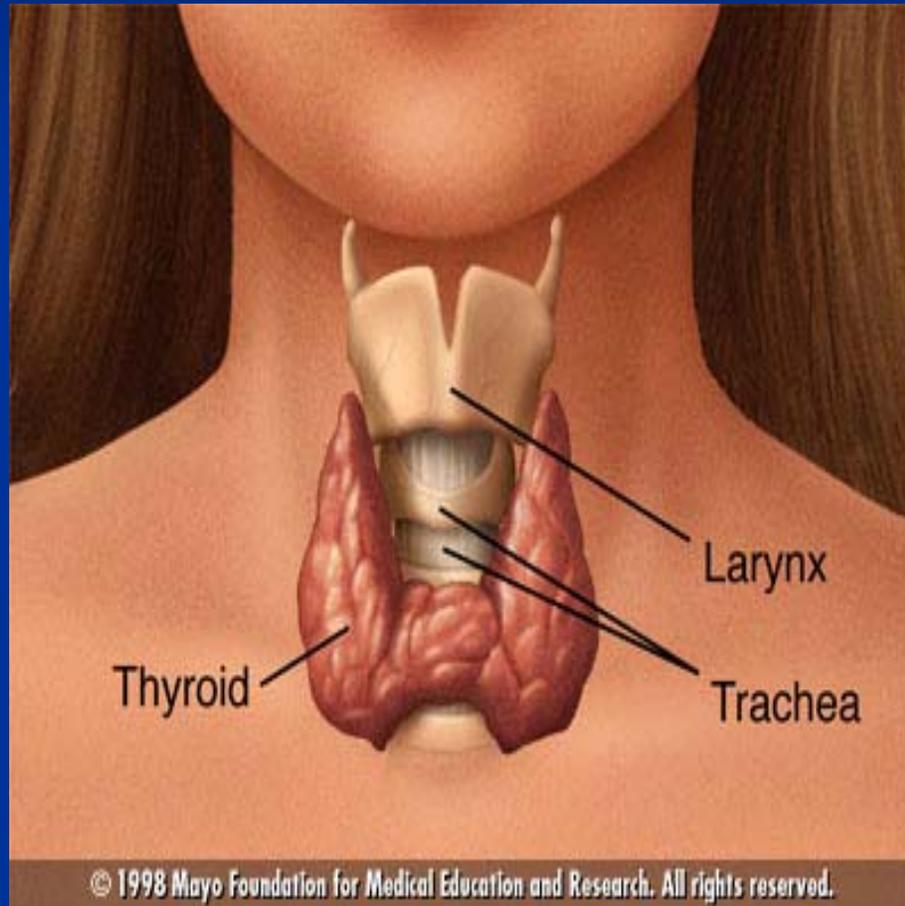


Management of Thyroid Cancer



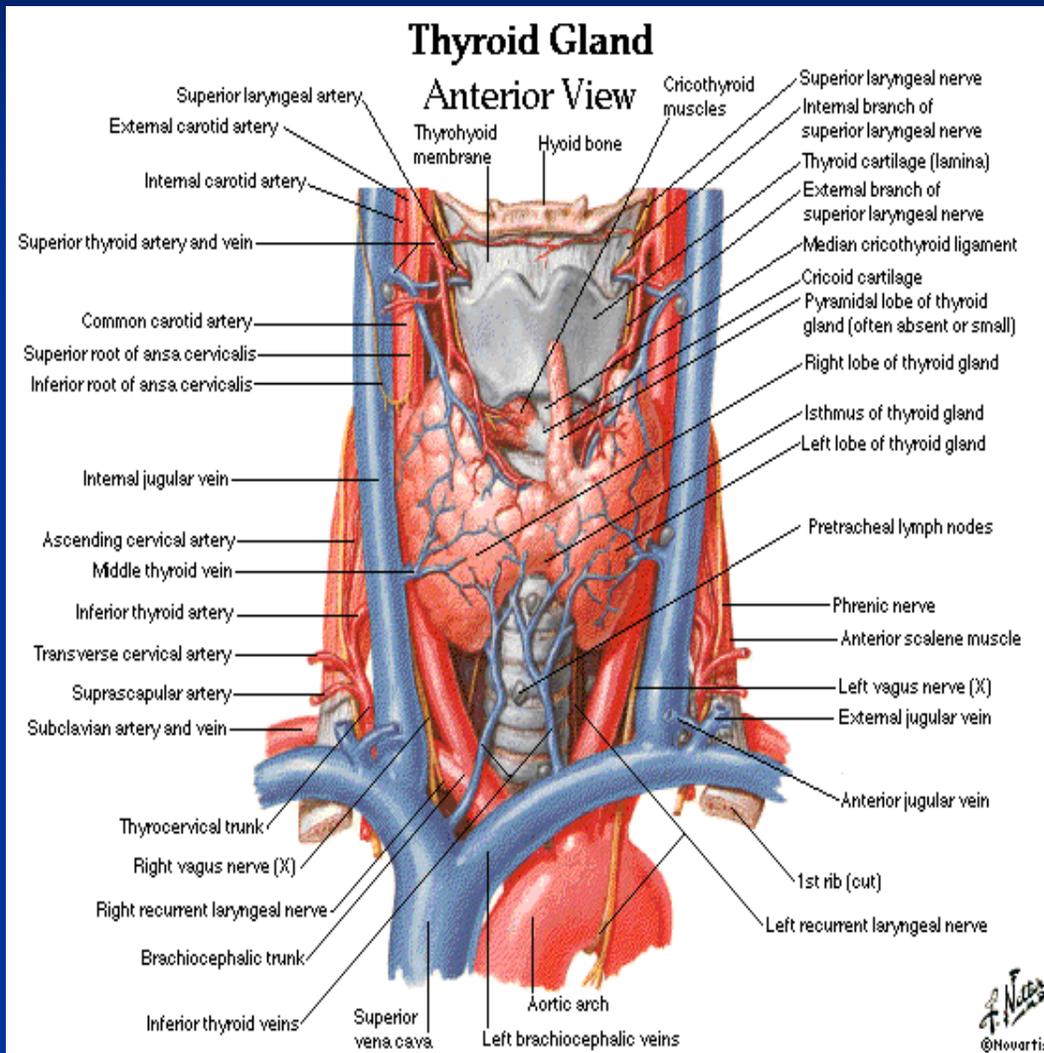
Sajani Shah MD
November 18, 2005
SUNY Downstate
Morbidity and Mortality
Conference

Thyroid Embryology



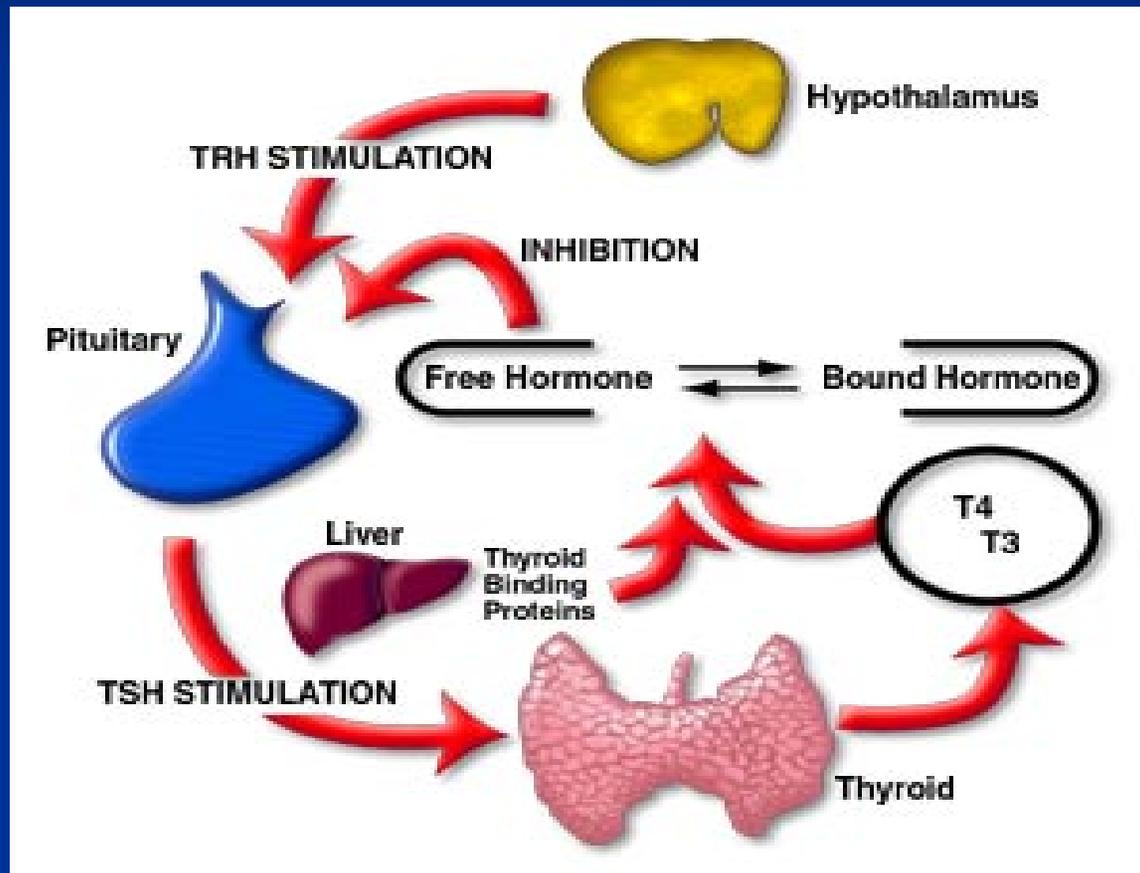
- Derived from endodermal tissue at base of tongue
- Embryonal remnants form *Thyroglossal duct; pyramidal lobe; lingual thyroid*
- Fuse with C-cells (neural crest origin), derived from the the 5th branchial arch
- C-cells scattered through posterior/superior lobes

Thyroid Anatomy



- Largest endocrine gland (20 - 25 g)
- Fills the tracheo-esophageal space
- Overlies RLN bilaterally
- Parathyroids lie at each pole (usually)

Thyroid Physiology



Introduction

- Thyroid Cancer accounts for 1.5% of all cancers in the US
- Six deaths per 1 million people occur annually.
- Occurs in about 40 per 1 million people per year
- The most common endocrine malignancy-accounts for 95% of all endocrine cancers
- Female to Male Ratio 2.5:1

Clinical Manifestation

- Most patients are euthyroid and present with a thyroid nodule
- Symptoms such as dysphagia, dyspnea and hoarseness usually indicate advanced disease
- Ipsilateral Cervical lymph glands may also be present.

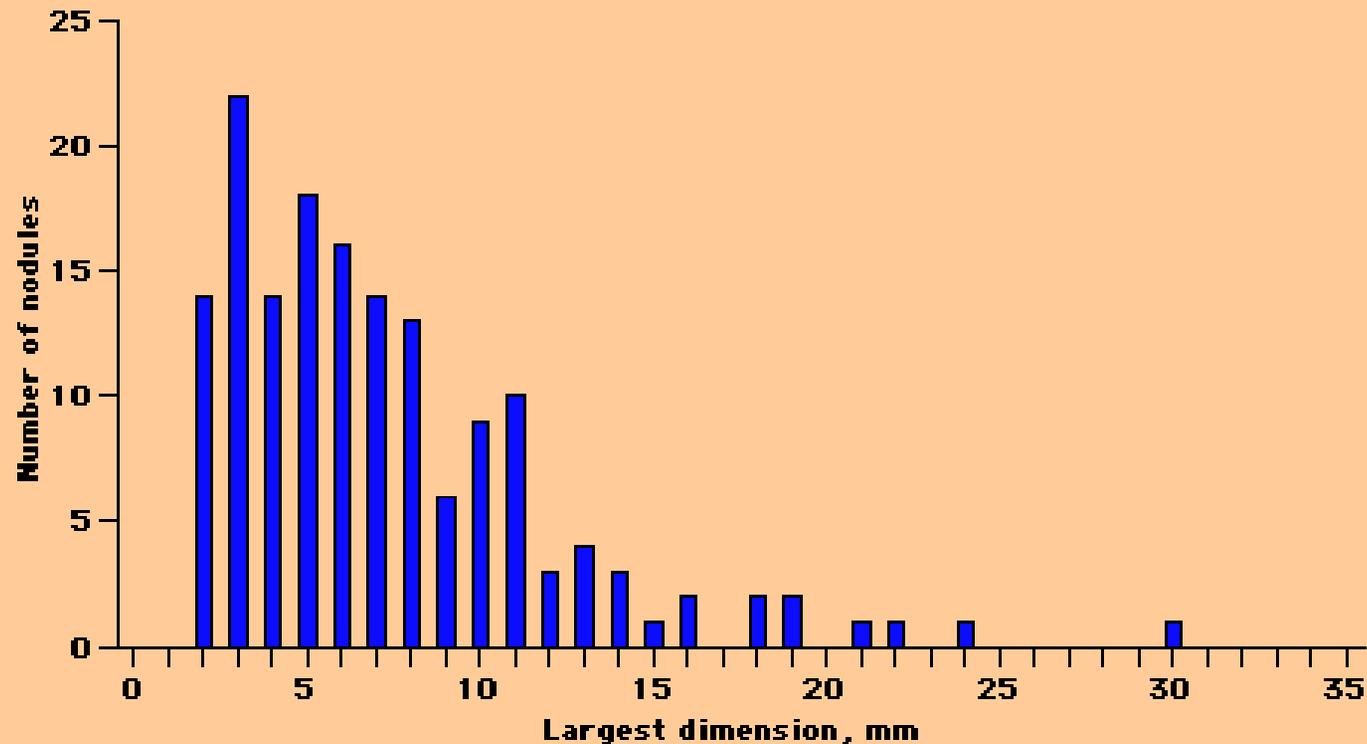
Risk Factors for Thyroid Cancer

- The only well-established risk factor for differentiated thyroid cancer is external head and neck **radiation**, especially during infancy
- Papillary thyroid carcinoma may occur in several **rare inherited syndromes**, including familial adenomatous polyposis, Gardner's syndrome, and Cowden's disease
- Patient's **Age and Gender**:
 - Malignancy more common in children and adults >60
 - Men

Radiation and Thyroid Cancer

- The association of irradiation and thyroid cancer has been known for years.
- The use of external-beam irradiation in children and young adults in the 1950s and 1960s for acne and tonsillitis has been shown to result in an increased incidence of papillary cancer, usually 5 years after exposure.
- Irradiation for soft tissue malignancy, such as Hodgkin's lymphoma, have an increased incidence of thyroid nodules and cancer.

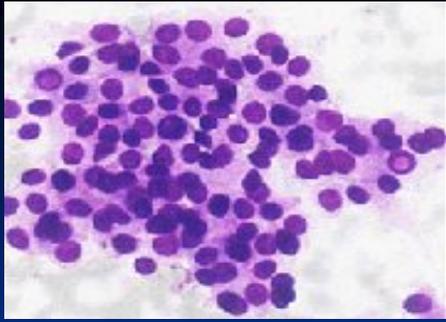
Radiation and Thyroid Nodule



Thyroid nodules in irradiated patients Size distribution of 157 thyroid nodules in 47 patients with a history of radiation exposure; seven others had no nodules. Eleven nodules were 1.5 cm or larger, five of which were palpable. (Data from Schneider, AB, Bekerman, C, Leland, J, et al, J Clin Endocrinol Metab 1997; 82:4020.)

Diagnosis

- Serum TSH
- Fine Needle Aspiration Cytology (FNA)
- High Resolution Thyroid US- helpful in detecting non palpable nodule and solid versus cystic lesion
- Thyroid Isotope Scanning- to assess functional activity of a nodule

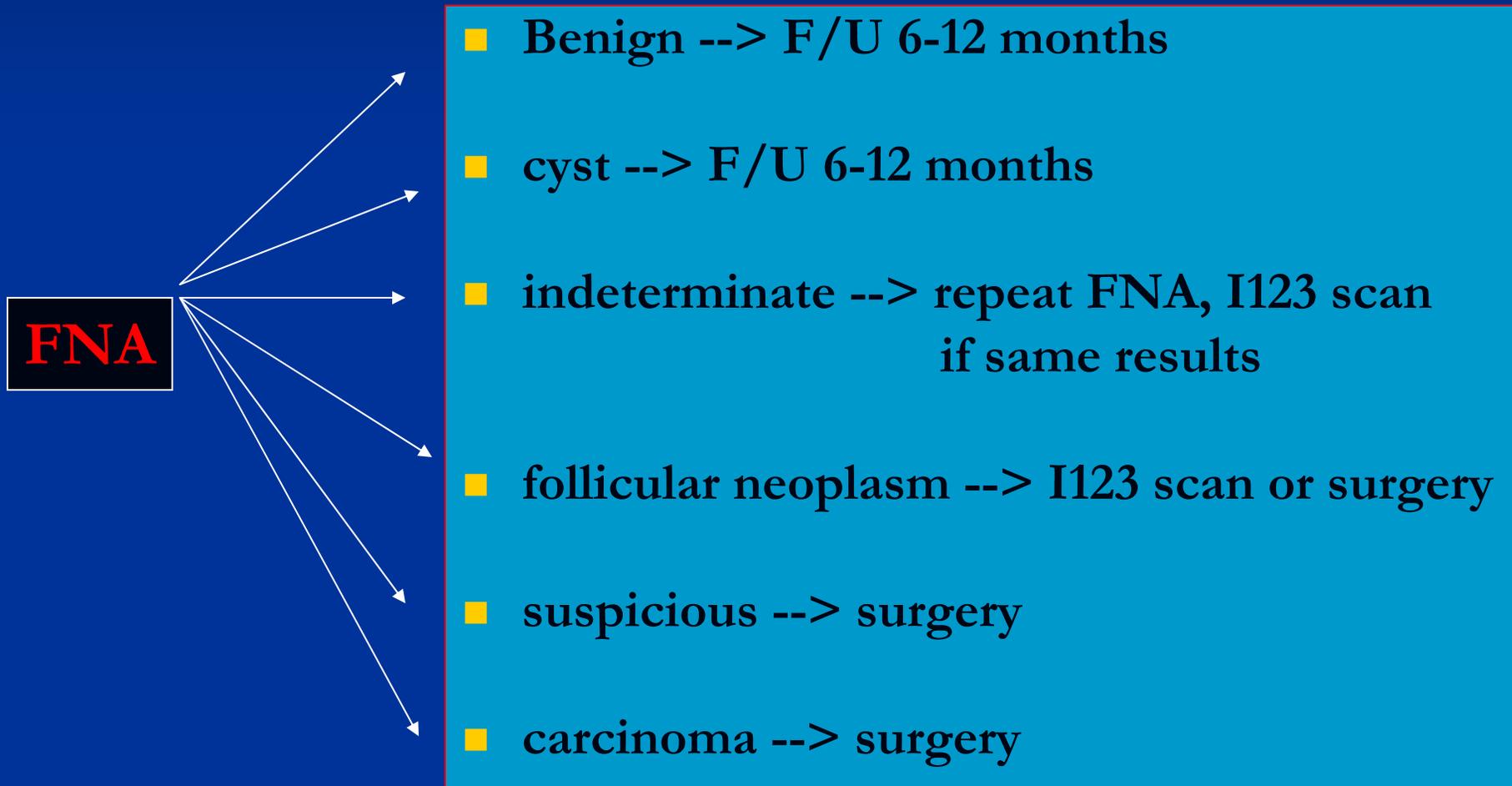


Fine Needle Aspiration

- Procedure of Choice – Fast, minimally invasive and few risk
- Incidence of False positive: 1%
- Incidence of False negative: 5%
- FNA is not a tissue diagnosis
- Limitation of FNA: cannot distinguish a benign follicular from a malignant lesion.

FNA Results of Thyroid Nodule

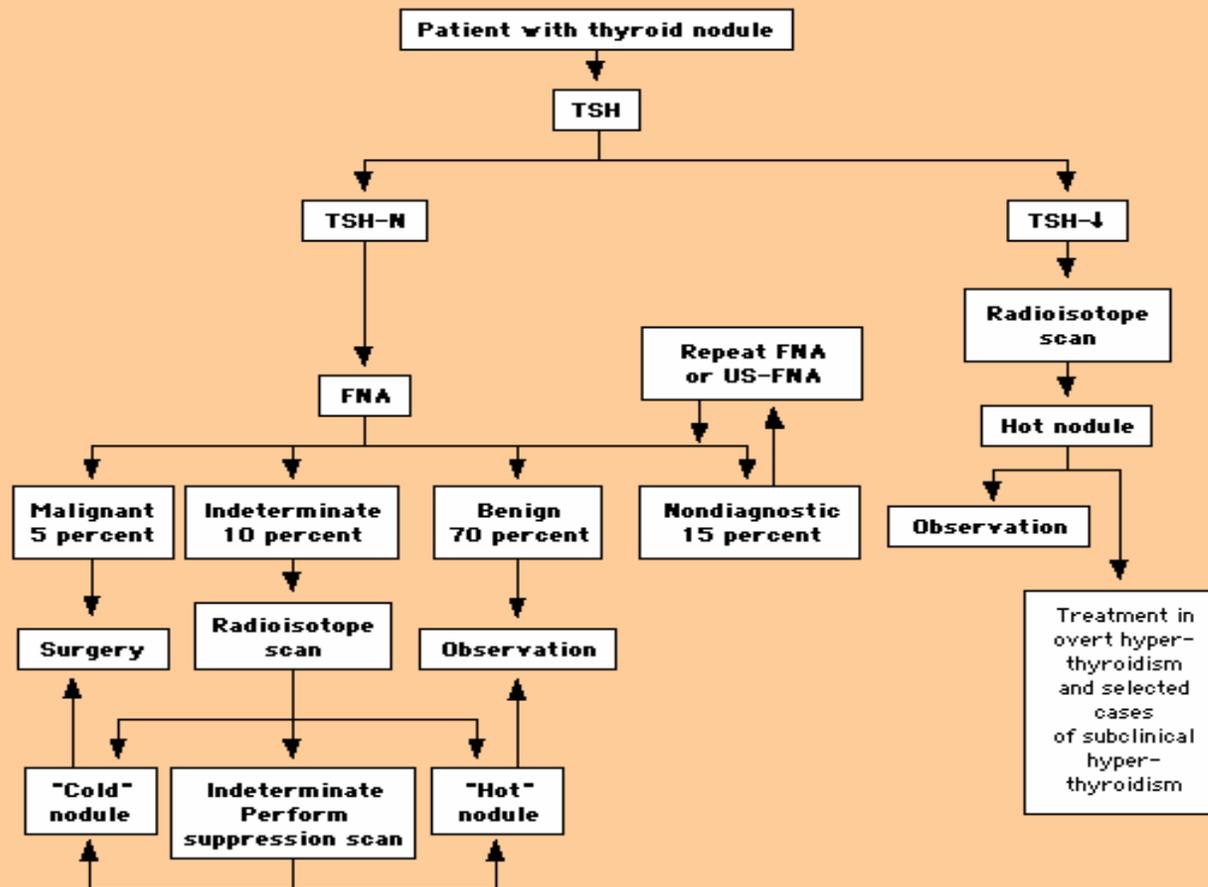
FNA



- Benign --> F/U 6-12 months
- cyst --> F/U 6-12 months
- indeterminate --> repeat FNA, I123 scan if same results
- follicular neoplasm --> I123 scan or surgery
- suspicious --> surgery
- carcinoma --> surgery

Management of Thyroid Nodule

Recommended Management of Thyroid Nodules†



FNA: Fine-needle aspiration; N: Normal; TSH: Thyroid-stimulating hormone (thyrotropin);
 US-FNA: Ultrasound-guided fine-needle aspiration.

† Modified from: Castro, MR, Gharib, H. Endocr Pract 2003; 9:128.

Classification and Incidence of Thyroid Cancer

Tumors of Follicular Cell Origin

■ Differentiated

| | |
|----------------|-----|
| ■ Papillary | 75% |
| ■ Follicular | 10% |
| ■ Hurthle Cell | 5% |

■ Undifferentiated

| | |
|--------------|----|
| ■ Anaplastic | 5% |
|--------------|----|

■ Tumors of Parafollicular

| | |
|-------------|----|
| ■ Medullary | 5% |
|-------------|----|

■ Other

| | |
|------------|-----|
| ■ Lymphoma | <1% |
|------------|-----|

STAGING FOR DIFFERENTIATED THYROID CANCER

- In differentiated thyroid carcinoma, several classification and staging systems have been introduced. However, no clear consensus has emerged favoring any one method over another
- **AMES system/AGES System/GAMES system**
- **TNM system**
- **MACIS system**
- **University of Chicago system**
- **Ohio State University system**
- **National Thyroid Cancer Treatment Cooperative Study (NTCTCS)**

PROGNOSIS

■ Prognostic schemes:

AMES (Lahey Clinic, Burlington, MA)

GAMES (Memorial Sloan-Kettering Cancer Center, NY)

AGES (Mayo Clinic, Rochester, MN)

■ GAMES scoring (PAPILLARY & FOLLICULAR CANCER)

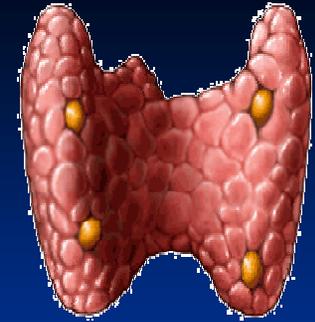
- **G** Grade
- **A** Age of patient when tumor discovered
- **M** Metastases of the tumor (other than Neck LN)
- **E** Extent of primary tumor
- **S** Size of tumor (>5 cm)

The patient is then placed into a high or low risk category

Prognostic Risk Classification for Patients with Well-Differentiated Thyroid Cancer (GAMES)

| | Low Risk | High Risk |
|--------|--|--|
| Age | <40 | >40 |
| Sex | Female | Male |
| Extent | No local extension, intrathyroidal, no capsular invasion | Capsular invasion, extrathyroidal extension |
| Mets | None | Regional or Distant |
| Grade | Well Differentiated | Poorly Differentiated |

TNM system



- Classification system in which age at diagnosis is considered a component of stage designation
- The TNM system (updated by the AJCC in 2002) is based primarily on pathologic findings and separates patients into four stages, with progressively poorer survival with increasing stage

TNM Staging

TNM Classification System for Differentiated Thyroid Carcinoma[†]

Definition

| | |
|-----|--|
| T1 | Tumor diameter <2 cm |
| T2 | Primary tumor diameter 2–4 cm |
| T3 | Primary tumor diameter >4 cm limited to the thyroid or with minimal extrathyroid extension |
| T4a | Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve |
| T4b | Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels |
| TX | Primary tumor size unknown, but without extrathyroidal invasion |
| | |
| N0 | No metastatic nodes |
| N1a | Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes |
| N1b | Metastasis to unilateral, bilateral, contralateral cervical or superior mediastinal node metastases |
| NX | Nodes not assessed at surgery |
| | |
| M0 | No distant metastases |
| M1 | Distant metastases |
| MX | Distant metastases not assessed |

Stages

| | Patient age <45 years | Patient age 45 years or older |
|-----------|-----------------------|--|
| Stage I | Any T, any N, M0 | T1, N0, M0 |
| Stage II | Any T, any N, M1 | T2, N0, M0 |
| Stage III | | T3, N0, M0 T1, N1a, M0 T2, N1a, M0 T3, N1a, M0 |
| Stage IVA | | T4a, N0, M0 T4a, N1a, M0 T1, N1b, M0 T2, N1b, M0 T3, N1b, M0 T4a, N1b, M0 |
| Stage IVB | | T4b, Any N, M0 |
| Stage IVC | | Any T, Any N, M1 |

[†] Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York, Inc.

- **University of Chicago system** — An easy-to-remember staging system for papillary carcinoma is the Clinical Class scheme proposed by De Groot and colleagues at the University of Chicago :

Class I — disease limited to the thyroid gland

Class II — lymph node involvement

Class III — extrathyroidal invasion

Class IV — distant metastases.

National Thyroid Cancer Treatment Cooperative Study (NTCTCS)

- The NTCTCS created a staging approach that was applied prospectively to a registry of patients drawn from 14 cooperating institutions . Clinical-pathologic staging was based upon:
 - patient age at diagnosis
 - tumor histology
 - tumor size
 - intrathyroidal multifocality
 - extraglandular invasion
 - metastases
 - tumor differentiation

MAICS Scoring

- Developed by the Mayo Clinic for staging.
- It is known to be the most accurate predictor of a patient's outcome with papillary thyroid cancer

(M = Metastasis, A = Age, I = Invasion, C = Completeness of Resection, S = Size)

| MAICS Score | | 20 year Survival |
|-------------|---|------------------|
| <6 | = | 99% |
| 6-7 | = | 89% |
| 7-8 | = | 56% |
| >8 | = | 24% |

Pathology of Thyroid Cancer

- **Differentiated thyroid cancer (DTC):**
 - Papillary - commonly spreads to nodes (40-50%), excellent prognosis
 - Follicular - slightly worse than papillary, can spread to bone, less to nodes (15%); Hurthle cell Ca is variant
- **Medullary** - sporadic vs. familial (MEN 2A)
 - total thyroidectomy is treatment
- **Anaplastic** - aggressive and fatal
 - surgical role is biopsy only

Prognosis

- Both Papillary and Follicular Cancer have good prognosis:
20 year survival rate are 90% and 70%

- Most important prognostic factor is age

- Bad Prognostic factor:
 - Tall Cell, Columnar
 - Large Tumors > 4cm
 - Extension beyond gland
 - Metastatic disease

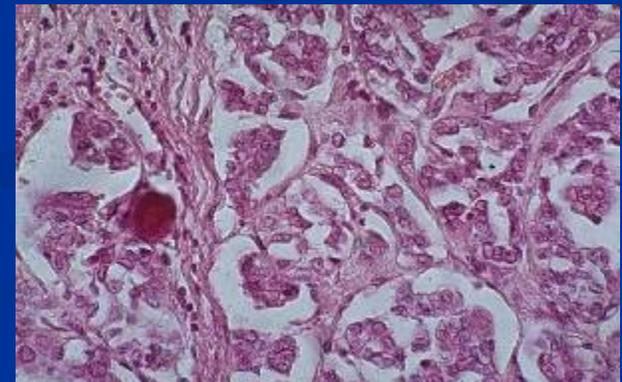
Papillary Cancer

- The most common malignant thyroid tumor.
- Accounts for 70-80% of all cancers
- Consists of Papillary, Follicular, Tall-cell, Columnar Cell and Diffuse sclerosing
- Women 2x > Men
- Age Presentation 38-45
- Accounts for 90% of radiation induced thyroid cancer



Papillary Cancer

- Histologic: Psammoma bodies, intranuclear grooves and cytoplasmic inclusions
- Multicentric: 30-50%
- Spread via Lymphatics- propensity for cervical node involvement
- Invasion of adjacent structures and distant mets uncommon



FOLLICULAR THYROID CANCER

- 15-20% Of Thyroid Cancers
- “Well Differentiated”
- Usually Encapsulated
- More Common Among Older Patients
- Female > Male
- More Aggressive & Less Curable Than Papillary
- Hematologic Spread
- 60% 10 Year Survival
- Types: Overtly Vs Minimally Invasive
Hurthle Cell

Hürthle Cell Neoplasms

- More aggressive than other differentiated thyroid carcinomas (higher mets/lower survival rates)
- Decreased affinity for I^{131}
- Need to differentiate from benign/malignant
- 65% of tumors > 4cm are malignant
- If malignant, needs total thyroidectomy and I^{131} with thyroglobulin assays
- Mets may be more sensitive to I^{131} than primary

Anaplastic cancer

- Undifferentiated
- Rapidly growing, often inoperable
- Invade locally, metastasize both locally and distantly
- Mean survival 6 months
- 5 year survival rate 7%

Lymphoma

- Rare, rapidly enlarging tumour
- Primary or secondary
- Seventh decade, 6:1 F/M ratio
- 5 year survival rate 75-80%, when confined to thyroid

Treatment

- The main treatment of papillary carcinoma of the thyroid is surgical resection.
- For lesions <1 cm, there is general agreement in the literature that **lobectomy plus isthmectomy** is the appropriate treatment.
- For adults with lesions larger than 2 cm, a **total thyroidectomy** is favored by most surgeons.
- Patients with history of exposure to ionizing radiation of the head and neck should have total thyroidectomy

Controversies in Treatment Total VS Lobectomy

- Controversy exists about the use of total thyroidectomy versus lobectomy and isthmectomy in adults with a 1- to 2-cm lesions
- Role of Lymph node dissection also debated

Rationale for Total Thyroidectomy for DTC

- Bilateral cancers are common (30-85%)
- improved effectiveness for I131 ablation
- lowers dose needed for I131 ablation
- allows f/u with thyroglobulin levels
- decreased recurrence in all groups
- improved survival in high risk pts.
- Decreased risk of pulmonary mets

Rationale for Lobectomy for DTC

- Most patients are low risk and excellent prognosis
- Role of adjuvant treatment not defined
- ↑ Complications of Total
- Occult multicentric tumor not clinically significant
- Most local recurrences → treated with surgery
- Excellent outcome with lobectomy in low risk patients

Central Lymph Node Dissection:

- Central compartment = the region bounded by the jugular veins, the hyoid bone, and the sternal notch
- All central nodes removed at time of procedure
- Removal of Central Nodes important in medullary and Hurthle Cell Ca
 - Microscopic spread is high
 - Do not take up I131 and cannot be ablated

Lateral Lymph Node Dissection

- Diseased nodes lateral to the jugular vein = modified radical neck dissection
- Removal of LN's anterior and posterolateral to the internal jugular vein from the mastoid to the subclavian vessels inferiorly and laterally to spinal accessory nerve (Level 2-5)
- Sparing the internal jugular vein, spinal accessory nerve, and sternocleidomastoid muscle

Treatment of Thyroid Cancer

- **Papillary cancer**

- < 1 cm

Lobectomy & isthmusectomy

- >2cm

Total thyroidectomy

- **Follicular cancer**

Total thyroidectomy

- **Hurthle**

Total thyroidectomy

- **Medullary**

Total thyroidectomy & central neck dissection

Recurrences

- Recurrence detected by exam,  serum thyroglobulin levels, or ^{131}I Total Body Scan
- Most recurrences occur within the first five years after initial treatment
- Local recurrence versus Distant
- The most common site of distant metastasis is the lung

Complications of Surgery

- Hypocalcemia -devascularization of parathyroid
 - about 5%, which resolves in 80% of these cases in about 12 months
- Recurrent Laryngeal Nerve Injury
either traction induced or division.
 - less than 3%
- Bleeding
 - wound hematomas



Postoperative management for thyroid cancer

Two principles:

- Radioiodine remnant ablation

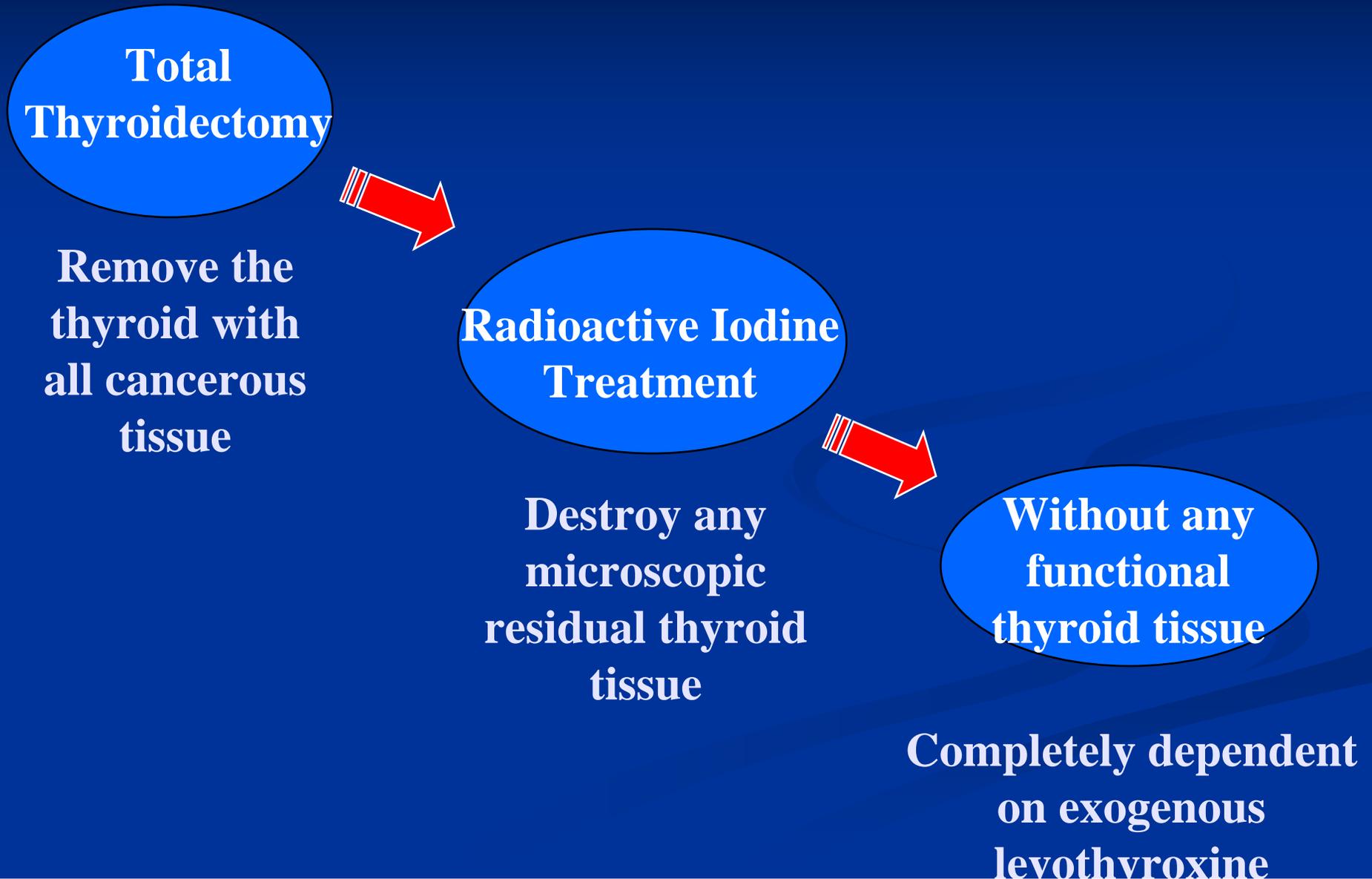
- Administration of Thyroid Hormone-
 - To suppress TSH and growth of any residual thyroid
 - To maintain patient euthyroid
 - Maintain TSH level 0.1uU/ml in low risk pts
 - Maintain TSH Level < 0.1uU/ml in high risk pts

Postoperative RAI

■ Recommendations:

- postoperative remnant ablation for all patients with differentiated thyroid carcinoma 45 years of age or older
- those with primary tumor 1.5 cm in diameter or more
- extrathyroidal disease, whether manifested by direct invasion through the capsule of the gland or local or regional metastases.

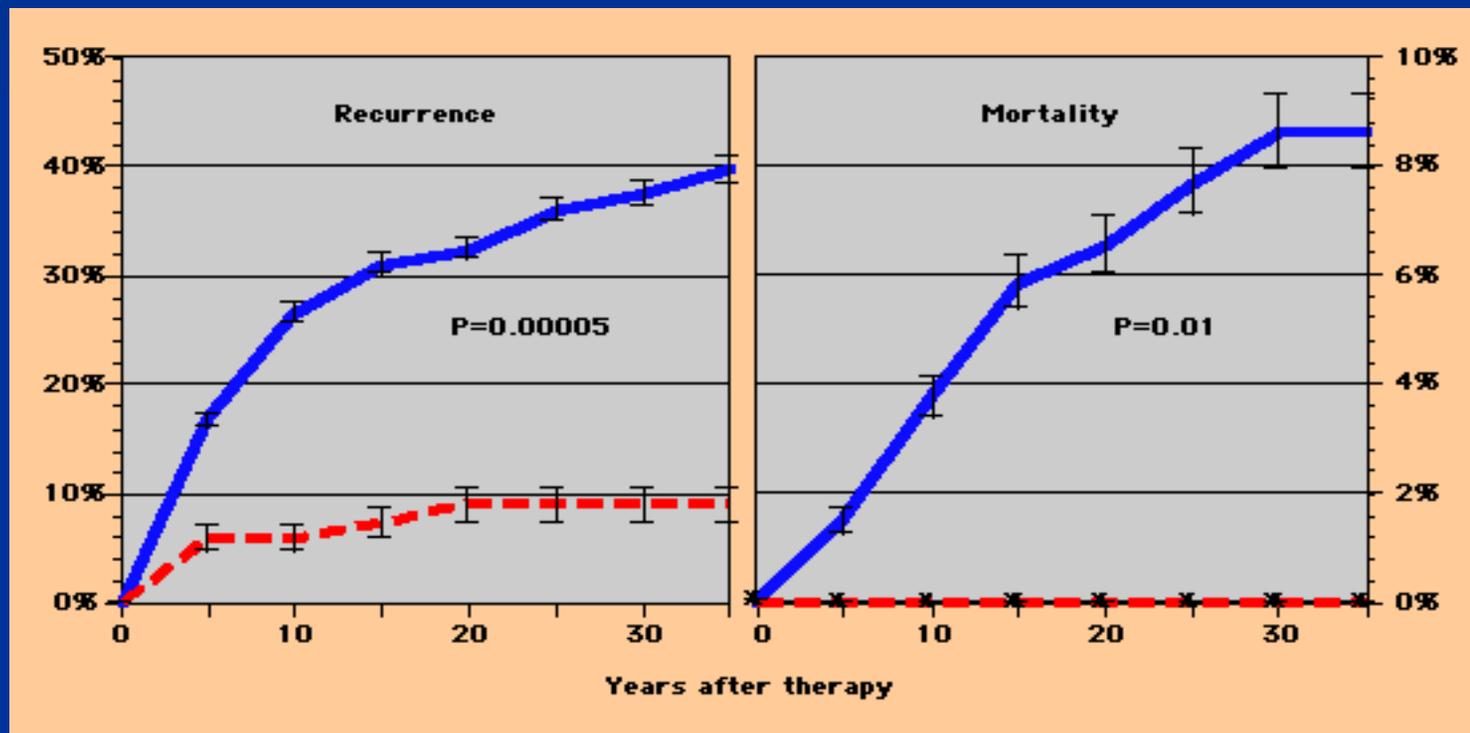
Standard Initial Treatment



Radioiodine therapy

- The nonsurgical treatment for papillary thyroid carcinoma is radioiodine (^{131}I).
- Radioiodine has three uses in the postoperative treatment of patients with thyroid cancer:
 - ablation of residual thyroid tissue
 - imaging for possible recurrent disease
 - treatment of residual or recurrent thyroid cancer

Radioiodine ablation reduces recurrence and mortality in stage II and Stage III thyroid cancer



Radioiodine ablation reduces recurrence and mortality in stage II and stage III thyroid cancer Long-term development of recurrent disease (left panel) or death (right panel) from thyroid cancer in patients without distant metastases at presentation, who received either ^{131}I ablation (red dashed lines) or no ablation (blue solid lines). (Data from Mazzaferri, EL, Jhiang, SM, Am J Med 1994; 97:418.)

External Beam Radiotherapy and Chemotherapy

- External Radiation required to control unresectable cancer.
- Chemotherapy may occasionally be beneficial in patients with progressive symptomatic thyroid carcinoma that is unresponsive or not amenable to surgery, radioiodine therapy, or external radiotherapy.

Chernobyl



On April 26, 1986 at 1.23 a.m. the world's worst nuclear disaster took place at the Chernobyl nuclear power station in northern Ukraine

Chernobyl: History

- 190 tons of highly radioactive uranium and graphite were expelled into the atmosphere
- Radioactive material was carried by the wind and rain into large areas of Belarus, Russia, and Ukraine.
- The result was an international ecological, medical, and economic calamity.

Chernobyl



- Over 70% of the radiation fell on the people of Belarus. They have been exposed to radioactivity **90 times** greater than that released by the Hiroshima bomb – the highest known exposure to radiation in the history of the atomic age.

Radiation effects on Thyroid Gland

- Thyroid cancer has been clearly linked to external ionizing radiation exposure
- Susceptibility to radiation-induced thyroid cancer is related to sex- higher in women and inversely related to age at exposure.
- Exposing the thyroid to radiation from internal sources (therapeutic doses of ^{131}I) has not been associated with thyroid cancer

Radiation-induced genetic mutations

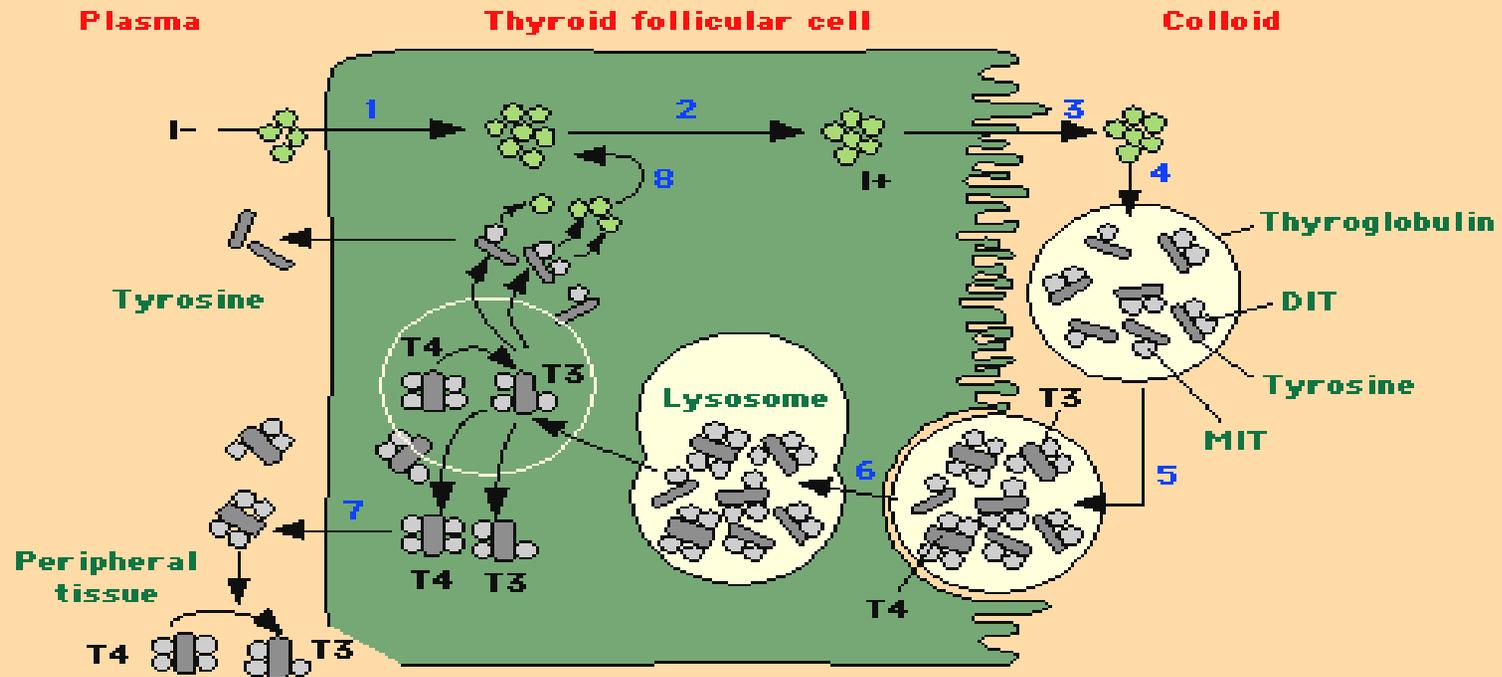
- Rearrangements of the tyrosine kinase domain of the RET proto-oncogene
- A high frequency of RET/PTC3- type rearrangement
- The biological and clinical significance RET activation remains controversial

Heterogeneity in the distribution of *RET/PTC* rearrangements within individual post-Chernobyl papillary thyroid carcinomas. *J Clin Endocrinol Metab* 89:4272–4279

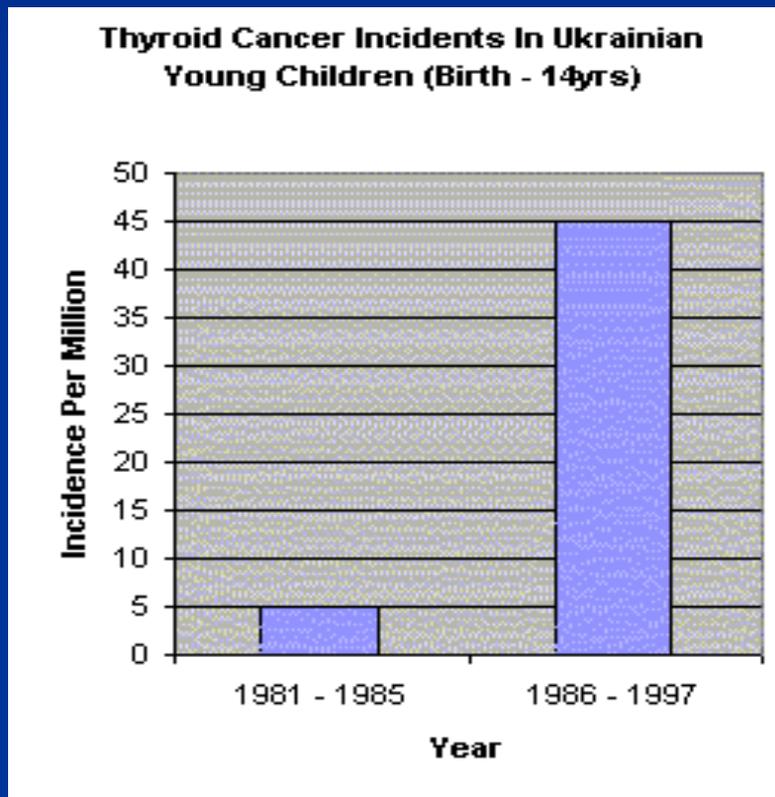
Chernobyl: Thyroid cancer

- The main consequence of the Chernobyl accident is thyroid cancer in children
- Children in southern Belarus and Ukraine, were exposed by milk from cows and leafy vegetables that had been contaminated with radioactive iodine.
- These children were also relatively more vulnerable because their usual diet, in general, was low in iodine.

- Since the thyroid gland concentrates iodine, it is highly susceptible to radiation damage from any intake of radioactive isotopes of iodine.



Incidence of Thyroid Cancer post-Chernobyl



- **Increase In Thyroid Cancer.** Between 1981 - 1985, the five years preceding the accident, the average thyroid cancer rate was **4-6 incidents** per million Ukrainian young children (birth to 15 years). However between 1986 - 1997 this rose to **45 incidents** per million

One Surgeon's 20 Year Experience

Dr. Alfonso

1985-2005

of Thyroidectomies: 1000

of Cancers: 310

30% Thyroid Cancer

Histologic Type:

| | | |
|----------------------|-------|-----|
| ■ Papillary Cancer | (238) | 79% |
| ■ Follicular Cancer | (25) | 9 % |
| ■ Hurthle Cell Tumor | (26) | 8% |
| ■ Medullary Cancer | (8) | 3% |
| ■ Anaplastic | (3) | 1% |

| | | |
|---------------------------|-------|-----|
| ■ Women: | (245) | 81% |
| ■ Men: | (55) | 19% |
| ■ Recurrences: | (24) | 8% |
| ■ Hx of radiation: | (32) | 10% |

Complications

- Temporary Hypocalcemia $8/300 = 2\%$
- Permanent Hypocalcemia $1/300 = .06\%$
- Nerve Palsy 0%
- Bleeding 0%

History of Previous Radiation

- Patients with hx radiation: 35 patients
- Radiation from Chernobyl: 27 patients
- $\frac{1}{2}$ of Chernobyl patients have bilateral disease

Recurrences

- Total # of Recurrences = 23
- Lymph node = 13
- Other Lobe = 9
- Liver = 1

Papillary Cancer:

An Unusual Distant Metastasis

Case Presentation

- HX:

Pt is a 29 year old native American Indian who presented with diffuse progressive neck enlargement. The patient attributed his enlarging neck to weight lifting.

- Pt denies any history of any previous radiation

- PMHX: Denies

PSHX: Denies

Case Presentation

- Family HX: None

- Physical:

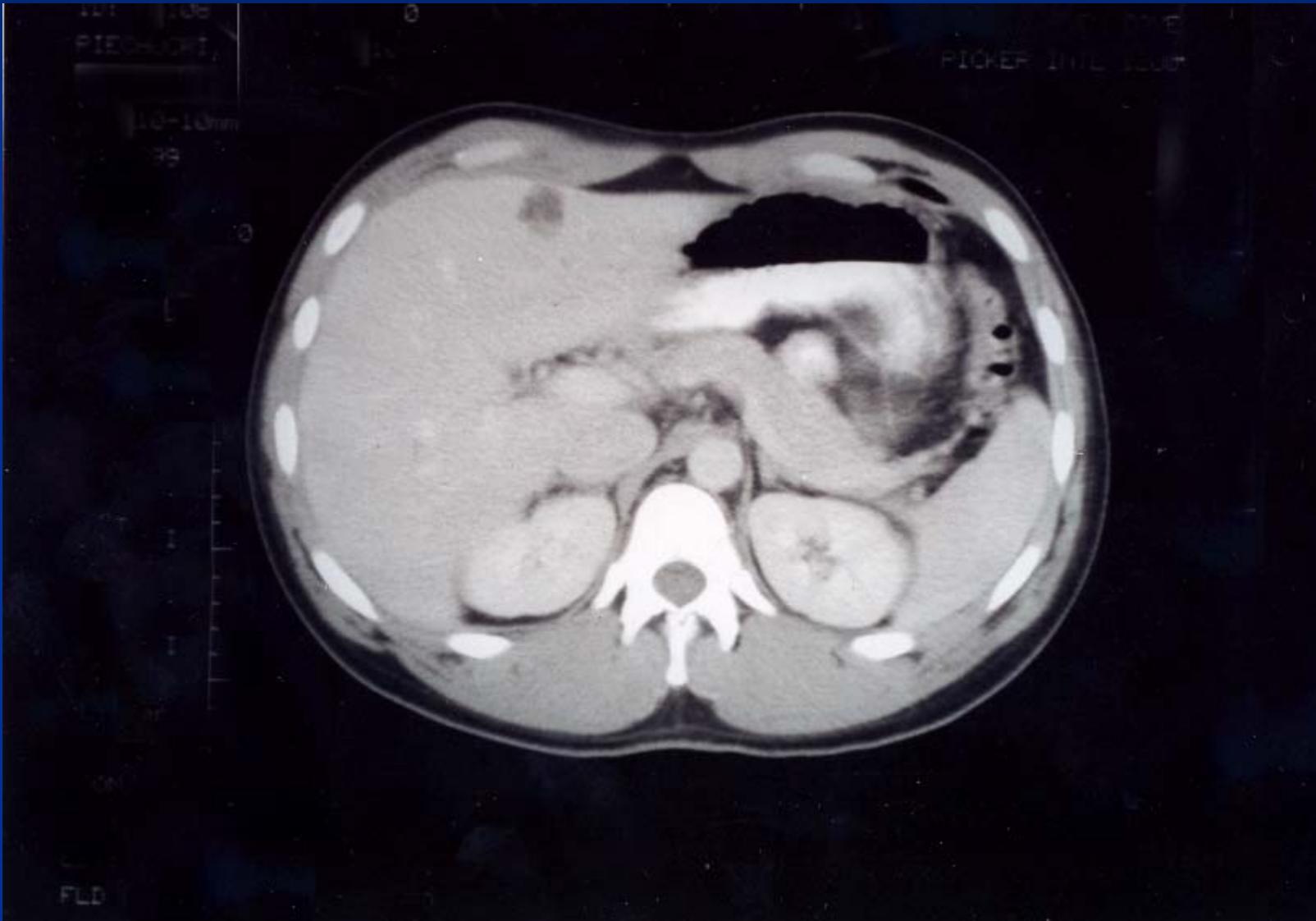
A palpable 2 cm nodule in Left Lobe of Thyroid
No lymph nodes palpable secondary to musculature

- FNA: Papillary Carcinoma

Postoperative Course

- Postoperative management:
 - Pt underwent radioiodine ablation
 - Maintained euthyroid
- Six months later:
 - Underwent ^{131}I Whole Body Scan
 - Showed uptake in liver
- Ct Scan of Abd/Pelvis:

CT Scan Abd/Pelvis



Treatment

- Ablation with I^{131} was attempted
- Two months later a follow-up Total Body Scan showed persistent activity of the Left Lobe of the Liver
- Repeated attempts unsuccessful

- Operative Course

- Resection of segment IV

- Margins negative

- Pathology: Colloid filled cyst filled with throglobulin

- Follow-up

- Pt disease free for 5 years

- Married with 2 children