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History

In 1812, Gay-Lussac discovered the element iodine as a factor caused goiter. By 1833, Boussingault prescribed iodized salt for prevention and treatment of goiter. In 1836, T.W. King, an English morphologist, presented descriptions of the thyroid follicle, its lymphatic and blood supply, and some predicted theories about the nature of colloid. In the 1870s, Fagge demonstrated the absence of thyroid function causes sporadic and congenital *cretinism*. William Gull and William Ord clarified the clinical and pathological role of the thyroid in *myxedema*.

The biggest contribution was from Theodor Kocher, a skillful surgeon from Bern, Switzerland. Kocher's technique became popular and was published widely. By 1882, Kocher's mortality rate was 2.4% and by the end of the 19th century this rate was as low as 0.18%. Kocher had over 5000 cases by the time of his death in 1917. Billroth added the bilateral partial resection technique to prevent hypothyroidism, nerve paralysis, and hypoparathyroidism (tetany). William Stewart Hallsted absorbed the thyroidectomy techniques of Billroth and Kocher and created his own skills of the thyroid resection in the United States since 1880. He was a pioneer American surgeon, who presented the techniques of thyroidectomy to its standard procedure by the time of his death in 1922.

Thyroid cancer was first described by Halsted in his extensive compilation of documented thyroidectomies by the terms sarcomatous degeneration, thyroid tumor or thyroid cancer cells. He described thyroid cancers as the silent growths, even though these sleeping tumors can suddenly become more aggressive, metastasize, recur and transform into highly lethal or high mortality cancers.

Anatomy

The thyroid gland is the first endocrine gland to form in the human embryo. In the fourth week, it begins as a thickened median endodermis caudally to the later site the median tongue bud. It then

migrates anteriorly and inferiorly onto the hyoid bone and laryngeal cartilages, through the *thyroglossal duct*. At the end of fifth week, the duct breaks down and the thyroid gland continues descending to its position, anterior to the trachea, by the seventh week. The thyroglossal duct then normally disappears by the tenth week.

The thyroid gland locates deep to the sternohyoid muscle, from the level C5 to T1 vertebrae or anterior to the 2nd and 3rd tracheal rings. It consists of two lobes, connected in the middle by a narrow isthmus, which is conical or pyramidal shape. In 50% of population, thyroid gland may stay as high as the level of the hyoid bone. Each lateral lobe is attached to the trachea by a consolidated connective tissue called *the lateral suspensory (Berry) ligament*. The posterior extensions of the each thyroid lobe are the *tubercles of Zuckerkandl*, which have an important relationship to the recurrent laryngeal nerve.

The thyroid gland was supplied by four main arteries:

- (1) *The superior thyroid arteries (paired)* originate from the external carotid artery (the first or second branch) or the common carotid artery. When it approaches the thyroid gland, the superior thyroid artery divides into anterior and posterior branches, which will then distribute numerous small branches to the gland and join with their counterparts from the opposite side.
- (2) *The inferior thyroid arteries (paired)* arise from the thyrocervical trunk and ascend into the neck on the medial aspect of the anterior scalene muscle, deep to the prevertebral fascia and cross vertically to the ascending recurrent laryngeal nerve. The inferior thyroid artery divides further into two branches: the upper branch supplies to the posterior aspect of the gland and the lower branch supplies to the lower pole of the gland.

In 1.5% to 12% of the cases, the *thyroid ima artery*, a variation of the inferior thyroid artery, may present usually in right side and ascend in front of the trachea. The superior and middle thyroid veins drain to the anterior facial vein and internal jugular vein. The inferior thyroid vein and thyroid ima vein form the innominate vein and drain into the branchiocephalic vein. The recurrent laryngeal nerves are close to the thyroid globes and the inferior thyroid arteries.

The lymphatic vessels of the thyroid gland drain into the internal jugular chain, the pericapsular region, the prelaryngeal, pretracheal and paratracheal lymph nodes. The lateral lymphatic vessels located along the superior thyroid vein pass to the inferior deep cervical lymph nodes such as retropharyngeal and retroesophageal areas. Nerve innervation of the thyroid gland is from the superior, middle, and inferior cervical sympathetic ganglia, which form the cardiac, and superior and inferior thyroid periaarterial plexuses.

Physiology

Three components participate in the euthyroidism control:

- (1) Thyroid gland responsible for the synthesis, storage, and secretion of thyroxine (T4) and 3,5,3'-triiodothyronine (T3: the most potent biologic agent).
- (2) The peripheral control of the T3, T4 metabolism, after their release into the circulation.
- (3) Thyroid stimulating hormone (TSH) and thyroid hormone-releasing hormone (TRH) mediate the thyroid hormone output in a classic negative feedback mechanism. *TSH*

regulates (1) the synthesis of thyroglobulin (Tg), (2) the uptake and organization of iodine, (3) the iodination of Tg to form T4 and T3, (4) the storage of T3 & T4 in the gland as *colloid*, and (5) the hydrolysis of the stored Tg to release T4 and T3 into the circulation.

Follicle, the functional unit of thyroid gland, is separated from the interstitium by a complete basement membrane. Lobule is a group of 20-30 follicles, separated to each other by a thin fibrous connective tissue layer. Follicular cells contain T4, T3, and other low molecular weight such as cytokeratins, vimentin, and epithelial membrane antigen. Follicular cells with rich eosinophilic cytoplasm are referred to as oncocytes, oxyphil cell, Askanazy cells or *Hurthle cells*. *C cells* or *parafollicular cells* are most abundant in a zone at the junction of the upper and middle thirds of the lateral lobes. They secrete calcitonin and other peptides (e.g. somatostatin, gastrin-releasing peptide, and thyrotropin-releasing hormone.)

Thyroid hormone biosynthesis requires 0.100 mg to 0.150 mg of inorganic iodide per day. The source of iodine is diet. Average, daily intake is from 0.3 to 0.7 mg per day (in the US). The total body pool is approximately 9 mg. About 8 mg located in colloid, which serves as a source of iodine when intake decreases. Circulating hormone is about 0.6 mg and free iodide in extracellular fluid is 0.15 mg. Most thyroid circulating hormone bound to a binding protein (TBG 80%, TTR15%, and albumin 5%). Only 0.3% of T4 and 0.3% of T3 is unbound.

The goal of peripheral thyroid hormone metabolism is to maintain the circulating and tissue T3 level, which appropriates for the thyroid hormone requirements. The unbound or free T3 crosses the cell membrane, by passive diffusion, through T3 receptors, which mediates the physiologic actions of thyroid hormone including growth, differentiation, calorigenesis, and TSH suppression.

Pathology

About 4% to 7% of the population has nodular thyroid disease. Approximately, 4% of these nodules are malignant and account for about 1% of all cancers. The incidence of thyroid nodules in female to male is 6.5% to 1.5%. However, the risk of being malignant thyroid nodules is twice as high in males as compare to females. Thyroid cancer develops most commonly between the ages 40 through 60.

Thyroid cancers are classified by their predominant histologic cell types, as follow: (1) well-differentiated malignant neoplasm (WDTC) accounts for 85% of thyroid cancers, including papillary, follicular, and Hurthle cell carcinomas, and (2) more aggressive variants include medullary carcinoma and anaplastic carcinoma (3) other tumors including lymphomas and metastatic tumors.

(1) *Papillary Thyroid Carcinoma (PTC)*: is the most common, accounting for 75% to 80% of thyroid cancer and 80% to 90% of radiation induced thyroid carcinomas. Female to male ratio is 3 to 1. Peak incidence is in the 30s to 40s year of age, with prolonged course and rarely caused death (1% - 10%). The 10-year survival rate is from 84% to 90%. Tumors are usually composed of mixed papillary fronds or follicular component. According to the size and location of the tumors, there are three subclasses of papillary carcinomas (1)

occult or less than 1.5 cm, (2) intrathyroidal, (3) extrathyroidal. The majority of papillary tumors are nonencapsulated, usually invade lymphatics and replace normal thyroid tissue. Grossly, these tumors often show central necrosis with fibrosis or hemorrhage; large tumors may have cystic degeneration and may resemble a benign thyroid cyst. Multicentricity develops in 75% of tumors, especially in patients with prior exposure to ionizing radiation. Papillary carcinomas have increased incidence in familial adenomatous polyposis syndromes such as Gardner's and Cowden's. Histologic findings of papillary tumors consist of columnar thyroidal epithelium set in papillary projection with well-formed fibrovascular cores or "*psammoma bodies*". Nuclei are vesicular and house-glass or "Orphan Annie" appearance. Factors affect surgical treatment including extrathyroidal extension, vascular and adjacent structural invasion or lymph node metastasis. There is a high rate of local regional lymph nodes (50%) but low risk of hematogenous dissemination. Spire et al. at MD Anderson Cancer Center determined that the most important prognostic factors for papillary carcinoma of thyroid are (1) *age*, (2) *sex*, (3) *histology of the cancer*, and (4) presence of *distant metastatic diseases*.

- (2) *Follicular Thyroid Carcinoma (FTC)* accounts for 5% of all thyroid cancers and 15% of primary epithelial malignant tumors of the thyroid, according to Segal et al. Peak incidence is in the fifth decade of life and female-to-male rate is 3:1. Follicular carcinoma tends to slow enlarging of non-tender nodules, hematogenous metastases to lung, bone and brain. Non-invasive tumors have a 10-year survival rate 86%, whereas invasive tumors have that of 44%. Grossly, follicular carcinomas are usually well encapsulated and grow in an expansive fashion. They undergo cystic degeneration, calcification, or hemorrhage. Microscopic finding is microfollicular pattern with vesicular nucleolus cells. The lumens of the acini are usually empty, without colloid. The most important feature of this type of cancer is the tendency to invade the thyroid capsule and blood vessels. The high-grade follicular carcinomas have marked hypercellularity and are difficult to differentiate with follicular adenoma. Therefore, multiple sections are required for identifying the capsular or vascular invasion. Follicular carcinoma is more aggressive than papillary carcinoma and is associated with a higher morbidity due to more rapid metastasis. In the study of Segal et al., the factors of (1) *age* (less than 40 years), (2) *tumor size* (<6 cm), (3) *invasion of blood vessels* (has significant effect the prognosis in the first 10 years) and (4) *distant metastases* (an important predictor for survival) show significant effects on the outcomes of follicular carcinomas.
- (3) *Hurthle (oxyphilic) cell Carcinoma* is the most aggressive well-differentiated neoplasm and accounts for about 5% of WDTC or 2% to 3% of all thyroid cancers. There is high incidence of bilateral thyroid lobe involvement and long-term lethal potential for local recurrence and mortality if the tumors were treated less aggressively. Female to male ratio is 2 to 1. Hurthle cell carcinomas have poor prognosis with five-year survival rate in about 50% to 60%.
- (4) *Medullary Carcinoma (MTC)* accounts for 5% to 10% of thyroid cancer. The tumor originates from calcitonin-producing parafollicular C-cell. Grossly, medullary tumors are gray to yellow, firm, well-circumscribed or invasive with bilateral multicentric involvement. Medullary carcinomas are classified as two groups:

- (1) *Sporadic (80%)*: have a poorer prognosis, usually unifocal, not associated with other endocrine tumors, occur in middle age to elderly patients, equal in both sexes; single nodule is common in sporadic form with clusters of cells and stromal amyloid in 85% to 90% cases,
- (2) *Family trait (20%)*: autosomal dominant inheritance, tumors associated with C-cell hyperplasia or the calcitonin-producing lesions; these tumors usually have early high calcitonin screening and better prognosis. The familial form of medullary cancers usually develop in the third decade of life with the female to male rate is 1.5 to 1. The familial medullary carcinomas are associated with other endocrine tumors such as:
 - (1) *Sipple's syndrome* or multiple endocrine neoplasm type II (MEN IIa), including (a) medullary thyroid carcinoma or C-cell hyperplasia, (b) adrenal medullary carcinoma and (c) hyperparathyroidism.
 - (2) *Wermer's syndrome* (MEN IIb), including (a) medullary thyroid carcinoma, (b) pheochromocytoma, (c) mucosal neuromas (of the tongue, lips, conjunctivae), ganglioneuromas of the intestines, characterized by special facial appearance, and marfanoid habitus.

Overall prognosis of MTC is poor due to early metastases to lymph nodes and distant metastases. The five-year survival rate is in the range of 60% to 70% and 10 year-survival rate is 40% to 50%. About 50% of medullary cancers have regional metastases to local lymph nodes at the time of diagnosis. Distant metastases include lung, liver, adrenal glands, and bones (osteoblastic, opposed to other cancers, e.g. prostate cancer, osteolysis).

- (5) *Anaplastic Thyroid Carcinoma (ATC)* or undifferentiated carcinoma accounts for 3% of all thyroid cancers, more common in elderly patients usually in their seventh decade. Females are more affected than males. Tumors have higher incidence in patients with pre-existing multinodular goiter (30%). The anaplastic thyroid cancer is the most aggressive thyroid cancer, is unencapsulated, and is associated with extended invasion outside the gland. Grossly, the neoplasm has fleshy, tan-white appearance, with hemorrhagic and necrotic areas. Histological cells with spindle or giant-cell variants. Patients with the anaplastic thyroid carcinomas have poor prognosis. Patients usually die within several months, due to airway obstruction, vascular invasion, distant metastases to lung and bone and resistant to the therapy.
- (6) *Malignant Lymphoma* accounts for 1% to 2% of thyroid cancers, increasing incidence in endemic goiter areas, most common in patients over 50 years of age. The female to male ratio is 3 to 1. It may develop from the pre-existing Hashimoto's thyroiditis and present as a rapidly growing mass in history of multinodular goiter. Rapid enlarging tumors can result in tracheal or esophageal compression. Grossly, tumors are large, yellow-tan, and scaly with hemorrhagic and necrosis areas. The most common variant of thyroid lymphomas are small-cell noncleaved type (or poorly differentiated malignant lymphoma) and the large-cell noncleaved follicular cell-type. The cell types and stages are the critical factors in prognosis, e.g. small cell, Hodgkin's, and

immunoblastic lymphomas have a favorable prognosis in early stage (stage I: 86% 5-year survival rate with lymphoma limited in the gland, 38% with lymph node involvement or invaded capsule, and rare with disseminated thyroid lymphoma).

- (7) *Metastatic Carcinoma* found in 2% to 4% of patients who die of cancers. Metastatic thyroid carcinomas are most common from malignant melanoma, lung, kidney, breast, and colon cancer. Malignant cells metastasize by lymphatic or vascular deposits of tumor emboli. To identify the metastatic lesions is important because when they exist surgical excision is not beneficial.

Prognostic Factors

**Histology*: the cell type is one of the most predominant prognostic factor and influences other risk factors.

**Age*: at the time of diagnosis is a significant effected risk factor, e.g. well-differentiated thyroid carcinoma has a greater tendency to invade the surrounding structures in patients older than 40. Mortality rate increases significantly in patients older than 60.

**Sex*: females are at a higher risk of developing thyroid nodules, however, males have a higher risk of thyroid cancer. Tumors are more aggressive and the prognoses are poorer in males than those in females.

**Size of primary lesions*: the larger the size of the tumor the greater the risk of vascular invasion or metastatic spread. Tumors greater than 1.5 cm carry a higher risk of recurrence and mortality.

* *Extracapsular* or vascular invasion and *metastatic* disease are poor prognosis factors. Regional metastasis in papillary carcinoma correlates positively with the incidence of local recurrence. Well-differentiated thyroid cancer, which invades and paralyzes the recurrent laryngeal nerve requires a wider resection. Distant metastases are rare in papillary cancers, but more often seen in follicular tumors, and are associated with poorer prognosis.

**History of radiation* is associated with higher risk of papillary carcinomas requiring more extensive resection to eradicate disease.

The Mayo clinic uses the “**AGES**” system incorporating age, grade, extracapsular tumor, and size. The Lahey clinic uses the “**AMES**” system incorporating age, metastasis, extracapsular, and size.

Diagnosis

The most common diagnostic measures include needle biopsy or aspiration, thyroid blood study, radiology imaging. Needle biopsy, a superior diagnostic technique, which provides accurate cytologic finding with no morbidity, has become the first step in thyroid nodule workup.

1. History and physical examination: a thorough history and head and neck examination should be the first evaluation of a thyroid mass. A malignant thyroid nodule usually presents as a painless mass. Other symptoms such as pain, hoarseness, dysphagia, dyspnea, stridor, hemoptysis, and rapid enlargement of the mass may occur with thyroid carcinomas but are not necessarily to be the signs of malignancy. A history of irradiation, especially in childhood, is an important risk for papillary carcinoma. External low dose

irradiation is the treatment for some diseases, e.g. acne, tonsillar hypertrophy, enlarged thymus, cervical adenitis, sinusitis and malignant disease. Previous thyroid diseases such as goiter, Hashimoto's disease and Grave's disease can be risk factors for thyroid cancer. Systemic disorder such as Gardner's syndrome, Cowden's disease, lymphoma, or other malignant diseases should be evaluated in relationship to thyroid nodules. Physical exam includes the full head and neck examination. A benign thyroid nodule is usually well-circumscribed, soft, non-tender, and movable free to surrounding tissue. A malignant tumor is harder, can be greater than 4 cm in diameter and may fixed to the surrounding and underlying tissues. Neck examination can reveal palpable metastatic cervical lymph nodes, especially in the anterior compartment (level III, IV, VI) and less common in level V. Chvostek's sign is helpful but not specific for hypocalcemia level because about 10% of the normal population can have false positive tests.

2. Needle biopsy:

- (1) *Core needle biopsy* provides adequate tissue for diagnosis in 90% of cases. Biopsy is guided by palpation. It is significantly more difficult, more traumatic and has more complication than fine needle biopsy
- (2) *Fine needle aspiration (FNA)* is more preferred because of less morbidity. Technique is performed on a palpable nodule or under ultrasonography guidance. Fine needle biopsy is an accurate diagnostic procedure in papillary, medullary, metastatic, anaplastic cancers, and malignant lymphomas. Differentiation between follicular and Hurthle cell neoplasms is based on capsular or vascular invasion. Ashcraft and Van Herle, in a comprehensive review compared the accuracy of fine needle aspiration and core biopsy, concluded that neither biopsy technique is superior, but fine needle aspiration has a lower yield of tissue and almost free of complication. In a recent report, fine needle aspiration has false negative rate of 0.3 to 10%, and a false positive rate of 0 to 2.5%. Therefore, a malignant specimen on fine needle aspiration is a strong indication for surgery; however, a negative result cannot rule out cancer. There are some *limitations of fine needle aspiration* to differentiate (1) adenomatoid nodule vs. follicular neoplasm, (2) papillary carcinoma with cystic change and benign cystic nodules, (3) large multinodular goiters and present malignancy, (4) Hashimoto's thyroiditis vs. oxyphilic cell (Hurthle) neoplasm, (5) multinodular goiter vs. Hurthle cell neoplasm, (6) Hashimoto's vs. malignant lymphoma, (7) malignant melanoma.

3. Blood test: thyroid function tests include (1) *thyroxin* or T4, (2) *triiodothyronine* or T3, and (3) *thyroid stimulating hormone* or TSH. *Serum calcium and phosphorous* levels may indicate hyperfunction of parathyroid gland adenoma, which may be associated with thyroid gland malignancy. *Thyroglobulin (Tg)* is usually measured as a baseline before and following up after surgery of well-differentiated thyroid carcinomas because it correlates with histologic types of tumors. Recurrent tumors are usually associated with high Tg level. *Calcitonin* is a useful test for diagnosis and screening in patients with medullary thyroid carcinoma and their family members; however, it is not a work up test. *Antimicrosomal and anti-Tg antibody titer* are unrealistic tests for screening or following

up a thyroid cancer because of high cost and low-specificity.

4. *Trial of suppression of TSH*, which is usually indicated in FNA negative for malignant nodules, applies thyroid hormone to suppress thyroid nodules. Levothyroxin suppression trial has showed decreasing volumes of thyroid nodules by 50% in approximately 40% of patients. The target of suppression test is to maintain released TSH levels between 0.1 and 0.5 mIU/L per day. Failure of suppression therapy is an indication for further workup or surgery therapy of the nodules.
5. Imaging studies:
 - Ultrasonography: is one of the most sensitive and effective tests for differentiation a thyroid and non-thyroid nodule in more than 80% of cases. It provides an accurate tri-dimensional location, follows up the nodular size, and indicates nodular location for the fine needle aspiration. US can detect the nodules as small as 2 to 3 mm and differentiate between solitary and multinodular diseases.
 - Radioisotope Scanning: to evaluate uptake of radioactive iodine or technetium of thyroid nodules compared with the remainder of the thyroid gland. Scintillation scanning has some value for routine evaluation of solitary thyroid nodules because the majority of both benign and malignant thyroid nodules are hyporeactive compared to adjacent tissues. Scanning with 123-I is more accurate but of greater cost and increases radiation exposure to the thyroid gland. However, radionuclide scanning is useful in the subgroups of patients with hyperthyroidism and autonomously functioning thyroid nodules. It is necessary to detect the remaining thyroid tissue after surgical resection as well as for presence of metastatic disease.
 - Magnetic resonance imaging (MRI): is very useful to detect residual, recurrent and metastatic cancers. T2 imaging is useful in differentiation between tumors and fibroses in operated neck tissue, and detection of muscle invasion. MRI also shows tracheal displacement and vascular relationship involved with large masses. Fat-saturation MRI can be used in suspected recurrent tumors, which are not identified by radioiodine scan.
 - Chest x-ray is helpful in detecting tracheal deviation, airway narrowing, and existent lung and bone metastasis. Patterns of calcification on chest x-ray are useful in identifying the types of cancer: (1) rim or eggshell calcification suggests a benign lesion, (2) bilateral calcification in superolateral aspect of the thyroid gland indicates MTC and (3) extensive irregular calcification suggests a multinodular goiter.
 - Pre-operative laryngoscopy evaluates vocal cord paralysis and should be documented in suspected carcinomas.

Staging of thyroid cancer

Staging is determined by physical exam, thyroid imaging, and endoscopic examination:

1. *Primary tumor*:
 - TX: primary tumor cannot be assessed
 - T0: no evidence of primary tumor

- T1: Tumor is limited to the thyroid and <1 cm
- T2: Tumor is limited to the thyroid and >1 cm but <4 cm
- T3: Tumor is limited to the thyroid and >4 cm
- T4: Tumor of any size extending beyond the thyroid capsule; T4a: solitary tumor, T4b: multifocal tumor

2. *Regional Lymph Node Metastasis:*

- NX: Regional lymph node cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis;
 - N1a: ipsilateral lymph node metastasis
 - N1b: bilateral, midline, or contralateral cervical or mediastinal lymph node metastasis

3. *Distant Metastasis:*

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis; specific metastatic sites (e.g. pulmonary (PUL), osseous (OSS), liver (HEP), brain (BRA), lymph nodes (LYM), etc)

Note: undifferentiated (anaplastic carcinoma) is considered by definition as stage IV tumors.

Clinical staging of papillary or follicular carcinoma:

- Patient under 45 years of age:
 - . Stage I: any T, any N, M0
 - . Stage II: any T, any N, M1
- Patient over 45 years of age:
 - . Stage I: T1, N0, M0
 - . Stage II: T2 or T3, N0, M0
 - . Stage III: T4, N0, M0, or any T, N1, M0
 - . Stage IV: any T, any N, M1

Clinical staging of medullary carcinoma:

- Stage I: T1, N0, M0
- Stage II: T2, T3, or T4, N0, M0
- Stage III: any T, N1, M0
- Stage IV: any T, any N, M1

Management

A. *Well-differentiated Thyroid Carcinoma: (Papillary, Follicular, and Hurthle cell)*

1. *Surgery:*

Tumor analysis should be done before the surgery regarding to the factors such as age, gender, extranodular invasion, distant metastasis, nodule size and involvement. A study at Memorial Sloan-Kettering Cancer Center from 1930 to 1980 identified female gender, multifocal primary tumor, and regional lymph node metastasis as favorable prognostic factors. On the contrary, age > 45, follicular histology, extrathyroidal extension, primary tumor >4 cm and presence of distant metastasis give worse prognoses.

All thyroid nodules should be approached as potential malignancies. Typically, total thyroidectomy is indicated for malignant lesions within one or the other lobe of the gland. Lobectomy is an option if frozen section (and subsequent permanent) histology returns a benign diagnosis.

According to Cannon, recurrent laryngeal nerve (RLN) is the key to thyroid operations. When the nerve cannot be found in the usual location, surgeons should dissect very carefully to identify the nerve near the superior pole of the thyroid gland. In the lateral aspect of the gland, the branches of the inferior thyroid artery and the parathyroid glands are dissected free of the thyroid globe, without interrupting their blood supply. Parathyroid autotransplantation is recommended when the glands or their blood supply are injured.

- *Total thyroidectomy* most commonly performed for WDTC. Total thyroidectomy allows for complete removal of primary tumor, reduced local recurrent rate to 26% (40% with lobectomy). Preparation for total thyroidectomy includes 131-I scanning, medication history, recurrent laryngeal nerve examination (pre-op documented recurrent laryngeal nerve function by Machida's scope or direct laryngoscopy), and pre-op Tg level.
- *Partial thyroidectomy* (lobectomy and isthmusectomy): is the basic minimal operation for thyroid cancers (nodulectomy is contraindicated). The procedure allows for identification and preservation of the parathyroid glands with blood supply and the recurrent laryngeal nerve. Indications for the procedure include unifocal, intrathyroidal, and nonmetastatic papillary carcinomas less than 1.0 cm in diameter; patient has no previous exposure to radiation and contralateral lobe is clinical normal. A study from Memorial Sloan-Kettering Cancer Center concluded that low-risk patients undergoing lobectomy are likely do as well as with total thyroidectomy and with less morbidity.
- *Near total thyroidectomy* leaves a minimal amount of thyroid tissue and preservation of the recurrent laryngeal nerve and parathyroid gland with their blood supply. This is the treatment for micro-carcinomas if multifocality or local lymph node metastasis is present. Micro-carcinomas are usually associated with bilateral tumor foci. Postoperative radioiodine scanning and therapy are necessary. Falk and McCaffrey reported that there were no differences in survival rate between complete excision with resection of recurrent laryngeal nerve and near total thyroidectomy with preservation of the nerve.
- *Role of neck dissection* in conjunction with thyroidectomy for WDTC is a controversial topic. Several studies showed that pathological evaluation of elective neck dissection has not improved the survival rate in papillary carcinoma. No neck dissection is necessary for the N0 neck and there is wide agreement on this among head and neck surgeons. Coburn and Wanebo reviewed retrospectively 108 patients in their clinic and concluded that patients age > 45, cervical lymph node positive, and positive mediastinal nodes need more aggressive treatment including modified neck dissection (preserves the jugular vein, SCM muscle, and spinal accessory nerve). Invasive tumors are removed

completely with preservation of involved organs (trachea and esophagus). Elective removal of lymph node is inadequate and should be avoided.

2. Adjuvant therapy:

- Post-op radioiodine (RAI): with appropriate dose, radiation therapy is safe in both children and adults. When patients have significant hypothyroidism (TSH > 50 mU/L), 4 to 5 mCi of ¹³¹I is given and the total body is scanned to look for residual thyroid tissue or metastasis. The scan and treatment are repeated until the scan is negative. Patient will receive follow up annually for several years. For the rest of life, patient's TSH should be held in low normal range by maintaining T4 level in high normal range. According to Attie et al., RAI uptake scanning is an essential indication after a thyroidectomy to determine the completeness of the surgical procedure and to detect residual or metastatic disease. Wong et al. reported ¹³¹I therapy prolonged lifespan even in disease-free patients after thyroidectomy.
- External beam radiation is useful in advanced locoregional WDTC whether superficial excision is complete or incomplete, if the tumor no longer picks up radioiodine, and in post-op adjuvant therapy for palliation of unresectable bone metastasis. The average dose is 50 Gy in 25 fractions over 5 weeks. Wu et al. reported that postoperative radiotherapy is more effective in well-differentiated thyroid carcinomas than in poorly differentiated carcinomas.

B. Undifferentiated Carcinoma:

These tumors are usually unresectable. Tracheotomy is considered when airway is compressed. Diagnosis is made by FNA and usually by open biopsy for completed cell study. A combination treatment of surgery, radiation or chemotherapy may help to control the tumors.

- Chemotherapy: undifferentiated thyroid carcinoma is generally not chemotherapy-sensitive. The most effective agent is adriamycin (doxorubicin). The approved combination by FDA includes adriamycin and cisplatin with hyperfractionated radiotherapy and debulking surgery may be used.
- Radiation therapy: anaplastic cancer does not concentrate ¹³¹I. The only radiation is external beam therapy. Without evidence of apparent metastasis at the time of initial treatment, the average survival rate for this tumor is only 6 months.

C. Medullary Thyroid Cancer:

Cervical metastasis at the time of diagnosis is observed in 50% of cases. Surgical resection includes the anterior compartment node dissection, which removes the lymphatics and adipose tissue from the hyoid bone to the sternal notch and laterally to the internal jugular vein. The lymph node groups removed are pre-tracheal, paratracheal, pre-cricoid, Delphian and perithyroidal nodes. With N(+) cervical lymph nodes, a selective lateral neck dissection of zones II, III, IV can be included.

Recurrent MTC is resistant to chemotherapy and radiation. Moley reported that chemotherapy cured 28% and controlled 69% of patients. At the MD Anderson hospital, radiation is used as an

adjuvant therapy in patients with soft tissue invasion, multiple positive nodes and metastatic MTC. When diagnose early and treat appropriately, the expected 10-year survival rate of MTC is about 90%. The most effective treatment is primary total thyroidectomy. Indications include the following reasons: (1) the C-cells have diffuse and bilateral anatomic distribution resulting in multifocal and bilobular tumors, (2) in the sporadic form, 30% of patients have bilateral involvement, (3) in the family cases, bilateral involvement is 100%.

D. Hurthle (oxyphilic) Cell Carcinoma:

The treatment of choice is total thyroidectomy because the tumor is aggressive and relatively unresponsive to radiation therapy. Another option is partial thyroidectomy. If the frozen section is negative for malignancy, the procedure is adequate. If it comes back positive, complete thyroidectomy should be done *within 2 weeks*. Patients have N(+) cervical lymph nodes need a routine modified neck dissection. Post-op thyroid suppression is helpful because Hurthle cell tumors have TSH receptors. Postoperative radioactive iodine is not indicated because these tumors take up ¹³¹I poorly.

Surgical complications

1. Nonmetabolic complications:

- Nerve injury: superior (SLN) and recurrent laryngeal nerves (RLN) are most commonly injured. The morbidity caused by nerve injury depends on the extent and nature of the damage. SLN normally courses medially to the superior thyroid artery. Teitelbaum et al. reported unilateral SLN injury in about 5% of thyroidectomies. SLN injury can be avoided by leaving superior pole vessels alone until the isthmus has been divided and the lobe has been substantially mobilized. Patients usually complain of unstable voice, difficulty with high pitch, dysphagia and aspiration due to decreased laryngeal sensation. Classic signs of bowing of the vocal cords, ipsilateral rotation of the posterior glottis and inferior displacement of the affected cord may be missed on indirect laryngoscopy. RLN injury can coexist with SLN paralysis one or both sides. The reasons for nerve injury are: (1) anatomic variations, (2) failure to recognize alteration in the normal course of the nerve because of pathologic conditions, (3) lack of meticulous hemostasis and fastidious anatomic dissection, and (4) suturing, stretching, and crushing injuries of the main trunk or branches. Unilateral RLN paralysis is not life threatening and is usually compensated by the shortening and movement of the opposite vocal cord across the midline and the fibrosis of the arytenoid muscle. Bilateral RLN injury can causes airway obstruction immediately or years later. The early symptoms are stridor and cyanosis shortly after extubation. These patients should be re-intubated.
- Hemorrhage: major post-op bleeding becomes apparent by excessive bloody discharge in the drain, swelling of the neck and cervical venous distension.
- Airway obstruction: is the major cause of morbidity and mortality in post-op thyroid surgery. Airway obstruction is caused by postoperative hematoma, laryngeal edema or bilateral vocal cord paralysis. Preceding symptoms are neck pain, swelling and stridor. Fiberoptic endoscopy can identify the extent of airway

obstruction. Management includes IV steroids over 24-48 hours, if there is no bilateral VC injury.

- Chyle leak is a rare complication of neck dissection and usually occurs in patients with previous neck irradiation or surgery.
- Pneumothorax is a rare complication, caused by injury to the apical pleura. It requires immediate recognition and applies of positive pressure respiration to keep the lungs expanded, as well as prompt closure of the wound to prevent recurrence.
- Postoperative nausea and vomiting (PONV) is associated with complications of general anesthesia, gender (more common in women), and intense operative vagal stimulation (e.g. surgical handling of neck structures. Fujii et al. reported that the incidence of PONV has been shown as high as 60% to 65% in patients undergoing thyroidectomy without prophylactic antiemetics. PONV can be avoided by prophylaxis treatment with 5-HT₃ antagonists (e.g. granisetron, ondansetron), droperidol, metoclopramide or other antiemetic agents.

2. *Metabolic complications:*

- Hypothyroidism: usually occur after a total or near total thyroidectomy, more common in Grave's disease.
- Hypocalcemia is caused by an inadvertent parathyroidectomy, in about 5% of thyroidectomies. It can be avoided by meticulous dissection and autotransplantation of the parathyroid glands.
- Thyroid storm: is a life threatening complication in patients with hyperthyroidism, and is caused by a disordering of hemeostasis owing to acute decompensation of the cardiovascular system, CNS, GI tract, and hepato-renal system. This complication is usually associated with a systemic illness (e.g. infection) in the postsurgical stage. It should be differentiated from malignant hyperthermia. Therapy includes (1) reduce hormone synthesis and release from the thyroid gland, (2) antagonize peripheral action of circulating hormones, (3) provide supportive care and (4) define and treat any precipitating conditions.

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