chromosome 10q11 occur in approximately a fifth of papillary thyroid cancers. The fusion oncoproteins generated are termed RET/PTC proteins (ret/papillary thyroid carcinoma), and constitutively activate RET and the downstream MAPK/ERK pathway. The frequency of ret/PTC translocations is significantly higher in papillary cancers arising in children and after radiation exposure. The gene NTRK1 (encoding the TrkA receptor), located on chromosome 1q, is similarly translocated in approximately 5% to 10% of papillary thyroid cancers.

Approximately a third to a half of papillary thyroid carcinomas harbor point mutations in the BRAF oncogene, also activating the MAPK/ERK pathway. In those cases the BRAF

mutations found were V600E mutation. After performing a multivariate analysis, it was found that the absence of tumor capsule was the only parameter associated (P=0.0005) with BRAF V600E mutation. According to recent studies, papillary cancers carrying the common V600E mutation tend to have a more aggressive long term course. BRAF mutations are frequent in papillary carcinoma and in undifferentiated cancers that have developed from papillary tumors.

Diagnosis

Papillary thyroid carcinoma is usually discovered on routine examination as an asymptomatic thyroid nodule that appears as a neck mass. In some instances, the mass may have produced local symptoms. This mass is normally referred to a fine needle aspiration biopsy (FNA) for investigation. FNA accuracy is very high and it is a process widely used in these cases. Other investigation methods include ultrasound imaging and nuclear scan. The ultrasound is a useful test to distinguish solid from cystic lesions and to identify calcifications. The thyroid ultrasound is also very effective to discover microcarcinomas, which refer to very small carcinomas (<1 cm). A significant number of such carcinomas are malignant.

Papillary thyroid carcinomas are also discovered when a hard nodule is found in multinodular goiter, when enlarged cervical lymph nodes are detected, or when there are unidentified metastatic lesions elsewhere in the body. Expanding lesions found in the thyroid gland, especially if they are painful, should be examined as they may indicate the presence of papillary thyroid carcinoma. Other clinical signs that could indicate papillary thyroid are: fixation to the trachea, stony hardness, damage to recurrent laryngeal or cervical sympathetic nerves. Seventy five percent of the population will have these thyroid nodules, and the majority will always be benign.

Chest x rays are not commonly performed. In cases of metastasis, some other tests are run to obtain sufficient information before a surgery. Such tests include the ultrasound and MRI of the neck as well as the CAT scanning. Other options that have shown good results in identifying tumors or related outcomes are the use of Thallium201 chloride, which helps identify metastatic tumor; Gallium, which is helpful to visualize lymphomas; I-meatiodobenzylguanidine, which has proven useful in imaging MTC; Tc-MIBI, which has been effective in detecting deposits of metastatic thyroid cancer; PET scans, which are also helpful for the imaging of metastatic disease. Chia *et al.* report that TSHR mRNA measured with FNA enhances the preoperative detection of cancer in patients with thyroid nodules, reducing unnecessary surgeries, and immediate postoperative levels can predict residual/metastatic disease.

Prognosis

Depending on source, the overall 5-year survival rate for papillary thyroid cancer is 96% or 97%, with a 10-year survival rate of 93%.

For a more specific prognosis for individual cases, there are at minimum 13 known scoring systems for prognosis; among the more often used are:

- AGES - Age, Grade, Extent of disease, Size
- AMES - Age, Metastasis, Extent of disease, Size
- MACIS - Metastasis, Age at presentation, Completeness of surgical resection, Invasion (extrathyroidal), Size (this is a modification of the AGES system). It is probably the most reliable staging method available.
- TNM staging - Tumor, node, metastasis. Remarkable about the TNM staging for (differentiated) thyroid carcinoma is that the scoring is different according to age.

MAICS

The MAICS system of estimating the prognosis of papillary thyroid cancer was developed by the Mayo Clinic, and was based on careful evaluation of a large group of patients. It is probably the most reliable staging method available.

It assigns scores to the main factors involved, and uses the sum of this score to calculate the prognosis:

Factors		Score
Distant **M**etastasis: spread of the cancer to areas outside the neck	Yes	3
	No	0
Age at the time the tumor was discovered	Less than 39 years	3.1
	Over 40 years	0.08 x age
Invasion into surrounding areas of the neck as seen by the naked eye	Yes	1
	No	0
Completeness of surgical resection (or removal) of the tumor	Incomplete	1
	Complete	0
Size of the tumor		0.3 x size in cm

Sum of MAICS Score	20 yr Survival
< 6.0	99%
6.0 - 6.99	89%
7.0 - 7.99	56%
> 8.0	24%

Most patients fall into the low risk category (MAICS score less than 6.0) and are cured of the cancer at the time of surgery.

Overall stage

By overall cancer staging into stages I to IV, papillary thyroid cancer has a 5-year survival rate of 100% for stages I and II, 93% for stage III and 51% for stage IV.

Treatment

Surgical treatment:

- Minimal disease (diameter up to 1.0 centimeters) - hemithyroidectomy (or unilateral lobectomy) and isthmectomy may be sufficient. There is some discussion whether this is still preferable over total thyroidectomy for this group of patients.
- Gross disease (diameter over 1.0 centimeters) - total thyroidectomy, and central compartment lymph node removal is the therapy of choice. Additional lateral neck nodes can be removed at the same time if an ultrasound guided FNA and thyrobulin TG cancer washing was positive on the pre-operative neck node ultrasound evaluation.

Arguments for total thyroidectomy are:

- Reduced risk of recurrence, if central compartment nodes are removed at the original surgery.
- Papillary carcinoma is a multifocal disease (hemithyroidectomy may leave disease in the other lobe)
- Ease of monitoring with thyroglobulin (sensitivity for picking up recurrence is increased in presence of total thyroidectomy, and ablation of remnant normal thyroid by low dose radioiodine 131 after following a low iodine diet (LID).
- Ease of detection of metastatic disease by thyroid and neck node ultrasound.

Thyroid total body scans are less reliable at finding recurrence than TG and ultrasound.

Papillary tumors tend to be more aggressive in patients over age 45. In such cases it might be required to perform a more extensive resection including portions of the trachea. Also, the sternocleidomastoid muscle, jugular vein, and accessory nerve are to be removed if such procedure allows apparently complete tumor resection. If a significant amount of residual tumor is left in the neck, external radiotherapy has been indicated and has proven useful especially in those cases when residual tumor does not take up radioiodine.

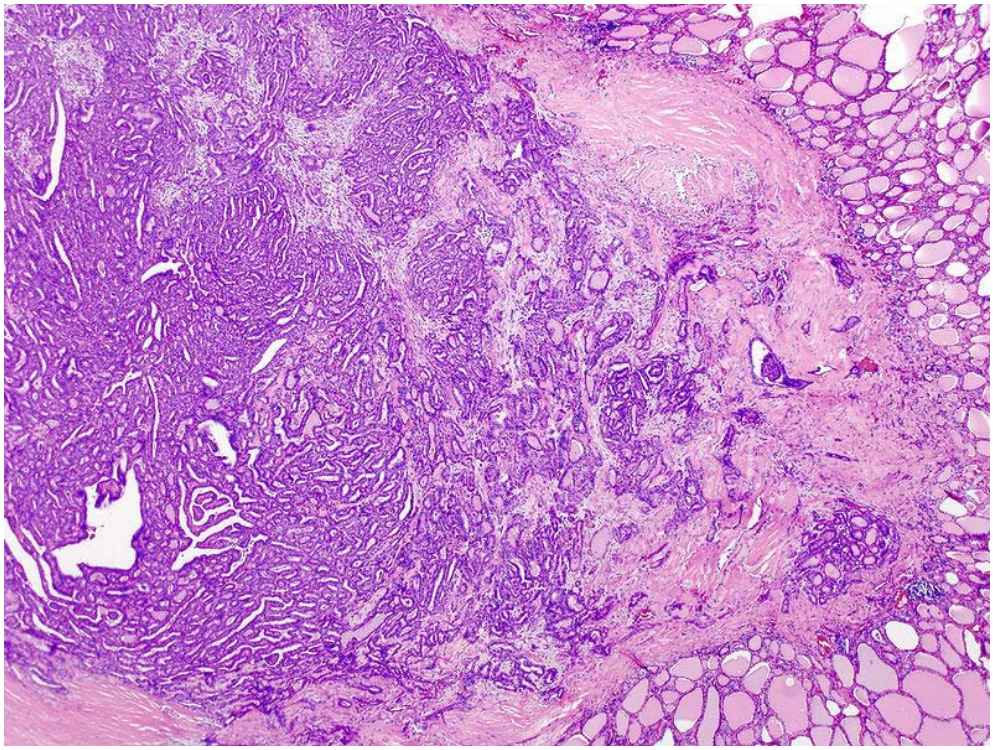
After surgical thyroid removal, the patient waits around 4–6 weeks to then have radioiodine therapy. This therapy is intended to both detect and destroy any metastasis

and residual tissue in the thyroid. The treatment may be repeated 6–12 months after initial treatment of metastatic disease where disease recurs or has not fully responded.

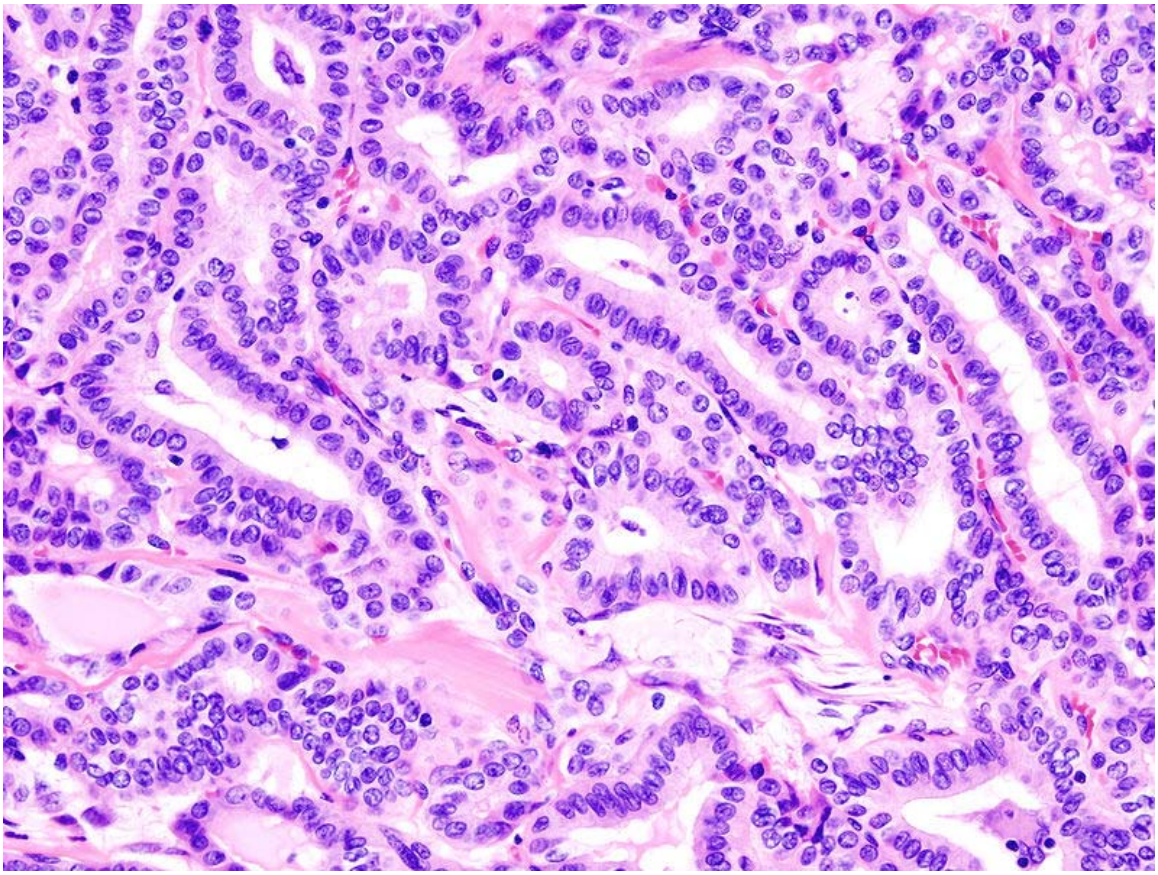
Patients are administered hormone replacement levothyroxine for life after surgery, especially after total thyroidectomy. Chemotherapy with cisplatin or doxorubicin has proven limited efficacy, however, it could be helpful for patients with bone metastases to improve their quality of life. Patients are also prescribed levothyroxine and radioiodine after surgery. Levothyroxine influences growth and maturation of tissues and it is involved in normal growth, metabolism, and development. In case of metastases, patients are prescribed antineoplastic agents which inhibit cell growth and proliferation and help in palliating symptoms in progressive disease.

After successful treatment, 35% of the patients may experience recurrence within a 40-year span. Also, patients may experience a high incidence of nodule metastasis, with 35% cases of cervical node metastases. Approximately 20% patients will develop multiple tumors within the thyroid gland.

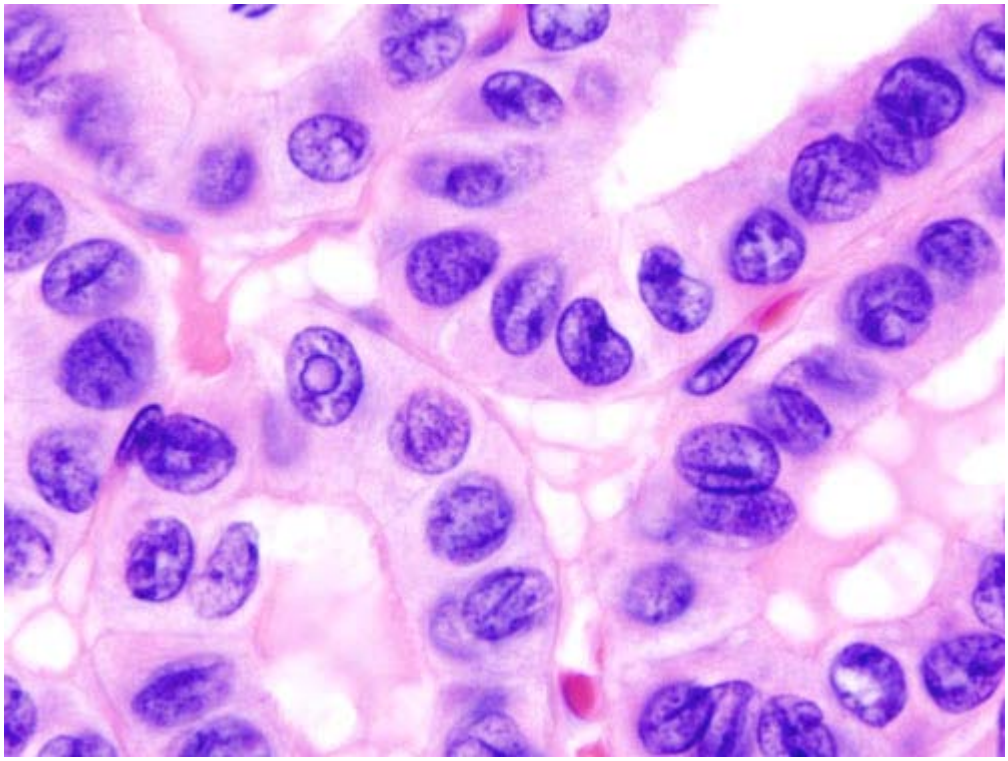
Additional images



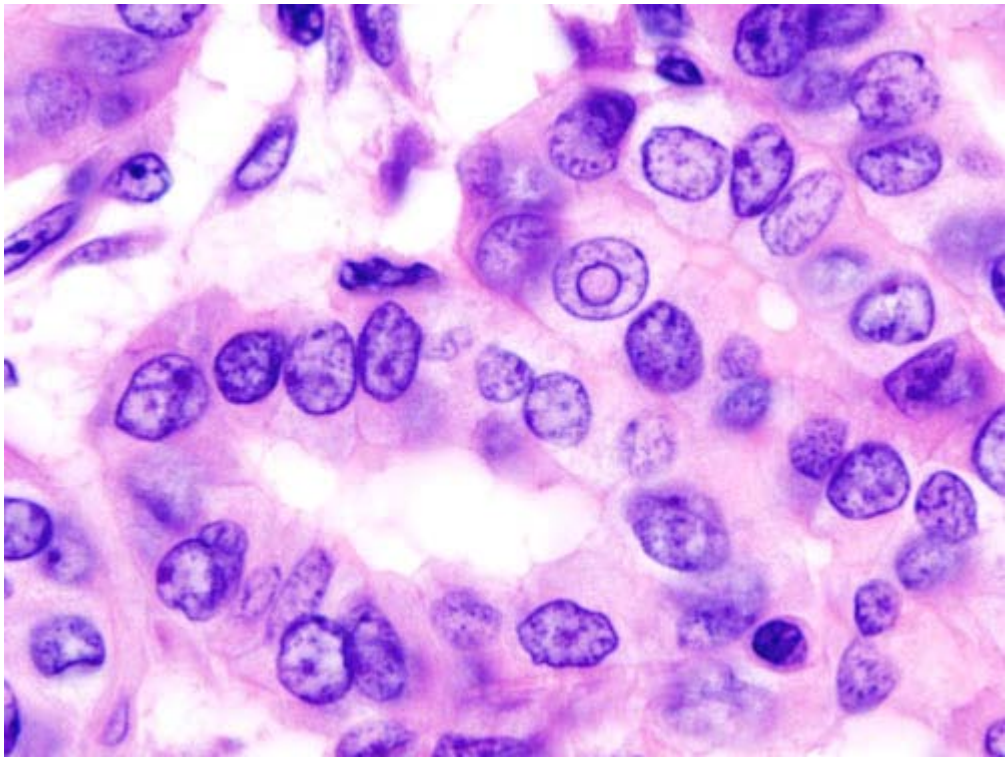
Micrograph of papillary thyroid carcinoma demonstrating prominent papillae with fibrovascular cores. H&E stain.



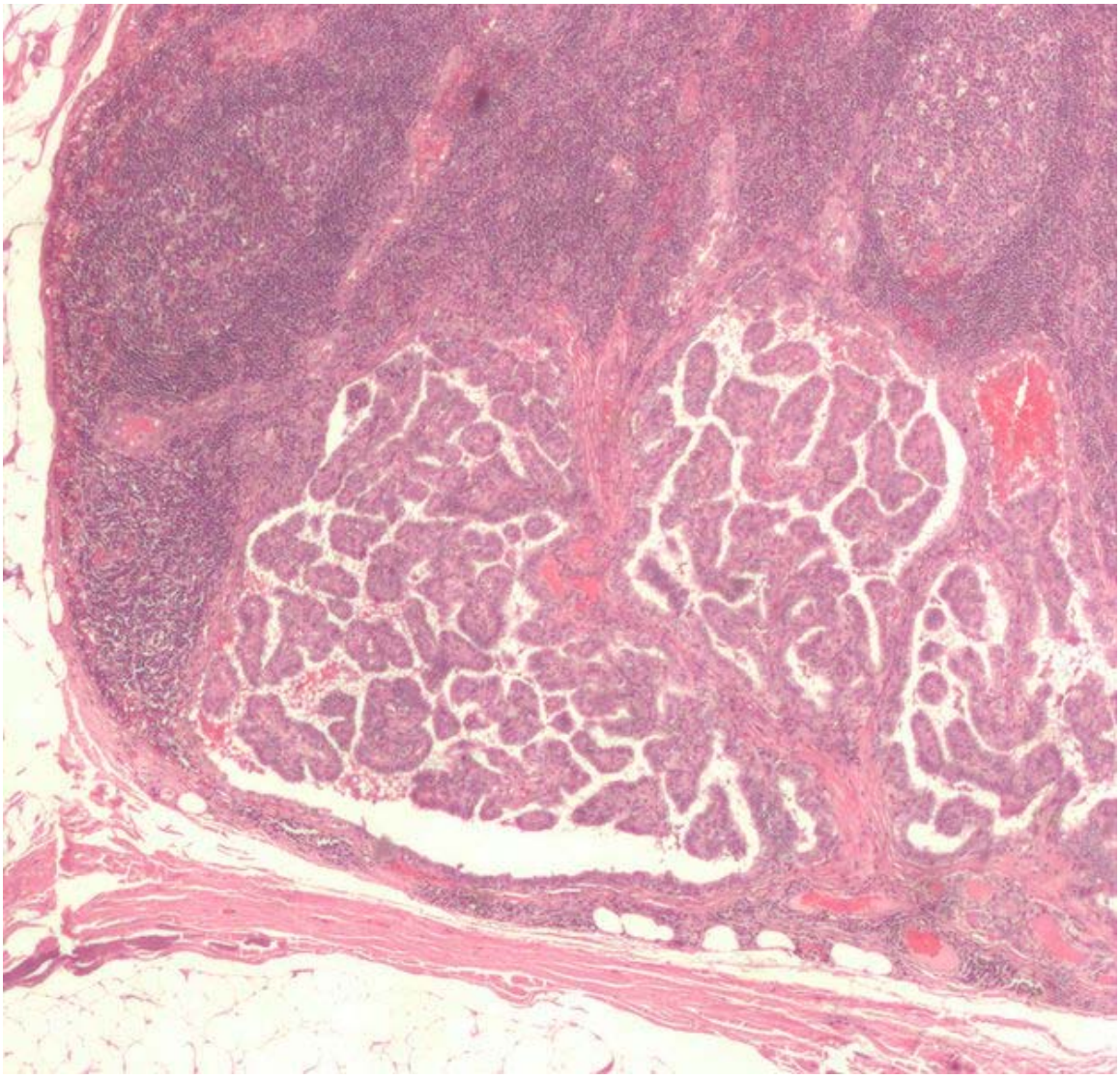
Micrograph showing that the papillae in papillary thyroid carcinoma are composed of cuboidal cells. H&E stain.



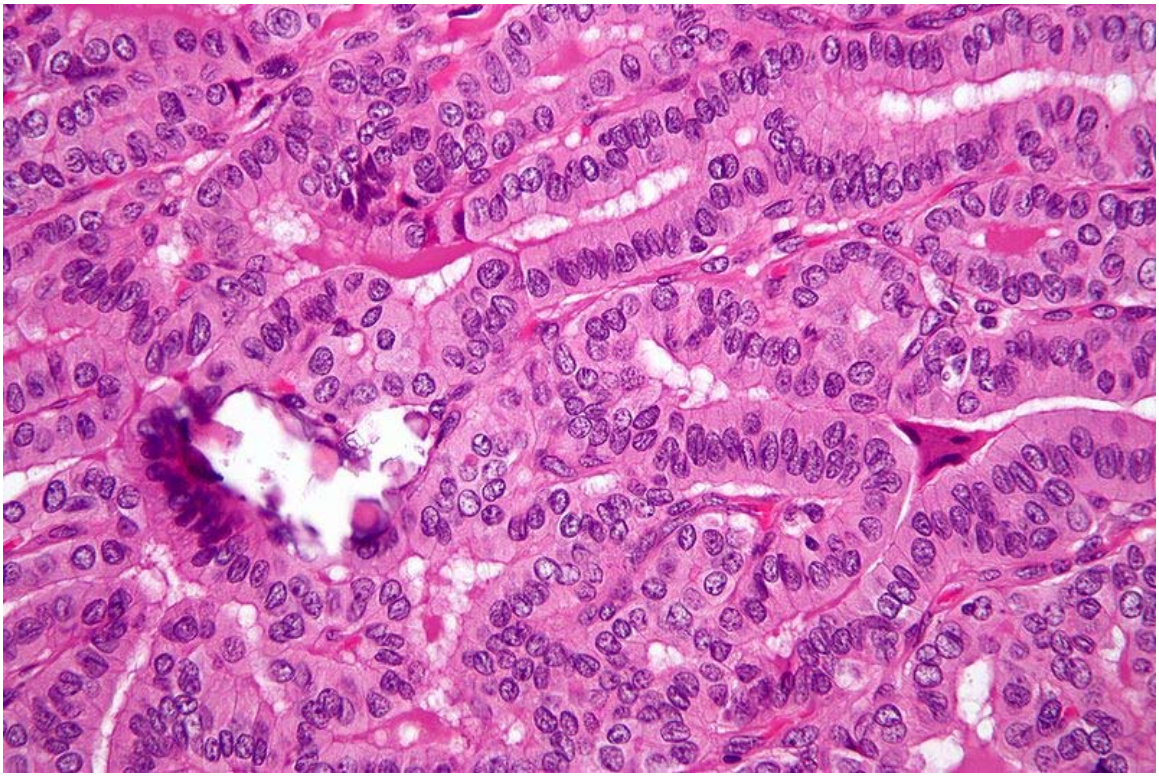
Micrograph (high power view) showing nuclear changes in papillary thyroid carcinoma (PTC), which include groove formation, optical clearing, eosinophilic inclusions and overlapping of nuclei. H&E stain.



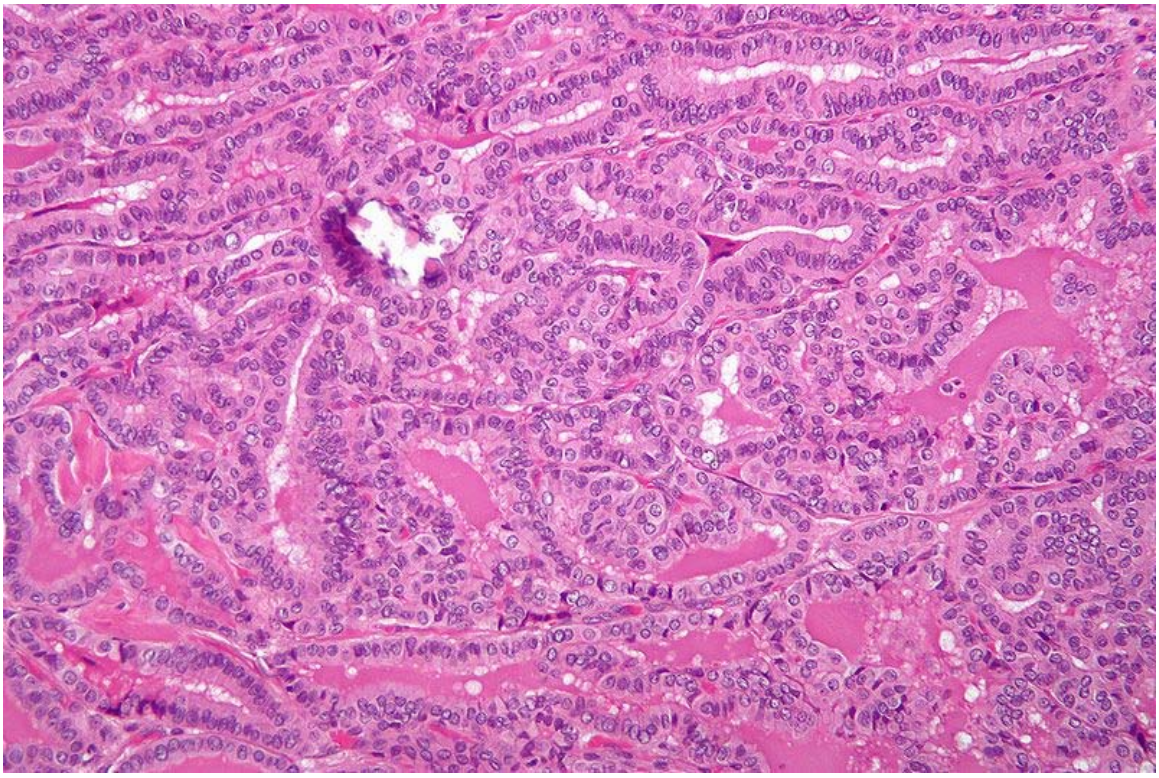
Micrograph (high power view) of PTC demonstrating nuclear clearing and overlapping nuclei. H&E stain.



Micrograph of metastatic papillary thyroid carcinoma to a lymph node. H&E stain.



Micrograph of **papillary thyroid carcinoma, tall cell variant** - high magnification. H&E stain.



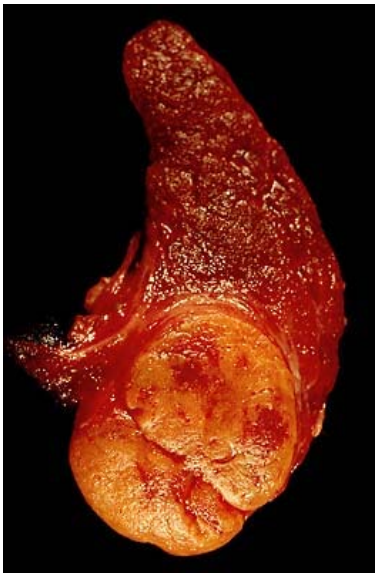
Micrograph of **papillary thyroid carcinoma, tall cell variant** - intermediate magnification. H&E stain.

Chapter 5

Follicular Thyroid Cancer and Anaplastic Thyroid Cancer

Follicular thyroid cancer

Follicular thyroid cancer



Gross pathological section of a follicular thyroid adenoma (tumor at the bottom).

ICD-10	C73.
ICD-9	193
OMIM	188470

eMedicine	med/804
MeSH	D013964

Follicular thyroid cancer accounts for 15% of thyroid cancer which occurs more commonly in women of over 50 years old. Thyroglobulin (Tg) can be used as a tumor marker for well-differentiated follicular thyroid cancer.

Classification

It is impossible to distinguish between follicular adenoma and carcinoma on cytological grounds. If fine needle aspiration cytology (FNAC) suggests follicular neoplasm, thyroid lobectomy should be performed to establish the histopathological diagnosis. Features sine qua non for the diagnosis of follicular carcinoma are capsular invasion and vascular invasion by tumor cells.

- Follicular carcinoma tends to metastasize to lung and bone via the bloodstream.
- Papillary thyroid carcinoma commonly metastasizes to cervical lymph nodes.

HMGA2 has been proposed as a marker to identify malignant tumors.

Treatment

Treatment is usually surgical, followed by radioiodine.

Initial treatment

- If follicular cells are found on cytological testing, it is common to carry out *hemithyroidectomy* to distinguish between follicular adenoma and follicular carcinoma on histopathological examination, proceeding to *completion thyroidectomy* and postoperative radioiodine ablation where carcinoma is confirmed. This way total thyroidectomy is not carried out unnecessarily.
- *Thyroidectomy* is invariably followed by radioiodine treatment at levels from 50 to 200 millicuries following two weeks of a low iodine diet (LID). Occasionally treatment must be repeated if annual scans indicate remaining cancerous tissue. Some physicians favor administering the maximum safe dose (calculated based on a number of factors), while others favor administering smaller doses, which may still be effective in ablating all thyroid tissue. I-131 is used for ablation of the thyroid tissue.

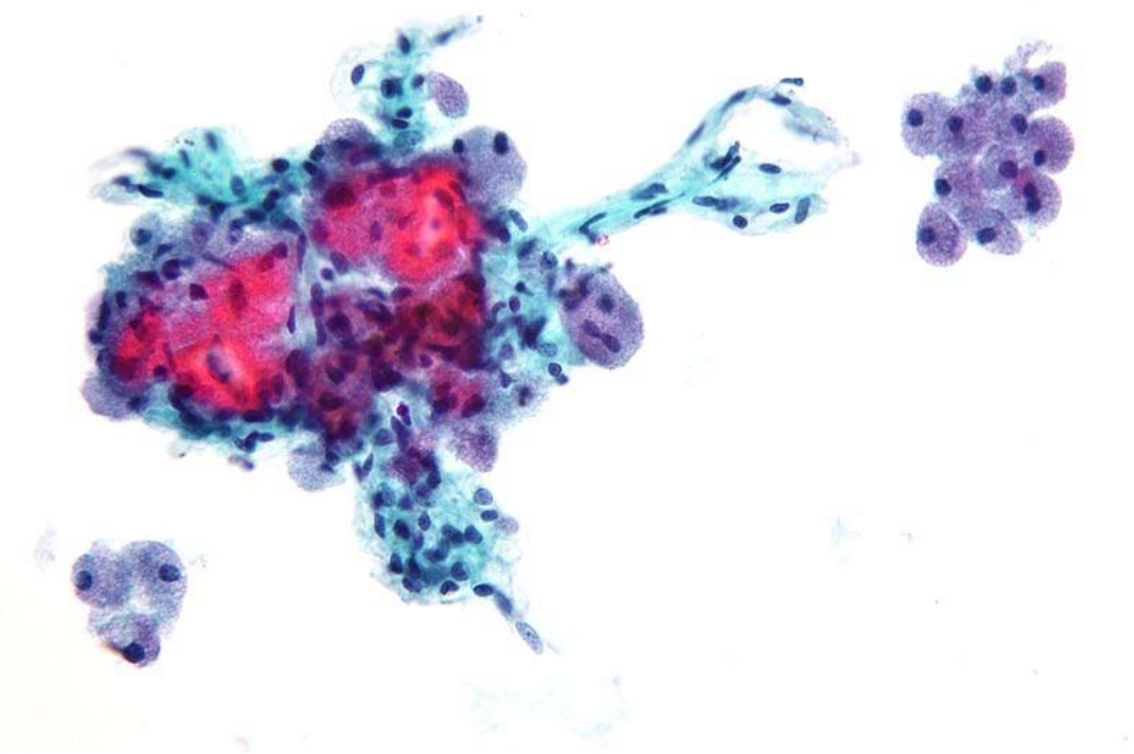
Minimally invasive thyroidectomy has been used in recent years in cases where the nodules are small.

Finding disease recurrence

Some studies have shown that thyroglobulin (Tg) testing combined with neck ultrasound is more productive in finding disease recurrence than full- or whole-body scans (WBS) using radioactive iodine. However, current protocol (in the USA) suggests a small number of clean annual WBS are required before relying on Tg testing plus neck ultrasound. When needed, whole body scans consist of withdrawal from thyroxine medication and/or injection of recombinant human Thyroid stimulating hormone (TSH). In both cases, a low iodine diet regimen must also be followed to optimize the takeup of the radioactive iodine dose. Low dose radioiodine of a few millicuries is administered. Full body nuclear medicine scan follows using a gamma camera. Scan doses of radioactive iodine may be I^{131} or I^{123}.

Recombinant human TSH, commercial name Thyrogen, is produced in cell culture from genetically engineered hamster cells.

Hurthle cell variant



Micrograph of a Hurthle cell neoplasm.

Hurthle cell thyroid cancer is often considered a variant of follicular cell carcinoma. Hurthle cell forms are more likely than follicular carcinomas to be bilateral and multifocal and to metastasize to lymph nodes. Like follicular carcinoma, unilateral hemithyroidectomy is performed for non-invasive disease, and total thyroidectomy for invasive disease

Prognosis

The overall 5-year survival rate for follicular thyroid cancer is 91%, and the 10-year survival rate is 85%.

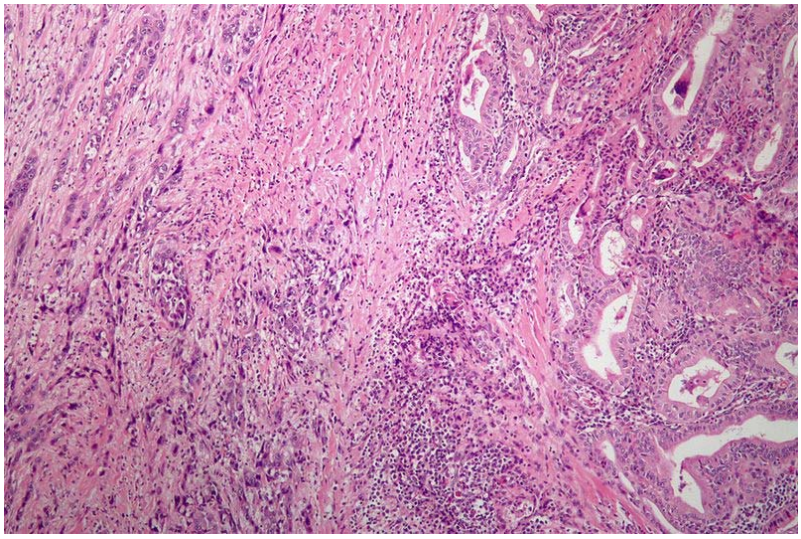
By overall cancer staging into stages I to IV, follicular thyroid cancer has a 5-year survival rate of 100% for stages I and II, 71% for stage III, and 50% for stage IV.

Associated mutations

Approximately one-half of follicular thyroid carcinomas have mutations in the Ras subfamily of oncogenes, most notably HRAS, NRAS, and KRAS. Also, a chromosomal translocation specific for follicular thyroid carcinomas is one between paired box gene 8 (PAX-8), a gene important in thyroid development, and the gene encoding peroxisome proliferator-activated receptor γ 1 (PPARγ1), a nuclear hormone receptor contributing to terminal differentiation of cells. The PAX8-PPARγ1 fusion is present in approximately one-third of follicular thyroid carcinomas, specifically those cancers with a t(2;3)(q13;p25) translocation, permitting juxtaposition of portions of both genes. Tumors tend carry either a RAS mutation or a PAX8-PPARγ1 fusion, and only rarely are both genetic abnormalities present in the same case. Thus, follicular thyroid carcinomas seem to arise by two distinct and virtually nonoverlapping molecular pathways.

Anaplastic thyroid cancer

Anaplastic thyroid cancer



Micrograph of **anaplastic thyroid carcinoma**. H&E stain.

ICD-10 C73.

ICD-9	193
eMedicine	med/2687
MeSH	D013964

Anaplastic thyroid cancer (ATC) is a form of thyroid cancer which has a very poor prognosis (14% ten-year survival rate) due to its aggressive behavior and resistance to cancer treatments.

Presentation

Anaplastic tumors have a high miotic rate and lymphovascular invasion. It rapidly invades surrounding tissues (such as the trachea). The presence of regional lymphadenopathy in older patients in whom needle aspiration biopsy reveals characteristic vesicular appearance of the nuclei would support a diagnosis of anaplastic carcinoma.

Prognosis

The overall 5-year survival rate of anaplastic thyroid cancer has been given as 7% or 14%, although the latter has been criticized as being overestimated.

Treatment of anaplastic-type carcinoma is generally palliative in its intent for a disease that is rarely cured and almost always fatal, with worse prognosis associated with large tumours, distant metastases, acute obstructive symptoms, and leukocytosis. Death is attributable to upper airway obstruction and suffocation in half of patients, and to a combination of complications of local and distant disease, or therapy, or both in the remainder.

Anaplastic thyroid cancer is extremely aggressive; in most cases death occurs in less than 1 year as a result of aggressive local growth and compromise of vital structures in the neck. ATC in most series has a median survival of 4 to 5 months from the time of diagnosis, with rare long-term survivors.

Treatment

Unlike its differentiated counterparts, anaplastic thyroid cancer is highly unlikely to be curable either by surgery or by any other treatment modality, and is in fact usually unresectable due to its high propensity for invading surrounding tissues.

Palliative treatment consists of radiation therapy usually combined with chemotherapy.

However, with today's technology, new drugs, such as combretastatin (fosbretabulin), bortezomib and TNF-Related Apoptosis Induced Ligand (TRAIL), are being introduced and trialed in clinical labs and human clinical studies. Based on encouraging Phase I and

II clinical trial results, with combretastatin (fosbretabulin), a type of drug that selectively destroys tumor blood vessels, a large, multi-national clinical trial is being undertaken to determine whether the drug can extend the survival of patients with ATC. Recent studies in Italy have shown positive results against ATC, but more tests outside the lab are needed to confirm this before it can be used in chemotherapy. There have been some case studies where patients with aggressive thyroid cancer have survived outside the mean expected survival time.

Post-operative radiotherapy

The role of external beam radiotherapy (EBRT) in thyroid cancer remains controversial and there is no level I evidence to recommend its use in the setting of differentiated thyroid cancers such as papillary and follicular carcinomas. Anaplastic thyroid carcinomas, however, are histologically distinct from differentiated thyroid cancers and due to the highly aggressive nature of ATC aggressive postoperative radiation and chemotherapy are typically recommended.

The National Comprehensive Cancer Network Clinical Practice Guidelines currently recommend that postoperative radiation and chemotherapy be strongly considered. No published randomised controlled trials have examined the addition of EBRT to standard treatment, namely surgery. Radioactive iodine is typically ineffective in the management of ATC as it is not an iodine-avid cancer.

Imbalances in age, sex, completeness of surgical excision, histological type and stage, between patients receiving and not receiving EBRT, confound retrospective studies. Variability also exists between treatment and non-treatment groups in the use of radio-iodine and post-treatment thyroid stimulating hormone (TSH) suppression and treatment techniques between and within retrospective studies.

Some recent studies have indicated that EBRT may be promising, though the number of patients studies has been small.

Clinical trials for investigational treatments are often considered by healthcare professionals and patients as first-line treatment.

Adjuvant therapy

In the absence of extracervical or unresectable disease, surgical excision should be followed by adjuvant radiotherapy. In the 18–24% of patients whose tumour seems both confined to the neck and grossly resectable, complete surgical resection followed by adjuvant radiotherapy and chemotherapy could yield a 75–80% survival at 2 years.

Chapter 6

Medullary Thyroid Cancer

Medullary thyroid cancer	
ICD-10	C73.
ICD-9	193
OMIM	155240
eMedicine	med/2272
MeSH	D013964

Medullary thyroid cancer (**MTC**) is a form of thyroid carcinoma which originates from the *parafollicular cells* (C cells), which produce the hormone calcitonin.

Approximately 25% of medullary thyroid cancer is genetic in nature, caused by a mutation in the RET proto-oncogene. This form is classified as familial MTC. When MTC occurs by itself it is termed sporadic MTC. When it coexists with tumors of the parathyroid gland and medullary component of the adrenal glands (pheochromocytoma) it is called multiple endocrine neoplasia type 2 (MEN2).

It was first characterized in 1959.

Markers

While the increased serum concentration of calcitonin is not harmful, it is useful as a marker which can be tested in blood.

A second marker, carcinoembryonic antigen (CEA), also produced by medullary thyroid carcinoma, is released into the blood and it is useful as a serum or blood tumor marker. In general measurement of serum CEA is less sensitive than serum calcitonin for detecting

the presence of a tumor, but has less minute to minute variability and is therefore useful as an indicator of tumor mass.

Genetics

Mutations (DNA changes) in the RET proto-oncogene, located on chromosome 10, lead to the expression of a mutated receptor tyrosine kinase protein, termed RET. RET is involved in the regulation of cell growth and development and its mutation is responsible for nearly all cases of hereditary or familial medullary thyroid carcinoma. Its mutation may also be responsible for the development of hyperparathyroidism and pheochromocytoma. Hereditary medullary thyroid cancer is inherited as an autosomal dominant trait, meaning that each child of an affected parent has a 50/50 probability of inheriting the mutant RET proto-oncogene from the affected parent. DNA analysis makes it possible to identify children who carry the mutant gene; surgical removal of the thyroid in children who carry the mutant gene is curative if the entire thyroid gland is removed at an early age, before there is spread of the tumor. The parathyroid tumors and pheochromocytomas are removed when they cause clinical symptomatology. Hereditary medullary thyroid carcinoma or multiple endocrine neoplasia (MEN2) accounts for approximately 25% of all medullary thyroid carcinomas.

Seventy-five percent of medullary thyroid carcinoma occurs in individuals without an identifiable family history and is assigned the term "sporadic". Individuals who develop sporadic medullary thyroid carcinoma tend to be older and have more extensive disease at the time of initial presentation than those with a family history (screening is likely to be initiated at an early age in the hereditary form). Approximately 25-60% of sporadic medullary thyroid carcinomas have a somatic mutation (one that occurs within a single "parafollicular" cell) of the RET proto-oncogene. This mutation is presumed to be the initiating event, although there could be other as yet unidentified causes.

Clinical features

The major clinical symptom of metastatic medullary thyroid carcinoma is diarrhea; occasionally a patient will have flushing episodes. Both occur particularly with liver metastasis. Occasionally, diarrhea or flushing will be the initial presenting complaint. The flushing that occurs in medullary thyroid carcinoma is indistinguishable from that associated with carcinoid syndrome. The presumed cause of flushing and diarrhea is the excessive production of calcitonin gene products (calcitonin or calcitonin gene-related peptide) and differs from the causation of flushing and diarrhea in carcinoid syndrome. Sites of spread of medullary thyroid carcinoma include local lymph nodes in the neck, lymph nodes in the central portion of the chest (mediastinum), liver, lung, and bone. Spread to other sites such as skin or brain occurs but is uncommon.

Treatment

Surgery can be effective when the condition is detected early, but a risk for recurrence remains.

Unlike differentiated thyroid carcinoma, there is no role for radioiodine treatment in medullary-type disease.

External beam radiotherapy should be considered for patients at high risk of regional recurrence, even after optimum surgical treatment. Brierley et al., conducted a retrospective study and found that external beam radiation was beneficial in some patients.

After a long period during which surgery and radiation therapy formed the major treatments for medullary thyroid carcinoma, clinical trials of several new tyrosine kinase inhibitors are now being studied. Preliminary results show clear evidence of response 10-30% of patients, providing hope for future advances. In the majority of responders there has been less than a 30% decrease in tumor mass yet the responses have been durable; responses have been stable for periods exceeding 3 years. The major side effects of this class of drug include hypertension, nausea, diarrhea, some cardiac electrical abnormalities, and thrombotic or bleeding episodes. Long-term safety of drugs effective for treatment of medullary thyroid carcinoma has not been established. None of the agents that show promise for treatment of medullary thyroid carcinoma have been approved by the US Food and Drug Administration for this purpose and most are available only through clinical trials.

Prognosis

The prognosis of MTC is poorer than that of follicular and papillary thyroid cancer when it has metastasized (spread) beyond the thyroid gland. Depending on source, the overall 5-year survival rate for medullary thyroid cancer is 80%, 83% or 86%, and the 10-year survival rate is 75%.

By overall cancer staging into stages I to IV, the 5-year survival rate is 100% at stage I, 98% at stage II, 81% at stage III and 28% at stage IV.

The prognostic value of measuring calcitonin and carcinoembryonic antigen (CEA) concentrations in the blood in patients with abnormal calcitonin levels postsurgery has been recently published (2005) in a retrospective study of 65 MTC patients, *et al.*. The post-surgical times ranged from 2.9 years to 29.5 years; all 65 patients **continued** to have abnormal calcitonin levels after total thyroidectomy and bilateral lymph node dissection. The prognosis of surviving MTC appears to be correlated with the rate at which a patient's postoperative calcitonin concentration doubles, rather than the pre- or postoperative absolute calcitonin level.

The result of the 65 patient study can be summarized with respect to the calcitonin doubling time (CDT):

CDT < 6 months: 3 patients out of 12 (25%) survived 5 years. 1 patient out of 12 (8%) survived 10 years. All died within 6 months to 13.3 years.

CDT between 6 months and 2 years: 11 patients out of 12 (92%) survived 5 years. 3 patients out of 8 (37%) survived 10 years. 4 patients out of 12 (25%) survived to the end of the study.

CDT > 2 years: 41 patients out of 41 (100%) were alive at the end of the study. These included 1 patient whose calcitonin was stable, and 11 patients who had decreasing calcitonin levels.

The 65 patients had a median age of 51 (range was 6 to 75), with 24 age 45 years or younger and 41 older than 45 years. The gender representation was 31 males and 34 females. All patients shared the following characteristics: 1) had total thyroidectomy and lymph node dissection; 2) had non-zero calcitonin levels after surgery; 3) had at least 4 serum calcitonin measurements after surgery; 4) had a status that could be confirmed at the conclusion of the study.

Chapter 7

Head and Neck Cancer

Head and neck cancer	
ICD-10	C07.-C14. C32.-C33.
ICD-9	150.9
MeSH	D006258

The term **head and neck cancer** refers to a group of biologically similar cancers originating from the upper aerodigestive tract, including the lip, oral cavity (mouth), nasal cavity, paranasal sinuses, pharynx, and larynx. 90% of head and neck cancers are squamous cell carcinomas (**SCCHN**), originating from the mucosal lining (epithelium) of these regions. Head and neck cancers often spread to the lymph nodes of the neck, and this is often the first (and sometimes only) manifestation of the disease at the time of diagnosis. Head and neck cancer is strongly associated with certain environmental and lifestyle risk factors, including tobacco smoking, alcohol consumption, UV light and occupational exposures, and certain strains of viruses, such as the sexually transmitted human papillomavirus. These cancers are frequently aggressive in their biologic behavior; patients with these types of cancer often develop a second primary tumor. Head and neck cancer is highly curable if detected early, usually with some form of surgery although chemotherapy and radiation therapy may also play an important role. The 2009 estimated number of head and neck cancer in the US is of 35,720 new cases.

Classification

Head and neck squamous cell carcinomas (HNSCC's) make up the vast majority of head and neck cancers, and arise from mucosal surfaces throughout this anatomic region. These include tumors of the nasal cavities, paranasal sinuses, oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx.

Oral cavity

Squamous cell cancers are common in the oral cavity, including the inner lip, tongue, floor of mouth, gingivae, and hard palate. Cancers of the oral cavity are strongly associated with tobacco use, especially use of chewing tobacco or "dip", as well as heavy alcohol use. Cancers of this region, particularly the tongue, are more frequently treated with surgery than are other head and neck cancers.

Surgeries for oral cancers include

- Maxillectomy (can be done with or without Orbital exenteration)
- Mandibulectomy (removal of the mandible or lower jaw or part of it)
- Glossectomy (tongue removal, can be total, hemi or partial)
- Radical neck dissection
- Moh's procedure
- Combinational e.g. glossectomy and laryngectomy done together.

The defect is covered/improved by using another part of the body and/or skin grafts and/or wearing a prosthesis.

Nasopharynx

Nasopharyngeal cancer arises in the nasopharynx, the region in which the nasal cavities and the Eustachian tubes connect with the upper part of the throat. While some nasopharyngeal cancers are biologically similar to the common HNSCC, "poorly differentiated" nasopharyngeal carcinoma is distinct in its epidemiology, biology, clinical behavior, and treatment, and is treated as a separate disease by many experts.

Oropharynx

Oropharyngeal squamous cell carcinomas (OSCC) begins in the oropharynx, the middle part of the throat that includes the soft palate, the base of the tongue, and the tonsils. Squamous cell cancers of the tonsils are more strongly associated with human papillomavirus infection than are cancers of other regions of the head and neck.

Hypopharynx

The hypopharynx includes the pyriform sinuses, the posterior pharyngeal wall, and the postcricoid area. Tumors of the hypopharynx frequently have an advanced stage at diagnosis, and have the most adverse prognoses of pharyngeal tumors. They tend to metastasize early due to the extensive lymphatic network around the larynx.

Larynx

Laryngeal cancer begins in the larynx or "voice box." Cancer may occur on the vocal folds themselves ("glottic" cancer), or on tissues above and below the true cords

("supraglottic" and "subglottic" cancers respectively). Laryngeal cancer is strongly associated with tobacco smoking.

Surgery can include partial laryngectomy (removal of part of the larynx) and total laryngectomy (removal of the whole larynx). If the whole larynx has been removed the person is left with a permanent tracheostomy and learns to speak again in a new way with the help of intensive teaching and speech therapy and/or an electronic device.

Also anyone who has had a glossectomy (tongue removal) will be taught to speak again in a new way and have intensive speech therapy.

Trachea

Cancer of the trachea is a rare malignancy which can be biologically similar in many ways to head and neck cancer, and is sometimes classified as such.

Most tumors of the salivary glands differ from the common carcinomas of the head and neck in etiology, histopathology, clinical presentation, and therapy, Other uncommon tumors arising in the head and neck include teratomas, adenocarcinomas, adenoid cystic carcinomas, and mucoepidermoid carcinomas. Rarer still are melanomas and lymphomas of the upper aerodigestive tract.

Signs and symptoms

Throat cancer usually begins with symptoms that seem harmless enough, like an enlarged lymph node on the outside of the neck, a sore throat or a hoarse sounding voice. However, in the case of throat cancer, these conditions may persist and become chronic. There may be a lump or a sore in the throat or neck that does not heal or go away. There may be difficult or painful swallowing. Speaking may become difficult. There may be a persistent earache. Other possible but less common symptoms include some numbness or paralysis of the face muscles.

Presenting symptoms include

- Mass in the neck
- Neck pain
- Bleeding from the mouth
- Sinus congestion, especially with nasopharyngeal carcinoma
- Bad breath
- Sore tongue
- Painless ulcer or sores in the mouth that do not heal
- White, red or dark patches in the mouth that will not go away
- Ear ache
- Unusual bleeding or numbness in the mouth
- Lump in the lip, mouth or gums
- Enlarged lymph glands in the neck

- Slurring of speech (if the cancer is affecting the tongue)
- Hoarse voice which persists for more than six weeks
- Sore throat which persists for more than six weeks
- Difficulty swallowing food
- Change in diet or weight loss

Causes

Alcohol and tobacco use are the most common risk factors for head and neck cancer in the United States. Alcohol and tobacco are likely synergistic in causing cancer of the head and neck. Smokeless tobacco is an etiologic agent for oral and pharyngeal cancers [Oropharyngeal cancer]. Cigar smoking is an important risk factor for oral cancers as well. Other potential environmental carcinogens include occupational exposures such as nickel refining, exposure to textile fibers, and woodworking. In one large, controlled study, marijuana use was shown to be associated with oral squamous cell carcinoma. In another study, marijuana use was even shown to be a potential protective factor against the development of head and neck squamous cell carcinoma. However, cigarette smokers have a lifetime increased risk for head and neck cancers that is 5- to 25-fold increased over the general population. The ex-smoker's risk for squamous cell cancer of the head and neck begins to approach the risk in the general population twenty years after smoking cessation. The high prevalence of tobacco and alcohol use worldwide and the high association of these cancers with these substances makes them ideal targets for enhanced cancer prevention.

Dietary factors

Dietary factors may contribute. Excessive consumption of processed meats and red meat were associated with increased rates of cancer of the head and neck in one study, while consumption of raw and cooked vegetables seemed to be protective.

Vitamin E was not found to prevent the development of leukoplakia, the white plaques that are the precursor for carcinomas of the mucosal surfaces, in adult smokers. Another study examined a combination of Vitamin E and beta carotene in smokers with early-stage cancer of the oropharynx, and found a worse prognosis in the vitamin users.

Betel-nut

Betel-nut chewing is associated with an increased risk of squamous cell cancer of the head and neck.

Recent evidence is accumulating pointing to a viral origin for some head and neck cancers.

Human papillomavirus

Human papillomavirus (HPV), in particular HPV16, is a causal factor for some head and neck squamous cell carcinoma (HNSCC). Approximately 15 to 25% of HNSCC contain genomic DNA from HPV, and the association varies based on the site of the tumor, especially HPV-positive oropharyngeal cancer, with highest distribution in the tonsils, where HPV DNA is found in (45 to 67%) of the cases, less often in the hypopharynx (13%–25%), and least often in the oral cavity (12%–18%) and larynx (3%–7%).

Some experts estimate that while up to 50% of cancers of the tonsil may be infected with HPV, only 50% of these are likely to be caused by HPV (as opposed to the usual tobacco and alcohol causes). The role of HPV in the remaining 25-30% is not yet clear.

Epstein-Barr virus

Epstein-Barr virus (EBV) infection is associated with nasopharyngeal cancer. Nasopharyngeal cancer occurs endemically in some countries of the Mediterranean and Asia, where EBV antibody titers can be measured to screen high-risk populations. Nasopharyngeal cancer has also been associated with consumption of salted fish, which may contain high levels of nitrites.

Gastroesophageal reflux disease

The presence of acid reflux disease (GERD - gastroesphogeal reflux disease) or larynx reflux disease can also be a major factor. In the case of acid reflux disease, stomach acids flow up into the esophagus and damage its lining, making it more susceptible to throat cancer.

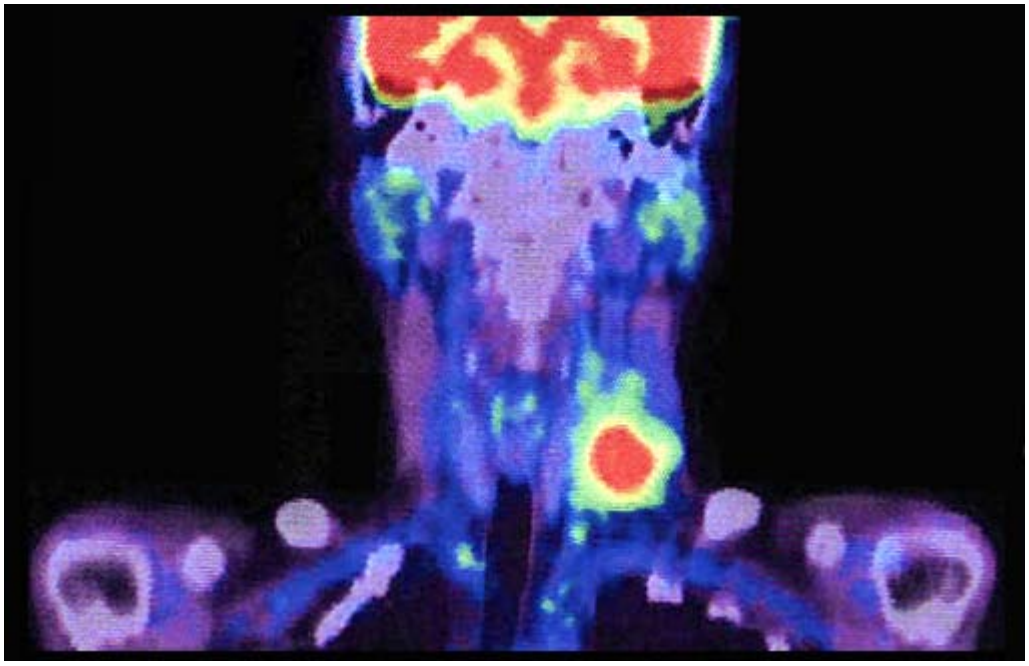
Ethnicity

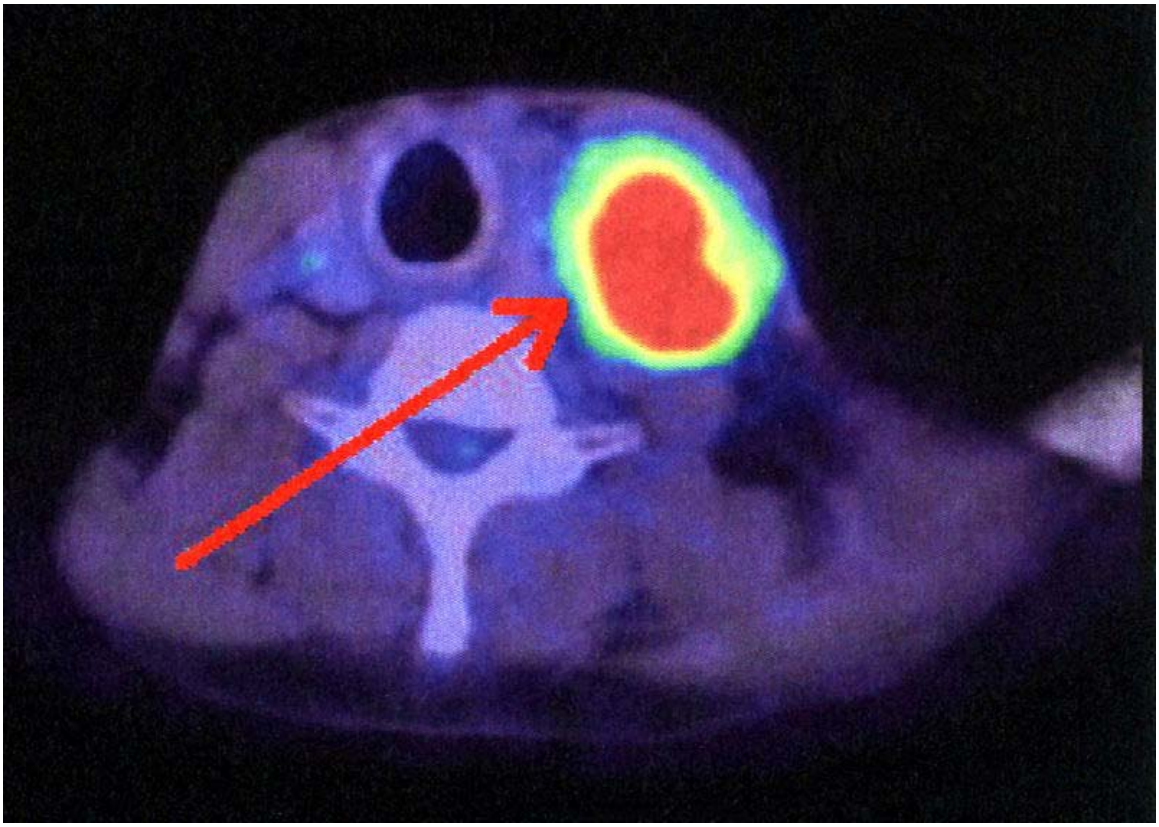
Ethnicity may also play a part, with African American men in the U.S. being found to be at a 50% higher risk of throat cancer than caucasian men.

Other possible causes

There are a wide variety of factors which can put someone at a heightened risk for throat cancer. Such factors include smoking or chewing tobacco or other things, such as gutkha, or paan, heavy alcohol consumption, poor diet resulting in vitamin deficiencies (worse if this is caused by heavy alcohol intake), weakened immune system, asbestos exposure, prolonged exposure to wood dust or paint fumes, exposure to petroleum industry chemicals, and being over the age of 55 years. Another risk factor includes the appearance of white patches or spots in the mouth, known as leukoplakia; in about ⅓ of the cases this develops into cancer.

Diagnosis





Left inferior internal jugular node metastases with extranodal invasion, two years after brachytherapy of tongue cancer. PET-CT scanning of a male patient in his 30's, 64

minutes after fludeoxyglucose (^{18}F) was administered, shows some fluff around the tumor.

A patient usually presents to the physician complaining of one or more of the above symptoms The patient will typically undergo a needle biopsy of this lesion, and a histopathologic information is available, a multidisciplinary discussion of the optimal treatment strategy will be undertaken between the radiation oncologist, surgical oncologist, and medical oncologist.

Histopathology

Throat cancers are classified according to their histology or cell structure, and are commonly referred to by their location in the oral cavity and neck. This is because where the cancer appears in the throat affects the prognosis - some throat cancers are more aggressive than others depending upon their location. The stage at which the cancer is diagnosed is also a critical factor in the prognosis of throat cancer.

Squamous cell carcinoma

Squamous cells are the epithelium (tissue layer) that is the surface cells of much of the body. Skin and mucous membranes are squamous cells. This is the most common form of larynx cancer, accounting for over 90% of throat cancer. Squamous cell carcinoma is most likely to appear in males over 40 years of age with a history of heavy alcohol use coupled with smoking.

Adenocarcinoma

Adenocarcinoma is a cancer of the columnar epithelium typical of the lower oesophagus. It is typical of Barrett's oesophagus but may be at another location. Adenocarcinoma is thought of as a product of Barrett's oesophagus.

Prevention

Avoidance of recognised risk factors (as described above) is the single most effective form of prevention. Regular dental examinations may identify pre-cancerous lesions in the oral cavity.

When diagnosed early, oral, head and neck cancers can be treated more easily and the chances of survival increase tremendously.

It is expected that HPV vaccines may reduce the risk of HPV induced head and neck cancer.

Management

General considerations

Improvements in diagnosis and local management, as well as targeted therapy, have led to improvements in quality of life and survival for head and neck cancer patients since 1992.

After a histologic diagnosis has been established and tumor extent determined, the selection of appropriate treatment for a specific cancer depends on a complex array of variables, including tumor site, relative morbidity of various treatment options, patient performance and nutritional status, concomitant health problems, social and logistic factors, previous primary tumors, and patient preference. Treatment planning generally requires a multidisciplinary approach involving specialist surgeons and medical and radiation oncologists.

Several generalizations are useful in therapeutic decision making, but variations on these themes are numerous. Surgical resection and radiation therapy are the mainstays of treatment for most head and neck cancers and remain the standard of care in most cases. For small primary cancers without regional metastases (stage I or II), wide surgical excision alone or curative radiation therapy alone is used. More extensive primary tumors, or those with regional metastases (stage III or IV), planned combinations of pre- or postoperative radiation and complete surgical excision are generally used. More recently, as historical survival and control rates are recognized as less than satisfactory, there has been an emphasis on the use of various induction or concomitant chemotherapy regimens.

Patients with head and neck cancer can be categorized into three clinical groups: those with localized disease, those with locally or regionally advanced disease, and those with recurrent and/or metastatic disease. Comorbidities (medical problems in addition to the diagnosed cancer) associated with tobacco and alcohol abuse can affect treatment outcome and the tolerability of aggressive treatment in a given patient.

Many different treatments and therapies are used in the treatment of throat cancer. The type of treatment and therapies used are largely determined by the location of the cancer in the throat area and also the extent to which the cancer has spread at time of diagnosis. Patients' also have the right to decide whether or not they wish to consent to a particular treatment. For example, some may decide to not undergo radiation therapy which has serious side effects if it means they will be extending their lives by only a few months or so. Others may feel that the extra time is worth it and wish to pursue the treatments.

Surgery

Surgery as a treatment is sometimes used in cases of throat cancer. In such cases an attempt is made to remove the cancerous cells. This can be particularly tricky if the cancer is near the larynx and can result in the patient being unable to speak. Surgery is

more commonly used to resection (remove) some of the lymph nodes to prevent further spread of the disease. A novel approach uses harvested hematopoietic stem cells (blood stem cells) and other harvested cells (if necessary, a silicon alloy can also be used or can be used in place of the cells) from the lining of the patient's stomach to form a new section of a trachea or esophagus.

CO2 laser surgery is also another form of treatment. Transoral laser microsurgery allows surgeons to remove tumors from the voice box with no external incisions. It also allows access to tumors that are not reachable with robotic surgery. A microscope helps the surgeon clearly view the margins of the tumor, minimizing the amount of normal tissue removed or damaged during surgery. This technique helps give the patient as much speech and swallowing function as possible after surgery.

Radiation therapy

Radiation mask used in treatment of throat cancer

Radiation therapy is the most common form of treatment. There are different forms of radiation therapy, including 3D conformal radiation therapy, intensity-modulated

radiation therapy, and brachytherapy, which are commonly used in the treatments of cancers of the head and neck. Most patients with head and neck cancer who are treated in the United States and Europe are treated with intensity-modulated radiation therapy using high energy photons.

Chemotherapy

Chemotherapy in throat cancer is not generally used to *cure* the cancer as such. Instead, it is used to provide an inhospitable environment for metastases so that they will not establish in other parts of the body. Typical chemotherapy agents are a combination of Taxol and Carboplatin. Erbitux is also used in the treatment of throat cancer.

Taxotere(Docetaxel) based chemotherapy has shown very good response in Locally advanced head and neck cancer. Taxotere is the only Taxane approved by US FDA for Head and neck cancer.

While not specifically a chemotherapy, Amifostine is often administered intravenously by a chemotherapy clinic prior to a patient's IMRT radiotherapy sessions. Amifostine protects the patient's gums and salivary glands from the effects of radiation. It should be noted that one of the side effects of Amifostine is that it **could protect tumors**. Another reason to use the newer more precise and better tumor damaging PMRT treatments.

Photodynamic therapy

Photodynamic therapy may have promise in treating mucosal dysplasia and small head and neck tumors. Amphinex is giving good results in early clinical trials for treatment of advanced head and neck cancer.

Targeted therapy

Targeted therapy, according to the National Cancer Institute, is "a type of treatment that uses drugs or other substances, such as monoclonal antibodies, to identify and attack specific cancer cells without harming normal cells." Some targeted therapy used in squamous cell cancers of the head and neck include cetuximab, bevacizumab, erlotinib, and reovirus.

The best quality data are available for cetuximab since the 2006 publication of a randomized clinical trial comparing radiation treatment plus cetuximab versus radiation treatment alone. This study found that concurrent cetuximab and radiotherapy improves survival and locoregional disease control compared to radiotherapy alone, without a substantial increase in side effects, as would be expected with the concurrent chemoradiotherapy, which is the current gold standard treatment for advanced head and neck cancer. Whilst this study is of pivotal significance, interpretation is difficult since cetuximab-radiotherapy was not directly compared to chemoradiotherapy. The results of ongoing studies to clarify the role of cetuximab in this disease are awaited with interest.

Another study evaluated the impact of adding cetuximab to conventional chemotherapy (cisplatin) versus cisplatin alone. This study found no improvement in survival or disease-free survival with the addition of cetuximab to the conventional chemotherapy.

However, another study which completed in March 2007 found that there was an improvement in survival.

The EXTREME (Erbitux in First-Line Treatment of Recurrent or Metastatic Head & Neck Cancer) study is a European multicenter phase III trial to determine whether adding cetuximab improves the impact of platinum-based chemotherapy. Between December 2004 and March 2007, researchers enrolled 442 patients in 17 countries who had stage III or IV recurrent and/or metastatic SCCHN, and who were not candidates for further surgery or radiation. About half of the patients had cancer in their pharynx (throat), and a quarter in their larynx (voice box), but none in the nasopharynx (upper part of the throat). The patients averaged 57 years of age. Only about 10 percent were women. Patients were randomly assigned to receive either chemotherapy (222 patients) or the same chemotherapy with cetuximab (220 patients). Chemotherapy consisted of 5-fluorouracil plus either carboplatin or cisplatin. Results: Patients treated with cetuximab reduced their risk of dying by 20 percent, surviving a median of 10.1 months compared to 7.4 months for those receiving chemotherapy alone.

A 2010 review concluded that the combination of cetuximab and platin/5-fluorouracil should be considered the current standard first-line regimen.

Head and neck cancer clinical trials employing bevacizumab, an inhibitor of the angiogenesis receptor VEGF, were recruiting patients As of March 2007.

Erlotinib is an oral EGFR inhibitor, and was found in one Phase II clinical trial to retard disease progression. Scientific evidence for the effectiveness of erlotinib is otherwise lacking to this point. A clinical trial evaluating the use of erlotinib in metastatic head and neck cancer is recruiting patients as of March, 2007.

Reovirus is an oncolytic virus that targets RAS activated cancer cells. Trial update on November 2008 showed stable disease or better in the first eight of nine patients with refractory head and neck cancer. Phase II trials are ongoing in England and the USA with phase III trials planned.

Prognosis

Although early-stage head and neck cancers (especially laryngeal and oral cavity) have high cure rates, up to 50% of head and neck cancer patients present with advanced disease. Cure rates decrease in locally advanced cases, whose probability of cure is inversely related to tumor size and even more so to the extent of regional node involvement. Consensus panels in America (AJCC) and Europe (UICC) have established staging systems for head and neck squamous cancers. These staging systems attempt to standardize clinical trial criteria for research studies, and attempt to define prognostic

categories of disease. Squamous cell cancers of the head and neck are staged according to the TNM classification system, where T is the size and configuration of the tumor, N is the presence or absence of lymph node metastases, and M is the presence or absence of distant metastases. The T, N, and M characteristics are combined to produce a "stage" of the cancer, from I to IVB.

Residual deficits

Even after successful definitive therapy, head and neck cancer patients face tremendous impacts on quality of life. Despite marked advances in reconstructive surgery and rehabilitation, intensity-modulated radiotherapy (IMRT) and conservation approaches to certain malignancies, some patients continue to have significant functional deficits.

Problem of second primaries

Survival advantages provided by new treatment modalities have been undermined by the significant percentage of patients cured of head and neck squamous cell carcinoma (HNSCC) who subsequently develop second primary tumors. The incidence of second primary tumors ranges in studies from 9.1% to 23% at 20 years. Second primary tumors are the major threat to long-term survival after successful therapy of early-stage HNSCC. Their high incidence results from the same carcinogenic exposure responsible for the initial primary process, called field cancerization.

Throat cancer has numerous negative effects on the body systems.

Digestive system

As it can impair a person's ability to swallow and eat, throat cancer affects the digestive system. The difficulty in swallowing can lead to a person to choke on their food in the early stages of digestion and interfere with the food's smooth travels down into the esophagus and beyond.

The treatments for throat cancer can also be harmful to the digestive system as well as other body systems. Radiation therapy can lead to nausea and vomiting, which can deprive a body of vital fluids (although these may be obtained through intravenous fluids if necessary). Frequent vomiting can lead to an electrolyte imbalance which has serious consequences for the proper functioning of the heart. Frequent vomiting can also upset the balance of stomach acids which has a negative impact on the digestive system, especially the lining of the stomach and esophagus.

Respiratory system

In the cases of some throat cancers, the air passages in the mouth and behind the nose may become blocked from lumps or the swelling from the open sores. If the throat cancer is near the bottom of the throat it has a high likelihood of spreading to the lungs and

interfering with the person's ability to breathe; this is even more likely if the patient is a smoker, because they are highly susceptible to lung cancer.

Others

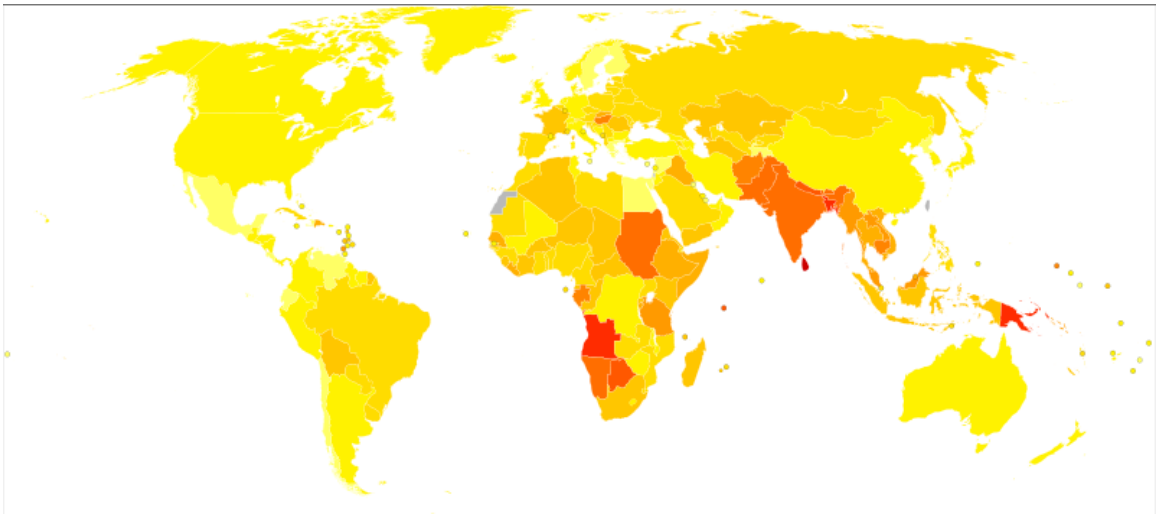
Like any cancer, metastasization affects many areas of the body, as the cancer spreads from cell to cell and organ to organ. For example, if it spreads to the bone marrow, it will prevent the body from producing enough red blood cells and affects the proper functioning of the white blood cells and the body's immune system; spreading to the circulatory system will prevent oxygen from being transported to all the cells of the body; and throat cancer can throw the nervous system into chaos, making it unable to properly regulate and control the body.

Symptoms and side effects

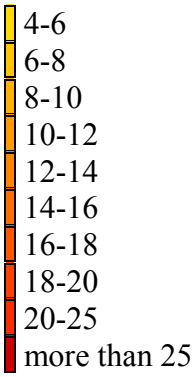
Patients with head and neck cancer may experience the following symptoms and treatment side effects

- Eating problems
- Pain associated with lesions
- Mucositis
- Nephrotoxicity and ototoxicity
- Xerostomia
- Gastroesophageal reflux
- Radiation induced osteonecrosis of the jaw

Epidemiology



Age-standardized death from oro-pharyngeal per 100,000 inhabitants in 2004.
no data
less than 2
2-4



The number of new cases of head and neck cancers in the United States was 40,490 in 2006, accounting for about 3% of adult malignancies. 11,170 patients died of their disease in 2006. The worldwide incidence exceeds half a million cases annually. In North America and Europe, the tumors usually arise from the oral cavity, oropharynx, or larynx, whereas nasopharyngeal cancer is more common in the Mediterranean countries and in the Far East. In Southeast China and Taiwan, head and neck cancer, specifically nasopharyngeal cancer is the most common cause of death in young men.

- In 2008, there were 22,900 cases of oral cavity cancer, 12,250 cases of laryngeal cancer, and 12,410 cases of pharyngeal cancer in the United States.
- In 2002, 7,400 Americans were projected to die of these cancers.
- More than 70% of throat cancers are at an advanced stage when discovered.
- Men are 89% more likely than women to be diagnosed with, and are almost twice as likely to die of, these cancers.
- African Americans are disproportionately affected by head and neck cancer, with younger ages of incidence, increased mortality, and more advanced disease at presentation. Laryngeal cancer incidence is higher in African Americans relative to white, Asian and Hispanic populations. There is a lower survival rate for similar tumor states in African Americans with head and neck cancer.
- Smoking and tobacco use are directly related to Oro-pharangeal (throat) cancer deaths.
- Head and neck cancer increases with age, especially after 50 years. Most patients are between 50 and 70 years old.

Chapter 8

Oral Cancer

Oral cancer	
ICD-10	C00.-C08.
ICD-9	140-146
DiseasesDB	9288

Oral cancer is a subtype of head and neck cancer, is any cancerous tissue growth located in the oral cavity. It may arise as a primary lesion originating in any of the oral tissues, by metastasis from a distant site of origin, or by extension from a neighboring anatomic structure, such as the nasal cavity or the maxillary sinus. Oral cancers may originate in any of the tissues of the mouth, and may be of varied histologic types: teratoma, adenocarcinoma derived from a major or minor salivary gland, lymphoma from tonsillar or other lymphoid tissue, or melanoma from the pigment producing cells of the oral mucosa. There are several types of oral cancers, but around 90% are squamous cell carcinomas, originating in the tissues that line the mouth and lips. Oral or mouth cancer most commonly involves the tongue. It may also occur on the floor of the mouth, cheek lining, gingiva (gums), lips, or palate (roof of the mouth). Most oral cancers look very similar under the microscope and are called squamous cell carcinoma. These are malignant and tend to spread rapidly.

Signs and symptoms

Skin lesion, lump, or ulcer:

- On the tongue, lip, or other mouth areas
- Usually small
- Most often pale colored, may be dark or discolored

- Early sign may be a white patch (leukoplakia) or a red patch (erythroplakia) on the soft tissues of the mouth
- Usually painless initially
- May develop a burning sensation or pain when the tumor is advanced

Additional symptoms that may be associated with this disease:

- Tongue problems
- Swallowing difficulty
- Mouth sores that do not resolve in 14 days
- Pain and paraesthesia are late symptoms.

Causes

Oncogenes are activated as a result of mutation of the DNA. The exact cause is often unknown. Regardless of the cause, treatment is the same: surgery, radiation with or without chemotherapy. Risk factors that predispose a person to oral cancer have been identified in epidemiological studies. India being member of International Cancer Genome Consortium is leading efforts to map oral cancer's complete genome.

In many Asian cultures chewing betel, paan and Areca is known to be a strong risk factor for developing oral cancer. In India where such practices are common, oral cancer represents up to 40% of all cancers, compared to just 4% in the UK.

Some oral cancers begin as leukoplakia a white patch (lesion), red patches, (erythroplakia) or non healing sores that have existed for more than 14 days. In the US oral cancer accounts for about 8 percent of all malignant growths. Men are affected twice as often as women, particularly men older than 40/60. In Indian subcontinent Oral submucous fibrosis is very common. This condition is characterized by limited opening of mouth and burning sensation on eating of spicy food. This is a progressive lesion in which the opening of the mouth becomes progressively limited, and later on even normal eating becomes difficult. It occurs almost exclusively in India and Indian communities living abroad.

Tobacco

Smoking and other tobacco use are associated with about 75 percent of oral cancer cases, caused by irritation of the mucous membranes of the mouth from smoke and heat of cigarettes, cigars, and pipes. Tobacco contains over 60 known carcinogens, and the combustion of it, and by products from this process, is the primary mode of involvement. Use of chewing tobacco or snuff causes irritation from direct contact with the mucous membranes.

Alcohol

Alcohol use is another high-risk activity associated with oral cancer. There is known to be a very strong synergistic effect on oral cancer risk when a person is both a heavy smoker and drinker. The risk is greatly increased compared to a heavy smoker, or a heavy drinker alone. Recent studies in Australia, Brazil and Germany point to alcohol-containing mouthwashes as also being etiologic agents in the oral cancer risk family. Constant exposure to these alcohol containing rinses, even in the absence of smoking and drinking, lead to significant increases in the development of oral cancer. A 2008 study suggests that acetaldehyde (a break-down product of alcohol) is implicated in oral cancer.

Human papillomavirus

Infection with human papillomavirus (HPV), particularly type 16 (there are over 120 types), is a known risk factor and independent causative factor for oral cancer. (Gilsion et al. Johns Hopkins) A fast growing segment of those diagnosed does not present with the historic stereotypical demographics. Historically that has been people over 50, blacks over whites 2 to 1, males over females 3 to 1, and 75% of the time people who have used tobacco products or are heavy users of alcohol. This new and rapidly growing sub population between 20 and 50 years old is predominantly non smoking, white, and males slightly outnumber females. Recent research from Johns Hopkins indicates that HPV is the primary risk factor in this new population of oral cancer victims. HPV16 (along with HPV18) is the same virus responsible for the vast majority of all cervical cancers and is the most common sexually transmitted infection in the US. Oral cancer in this group tends to favor the tonsil and tonsillar pillars, base of the tongue, and the oropharnyx. Recent data suggest that individuals that come to the disease from this particular etiology have some slight survival advantage.

Diagnosis

An examination of the mouth by the health care provider or dentist shows a visible and/or palpable (can be felt) lesion of the lip, tongue, or other mouth area. As the tumor enlarges, it may become an ulcer and bleed. Speech/talking difficulties, chewing problems, or swallowing difficulties may develop. A feeding tube is often necessary to maintain adequate nutrition. This can sometimes become permanent as eating difficulties can include the inability to swallow even a sip of water.

There are a variety of screening devices that may assist dentists in detecting oral cancer, including the Velscope, Vizilite Plus and the identafi 3000. While a dentist, physician or other health professional may suspect a particular lesion is malignant, there is no way to tell by looking alone - since benign and malignant lesions may look identical to the eye. A non-invasive brush biopsy (BrushTest) can be performed to rule out the presence of dysplasia (pre-cancer) and cancer on areas of the mouth that exhibit an unexplained color variation or lesion. The only definitive method for determining if cancerous or precancerous cells are present is through biopsy and microscopic evaluation of the cells

in the removed sample. A tissue biopsy, whether of the tongue or other oral tissues and microscopic examination of the lesion confirm the diagnosis of oral cancer or precancer.

Management

Surgical excision (removal) of the tumor is usually recommended if the tumor is small enough, and if surgery is likely to result in a functionally satisfactory result. Radiation therapy with or without chemo is often used in conjunction with surgery, or as the definitive radical treatment, especially if the tumour is inoperable. Surgeries for oral cancers include

- Maxillectomy (can be done with or without Orbital exenteration)
- Mandibulectomy (removal of the mandible or lower jaw or part of it)
- Glossectomy (tongue removal, can be total, hemi or partial)
- Radical neck dissection
- Moh's procedure or CCPDMA
- Combinational e.g. glossectomy and laryngectomy done together.
- Feeding tube to sustain nutrition.

Owing to the vital nature of the structures in the head and neck area, surgery for larger cancers is technically demanding. Reconstructive surgery may be required to give an acceptable cosmetic and functional result. Bone grafts and surgical flaps such as the radial forearm flap are used to help rebuild the structures removed during excision of the cancer. An oral prothesis may also be required. Most oral cancer patients depend on a feeding tube for their hydration and nutrition. Some will also get a port for the chemo to be delivered. Many oral cancer patients are disfigured and suffer from many long term after effects. The after effects often include fatigue, speech problems, trouble maintaining weight, thyroid issues, swallowing difficulties, inability to swallow, memory loss, weakness, dizziness, high frequency hearing loss and sinus damage.

Survival rates for oral cancer depend on the precise site, and the stage of the cancer at diagnosis. Overall, survival is around 50% at five years when all stages of initial diagnosis are considered. Survival rates for stage 1 cancers are 90%, hence the emphasis on early detection to increase survival outcome for patients.

Following treatment, rehabilitation may be necessary to improve movement, chewing, swallowing, and speech. speech and language pathologists may be involved at this stage.

Chemotherapy is useful in oral cancers when used in combination with other treatment modalities such as radiation therapy. It is not used alone as a monotherapy. When cure is unlikely it can also be used to extend life and can be considered palliative but not curative care. Biological agents, such as Cetuximab have recently been shown to be effective in the treatment of squamous cell head and neck cancers, and are likely to have an increasing role in the future management of this condition when used in conjunction with other treatments.

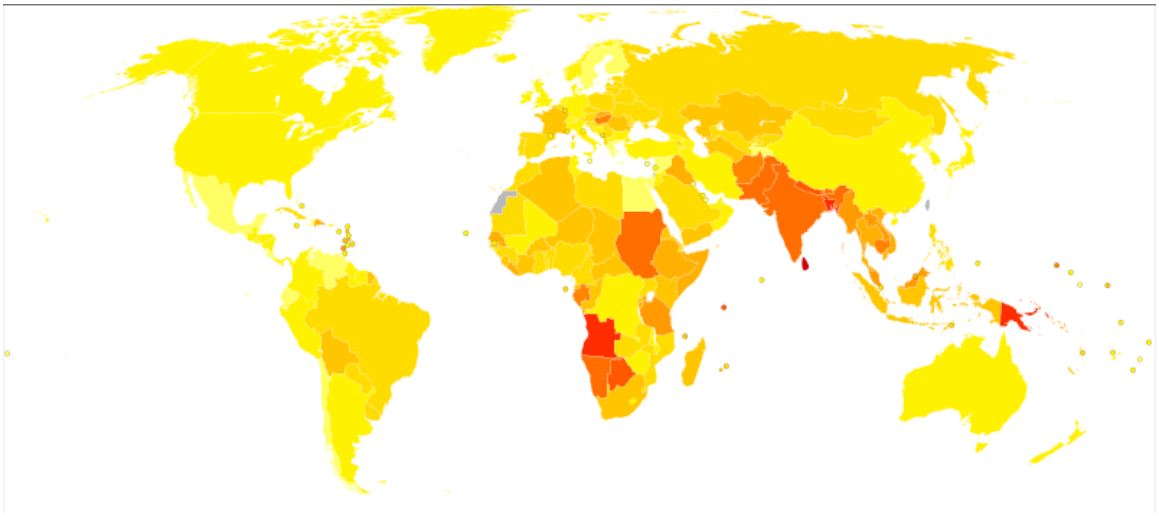
Treatment of oral cancer will usually be by a multidisciplinary team, with treatment professionals from the realms of radiation, surgery, chemotherapy, nutrition, dental professionals, and even psychology all possibly involved with diagnosis, treatment, rehabilitation, and patient care.

The Oral Cancer Foundation is a website devoted to in depth medical information about all oral cancers including treatment, side effects and even lists of the nation's best cancer treatment centers. The Oral Cancer Foundation has a forum where patients and their caregivers assist each other. It is monitored by the founder and administrators who ensure accurate up to date information is exchanged. This website has the most comprehensive amount of information devoted to oral cancer.

Prognosis

- Postoperative disfigurement of the face, head and neck
- Complications of radiation therapy, including dry mouth and difficulty swallowing
- Other metastasis (spread) of the cancer
- Significant weight loss

Epidemiology



Age-standardized death from oro-pharyngeal per 100,000 inhabitants in 2004.

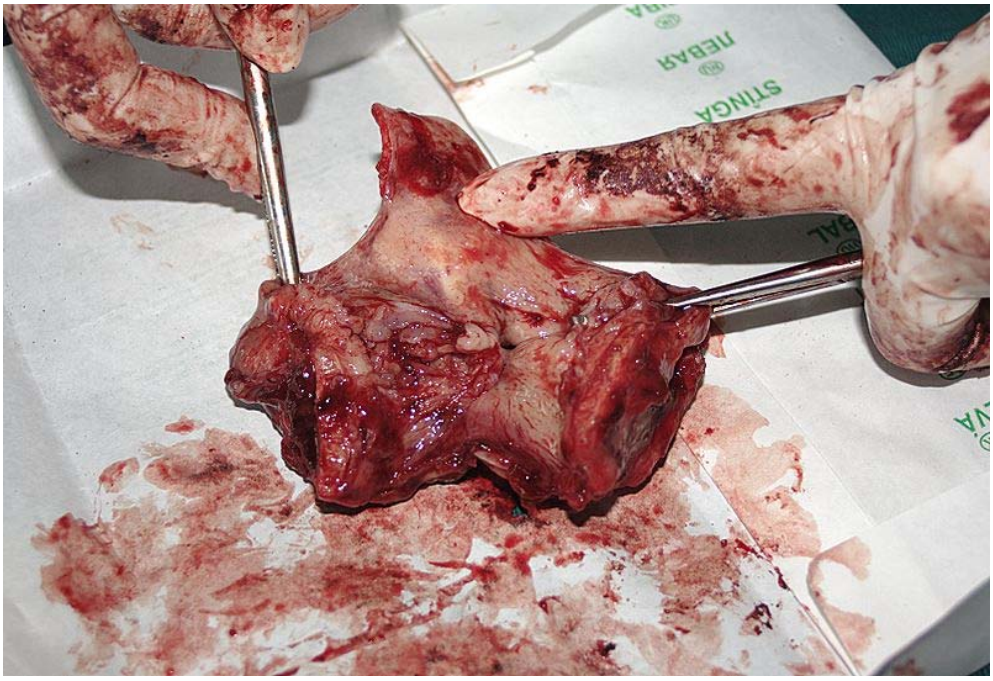
- no data
- less than 2
- 2-4
- 4-6
- 6-8
- 8-10
- 10-12
- 12-14
- 14-16

In 2008, in the United States alone, about 34,000 individuals were diagnosed with oral cancer. 66% of the time these will be found as late stage three and four disease. Low public awareness of the disease is a significant factor, but these cancers could be found at early highly survivable stages through a simple, painless, 5 minute examination by a trained medical or dental professional.

Chapter 9

Laryngeal Cancer

Laryngeal cancer



Larynx cancer.

ICD-10	C32.
ICD-9	161
MeSH	D007822

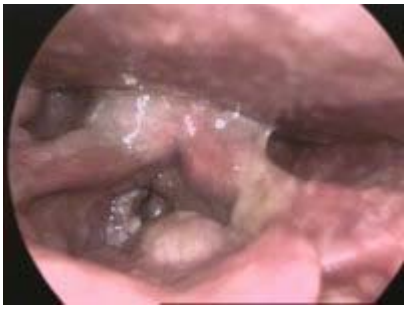
Laryngeal cancer may also be called **cancer of the larynx** or **laryngeal carcinoma**. Most laryngeal cancers are squamous cell carcinomas, reflecting their origin from the

squamous cells which form the majority of the laryngeal epithelium. Cancer can develop in any part of the larynx, but the cure rate is affected by the location of the tumor. For the purposes of tumour staging, the larynx is divided into three anatomical regions: the glottis (true vocal cords, anterior and posterior commissures); the supraglottis (epiglottis, arytenoids and aryepiglottic folds, and false cords); and the subglottis.

Most laryngeal cancers originate in the glottis. Supraglottic cancers are less common, and subglottic tumours are least frequent.

Laryngeal cancer may spread by direct extension to adjacent structures, by metastasis to regional cervical lymph nodes, or more distantly, through the blood stream. Distant metastates to the lung are most common.

Risk factors



Larynx cancer - endoscopic view

Smoking is the most important risk factor for laryngeal cancer. Death from laryngeal cancer is 20 times more likely for heaviest smokers than for nonsmokers. Heavy chronic consumption of alcohol, particularly alcoholic spirits, is also significant. When combined, these two factors appear to have a synergistic effect. Some other quoted risk factors are likely, in part, to be related to prolonged alcohol and tobacco consumption. These include low socioeconomic status, male sex, and age greater than 55 years.

People with a history of head and neck cancer are known to be at higher risk (about 25%) of developing a second cancer of the head, neck, or lung. This is mainly because in a significant proportion of these patients, the aerodigestive tract and lung epithelium have been exposed chronically to the carcinogenic effects of alcohol and tobacco. In this situation, a field change effect may occur, where the epithelial tissues start to become diffusely dysplastic with a reduced threshold for malignant change. This risk may be reduced by quitting alcohol and tobacco.

Symptoms

The symptoms of laryngeal cancer depend on the size and location of the tumor. Symptoms may include the following:

- Hoarseness or other voice changes

- A lump in the neck
- A sore throat or feeling that something is stuck in the throat
- Persistent cough
- Stridor
- Bad breath
- Ear ache ("*referred*")

Incidence

Two in 20,000 (12,500 new cases per year) in USA. The American Cancer Society estimates that 9,510 men and women (7,700 men and 1,810 women) will be diagnosed with and 3,740 men and women will die of laryngeal cancer in 2006.

Laryngeal cancer is listed as a "rare disease" by the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH). This means that laryngeal cancer affects fewer than 200,000 people in the U.S.

Each year, about 2,200 people in the U.K. are diagnosed with laryngeal cancer.

Diagnosis

Diagnosis is made by the doctor on the basis of a medical history, physical examination, and special investigations which may include a chest x-ray, CT or MRI scans, and tissue biopsy. The examination of the larynx requires some expertise, which may require specialist referral.

The physical exam includes a systematic examination of the whole patient to assess general health and to look for signs of associated conditions and metastatic disease. The neck and supraclavicular fossa are palpated to feel for cervical adenopathy, other masses, and laryngeal crepitus. The oral cavity and oropharynx are examined under direct vision. The larynx may be examined by indirect laryngoscopy using a small angled mirror with a long handle (akin to a dentist's mirror) and a strong light. Indirect laryngoscopy can be highly effective, but requires skill and practice for consistent results. For this reason, many specialist clinics now use fibre-optic nasal endoscopy where a thin and flexible endoscope, inserted through the nostril, is used to clearly visualise the entire pharynx and larynx. Nasal endoscopy is a quick and easy procedure performed in clinic. Local anaesthetic spray may be used.

If there is a suspicion of cancer, biopsy is performed, usually under general anaesthetic. This provides histological proof of cancer type and grade. If the lesion appears to be small and well localised, the surgeon may undertake excision biopsy, where an attempt is made to completely remove the tumour at the time of first biopsy. In this situation, the pathologist will not only be able to confirm the diagnosis, but can also comment on the completeness of excision, i.e., whether the tumour has been completely removed. A full endoscopic examination of the larynx, trachea, and esophagus is often performed at the time of biopsy.

For small glottic tumours further imaging may be unnecessary. In most cases, tumour staging is completed by scanning the head and neck region to assess the local extent of the tumour and any pathologically enlarged cervical lymph nodes.

The final management plan will depend on the site, stage (tumour size, nodal spread, distant metastasis), and histological type. The overall health and wishes of the patient must also be taken into account.

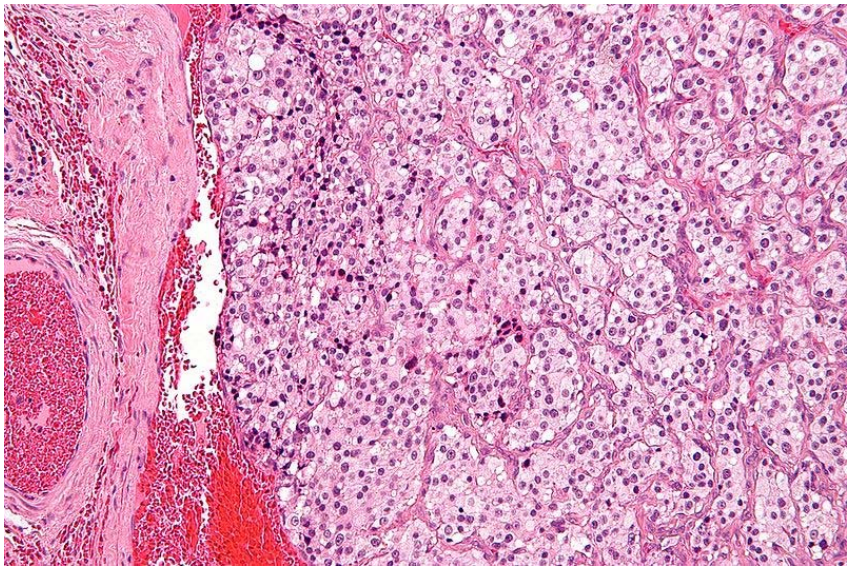
Treatment

Specific treatment depends on the location, type, and stage of the tumour. Treatment may involve surgery, radiotherapy, or chemotherapy, alone or in combination. This is a specialised area which requires the coordinated expertise of ear, nose and throat (ENT) surgeons (otolaryngologists) and oncologists.

Chapter 10

Paraganglioma

Paraganglioma



Micrograph of a *carotid body tumor* (a type of paraganglioma).

ICD-10	C75.4, C75.5, D35.5, D35.6, D44.6, D44.7
ICD-9	194.5, 194.6, 227.5, 227.6, 237.3
ICD-O:	M8680/0 - M8693/9
DiseasesDB	33480
eMedicine	med/2994
MeSH	D010235

A **paraganglioma** is a rare neuroendocrine neoplasm that may develop at various body sites (including the head, neck, thorax and abdomen). About 97% are benign and cured by surgical removal; the remaining 3% are malignant because they are able to produce distant metastases. Paragangliomas are still sometimes referred to using older, obsolete terminology (for example as "chemodectomas" or "glomus tumors", the latter not to be confused with glomus tumors of the skin).

Cellular origin and classification

Paragangliomas originate from chromaffin cells in paraganglia or chromaffin-negative glomus cells derived from the embryonic neural crest, functioning as part of the sympathetic nervous system (a branch of the autonomic nervous system). These cells normally act as special chemoreceptors located along blood vessels, particularly in the carotid bodies (at the bifurcation of the common carotid artery in the neck) and in aortic bodies (near the aortic arch).

Accordingly, paragangliomas are categorised as originating from a neural cell line in the World Health Organization classification of neuroendocrine tumors. In the categorization proposed by Wick, paragangliomas belong to group II. Given the fact that they originate from cells of the orthosympathetic system, paragangliomas are closely related to phaeochromocytomas, which however are chromaffine-positive.

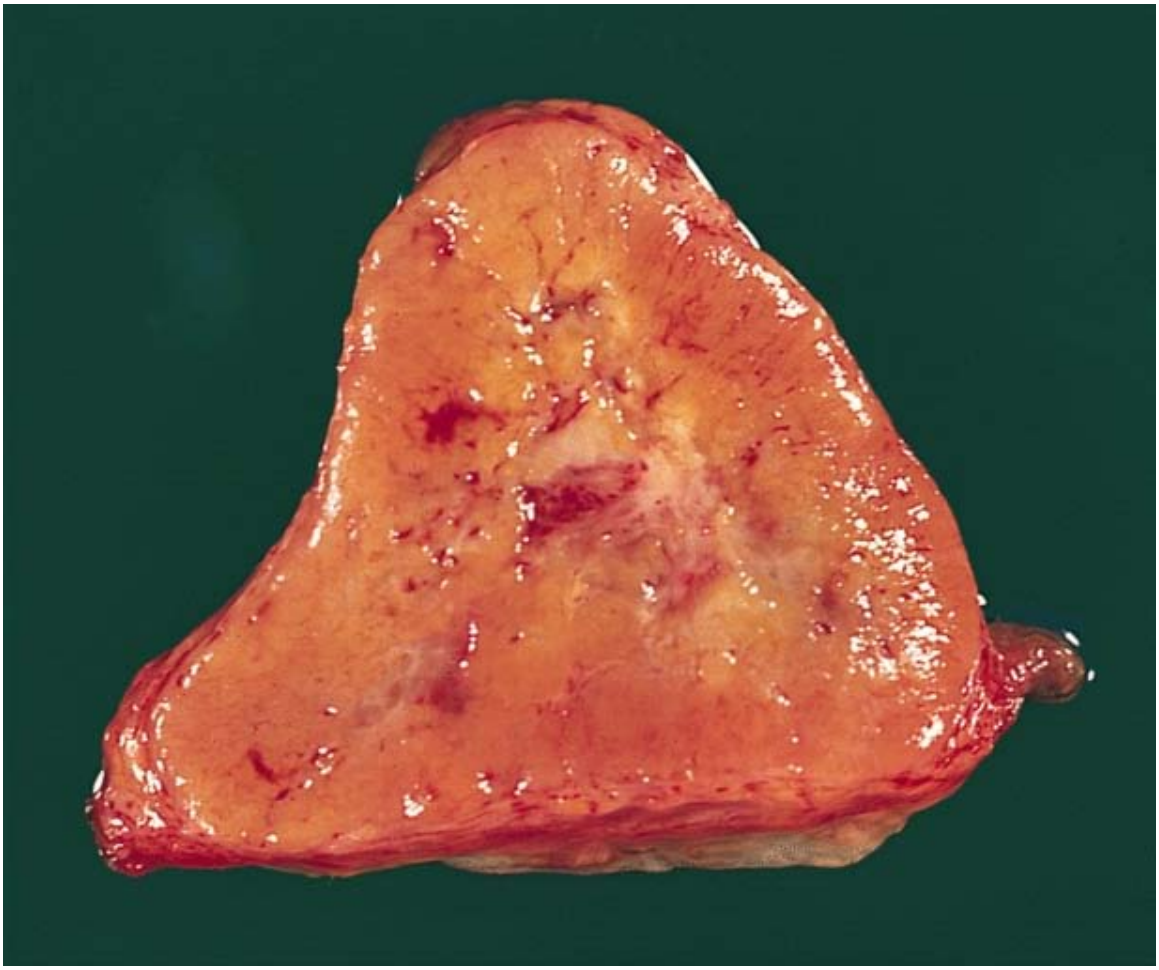
Clinical presentation

Most paragangliomas are either asymptomatic or present as a painless mass. While all contain neurosecretory granules, only in 1–3% of cases is secretion of hormones such as catecholamines abundant enough to be clinically significant; in that case manifestations often resemble those of phaeochromocytomas.

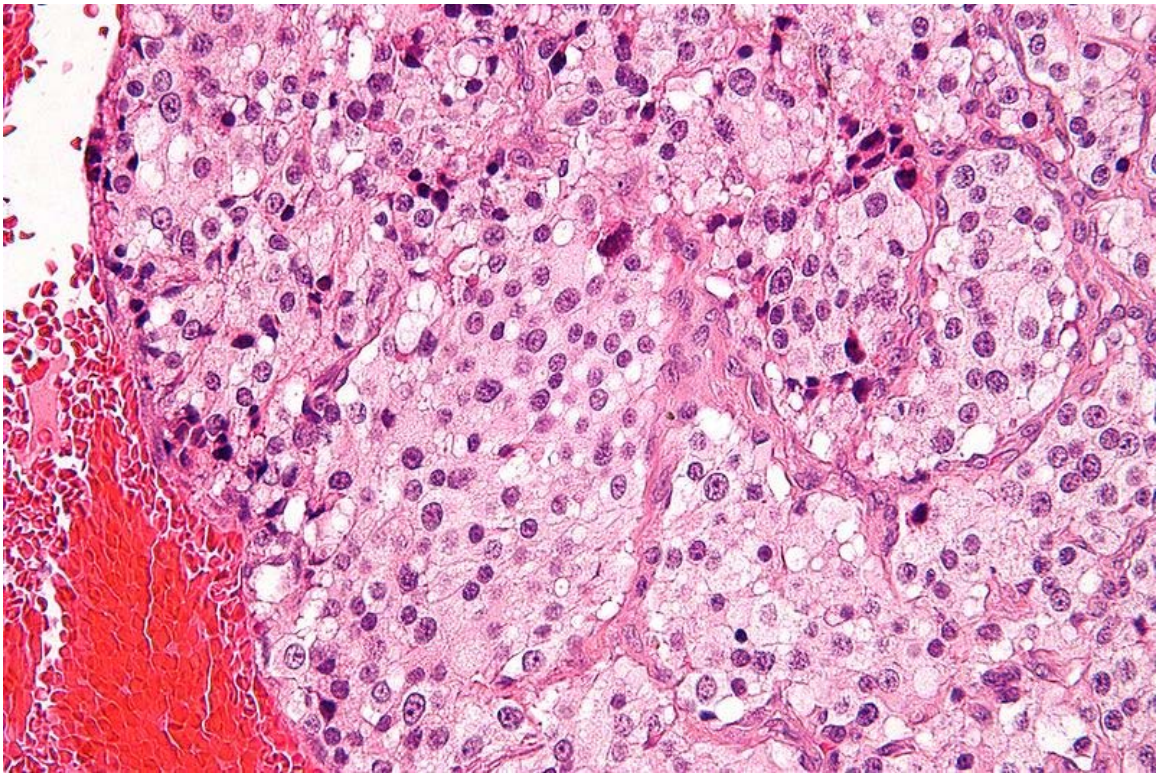
Inheritance

About 75% of paragangliomas are sporadic; the remaining 25% are hereditary (and have an increased likelihood of being multiple and of developing at an earlier age). Mutations of the genes SDHD (previously known as PGL1), PGL2, and SDHC (previously PGL3) have been identified as causing familial head and neck paragangliomas. Mutations of SDHB play an important role in familial adrenal pheochromocytoma and extra-adrenal paraganglioma (of abdomen and thorax), although there is considerable overlap in the types of tumors associated with SDHB and SDHD gene mutations. Paragangliomas may also occur in MEN type 2A and 2B.

Pathology



Mediastinal paraganglioma. The cut surface of a 3.9 x 3.5 x 2.5 cm tumor is triangular, with a bulging peripheral portion and a somewhat fibrotic center. It was surrounded by the heart, left lower lobe of the lung, aorta, esophagus, and diaphragm, and had been 1.8 cm in diameter 7 years before.



Micrograph of a *carotid body tumor* with the characteristic *Zellballen*. H&E stain.

The paragangliomas appear grossly as sharply circumscribed polypoid masses and they have a firm to rubbery consistency. They are highly vascular tumors and may have a deep red color.

On microscopic inspection, the tumor cells are readily recognized. Individual tumor cells are polygonal to oval and are arranged in distinctive cell balls, called *Zellballen*. These cell balls are separated by fibrovascular stroma and surrounded by sustentacular cells.

By light microscopy, the differential diagnosis includes related neuroendocrine tumors, such as carcinoid tumor, neuroendocrine carcinoma, and medullary carcinoma of the thyroid; middle ear adenoma; and meningioma.

With immunohistochemistry, the chief cells located in the cell balls are positive for chromogranin, synaptophysin, neuron specific enolase, serotonin, neurofilament and Neural cell adhesion molecule; they are S-100 protein negative. The sustentacular cells are S-100 positive and focally positive for glial fibrillary acid protein. By histochemistry, the paraganglioma cells are argyrophilic, periodic acid Schiff negative, mucicarmine negative, and argentaffin negative.

Sites of origin

About 85% of paragangliomas develop in the abdomen; only 12% develop in the chest and 3% in the head and neck region (the latter are the most likely to be symptomatic). While most are single, rare multiple cases occur (usually in a hereditary syndrome). Paragangliomas are described by their site of origin and are often given special names:-

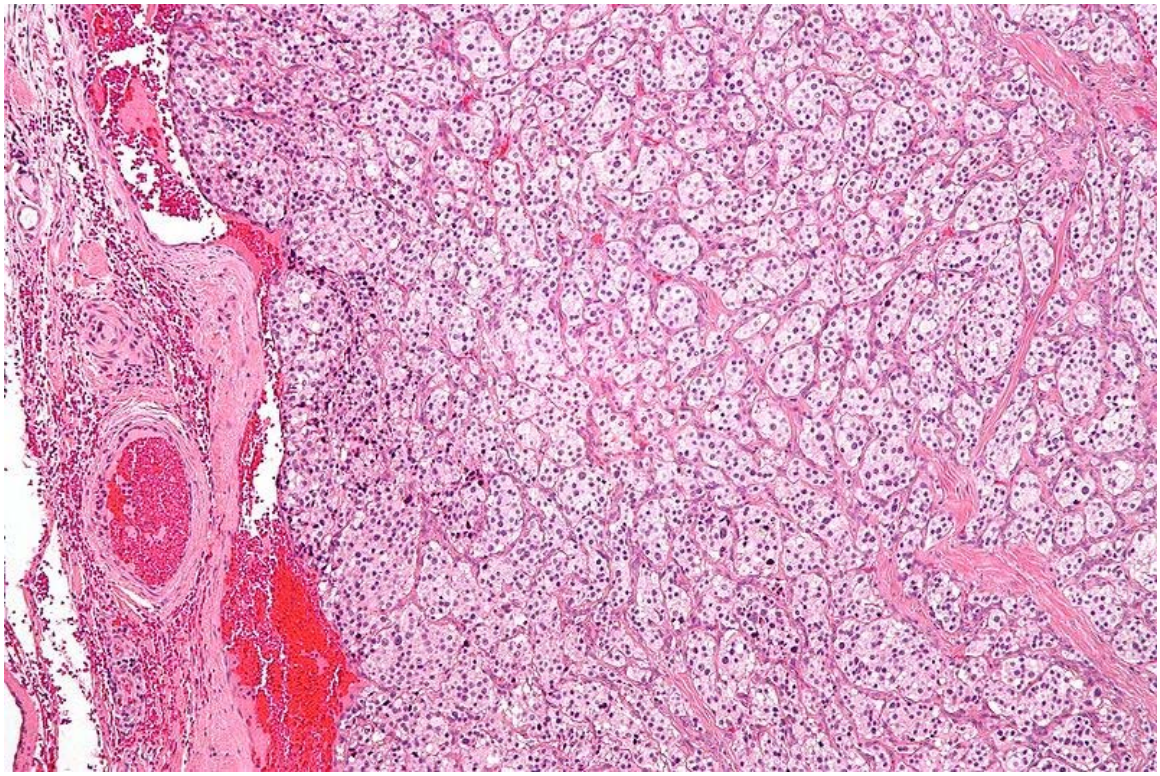
- **Carotid paraganglioma** (carotid body tumor): Is the most common of the head and neck paragangliomas. It usually presents as a painless neck mass, but larger tumors may cause cranial nerve palsies, usually of the vagus nerve and hypoglossal nerve.
- **Glomus tympanicum** and **Glomus jugulare**: Both commonly present as a middle ear mass resulting in tinnitus (in 80%) and hearing loss (in 60%). The cranial nerves of the jugular foramen may be compressed, resulting swallowing difficulty, or ipsilateral weakness of the upper trapezius and sternocleiodomastoid muscles (from compression of the spinal accessory nerve). These patients present with a reddish bulge behind an intact ear drum. This condition is also known as the "Red drum". On application of pressure to the external ear canal with the help of a pneumatic ear speculum the mass could be seen to blanch. This sign is known as "Brown's sign".
- **Vagal paraganglioma**: These are the least common of the head and neck paragangliomas. They usually present as a painless neck mass, but may result in dysphagia and hoarseness.
- **Pulmonary paraglioma**: These occur in the lung and may be either single or multiple.

- **Other sites**: Rare sites of involvement are the larynx, nasal cavity, paranasal sinuses, thyroid gland, and the thoracic inlet, as well as the bladder in extremely rare cases.

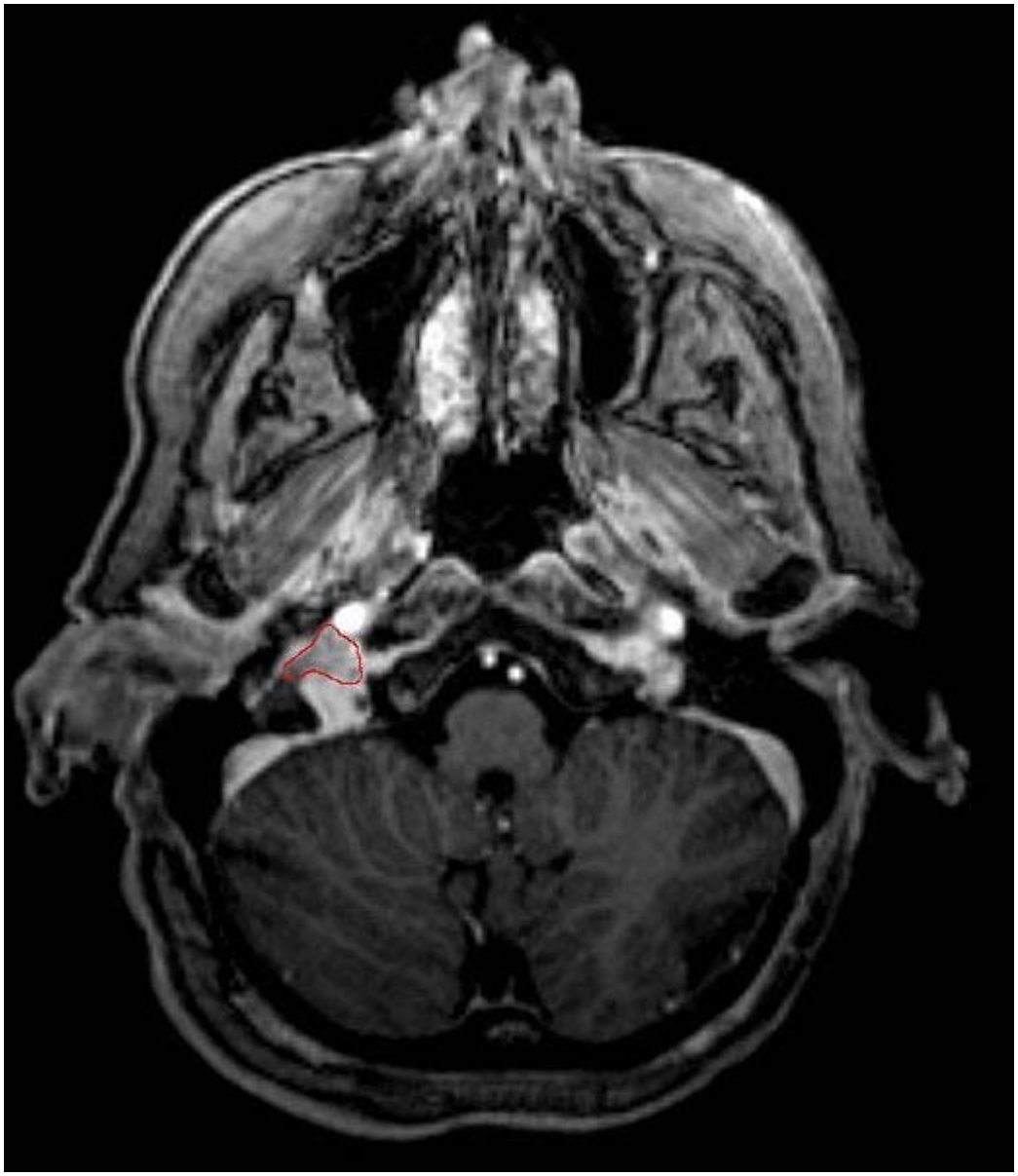
Treatment

The main treatment modalities are surgery, embolization and radiotherapy.

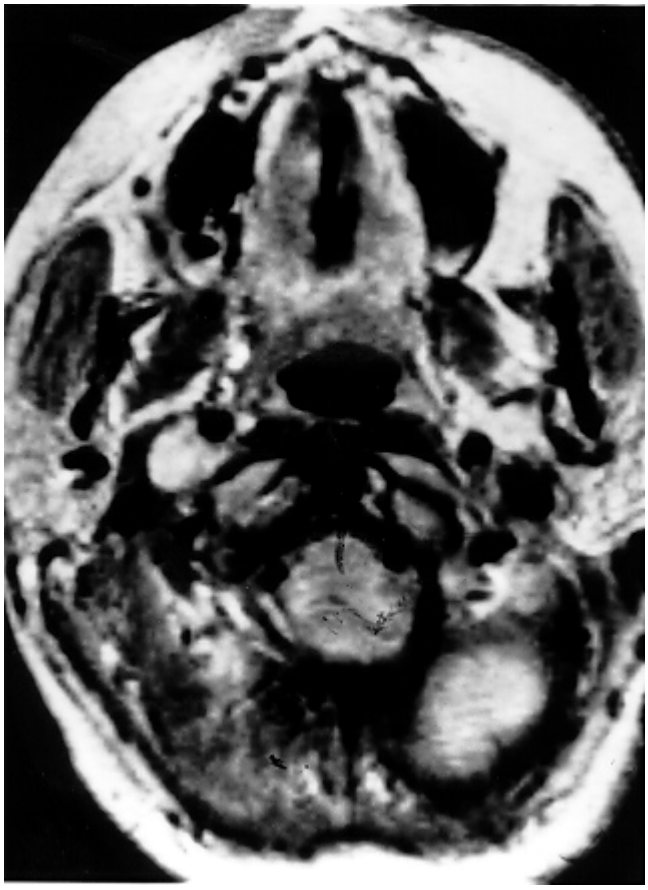
Additional images



Micrograph of a *carotid body tumor*.



Glomus Jugulare Tumor.

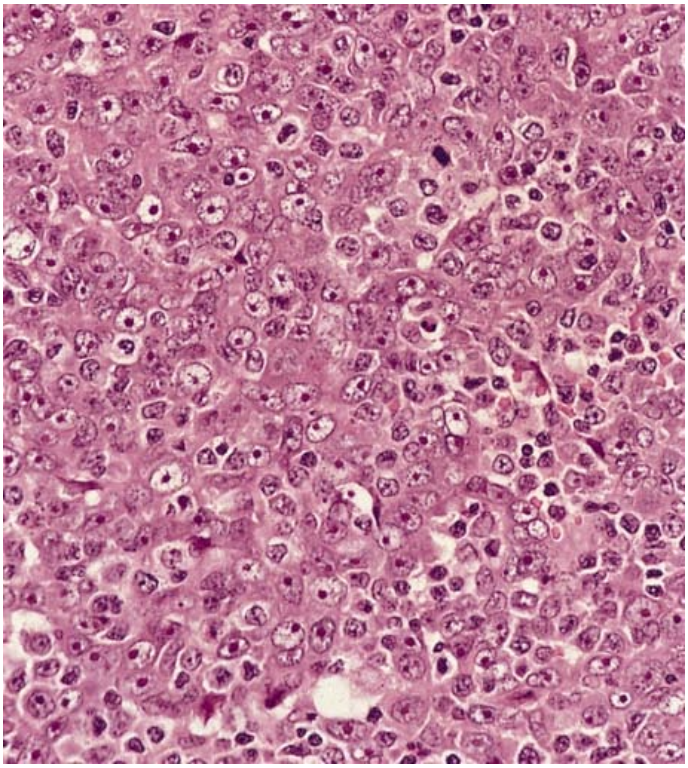


Ectopic functional paraganglioma (glomus jugulare) in a patient with VHL. T2 weighted MRI at the same location demonstrates a high signal mass consistent with a paraganglioma. Extra adrenal paragangliomas can be found in VHL (arrow).

Chapter 11

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma



Metastatic nasopharyngeal carcinoma in a lymph node

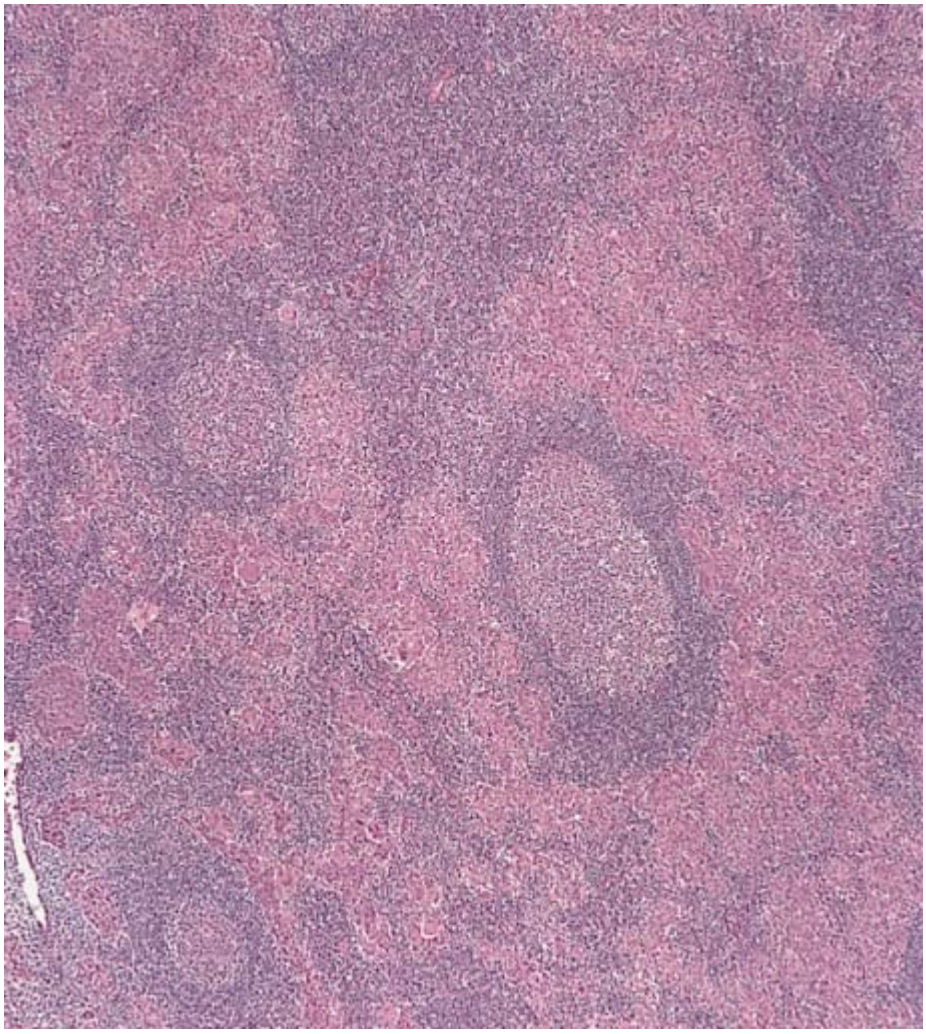
ICD-10	C11.
ICD-9	147
OMIM	161550

DiseasesDB	8814
eMedicine	ped/1553
MeSH	D009303

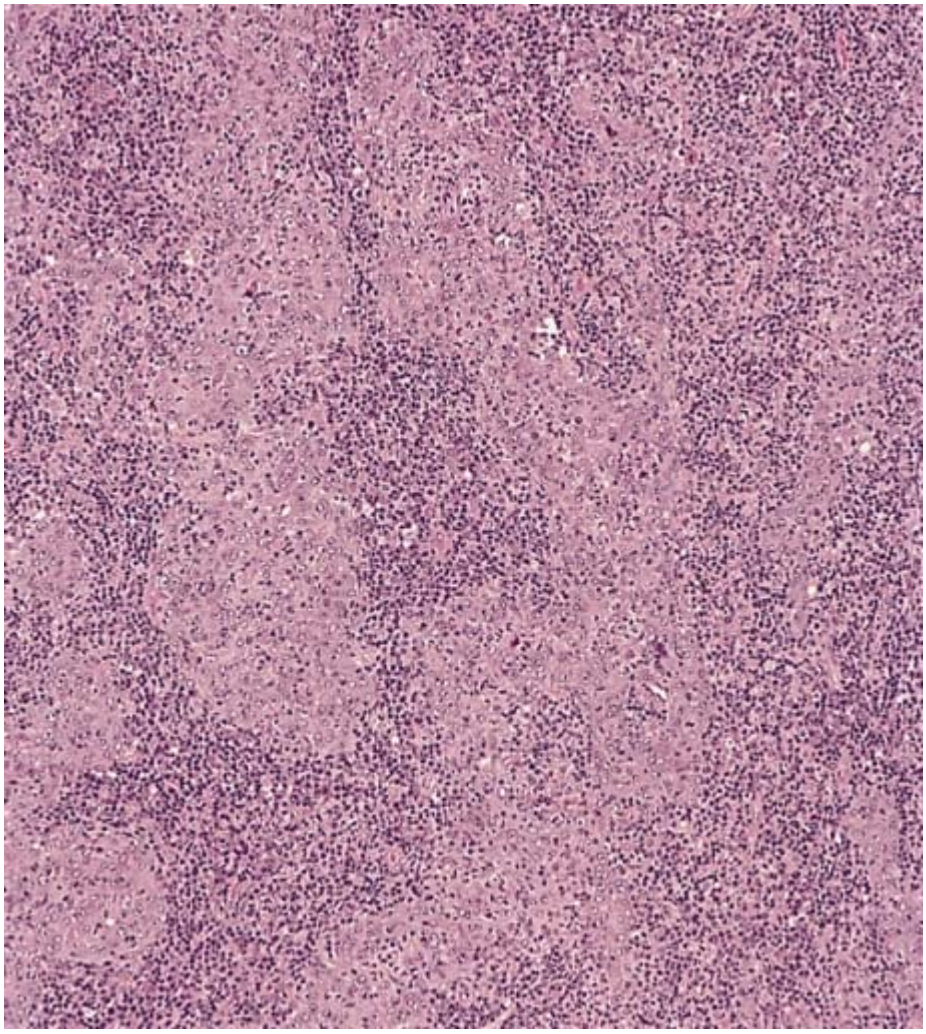
Nasopharyngeal carcinoma (NPC) is a cancer originating in the nasopharynx, the uppermost region of the pharynx or "throat", where the nasal passages and auditory tubes join the remainder of the upper respiratory tract. NPC differs significantly from other cancers of the head and neck in its occurrence, causes, clinical behavior, and treatment. It is vastly more common in certain regions of East Asia and Africa than elsewhere, with viral, dietary and genetic factors implicated in its causation.

Classification

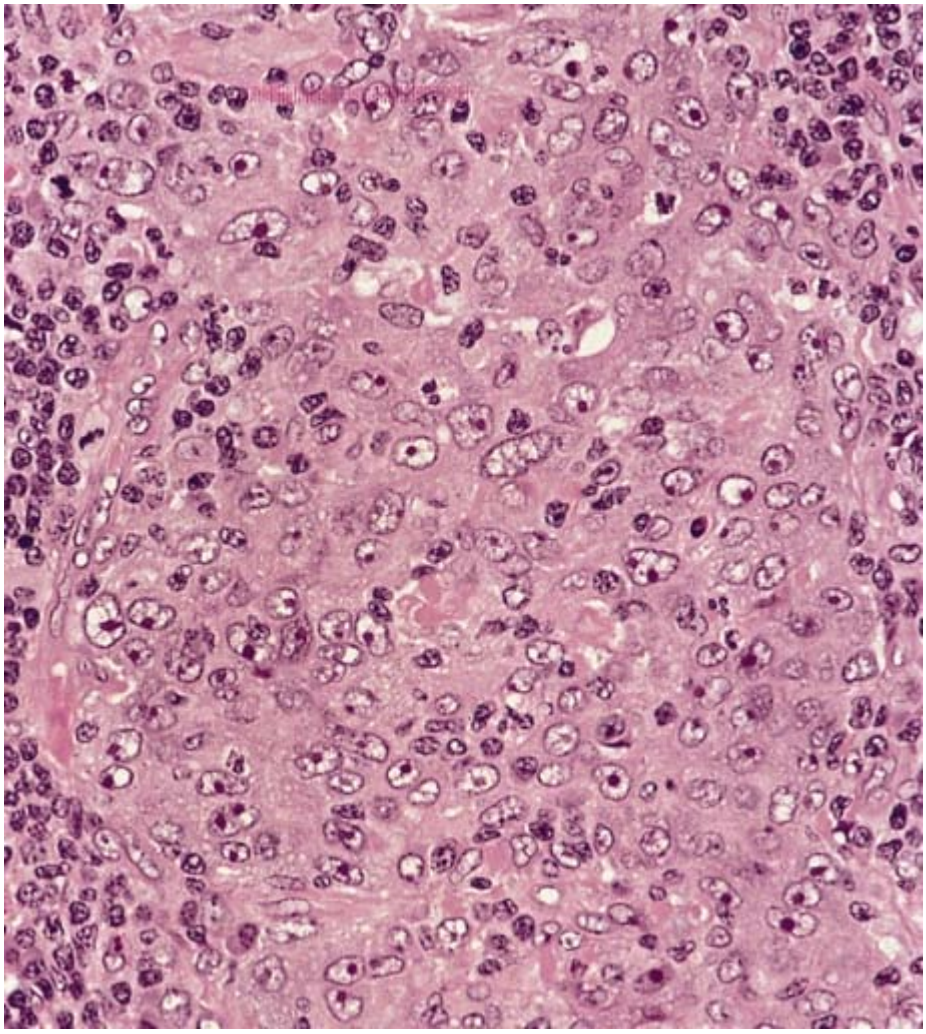
Nasopharyngeal carcinoma, commonly known as nasopharyngeal cancer, is classified as a malignant neoplasm, or cancer, arising from the mucosal epithelium of the nasopharynx, most often within the *lateral nasopharyngeal recess* or *fossa of Rosenmüller*. There are three microscopic subtypes of NPC: a well-differentiated *keratinizing* type, a moderately-differentiated *nonkeratinizing* type, and an *undifferentiated* type, which typically contains large numbers of non-cancerous lymphocytes (chronic inflammatory cells), thus giving rise to the name *lymphoepithelioma*. The undifferentiated form is most common, and is most strongly associated with Epstein-Barr virus infection of the cancerous cells.



Undifferentiated nasopharyngeal carcinoma - low power



Undifferentiated nasopharyngeal carcinoma - med. power



Undifferentiated nasopharyngeal carcinoma - high power

Symptoms and signs

Cervical lymphadenopathy is the initial presentation in many patients, and the diagnosis of NPC is often made by lymph node biopsy. Symptoms related to the primary tumor include trismus, pain, otitis media, nasal regurgitation due to paresis of the soft palate, hearing loss and cranial nerve palsies. Larger growths may produce nasal obstruction or bleeding and a "nasal twang". Metastatic spread may result in bone pain or organ dysfunction. Rarely, a paraneoplastic syndrome of osteoarthropathy may occur with widespread disease.

Causes

EBV (Epstein-Barr virus) NPC is the most common epithelial cancer in adults. The detection of nuclear antigen associated with Epstein-Barr virus (EBNA) and viral DNA in NPC type 2 and 3, has revealed that EBV can infect epithelial cells and is associated with

their transformation . The etiology of NPC (particularly the endemic form) seems to follow a multi-step process, in which EBV, ethnic background, and environmental carcinogens all seem to play an important role. Lo et al. showed that EBV DNA was detectable in the plasma samples of 96% of patients with non-keratinizing NPC, compared with only 7% in controls . More importantly, EBV DNA levels appear to correlate with treatment response and they may predict disease recurrence, suggesting that they may be an independent indicator of prognosis. In adults, other likely etiological factors include genetic susceptibility, consumption of food (in particular salted fish) containing carcinogenic volatile nitrosamines, and as in children, EBV .

Treatment

Surgery. Due to the anatomical position of NPC and its tendency to present with cervical lymph node metastases, it is not amenable to surgery for local control. Biopsy of the involved lymph node is the usual surgical procedure. The nasopharyngeal primary tumor is rarely biopsied.

Chemotherapy. Several factors are taken into account in deciding the chemotherapy regimen. Firstly, efficacy: the figures for event-free survival are similar for most small chemotherapy series but therapy usually involves fairly high-dose radiotherapy to the nasopharynx – 60 to 65 Gy. However, the most promising results with a recent update, are those obtained using the Mertens protocol NPC-91-GPOH (Society of Pediatric Oncology and Hematology). This protocol should therefore be considered as the best current treatment. Uniquely, the NPC-91-GPOH protocol includes immunotherapy with interferon-beta after chemotherapy and radiotherapy, which may explain its superior results compared to regimens without interferon treatment . Secondly, late effects: in terms of chemotherapy, the Manchester regimen – doxorubicin, methotrexate and cyclophosphamide – would produce infertility in boys (total dose of cyclophosphamide 12 gm/m2) and possible anthracycline toxicity (total dose of doxorubicin 360 mg/m2) . The NPC-91-GPOH protocol might produce some infertility in older boys but the total dose of cisplatinum is only 300 mg/m2. Furthermore, the incidence of renal toxicity should be relatively low but auditory toxicity would be higher because of the additional effect of irradiation on the auditory apparatus. The degree of pituitary dysfunction obviously depends on the radiotherapy field and, potentially, on the dose of radiotherapy but some degree of hypopituitarism is expected. Furthermore, irradiation to the neck would result in hypothyroidism for the majority of patients and irradiation to the oropharynx would result in xerostomia and resultant poor dentition. The later may be relieved by amifostine, as demonstrated in adult studies.

Radiotherapy. Although treatment with radiotherapy controls the primary tumor [28-30], it does not prevent the appearance of distant metastases [28,31]. Radiotherapy is given with megavoltage equipment after initial chemotherapy. A maximum dose of 45 Gy is given to the clinical target volume, which is a 1 cm margin around the MRI-detected primary site, and inferiorly down to the clavicles to include the lymph nodes. Treatment is given in two phases:

- Phase I – parallel pair (mostly lateral unless the tumor extends anteriorly between the eyes). Eyes, brain and brain stem are shielded as much as possible. A mid-plane dose of 30 Gy in 15 fractions is given.
- Phase II – a lateral parallel pair or three-fields technique is used for the primary site, delivering 15 Gy in seven fractions to the clinical target volume of the tumor with a 1 cm margin. Brain stem and eyes should be shielded. Any overlap with the neck field should be shielded. A matching anterior neck node field is used to deliver a prescribed maximum subcutaneous dose of 15 Gy in seven fractions. The spinal cord should be shielded in this field. This prescription for radiotherapy is used in Manchester, but it is recognized that higher doses may be used in some centers, possibly to a total of 60 Gy to the tumor volume. In an current GPOH study, patients in complete remission (CR) after three courses of chemotherapy, will have their radiotherapy dosage reduced to 54 Gy instead of 59 Gy.

Recommendation. In the current GPOH protocol NPC-2003-GPOH, low-risk patients with Stage I and II tumors receive radiotherapy only, followed by 105 μg/Kg of adjuvant interferon beta (IFNbeta), intravenously (i.v.), three times a week for 6 months. High-risk patients receive cisplatinum (100 mg/m2 over 6 hours on day 1 with standard hydration), mannitol and electrolyte replacement, and folinic acid (25 mg/m2 every 6 hours for a total of six doses) as well as 5-fluorouracil (1000 mg/m2 per day from day 2 for 5 days) as a continuous infusion. They receive three courses of chemotherapy every 21 days or on full blood count recovery, followed by irradiation and IFNbeta as for low-risk patients. Methotrexate has been dropped because of severe mucositis. Patients not in CR after three courses of chemotherapy will receive concomitant cisplatinum (20 mg/m2/day for 3 days with radiotherapy for two courses).

Prognosis

Prognostic factors Stage at presentation is the most prognostic factor. The 5-year disease-specific survival (DSS) is as follow: • For stage I à 98% • For stage II A-B à 95% • For stage III à 86% • For stage IV A-B à 73% (…)

Factors that may influence prognosis include the clinical stage, patient age and gender, presence of keratinization, lymph node metastasis, and possibly genetic factors. • Better prognosis is associated with lower clinical stage, younger patient age, and female gender. • While worse prognosis is seen with high-stage tumors, old patients and male gender(..) Presentation with lymphadenomegalia implies that the disease has spread beyond the primary site. However, in childhood the presence of metastatic disease in cervical lymph nodes at diagnosis does not adversely affect prognosis [30-33]. Factors associated with a poor prognosis • skull base involvement [33-35] • extent of the primary tumor [31,32] • cranial nerve involvement [33,34] Reddy *et al.* (..) evaluated 50 patients with NPC and found that the patients with the keratinizing type of NPC had a higher incidence of locally advanced tumor but a lower incidence of lymphatic and/or distant spread. Despite these findings, the patient with the keratinizing NPC had a poorer 5-year survival rate than those with the other histologic subtypes due to a higher incidence of deaths secondary to local uncontrollable disease and nodal metastasis. (…) NPC frequently

metastasize to regional lymph nodes and the presence of lymph node metastasis decrease survival by 10-20%.(..) Similarly, a large percentage of NPC, particularly of the undifferentiated type, metastasize to sites below the clavicle, including lung, bones (rib and spine), and liver.

Epidemiology

NPC is uncommon in the United States and most other nations, but is extremely common in southern regions of China, particularly in Guangdong accounting for 18% of all cancers in China. It is sometimes referred to as **Cantonese cancer** because it occurs in about 25 cases per 100,000 people in this region, 25 times higher than the rest of the world. It is also quite common in Taiwan. This could be due to the South East Asian diet which typically includes consumption of salted vegetables, fish and meat. While NPC is seen primarily in middle-aged persons in Asia, a high proportion of African cases appear in children. The cause of increased risk for NPC in these endemic regions is not entirely clear.

Chapter 12

Uveal Melanoma

Uveal Melanoma	
ICD-10	C69.
ICD-9	190
ICD-O:	M8720/3
OMIM	155720
DiseasesDB	2614
MedlinePlus	001022
eMedicine	oph/403
MeSH	D014604

Uveal melanoma is a cancer (melanoma) of the eye involving the iris, ciliary body, or choroid (collectively referred to as the uvea). Tumors arise from the pigment cells (melanocytes) that reside within the uvea giving color to the eye. These melanocytes are distinct from the Retinal pigment epithelium cells underlying the retina that do not form melanomas.

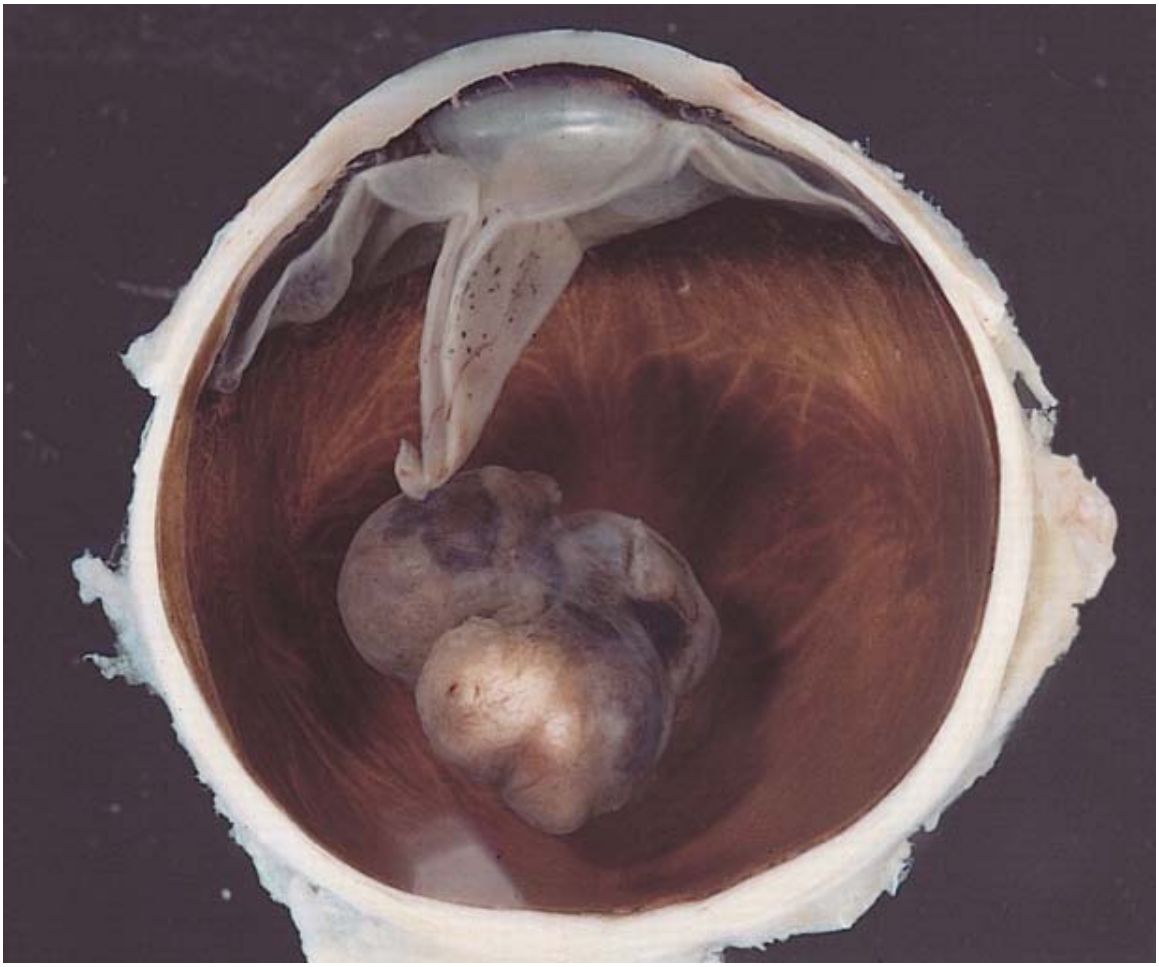
Types

Uveal melanomas may arise from any of the three parts of the uvea, and are sometimes referred to by their location, as Choroidal melanoma, ciliary body melanoma, or iris melanoma. Large tumors often encompass multiple parts of the uvea and can be named accordingly. True iris melanomas, originating from within the iris as opposed to originating elsewhere and invading the iris, are distinct in their etiology and prognosis, such that the other tumors are often referred to collectively as Posterior uveal melanomas.

Iris melanoma

Uveal tumors can originate from melanocytes residing within the iris. Benign melanocytic tumors, such as iris freckles and moles (nevi), are common and pose no health risks, unless they show signs of malignancy, in which case they are classified as iris melanomas. Though derived from uveal melanocytes, iris melanomas share more in common with cutaneous (skin) melanomas, in that they frequently harbor BRAF mutations associated with ultraviolet damage. Iris melanomas are much less likely to metastasize than other uveal melanomas, and less likely to impair vision if detected and treated early.

Posterior uveal melanoma



Variably pigmented, mushroom-shaped choroidal tumor has ruptured the Bruch membrane and grown into the subretinal space.

Benign melanocytic tumors of the choroid, such as choroidal freckles and nevi, are very common and pose no health risks, unless they show signs of malignancy, in which case they are considered melanomas. Uveal melanoma is distinct from most skin melanomas associated with ultraviolet exposure; however, it shares several similarities with non-sun-

exposed melanomas, such as acral melanomas and mucosal melanomas. BRAF mutations are extremely rare in posterior uveal melanomas; instead, uveal melanomas frequently harbor GNAQ/GNA11 mutations, a trait shared with blue nevi, Nevus of Ota, and Ocular melanosis. As seen in BRAF, mutations in GNAQ/GNA11 are early events in tumorigenesis and are not prognostic for tumor stage or later metastatic spread. In contrast, mutations in the gene BAP1 are strongly linked to metastatic spread and patient survival. Incidence of posterior uveal melanoma is highest among people with light skin and blue eyes. Other risk factors, such as blue light exposure and arc welding have been put forward, but are still debated in the field. Mobile phone use is not a risk factor for uveal melanoma.

Treatment

The treatment protocol for uveal melanoma has been directed by many clinical studies, the most important being "The Collaborative Ocular Melanoma Study" (COMS). The treatment varies depending upon many factors, chief among them, the size of the tumor. Primary treatment can involve removal of the affected eye (enucleation); however, this is now reserved for cases of extreme tumor burden or other secondary problems. Advances in radiation therapies have significantly decreased the number of patients treated by enucleation in developed countries. The most common radiation treatment is plaque brachytherapy, in which a small disc-shaped shield (plaque) encasing radioactive seeds (most often Iodine-125, though Ruthenium-106 and Palladium-103 are also used) is attached to the outside surface of the eye, overlying the tumor. The plaque is left in place for a few days and then removed. The risk of metastasis after plaque radiotherapy is the same as that of enucleation, suggesting that micrometastatic spread occurs prior to treatment of the primary tumor. Other modalities of treatment include transpupillary thermotherapy, external beam proton therapy, resection of the tumor, Gamma Knife stereotactic radiosurgery or a combination of different modalities. Different surgical resection techniques can include trans-scleral partial choroidectomy, and transretinal endoresection.

Prognostic factors

Several clinical and pathological prognostic factors have been identified that are associated with higher risk of metastasis of uveal melanomas. These include large tumor size, ciliary body involvement, presence of orange pigment overlying the tumor, and older patient age. Likewise several histological and cytological factors are associated with higher risk of metastasis including presence and extent of cells with epithelioid morphology, presence of looping extracellular matrix patterns, increased infiltration of immune cells, as well as staining with several immunohistochemical markers.

The most important genetic alteration associated with poor prognosis in uveal melanoma is inactivation of BAP1, which most often occurs through mutation of one allele and subsequent loss of an entire copy of Chromosome 3 (Monosomy 3) to unmask the mutant copy. Because of this function in inactivation of BAP1, monosomy 3 correlates strongly with metastatic spread Where BAP1 mutation status is not available, gains on

chromosomes 6 and 8 can be used to refine the predictive value of the Monosomy 3 screen, with gain of 6p indicating a better prognosis and gain of 8q indicating a worse prognosis in disomy 3 tumors. In rare instances, monosomy 3 tumors may duplicate the BAP1-mutant copy of the chromosome to return to a disomic state referred to as isodisomy. Thus, isodisomy 3 is prognostically equivalent to monosomy 3, and both can be detected by tests for chromosome 3 loss of heterozygosity. Monosomy 3, along with other chromosomal gains, losses, amplifications, and LOH, can be detected in fresh or paraffin embedded samples by virtual karyotyping.

The most accurate prognostic factor is molecular classification by gene expression profiling of uveal melanomas. This analysis has been used to identify two subclasses of uveal melanomas: class 1 tumors that have a very low risk of metastasis and class 2 tumors that have a very high risk of metastasis. Gene expression profiling outperforms all of the above-mentioned factors at predicting metastatic spread of the primary tumor, including monosomy 3.

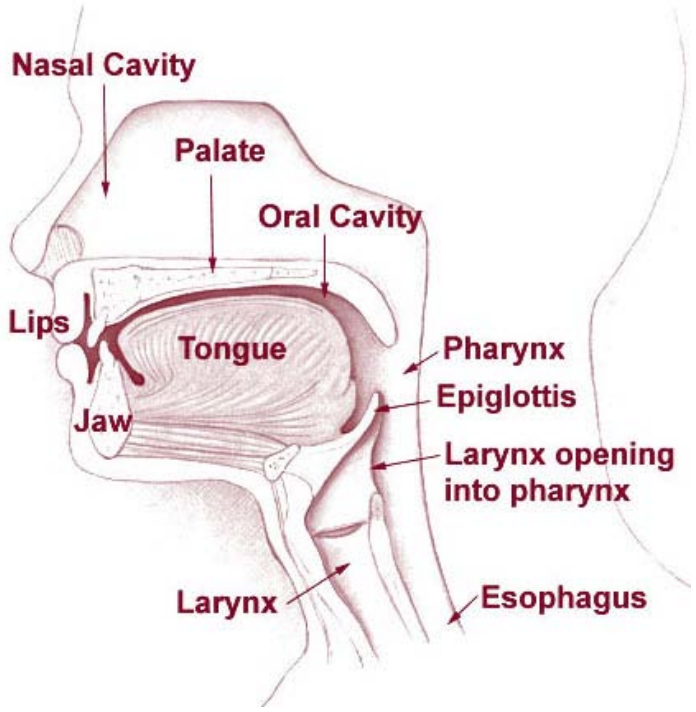
Metastasis

The primary site of metastasis for uveal melanoma is the liver in most patients, less likely the lungs. Approximately 50% of patients will develop metastases within 15 years after treatment of the primary tumor. The average survival time after diagnosis of liver metastases is 8 to 10 months.

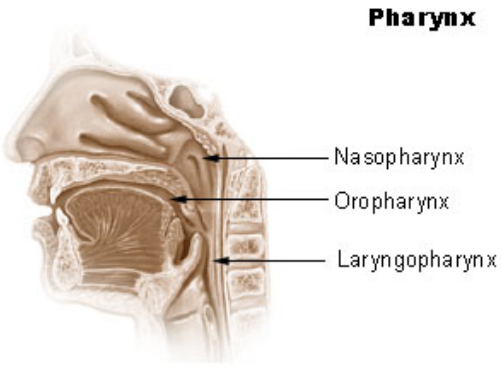
Chapter 13

Oropharyngeal Cancer

Oropharyngeal cancer



Head and neck.



Pharynx

Artery	pharyngeal branches of ascending pharyngeal artery, ascending palatine, descending palatine, pharyngeal branches of inferior thyroid
Vein	pharyngeal veins
Nerve	pharyngeal plexus

MeSH *Pharynx*

Oropharyngeal cancer is a disease which malignant cells form in the tissue of oropharynx. Oropharynx is a middle part of the throat which includes the base of the tongue, the tonsils, the soft palate, and the walls of the pharynx.

Studies

For patients with advanced oropharyngeal cancer the combination of radiotherapy and chemotherapy appears to be as efficient as surgurical management. Shiley and her coworkers had a study to compare how the two approaches maintain swallowing function. They studied 27 patients who underwent the advanced stage (III and IV) of oropharyngeal cancer. Among those patients, 67% had base of tongue lesions and 82% of them used gastrostomy tube either before or during the treatment. Three months after the chemoradiation, 33% of the patients were consuming all nutrition orally, 45% had some oral intake but still had the tube feeding, and 22% had no oral intake at all. The results showed that the short-term incidence of gastrostomy tube dependence after chemo radiation was similar to that after surgical management of oropharyngeal cancer at their institution.

Symptoms of Oropharyngeal cancer

Following are the possible sign of oropharyngeal cancer.

- A sore throat that persists

- Pain or difficulty with swallowing
- Unexplained weight loss
- Voice changes
- Ear pain
- A lump in the back of the throat or mouth
- A lump in the neck
- A dull pain behind the sternum
- Cough

Risks of Oropharyngeal cancer

Following are the risk factors that can increase the risk of developing oropharyngeal cancer.

- Smoking and chewing tobacco.
- Heavy alcohol use.
- A diet low in fruits and vegetables.
- Drinking maté, a stimulant drink common in South America.
- Chewing betel quid, a stimulant commonly used in parts of Asia.
- Being infected with human papilloma virus (HPV).

Prognosis

The prognosis for people with oropharyngeal cancer depends on the age and health of the person and the stage of the disease. It is important for people with oropharyngeal cancer to have follow-up exams for the rest of their lives as cancer can occur in nearby areas. In addition, it is important to eliminate risk factors such as smoking and drinking alcohol, which increase the risk for second cancers.

Ways of the cancer spreading in the body

There are three ways of cancer spreading in the body.

- Cancer invades the surrounding normal tissues.
- Cancer invades the lymph system and travels through the lymph vessels to other places in the body.
- Cancer invades the veins and capillaries and travels through the blood to other places in the body.

Stages of the Oropharyngeal cancer

Stage 0 carcinoma in situ

Abnormal cells are found in the lining of the oropharynx, These may become cancer and spread into nearby normal tissue.

Stage 1

Cancer has formed and is 2 centimeters or smaller and has not spread outside the oropharynx.

Stage 2

Cancer has formed and is larger than 2 centimeters, but not larger than 4 centimeters. Also it has not yet spread outside the oropharynx.

Stage 3

- Cancer is larger than 4 centimeters and has not spread outside the oropharynx
- Any size and has spread to only one lymph node on the same side of the neck as the cancer. The lymph node with cancer is 3 centimeters or smaller.

Stage 4A

- Cancer has spread to tissues near the oropharynx, including the voice box, roof of the mouth, lower jaw, muscle of the tongue, or central muscles of the jaw, and may have spread to one or more nearby lymph nodes, none larger than 6 centimeters.
- Cancer is any size and has spread to one lymph node that is larger than 3 centimeters but not larger than 6 centimeters on the same side of the neck as the cancer, or to more than one lymph node, none larger than 6 centimeters, on one of both sides of the neck.

Stage 4B

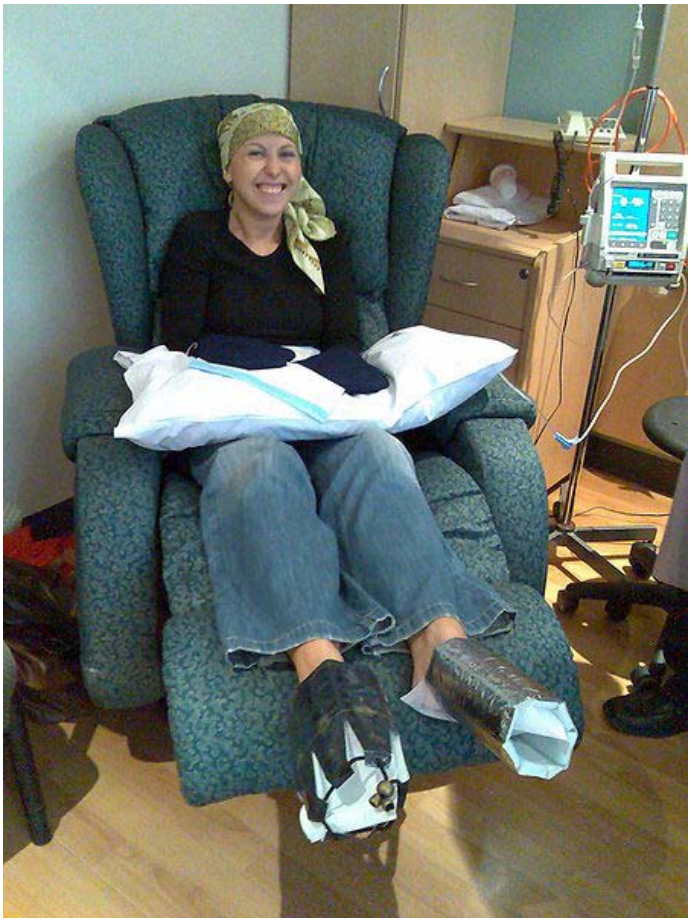
- Cancer surrounds the main artery in the neck or has spread to bones in the jaw or skull, to muscle in the side of the jaw, or to the upper part of the throat behind the nose, and may have spread to nearby lymph nodes
- Cancer has spread to a lymph node that is larger than 6 centimeters and may have spread to tissues around the oropharynx.

Stage 4C

Cancer has spread to other parts of the body; the tumor may be any size and may have spread to lymph nodes.

Chapter 14

Chemotherapy



A woman being treated with docetaxel chemotherapy for breast cancer. Cold mittens and wine coolers are placed on her hands and feet to reduce harm to her nails.

Chemotherapy, in the most simple sense, is the treatment of an ailment by chemicals especially by killing micro-organisms or cancerous cells. In popular usage, it refers to antineoplastic drugs used to treat cancer or the combination of these drugs into a

cytotoxic standardized treatment regimen. In its non-oncological use, the term may also refer to antibiotics (*antibacterial chemotherapy*). In that sense, the first modern chemotherapeutic agent was arsphenamine, an arsenic compound discovered in 1909 and used to treat syphilis. This was later followed by sulfonamides (sulfa drugs) and penicillin.

Most commonly, chemotherapy acts by killing cells that divide rapidly, one of the main properties of most cancer cells. This means that it also harms cells that divide rapidly under normal circumstances: cells in the bone marrow, digestive tract and hair follicles; this results in the most common side effects of chemotherapy : myelosuppression (decreased production of blood cells, hence also immunosuppression), mucositis (inflammation of the lining of the digestive tract), and alopecia (hair loss).

Other uses of cytostatic chemotherapy agents (including the ones mentioned below) are the treatment of autoimmune diseases such as multiple sclerosis, dermatomyositis, polymyositis, lupus, rheumatoid arthritis and the suppression of transplant rejections.

Newer anticancer drugs act directly against abnormal proteins in cancer cells; this is termed targeted therapy.

History

The use of minerals and plant-based medicines are believed to date back to prehistoric medicine.

The first use of drugs to treat cancer, however, was in the early 20th century, although it was not originally intended for that purpose. Mustard gas was used as a chemical warfare agent during World War I and was studied further during World War II. During a military operation in World War II, a group of people were accidentally exposed to mustard gas and were later found to have very low white blood cell counts. It was reasoned that an agent that damaged the rapidly growing white blood cells might have a similar effect on cancer. Therefore, in the 1940s, several patients with advanced lymphomas (cancers of certain white blood cells) were given the drug by vein, rather than by breathing the irritating gas. Their improvement, although temporary, was remarkable. That experience led researchers to look for other substances that might have similar effects against cancer. As a result, many other drugs have been developed to treat cancer, and drug development since then has exploded into a multibillion-dollar industry, although the principles and limitations of chemotherapy discovered by the early researchers still apply.

Principles

Cancer is the uncontrolled growth of cells coupled with malignant behavior: invasion and metastasis. Cancer is thought to be caused by the interaction between genetic susceptibility and environmental toxins.

In the broad sense, most *chemotherapeutic* drugs work by impairing mitosis (cell division), effectively targeting fast-dividing cells. As these drugs cause damage to cells they are termed *cytotoxic*. Some drugs cause cells to undergo apoptosis (so-called "self programmed cell death").

Scientists have yet to identify specific features of malignant and immune cells that would make them uniquely targetable (barring some recent examples, such as the Philadelphia chromosome as targeted by imatinib). This means that other fast-dividing cells, such as those responsible for hair growth and for replacement of the intestinal epithelium (lining), are also often affected. However, some drugs have a better side effect profile than others, enabling doctors to adjust treatment regimens to the advantage of patients in certain situations.

As chemotherapy affects cell division, tumors with high *growth fractions* (such as acute myelogenous leukemia and the aggressive lymphomas, including Hodgkin's disease) are more sensitive to chemotherapy, as a larger proportion of the targeted cells are undergoing cell division at any time. Malignancies with slower growth rates, such as indolent lymphomas, tend to respond to chemotherapy much more modestly.

Drugs affect "younger" tumors (i.e., more differentiated) more effectively, because mechanisms regulating cell growth are usually still preserved. With succeeding generations of tumor cells, differentiation is typically lost, growth becomes less regulated, and tumors become less responsive to most chemotherapeutic agents. Near the center of some solid tumors, cell division has effectively ceased, making them insensitive to chemotherapy. Another problem with solid tumors is the fact that the chemotherapeutic agent often does not reach the core of the tumor. Solutions to this problem include radiation therapy (both brachytherapy and teletherapy) and surgery.

Over time, cancer cells become more resistant to chemotherapy treatments. Recently, scientists have identified small pumps on the surface of cancer cells that actively move chemotherapy from inside the cell to the outside. Research on p-glycoprotein and other such chemotherapy efflux pumps, is currently ongoing. Medications to inhibit the function of p-glycoprotein are undergoing testing as of June, 2007 to enhance the efficacy of chemotherapy.

Treatment schemes

There are a number of strategies in the administration of chemotherapeutic drugs used today. Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms.

Combined modality chemotherapy is the use of drugs with other cancer treatments, such as radiation therapy or surgery. Most cancers are now treated in this way. *Combination chemotherapy* is a similar practice that involves treating a patient with a number of different drugs simultaneously. The drugs differ in their mechanism and side effects. The biggest advantage is minimising the chances of resistance developing to any one agent.

In *neoadjuvant chemotherapy* (*preoperative* treatment) initial chemotherapy is designed to shrink the primary tumour, thereby rendering local therapy (surgery or radiotherapy) less destructive or more effective.

Adjuvant chemotherapy (*post*operative treatment) can be used when there is little evidence of cancer present, but there is risk of recurrence. This can help reduce chances of developing resistance if the tumour does develop. It is also useful in killing any cancerous cells which have spread to other parts of the body. This is often effective as the newly growing tumours are fast-dividing, and therefore very susceptible.

Palliative chemotherapy is given without curative intent, but simply to decrease tumor load and increase life expectancy. For these regimens, a better toxicity profile is generally expected.

All chemotherapy regimens require that the patient be capable of undergoing the treatment. Performance status is often used as a measure to determine whether a patient can receive chemotherapy, or whether dose reduction is required. Because only a fraction of the cells in a tumor die with each treatment (fractional kill), repeated doses must be administered to continue to reduce the size of the tumor. Current chemotherapy regimens apply drug treatment in cycles, with the frequency and duration of treatments limited by toxicity to the patient.

Types

The majority of chemotherapeutic drugs can be divided in to alkylating agents, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, and other antitumour agents. All of these drugs affect cell division or DNA synthesis and function in some way.

Some newer agents do not directly interfere with DNA. These include monoclonal antibodies and the new tyrosine kinase inhibitors e.g. *imatinib mesylate* (*Gleevec* or *Glivec*), which directly targets a molecular abnormality in certain types of cancer (chronic myelogenous leukemia, gastrointestinal stromal tumors). These are examples of targeted therapies.

In addition, some drugs that modulate tumor cell behaviour without directly attacking those cells may be used. Hormone treatments fall into this category.

Where available, Anatomical Therapeutic Chemical Classification System codes are provided for the major categories.

Alkylating agents (L01A)

Alkylating agents are so named because of their ability to alkylate many nucleophilic functional groups under conditions present in cells. Cisplatin and carboplatin, as well as oxaliplatin, are alkylating agents. They impair cell function by forming covalent bonds

with the amino, carboxyl, sulfhydryl, and phosphate groups in biologically important molecules.

Other agents are mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide. They work by chemically modifying a cell's DNA.

Anti-metabolites (L01B)

Anti-metabolites masquerade as purines ((azathioprine, mercaptopurine)) or pyrimidines—which become the building blocks of DNA. They prevent these substances from becoming incorporated in to DNA during the "S" phase (of the cell cycle), stopping normal development and division. They also affect RNA synthesis. Due to their efficiency, these drugs are the most widely used cytostatics.

Plant alkaloids and terpenoids (L01C)

These alkaloids are derived from plants and block cell division by preventing microtubule function. Microtubules are vital for cell division, and, without them, cell division cannot occur. The main examples are vinca alkaloids and taxanes.

Vinca alkaloids (L01CA)

Vinca alkaloids bind to specific sites on tubulin, inhibiting the assembly of tubulin into microtubules (M phase of the cell cycle). They are derived from the Madagascar periwinkle, *Catharanthus roseus* (formerly known as *Vinca rosea*). The vinca alkaloids include:

- Vincristine
- Vinblastine
- Vinorelbine
- Vindesine

Podophyllotoxin (L01CB)

Podophyllotoxin is a plant-derived compound which is said to help with digestion as well as used to produce two other cytostatic drugs, etoposide and teniposide. They prevent the cell from entering the G1 phase (the start of DNA replication) and the replication of DNA (the S phase). The exact mechanism of its action is not yet known.

The substance has been primarily obtained from the American Mayapple (*Podophyllum peltatum*). Recently it has been discovered that a rare Himalayan Mayapple (*Podophyllum hexandrum*) contains it in a much greater quantity, but, as the plant is endangered, its supply is limited. Studies have been conducted to isolate the genes involved in the substance's production, so that it could be obtained recombinantly.

Taxanes (L01CD)

The prototype taxane is the natural product paclitaxel, originally known as Taxol and first derived from the bark of the Pacific Yew tree. Docetaxel is a semi-synthetic analogue of paclitaxel. Taxanes enhance stability of microtubules, preventing the separation of chromosomes during anaphase.

Topoisomerase inhibitors (L01CB and L01XX)

Topoisomerases are essential enzymes that maintain the topology of DNA. Inhibition of type I or type II topoisomerases interferes with both transcription and replication of DNA by upsetting proper DNA supercoiling.

- Some type I topoisomerase inhibitors include *camptothecins*: irinotecan and topotecan.

- Examples of type II inhibitors include amsacrine, etoposide, etoposide phosphate, and teniposide. These are semisynthetic derivatives of epipodophyllotoxins, alkaloids naturally occurring in the root of American Mayapple (*Podophyllum peltatum*).

Antineoplastics (L01D)

These include the immunosuppressant dactinomycin (which is used in kidney transplantations), doxorubicin, epirubicin, bleomycin and others.

Newer and experimental approaches

Hematopoietic stem cell transplant approaches

Stem cell harvesting and autologous or hematopoietic stem cell transplantation has been used to allow for higher doses of chemotherapeutic agents where dosages are primarily limited by hematopoietic damage. Years of research in treating solid tumors, particularly breast cancer, with hematopoeitic stem cell transplants, has yielded little proof of efficacy. Hematological malignancies such as myeloma, lymphoma, and leukemia remain the main indications for stem cell transplants.

Isolated infusion approaches

Isolated limb perfusion (often used in melanoma), or isolated infusion of chemotherapy into the liver or the lung have been used to treat some tumours. The main purpose of these approaches is to deliver a very high dose of chemotherapy to tumor sites without causing overwhelming *systemic* damage. These approaches can help control solitary or limited metastases, but they are by definition *not* systemic, and, therefore, do not treat distributed metastases or micrometastases.

Targeted delivery mechanisms

Specially targeted delivery vehicles aim to increase effective levels of chemotherapy for tumor cells while reducing effective levels for other cells. This should result in an increased tumor kill and/or reduced toxicity.

Specially targeted delivery vehicles have a differentially higher affinity for tumor cells by interacting with tumor-specific or tumour-associated antigens.

In addition to their targeting component, they also carry a payload - whether this is a traditional chemotherapeutic agent, or a radioisotope or an immune stimulating factor. Specially targeted delivery vehicles vary in their stability, selectivity, and choice of target, but, in essence, they all aim to increase the maximum effective dose that can be delivered to the tumor cells. Reduced systemic toxicity means that they can also be used in sicker patients, and that they can carry new chemotherapeutic agents that would have been far too toxic to deliver via traditional systemic approaches.

Light water

Light water or Deuterium-Depleted Water (DDW) is a form of water with lower-than-normal levels of the isotope deuterium. Whereas deuterium-rich heavy water is harmful to many animals, experiments have shown that consumption of light water may be beneficial to humans, particularly those undergoing chemotherapy. A 1999 Romanian study found that water with only 30ppm deuterium produced marked improvement in survival rates of mice bombarded with ionizing radiation. A study of four patients with brain metastases from lung cancer found a three-month regimen of light water "noticeably prolonged" their survival time. A 2010 Hungarian study found significant improvement in the survival times of prostate cancer patients treated with light water.

Nanoparticles

Nanoparticles have emerged as a useful vehicle for poorly soluble agents such as paclitaxel. Protein-bound paclitaxel (e.g., Abraxane) or nab-paclitaxel was approved by the U.S. Food and Drug Administration (FDA) in January 2005 for the treatment of refractory breast cancer. This formulation of paclitaxel uses human albumin as a vehicle and not the Cremophor vehicle used in Taxol. Nanoparticles made of magnetic material can also be used to concentrate agents at tumour sites using an externally applied magnetic field.

Dosage

Dosage of chemotherapy can be difficult: If the dose is too low, it will be ineffective against the tumor, whereas, at excessive doses, the toxicity (side effects, neutropenia) will be intolerable to the patient. This has led to the formation of detailed "dosing schemes" in most hospitals, which give guidance on the correct dose and adjustment in case of

toxicity. In immunotherapy, they are in principle used in smaller dosages than in the treatment of malignant diseases.

In most cases, the dose is adjusted for the patient's body surface area, a measure that correlates with blood volume. The BSA is usually calculated with a mathematical formula or a nomogram, using a patient's weight and height, rather than by direct measurement.

Delivery

Most chemotherapy is delivered intravenously, although a number of agents can be administered orally (e.g., melphalan, busulfan, capecitabine). In some cases, isolated limb perfusion (often used in melanoma), or isolated infusion of chemotherapy into the liver or the lung have been used. The main purpose of these approaches is to deliver a very high dose of chemotherapy to tumour sites without causing overwhelming systemic damage.

Depending on the patient, the cancer, the stage of cancer, the type of chemotherapy, and the dosage, intravenous chemotherapy may be given on either an inpatient or an outpatient basis. For continuous, frequent or prolonged intravenous chemotherapy administration, various systems may be surgically inserted into the vasculature to maintain access. Commonly used systems are the Hickman line, the Port-a-Cath or the PICC line. These have a lower infection risk, are much less prone to phlebitis or extravasation, and abolish the need for repeated insertion of peripheral cannulae.

Harmful and lethal toxicity from chemotherapy limits the dosage of chemotherapy that can be given. Some tumors can be destroyed by sufficiently high doses of chemotherapeutic agents. However, these high doses cannot be given because they would be fatal to the patient.

Adverse effects

Chemotherapeutic techniques have a range of side effects that depend on the type of medications used. The most common medications mainly affect the fast-dividing cells of the body, such as blood cells and the cells lining the mouth, stomach, and intestines. Common side effects include:

- Depression of the immune system, which can result in potentially fatal infections. Although patients are encouraged to wash their hands, avoid sick people, and to take other infection-reducing steps, about 85% of infections are due to naturally occurring microorganisms in the patient's own gut and skin. This may manifest as systemic infections, such as sepsis, or as localized outbreaks, such as shingles. Sometimes, chemotherapy treatments are postponed because the immune system is suppressed to a critically low level.
- Fatigue. The treatment can be physically exhausting for the patient, who might already be very tired from cancer-related fatigue. It may produce mild to severe

anemia. Treatments to mitigate anemia include hormones to boost blood production (erythropoietin), iron supplements, and blood transfusions.
- Tendency to bleed easily. Medications that kill rapidly dividing cells or blood cells are likely to reduce the number of platelets in the blood, which can result in bruises and bleeding. Extremely low platelet counts may be temporarily boosted through platelet transfusions. Sometimes, chemotherapy treatments are postponed to allow platelet counts to recover.
- Gastrointestinal distress. Nausea and vomiting are common side effects of chemotherapeutic medications that kill fast-dividing cells. This can also produce diarrhea or constipation. Malnutrition and dehydration can result when the patient doesn't eat or drink enough, or when the patient vomits frequently, because of gastrointestinal damage. This can result in rapid weight loss, or occasionally in weight gain, if the patient eats too much in an effort to allay nausea or heartburn. Weight gain can also be caused by some steroid medications. These side effects can frequently be reduced or eliminated with antiemetic drugs. Self-care measures, such as eating frequent small meals and drinking clear liquids or ginger tea, are often recommended. This is a temporary effect, and frequently resolves within a week of finishing treatment.
- Hair loss. Some medications that kill rapidly dividing cells cause dramatic hair loss; other medications may cause hair to thin. These are temporary effects: hair usually starts growing back a few weeks after the last treatment, sometimes with a tendency to curl that may be called a "chemo perm".

Damage to specific organs may occur, with resultant symptoms:

- Cardiotoxicity (heart damage)
- Hepatotoxicity (liver damage)
- Nephrotoxicity (kidney damage)
- Ototoxicity (damage to the inner ear), producing vertigo
- Encephalopathy (brain dysfunction)

Immunosuppression and myelosuppression

Virtually all chemotherapeutic regimens can cause depression of the immune system, often by paralysing the bone marrow and leading to a decrease of white blood cells, red blood cells, and platelets. The latter two, when they occur, are improved with blood transfusion. Neutropenia (a decrease of the neutrophil granulocyte count below 0.5 x 10^9/litre) can be improved with synthetic G-CSF (granulocyte-colony stimulating factor, e.g., filgrastim, lenograstim).

In very severe myelosuppression, which occurs in some regimens, almost all the bone marrow stem cells (cells that produce white and red blood cells) are destroyed, meaning *allogenic* or *autologous* bone marrow cell transplants are necessary. (In autologous BMTs, cells are removed from the patient before the treatment, multiplied and then re-injected afterwards; in *allogenic* BMTs the source is a donor.) However, some patients still develop diseases because of this interference with bone marrow.

In Japan the government has approved the use of some medicinal mushrooms like *Trametes versicolor*, to counteract depression of the immune system in patients undergoing chemotherapy. The United States' top-ranked cancer hospital, the MD Anderson, has reported that polysaccharide-K (PSK; an extract from *Trametes versicolor*) is a "promising candidate for chemoprevention due to the multiple effects on the malignant process, limited side effects and safety of daily oral doses for extended periods of time." PSK is already used in pharmaceuticals designed to complement chemotherapy such as MC-S. The MD Anderson has also reported that there are 40 human studies, 55 animal studies, 37 *in vitro* studies, and 11 reviews published concerning *Trametes versicolor* or its extract PSK.

Nausea and vomiting

Chemotherapy-induced nausea and vomiting (CINV) is common with many treatments and some forms of cancer. However, some chemotherapy regimens do not have this side effect, and very effective drugs to stop or noticeably reduce this adverse effect are available.

A class of drugs called 5-HT_3 antagonists are the most effective antiemetics and constitute the single greatest advance in the management of nausea and vomiting in patients with cancer. These drugs block one or more of the nerve signals that cause nausea and vomiting. During the first 24 hours after chemotherapy, the most effective approach appears to be blocking the 5-HT_3 nerve signal. Approved 5-HT_3 inhibitors include dolasetron, granisetron, and ondansetron (Zofran). The newest 5-HT_3 inhibitor, palonosetron, also prevents delayed nausea and vomiting, which occurs during the 2–5 days after treatment. Since some patients have trouble swallowing pills, these drugs are often available by injection, as orally disintegrating tablets, or as transdermal patchs.

The substance P inhibitor aprepitant, which became available in 2005, is also effective in controlling the nausea of cancer chemotherapy.

Some studies and patient groups say that the use of cannabinoids derived from marijuana during chemotherapy greatly reduces the associated nausea and vomiting, and enables the patient to eat. Some synthetic derivatives of the active substance in marijuana (Tetrahydrocannabinol or THC) such as Marinol may be practical for this application. Natural marijuana, known as medical cannabis is also used and recommended by some oncologists, though its use is regulated and not legal everywhere.

Secondary neoplasm

Development of secondary neoplasia after successful chemotherapy and/or radiotherapy treatment can occur. The most common secondary neoplasm is secondary acute myeloid leukemia, which develops primarily after treatment with alkylating agents or topoisomerase inhibitors. Other studies have shown a 13.5 fold increase from the general population in the incidence of secondary neoplasm occurrence after 30 years from treatment.

Infertility

Some types of chemotherapy are gonadotoxic and may cause infertility. Chemotherapies with high risk include procarbazine and other alkylating drugs such as cyclophosphamide, ifosfamide, busulfan, melphalan, chlorambucil and chlormethine. Drugs with medium risk include doxorubicin and platinum analogs such as cisplatin and carboplatin. On the other hand, therapies with low risk of gonadotoxicity include plant derivatives such as vincristine and vinblastine, antibiotics such as bleomycinand dactinomycin and antimetabolites such as methotrexate, mercaptopurine and 5-fluoruracil.

Patients may choose between several methods of fertility preservation prior to chemotherapy, including cryopreservation of semen, ovarian tissue, oocytes or embryos.

Other side effects

In particularly large tumors, such as large lymphomas, some patients develop tumor lysis syndrome from the rapid breakdown of malignant cells. Although prophylaxis is available and is often initiated in patients with large tumors, this is a dangerous side effect that can lead to death if left untreated.

Less common side effects include pain, red skin (erythema), dry skin, damaged fingernails, a dry mouth (xerostomia), water retention, and sexual impotence. Some medications can trigger allergic or pseudoallergic reactions.

Some patients report fatigue or non-specific neurocognitive problems, such as an inability to concentrate; this is sometimes called post-chemotherapy cognitive impairment, referred to as "chemo brain" by patients' groups.

Specific chemotherapeutic agents are associated with organ-specific toxicities, including cardiovascular disease (e.g., doxorubicin), interstitial lung disease (e.g., bleomycin) and occasionally secondary neoplasm (e.g., MOPP therapy for Hodgkin's disease).

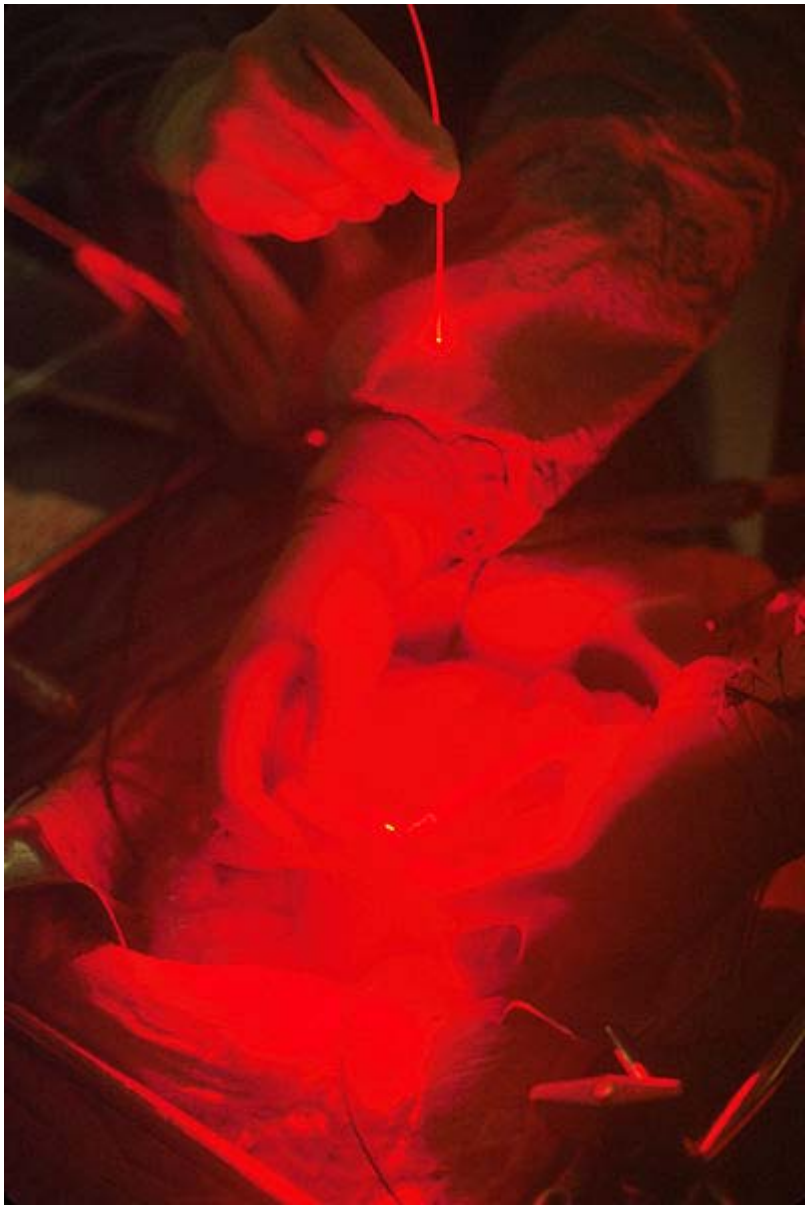
In other animals

Chemotherapy is used in veterinary medicine similar to in human medicine.

Chapter 15

Photodynamic Therapy and Targeted Therapy

Photodynamic therapy



Close up of surgeons' hands in an operating room with a "beam of light" traveling along fiber optics for photodynamic therapy. Its source is a laser beam which is split at two different stages to create the proper "therapeutic wavelength". A patient would be given a photo sensitive drug (photofrin) containing cancer killing substances which are absorbed by cancer cells. During the surgery, the light beam is positioned at the tumor site, which then activates the drug that kills the cancer cells, thus photodynamic therapy (PDT).

Photodynamic therapy (PDT), matured as a feasible medical technology in the 1980s at several institutions throughout the world, is used to eradicate premalignant and early-stage cancer and reduce the tumour size in end-stage cancers involving three key components: a photosensitizer, light, and tissue oxygen.

It is an approved treatment for wet macular degeneration, and is also being investigated for treatment of psoriasis.

Treatment of internal organs may be achieved through the use of endoscopes and fiber optic catheters to deliver light, and intravenously-administered photosensitizers.

A great deal of research and clinical study is now underway to determine optimal combinations of photosensitizers, light sources, and treatment parameters for a wide variety of different cancers.

It is currently being tested as a treatment for severe acne.

History

The German physician Friedrich Meyer–Betz performed the first study with what was first called **photoradiation therapy** (PRT) with porphyrins in humans in 1913. Meyer–Betz tested the effects of haematoporphyrin-PRT on his own skin.

Thomas Dougherty of Roswell Park Cancer Center, among others worldwide, became a highly visible advocate and educator. Early patients were treated at Roswell, Los Angeles Children's Hospital, Los Angeles County Hospital, and other clinics and Hospitals in the USA and overseas.

It was John Toth, as product manager for Cooper Medical Devices Corp/Cooper Lasersonics, who acknowledged the "photodynamic chemical effect" of the therapy with early clinical argon dye lasers and wrote the first "white paper" renaming the therapy as "Photodynamic Therapy" (PDT). This was done to support efforts in setting up 10 clinical sites in Japan where the term "radiation" had negative connotations. PDT received even greater interest as result of Thomas Dougherty helping expand clinical trials and forming the International Photodynamic Association, in 1986.

Mechanism of action

A photosensitizer is a chemical compound that can be excited by light of a specific wavelength. This excitation uses visible or near-infrared light. In photodynamic therapy, either a photosensitizer or the metabolic precursor of one is administered to the patient. The tissue to be treated is exposed to light suitable for exciting the photosensitizer. Usually, the photosensitizer is excited from a ground singlet state to an excited singlet state. It then undergoes intersystem crossing to a longer-lived excited triplet state. One of the few chemical species present in tissue with a ground triplet state is molecular oxygen. When the photosensitizer and an oxygen molecule are in proximity, an energy transfer can take place that allows the photosensitizer to relax to its ground singlet state, and create an excited singlet state oxygen molecule. Singlet oxygen is a very aggressive chemical species and will very rapidly react with any nearby biomolecules. (The specific targets depend heavily on the photosensitizer chosen.) Ultimately, these destructive reactions will kill cells through apoptosis or necrosis.

This mechanism is identical to the mechanism of the disease erythropoietic protoporphyria, which causes blistering in response to sun exposure due to a genetic defect in the same metabolic pathway.

Example treatment of skin cancer

As an example, consider PDT as a treatment for basal cell carcinoma (BCC). BCC is the most common form of skin cancer in humans. Conventional treatment of BCC involves surgical excision, cryogenic treatment with liquid nitrogen, or localized chemotherapy with 5-fluorouracil or other agents.

A PDT treatment would involve the following steps.

- A photosensitizer precursor (aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) or levulinic acid (LA)) is applied.
- A waiting period of a few hours is allowed to elapse, during which time
    - ALA will be taken up by cells, and
    - ALA will be converted by the cells to protoporphyrin IX, a photosensitizer.
- The physician shines a bright red light (from an array of light-emitting diodes or a diode laser) on the area to be treated. The light exposure lasts a few minutes to a few tens of minutes.
    - Protoporphyrin IX absorbs light, exciting it to an excited singlet state;
    - Intersystem crossing occurs, resulting in excited triplet protoporphyrin IX;
    - Energy is transferred from triplet protoporphyrin IX to triplet oxygen, resulting in singlet (ground state) protoporphyrin IX and excited singlet oxygen;
    - Singlet oxygen reacts with biomolecules, fatally damaging some cells in the treatment area.
- Within a few days, the exposed skin and carcinoma will scab over and flake away.

- In a few weeks, the treated area has healed, leaving healthy skin behind. For extensive malignancies, repeat treatments may be required. It is also common to experience pain from the area treated.
- After the treatment the patient will need to avoid excessive exposure to sunlight for a period of time.

Advantages and limitations

Unlike chemotherapy for cancer the effect of PDT can be localised. Specificity of treatment is achieved in three ways.

- First, light is delivered only to tissues that a physician wishes to treat. In the absence of light, there is no activation of the photosensitizer and no cell killing.
- Second, photosensitizers may be administered in ways that restrict their mobility.
- Finally, photosensitizers may be chosen which are selectively absorbed at a greater rate by targeted cells. ALA is taken up much more rapidly by metabolically active cells. Since malignant cells tend to be growing and dividing much more quickly than healthy cells, the ALA targets the unhealthy cells.

PDT can be much cheaper than the alternative radiotherapy or surgical operation and after care. Post operative recovery is typically hours or days rather than weeks.

A major limitation of PDT is that the light needed to activate most photosensitizers can not penetrate through more than one third of an inch (1 cm) of tissue using standard laser technology and low powered LED technology. Laser application of PDT is generally limited to the treatment of tumours on or under the skin, or on the lining of some internal organs. Moreover it is less effective in treatment of large tumours and metastasis for the same reason. However, new high-powered LED technology has been lab-tested to provide a depth of 2 inches from surface in a simulated breast tissue. Also, hollow needles have been used by some units to get the light into deeper tissues.

Photosensitizers

A wide array of photosensitizers for PDT exist. They can be divided into porphyrins, chlorophylls and dyes. Some examples include aminolevulinic acid (ALA), Silicon Phthalocyanine Pc 4, m-tetrahydroxyphenylchlorin (mTHPC), and mono-L-aspartyl chlorin e6 (NPe6).

Several photosensitizers are commercially available for clinical use, such as Photofrin, Visudyne, Levulan, Foscan, Metvix, Hexvix®, Cysview™, and Laserphyrin, with others in development, e.g. Antrin, Photochlor, Photosens, Photrex, Lumacan, Cevira, Visonac, BF-200 ALA. Amphinex.

Although these photosensitizers can be used for wildly different treatments, they all aim to achieve certain characteristics:

- High absorption at long wavelengths
    - Tissue is much more transparent at longer wavelengths (~700-850 nm). Absorbing at longer wavelengths would allow the light to penetrate deeper, and allow the treatment of larger tumors.
- High singlet oxygen quantum yield
- Low photobleaching
- Natural fluorescence
    - Many optical dosimetry techniques, such as fluorescence spectroscopy, depend on the drug being naturally fluorescent
- High chemical stability
- Low dark toxicity
    - The photosensitizer should not be harmful to the target tissue until the treatment beam is applied.
- Preferential uptake in target tissue

The major difference between different types of photosensitizers is in the parts of the cell that they target. Unlike in radiation therapy, where damage is done by targeting cell DNA, most photosensitizers target other cell structures. For example, mTHPC has been shown to localize in the nuclear envelope and do its damage there. In contrast, ALA has been found to localize in the mitochondria and Methylene Blue in the lysosomes.

Targeted PDT

Some photosensitisers naturally accumulate in the endothelial cells of vascular tissue allowing 'vascular targeted' PDT, but there is also research to target the photosensitiser to the tumour (usually by linking it to antibodies or antibody fragments). It is currently only in pre-clinical studies.

Other research

To allow treatment of deeper tumours some researchers are using internal chemiluminescence to activate the photosensitiser.

PDT is currently in clinical trials to be used as a treatment for severe acne. Initial results show have shown for it to be effective as a treatment only for severe acne, though some question whether it is better than existing acne treatments. The treatment causes severe redness and moderate to severe pain and burning sensation.

Targeted therapy

Targeted therapy is a type of medication that blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis and tumor growth,

rather than by simply interfering with rapidly dividing cells (e.g. with traditional chemotherapy). Targeted cancer therapies may be more effective than current treatments and less harmful to normal cells.

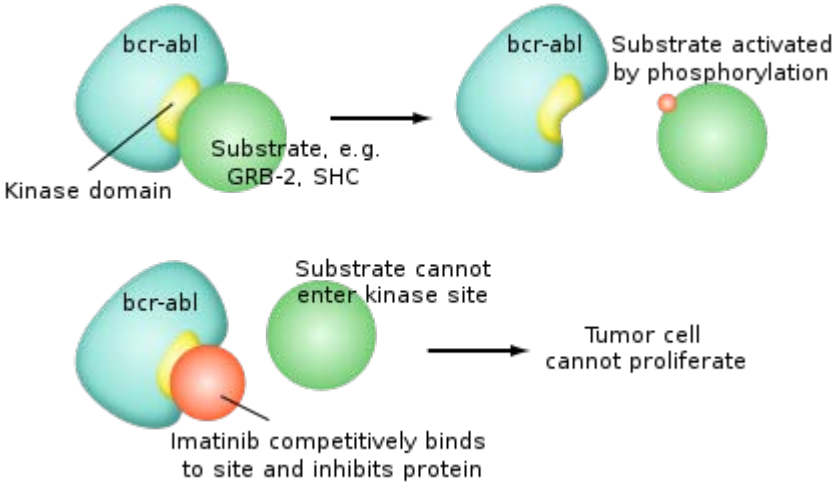
The definitive experiments that showed that targeted therapy would reverse the malignant phenotype of tumor cells involved treating Her2/neu transformed cells with monoclonal antibodies in vitro and in vivo by Mark Greene's laboratory.

Some have challenged use of the term, stating that drugs usually associated with the term are insufficiently selective. The phrase occasionally appears in scare quotes.

Types

The main categories of targeted therapy are *small molecules* and *monoclonal antibodies.*

Small molecules



Mechanism of imatinib

- Imatinib mesylate (Gleevec, also known as STI–571) is approved for chronic myelogenous leukemia, gastrointestinal stromal tumor and some other types of cancer. Early clinical trials indicate that imatinib may be effective in treatment of dermatofibrosarcoma protuberans.
- Gefitinib (Iressa, also known as ZD1839), targets the epidermal growth factor receptor (EGFR) tyrosine kinase and is approved in the U.S. for non small cell lung cancer. EGFR is also overexpressed in the cells of other solid tumors, such as lung and breast cancers. This leads to inappropriate activation of the apoptotic Ras signal transduction cascade, eventually leading to uncontrolled cell proliferation.Gefitinib inhibits EGFR tyrosine kinase by binding to the adenosine triphosphate (ATP)-binding site of the enzyme. Thus the function of the EGFR

tyrosine kinase in activating the Ras signal transduction cascade is inhibited; and malignant cells are inhibited.
- Erlotinib (marketed as Tarceva). Erlotinib inhibits epidermal growth factor receptor, and works through a similar mechanism as gefitinib. Erlotinib has been shown to increase survival in metastatic non small cell lung cancer when used as second line therapy. Because of this finding, erlotinib has replaced gefitinib in this setting.
- Bortezomib (Velcade) is an apoptosis-inducing drug that causes cancer cells to undergo cell death by interfering with proteins. It is approved in the U.S. to treat multiple myeloma that has not responded to other treatments.
- The selective estrogen receptor modulator tamoxifen has been described as the foundation of targeted therapy.
- Newer BCL-2 antagonists, such as Obatoclax, ABT-263, and Gossypol.
- PARP inhibitors (e.g. Iniparib, Olaparib in clinical trials)
- Janus kinase inhibitors
- Apatinib is a selective VEGF Receptor 2 inhibitor which has shown encouraging anti-tumor activity in a broad range of malignancies in clinical trials. Apatinib is currently in clinical development for metastatic gastric carcinoma, metastatic breast cancer and advanced hepatocellular carcinoma.
- salinomycin has demonstrated potency in killing cancer stem cells in both laboratory-created and naturally occurring breast tumors in mice.

Monoclonal antibodies

Several are in development and a few have been licenced by the FDA. Examples of licenced monoclonal antibodies include:

- Rituximab (marketed as MabThera or Rituxan) targets CD20 found on B cells. It is used in non Hodgkin lymphoma
- Trastuzumab (Herceptin) targets the Her2/neu (also known as ErbB2) receptor expressed in some types of breast cancer
- Cetuximab (marketed as Erbitux) targets the epidermal growth factor receptor. It is used in the treatment of colon cancer and non-small cell lung cancer.
- Bevacizumab (marketed as Avastin) targets circulating VEGF ligand. It is approved for use in the treatment of colon cancer, breast cancer, non-small cell lung cancer, and is investigational in the treatment of sarcoma. Its use for the treatment of brain tumors has been recommended.

Antibody-drug conjugates are being developed.

Progress and future

Many oncologists believe that targeted therapies are the chemotherapy of the future. As solid tumor cancer continues to be viewed as a chronic condition, methods for long-term treatment, with less side-effects, continue to be investigated.

In the U.S., the National Cancer Institute's *Molecular Targets Development Program* (MTDP) to identify and evaluate molecular targets that may be candidates for drug development.

The next stage of targeted therapies will focus on finding which patients will respond to which targeted therapies. This is called the identification of "sub-populations", stratified medicine or even personalized medicine. The route to identify these sub-populations is through biomarkers and surrogate endpoints.