Thyroid Cancer

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Introduction

- Consistent techniques of thyroid surgery date back approximately 100 years.
- Theodor Kocher of Bern, Switzerland made major contributions to thyroid the understanding of thyroid disease and thyroid surgery.
  - 1872 - performed his first thyroidectomy
  - 1901 - had performed 2,000 thyroid procedure
  - 1901 - overall operative mortality had decreased from 50% to 4.5%
  - 1909 - won the nobel prize for his work

(Cady, 1991, Soh, 1996)
Statistics of Thyroid Cancer

- **1.0%-1.5%** of all new cancer cases in the United States (Sessions, 1993; Silverberg, 1989) – ten fold less than that of lung, breast, or colorectal cancer

- **8,000-14,000** new cases diagnosed each year (Sessions, 1993; Geopfert, 1998)

- **3%** of patients who die of other causes have occult thyroid cancer and **10%** have microscopic cancers (Robbins, 1991)

- **35%** of thyroid gland at autopsy in some studies have papillary carcinomas (<1.0cm) (Mazzaferri, 1993)

- **1,000-1,200** patients in the U.S. die each year of thyroid cancer (Goldman, 1996)
Statistics of Thyroid Cancer (continued…)

- 4%-7% of adults in North America have palpable thyroid nodules (Mazzaferri, 1993, Vander, 1968)
- 4:1 women to men (Mazzaferri, 1993)
- Overall, fewer than 5% of nodules are malignant (Mazzaferri, 1988)
History

◆ Symptoms

◆ The most common presentation of a thyroid nodule, benign or malignant, is a painless mass in the region of the thyroid gland (Goldman, 1996).

◆ Symptoms consistent with malignancy

  • Pain
  • dysphagia
  • Stridor
  • hemoptysis
  • rapid enlargement
  • hoarseness
Risk factors

Thyroid exposure to irradiation

• low or high dose external irradiation (40-50 Gy [4000-5000 rad])

• especially in childhood for:
  – large thymus, acne, enlarged tonsils, cervical adenitis, sinusitis, and malignancies

• 30%-50% chance of a thyroid nodule to be malignant (Goldman, 1996)

• Schneider and co-workers (1986) studied, with long term F/U, 3000 patients who underwent childhood irradiation.
  – 1145 had thyroid nodules
  – 318/1145 had thyroid cancer (mostly papillary)
History (continued…)

**Risk factors** (continued…)

**Age and Sex**

- Benign nodules occur most frequently in women 20-40 years (Campbell, 1989)
- 5%-10% of these are malignant (Campbell, 1989)
- Men have a higher risk of a nodule being malignant
- Belfiore and co-workers found that:
  - the odds of cancer in men quadrupled by the age of 64
  - a thyroid nodule in a man older than 70 years had a 50% chance of being malignant
History (continued...)

- **Family History**
  - History of family member with medullary thyroid carcinoma
  - History of family member with other endocrine abnormalities (parathyroid, adrenals)
  - History of familial polyposis (Gardner’s syndrome)
Evaluation of the thyroid Nodule

*(Physical Exam)*

- Examination of the thyroid nodule:
  - consistency - hard vs. soft
  - size - < 4.0 cm
  - Multinodular vs. solitary nodule
    - multinodular - 3% chance of malignancy (Goldman, 1996)
    - solitary nodule - 5%-12% chance of malignancy (Goldman, 1996)
  - Mobility with swallowing
  - Mobility with respect to surrounding tissues
  - Well circumscribed vs. ill defined borders
Physical Exam (continued…)

- Examine for ectopic thyroid tissue
- Indirect or fiberoptic laryngoscopy
  - vocal cord mobility
  - evaluate airway
  - preoperative documentation of any unrelated abnormalities

- Systematic palpation of the neck
  - Metastatic adenopathy commonly found:
    - in the central compartment (level VI)
    - along middle and lower portion of the jugular vein (regions III and IV) and

- Attempt to elicit Chvostek’s sign
Evaluation of the Thyroid Nodule

(Blood Tests)

- Thyroid function tests
  - thyroxine (T4)
  - triiodothyronine (T3)
  - thyroid stimulating hormone (TSH)
- Serum Calcium
- Thyroglobulin (TG)
- Calcitonin
Evaluation of the Thyroid Nodule

(Radioimaging)

- Radioimaging usually not used in initial work-up of a thyroid nodule
  - Chest radiograph
  - Computed tomography
  - Magnetic resonance imaging
Evaluation of the Thyroid Nodule (Ultrasonography)

◆ Advantages
  ◆ Most sensitive procedure for identifying lesions in the thyroid (2-3mm)
  ◆ 90% accuracy in categorizing nodules as solid, cystic, or mixed (Rojeski, 1985)
  ◆ Best method of determining the volume of a nodule (Rojeski, 1985)
  ◆ Can detect the presence of lymph node enlargement and calcifications
  ◆ Noninvasive and inexpensive
Ultrasonography (Continued…)

- **When to use Ultrasonography:**
  - Long term follow-up for the following:
    - to evaluate the involution of a multinodular gland or a solitary benign nodule under suppression therapy
    - monitor for reaccumulation of a benign cystic lesion
    - follow thyroid nodules enlargement during pregnancy
  - **Evaluation of a thyroid nodule:**
    - help localize a lesion and direct a needle biopsy when a nodule is difficult to palpate or is deep-seated
    - Determine if a benign lesion is solid or cystic
Ultrasonography (Continued…)

Disadvantages

- Unable to reliably diagnose true cystic lesions
- Cannot accurately distinguish benign from malignant nodules
Prior to FNA, was the initial diagnostic procedure of choice

Performed with: technetium 99m pertechnetate or radioactive iodine

- Technetium 99m pertechnetate
  - cost-effective
  - readily available
  - short half-life
  - trapped but not organified by the thyroid - cannot determine functionality of a nodule
Radioisotope Scanning (Continued…)

- Radioactive iodine
  - radioactive iodine (I-131, I-125, I-123)
  - is trapped and organified
  - can determine functionality of a thyroid nodule
Radioisotope Scanning (continued...)

- Limitations
  - Not as sensitive or specific as fine needle aspiration in distinguishing benign from malignant nodule
    - 90%-95% of thyroid nodules are hypofunctioning, with 10%-20% being malignant (Geopfert, 1994, Sessions, 1993)
    - Campbell and Pillsbury (1989) performed a meta-analysis of 10 studies correlating the results of radionuclide scans in patients with solitary thyroid nodules with the pathology reports following surgery and found:
      - 17% of cold nodules, 13% of warm or cool nodules, and 4% of hot nodules to be malignant
Radioisotope Scanning (continued…)

Specific uses of thyroid scanning:

- Preoperative evaluation
  - When patients have benign (by FNA), solid (by U/S) lesions
  - When patients have nonoxyphilic follicular neoplasms

- Postoperative evaluation
  - Immediately postop for localization of residual cancer or thyroid tissue
  - Follow-up for tumor recurrence or metastasis

(Geopfert, 1994)
Evaluation of the Thyroid Nodule

*(Fine-Needle Aspiration)*

- Currently considered to be the best first-line diagnostic procedure in the evaluation of the thyroid nodule:
- Advantages:
  - Safe
  - Cost-effective
  - Minimally invasive
  - Leads to better selection of patients for surgery than any other test (Rojeski, 1985)
Fine-Needle Aspiration (continued…)

- FNA halved the number of patients requiring thyroidectomy (Mazzaferri, 1993)
- FNA has double the yield of cancer in those who do undergo thyroidectomy (Mazzaferri, 1993)
Pathologic results are categorized as:
- positive,
- negative, or
- indeterminate

Hossein and Goellner (1993) use four categories. They pooled data from seven series and came up with the following rates:
- benign - 69%
- suspicious - 10%
- malignant - 4%
- nondiagnostic - 17%
Fine-Needle Aspiration (continued…)

- Limitations
  - skill of the aspirator
    - Sampling error in lesions <1cm, >4cm, multinodular lesions, and hemorrhagic lesions
    - Error can be diminished using ultrasound guidance
  - expertise of the cytologist
  - difficulty in distinguishing some benign cellular adenomas from their malignant counterparts (follicular and Hurthle cell)

- False negative results = 1%-6% (Mazzeferri, 1993)

- False positive results = 3%-6% (Rojeski, 1985, Mazzeferri, 1993, Hall, 1989)
Evaluation of the Thyroid Nodule
(Thyroid-Stimulating Hormone Suppression)

◆ Mechanism/Rationale

• Exogenous thyroid hormone feeds back to the pituitary to decrease the production of TSH
• Cancer is autonomous and does not require TSH for growth whereas benign processes do
• Thyroid masses that shrink with suppression therapy are more likely to be benign
• Thyroid masses that continue to enlarge are likely to be malignant
Thyroid Suppression (continued…)

Limitations:

- 16% of malignant nodules are suppressible
- Only 21% of benign nodules are suppressible
- Provides little use in distinguishing benign from malignant nodules

(Geopfert, 1998)
Thyroid Suppression (continued…)

- **Uses:**
  - Preoperative
    - patients with nonoxyphilic follicular neoplasms
    - patients with solitary benign nodules that are nontoxic (particularly men and premenopausal women)
    - women with repeated nondiagnostic tests
  - Postoperative
    - Use in follicular, papillary and Hurthle cell carcinomas

(Geopfert, 1998, Mazzaferri, 1993)
Thyroid Suppression (continued…)

How to use thyroid suppression

- administer levothyroxine
- maintain TSH levels at <0.1 mIU/L
- use ultrasound to monitor size of nodule
  - if the nodule shrinks, continue L-thyroxine maintaining TSH at low-normal levels
  - if the nodule has remained the same size after 3 months, reaspirate
  - if the nodule has increased in size, excise it

(Geopfert, 1998,)
Classification of Malignant Thyroid Neoplasms

- Papillary carcinoma
  - Follicular variant
  - Tall cell
  - Diffuse sclerosing
  - Encapsulated
- Follicular carcinoma
  - Overtly invasive
  - Minimally invasive
- Hurthle cell carcinoma
- Anaplastic carcinoma
  - Giant cell
  - Small cell
- Medullary Carcinoma
- Miscellaneous
  - Sarcoma
  - Lymphoma
  - Squamous cell carcinoma
  - Mucoepidermoid carcinoma
  - Clear cell tumors
  - Pasma cell tumors
  - Metastatic
    - Direct extension
    - Kidney
    - Colon
    - Melanoma
Well-Differentiated Thyroid Carcinomas (WDTC) - Papillary, Follicular, and Hurthle cell

- Pathogenesis - unknown
- Papillary has been associated with the RET proto-oncogene but no definitive link has been proven (Geopfert, 1998)
- Certain clinical factors increase the likelihood of developing thyroid cancer
  - Irradiation - papillary carcinoma
  - Prolonged elevation of TSH (iodine deficiency) - follicular carcinoma (Goldman, 1996)
    - relationship not seen with papillary carcinoma
    - mechanism is not known
WDTC - Papillary Carcinoma

- 60%-80% of all thyroid cancers (Geopfert, 1998, Merino, 1991)
- Histologic subtypes
  - Follicular variant
  - Tall cell
  - Columnar cell
  - Diffuse sclerosing
  - Encapsulated
- Prognosis is 80% survival at 10 years (Goldman, 1996)
- Females > Males
- Mean age of 35 years (Mazzaferri, 1994)
Lymph node involvement is common
- Major route of metastasis is lymphatic
- 46%-90% of patients have lymph node involvement (Goepfert, 1998, Scheumann, 1984, De Jong, 1993)
- Clinically undetectable lymph node involvement does not worsen prognosis (Harwood, 1978)
Microcarcinomas - a manifestation of papillary carcinoma

- Definition - papillary carcinomas smaller than 1.0 cm
- Most are found incidentally at autopsy
- Autopsy reports indicate that these may be present in up to 35% of the population (Mazzaferri, 1993)
- Usually clinically silent
- Most agree that the morbidity and mortality from microcarcinoma is minimal and near that of the normal population
- One study showed a 1.3% mortality rate (Hay, 1990)
WDTC - Papillary Carcinoma
(continued…)

- **Pathology**
  - Gross - vary considerably in size
    - often *multi-focal*
    - unencapsulated but often have a pseudocapsule
  - Histology - closely packed papillae with little colloid
    - *psammoma bodies*
    - nuclei are oval or elongated, pale staining with ground glass appearance - *Orphan Annie cells*
WDTC - Follicular Carcinoma

◆ 20% of all thyroid malignancies
◆ Mean age of 39 years (Mazzaferri, 1994)
◆ Prognosis - 60% survive to 10 years (Geopfert, 1994)
◆ Metastasis - angioinvasion and hematogenous spread
  • 15% present with distant metastases to bone and lung
◆ Lymphatic involvement is seen in 13% (Goldman, 1996)
WDTC - Follicular Carcinoma
(Continued…)

- Pathology
  - Gross - encapsulated, solitary
  - Histology - very well-differentiated (distinction between follicular adenoma and carcinoma is difficult)
    - Definitive diagnosis - evidence of vascular and capsular invasion
  - FNA and frozen section cannot accurately distinguish between benign and malignant lesions
WDTC - Hurthle Cell Carcinoma

- Variant of follicular carcinoma
- First described by Askanazy
  - “Large, polygonal, eosinophilic thyroid follicular cells with abundant granular cytoplasm and numerous mitochondria” (Goldman, 1996)
- Definition (Hurthle cell neoplasm) - an encapsulated group of follicular cells with at least a 75% Hurthle cell component
- Carcinoma requires evidence of vascular and capsular invasion
- 4%-10% of all thyroid malignancies (Sessions, 1993)
WDTC - Hurthle Cell Carcinoma
(Continued…)

- Women > Men
- Lymphatic spread seen in 30% of patients
  (Goldman, 1996)
- Distant metastases to bone and lung is seen in 15% at the time of presentation
 persists Prognosis

Based on age, sex, and findings at the time of surgery (Geopfert, 1998)

Several prognostic schemes represented by acronyms have been developed by different groups:

- **AMES** (Lahey Clinic, Burlington, MA)
- **GAMES** (Memorial Sloan-Kettering Cancer Center, New York, NT)
- **AGES** (Mayo Clinic, Rochester, MN)
WDTC - Prognosis  (Continued…)

- Depending on variables, patients are categorized in to one of the following three groups:

1) **Low risk group** - men younger than 40 years and women younger than 50 years regardless of histologic type

- recurrence rate - 11%
- death rate - 4%

(Cady and Rossi, 1988)
1) **Intermediate risk group** - Men older than 40 years and women older than 50 years who have papillary carcinoma
   - recurrence rate - 29%
   - death rate - 21%

2) **High risk group** - Men older than 40 years and women older than 50 years who have follicular carcinoma
   - recurrence rate - 40%
   - death rate - 36%
Medullary Thyroid Carcinoma

- 10% of all thyroid malignancies
- 1000 new cases in the U.S. each year
- Arises from the parafollicular cell or C-cells of the thyroid gland
  - derivatives of neural crest cells of the branchial arches
  - secrete calcitonin which plays a role in calcium metabolism
Medullary Thyroid Carcinoma (Continued…)

- Developes in 4 clinical settings:
  - Sporadic MTC (SMTC)
  - Familial MTC (FMTC)
  - Multiple endocrine neoplasia IIa (MEN IIa)
  - Multiple endocrine neoplasia IIb (MEN IIb)
Medullary Thyroid Carcinoma (continued…)

◆ **Sporadic MTC:**

- 70%-80% of all MTCs (Colson, 1993, Marzano, 1995)
- Mean age of 50 years (Russell, 1983)
- 75% 15 year survival (Alexander, 1991)
- Unilateral and Unifocal (70%)
- Slightly more aggressive than FMTC and MEN IIa
- 74% have extrathyroid involvement at presentation (Russell, 1983)
Medullary Thyroid Carcinoma
(Continued…)

- **Familial MTC:**
  - Autosomal dominant transmission
  - Not associated with any other endocrinopathies
  - Mean age of 43
  - Multifocal and bilateral
  - Has the best prognosis of all types of MTC
  - 100% 15 year survival

(Farndon, 1986)
Medullary Thyroid Carcinoma
(continued…)

◆ *Multiple endocrine neoplasia IIa (Sipple’s Syndrome)*:
  - MTC, Pheochromocytoma, parathyroid hyperplasia
  - Autosomal dominant transmission
  - Mean age of 27
  - 100% develop MTC (Cance, 1985)
  - 85%-90% survival at 15 years (Alexander, 1991, Brunt, 1987)
Medullary Thyroid Carcinoma
(continued…)

- Multiple endocrine neoplasia IIb (Wermer’s Syndrome, MEN III, mucosal syndrome):

  - Pheochromocytoma, multiple mucosal neuromas, marfanoid body habitus
  - 90% develop MTC by the age of 20
  - Most aggressive type of MTC
  - 15 year survival is <40%-50%

  (Carney, 1979)
Medullary Thyroid Carcinoma
(continued…)

✦ Diagnosis

- Labs: 1) basal and pentagastrin stimulated serum calcitonin levels (>300 pg/ml)
- 2) serum calcium
- 3) 24 hour urinary catecholamines (metanephrines, VMA, nor-metanephrines)
- 4) carcinoembryonic antigen (CEA)

- Fine-needle aspiration
- Genetic testing of all first degree relatives
  - RET proto-oncogene
Anaplastic Carcinoma of the Thyroid

- Highly lethal form of thyroid cancer
- Median survival <8 months (Jereb, 1975, Junor, 1992)
- 1%-10% of all thyroid cancers (Leeper, 1985, LiVolsi, 1987)
- Affects the elderly (30% of thyroid cancers in patients >70 years) (Sou, 1996)
- Mean age of 60 years (Junor, 1992)
- 53% have previous benign thyroid disease (Demeter, 1991)
- 47% have previous history of WDTC (Demeter, 1991)
Anaplastic Carcinoma of the Thyroid

Pathology

- Classified as large cell or small cell
- Large cell is more common and has a worse prognosis
- Histology - sheets of very poorly differentiated cells
  - little cytoplasm
  - numerous mitoses
  - necrosis
  - extrathyroidal invasion
Management

- Surgery is the definitive management of thyroid cancer, excluding most cases of ATC and lymphoma.

- Types of operations:
  - lobectomy with isthmusectomy - minimal operation required for a potentially malignant thyroid nodule
  - total thyroidectomy - removal of all thyroid tissue - preservation of the contralateral parathyroid glands
  - subtotal thyroidectomy - anything less than a total thyroidectomy
Management (WDTC) - Papillary and Follicular

- Subtotal vs. total thyroidectomy
Rationale for total thyroidectomy

1) 30%-87.5% of papillary carcinomas involve opposite lobe (Hirabayashi, 1961, Russell, 1983)
2) 7%-10% develop recurrence in the contralateral lobe (Soh, 1996)
3) Lower recurrence rates, some studies show increased survival (Mazzaferri, 1991)
4) Facilitates earlier detection and tx for recurrent or metastatic carcinoma with iodine (Soh, 1996)
5) Residual WDTC has the potential to dedifferentiate to ATC
Management (WDTC) - Papillary and Follicular (Continued…)

◆ Rationale for subtotal thyroidectomy
  
  • 1) Lower incidence of complications
    • Hypoparathyroidism (1%-29%) (Schroder, 1993)
    • Recurrent laryngeal nerve injury (1%-2%) (Schroder, 1993)
    • Superior laryngeal nerve injury
  
  • 2) Long term prognosis is not improved by total thyroidectomy (Grant, 1988)
Management (WDTC) - Papillary and Follicular (continued)

- **Indications for total thyroidectomy**
  - 1) Patients older than 40 years with papillary or follicular carcinoma
  - 2) Anyone with a thyroid nodule with a history of irradiation
  - 3) Patients with bilateral disease
Managing lymphatic involvement

- pericapsular and tracheoesophageal nodes should be dissected and removed in all patients undergoing thyroidectomy for malignancy
- Overt nodal involvement requires exploration of mediastinal and lateral neck
- if any cervical nodes are clinically palpable or identified by MR or CT imaging as being suspicious a neck dissection should be done (Goldman, 1996)
- Prophylactic neck dissections are not done (Gluckman)
Management (WDTC) - Papillary and Follicular (continued)

- **Postoperative therapy/follow-up**
  - **Radioactive iodine** (administration)
    - Scan at 4-6 weeks postop
    - repeat scan at 6-12 months after ablation
    - repeat scan at 1 year then...
    - every 2 years thereafter
Postoperative therapy/follow-up

- Thyroglobulin (TG) (Gluckman)
  - measure serum levels every 6 months
  - Level >30 ng/ml are abnormal

- Thyroid hormone suppression (control TSH dependent cancer) (Goldman, 1996)
  - should be done in -
    1) all total thyroidectomy patients
    2) all patients who have had radioactive ablation of any remaining thyroid tissue
Total thyroidectomy is recommended because:

1) Lesions are often Multifocal
2) They are more aggressive than WDTCs
3) Most do not concentrate iodine
Management (WDTC) - Hurthle Cell Carcinoma (continued)

- Postoperative management
  - Thyroid suppression
  - Measure serum thyroglobulin every 6 months
  - Postoperative radioactive iodine is usually not effective (10% concentrate iodine) (Clark, 1994)
Medullary Thyroid Carcinoma (Management)

- **Recommended surgical management**
  - total thyroidectomy
  - central lymph node dissection
  - lateral jugular sampling
    - if suspicious nodes - modified radical neck dissection

- **If patient has MEN syndrome**
  - remove pheochromocytoma before thyroid surgery
Medullary Thyroid Carcinoma
(Management)

Postoperative management

- disease surveillance
  - serial calcitonin and CEA
    - 2 weeks postop
    - 3/month for one year, then…
    - biannually

- If calcitonin rises
  - metastatic work-up
  - surgical excision
  - if metastases - external beam radiation
Anaplastic Carcinoma
(Management)

- Most have extensive extrathyroidal involvement at the time of diagnosis
  - surgery is limited to biopsy and tracheostomy

- Current standard of care is:
  - maximum surgical debulking, possible
  - adjuvant radiotherapy and chemotherapy (Jereb and Sweeney, 1996)