INTEGRATED ACADEMIC STUDIES OF MEDICINE

IASM

FACULTY OF MEDICAL SCIENCES

Therapy of thyroid cancer

Epidemiology

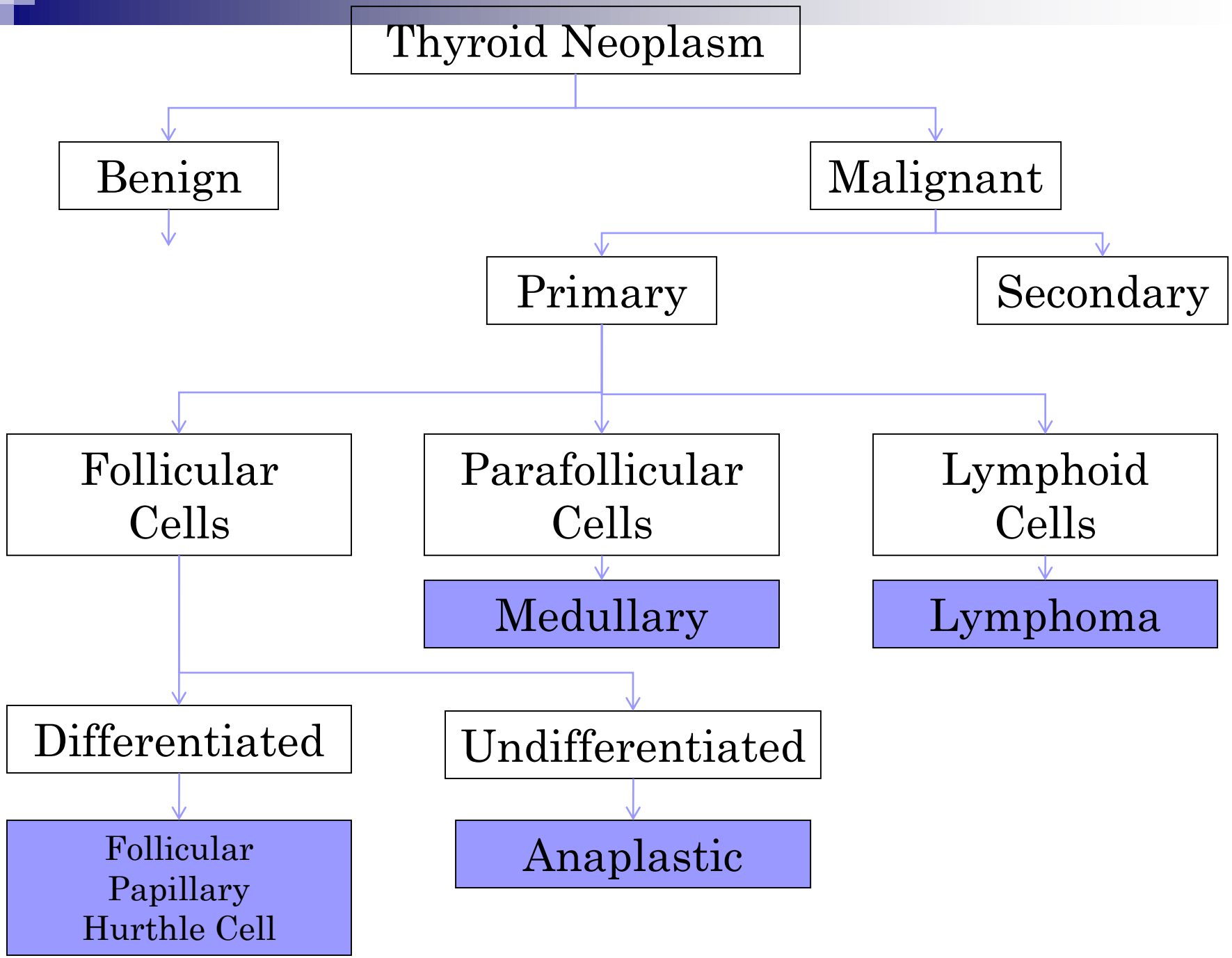
- Commonest endocrine malignancy
  - 1% of all malignancies
  - 0.5-1 per 100000
- Good prognosis
- Extent of treatment is hotly debated
  - No randomized trials
- Annual Incidence is 3.7 per 100,000
- Sex Ratio is 3:1 (Female:Male)
- Can occur at any age group

Causes and Risk Factors

- Genetics:
  - Abnormal *RET* oncogene may cause MTC.
  - MEN 2A, 2B Syndrome.
- Family History:
  - Hx of goiters increase risk for Papillary Ca.
  - Gardner's Syndrome and FAP increase risk for Papillary Ca.
- Radiation Exposure:
  - Radiation therapy to Head or Neck.
  - Exposure to Radioactive Iodine during childhood, or other radioactive substances (Chernobyl) ↑ risk for particularly Papillary carcinoma.

Causes and Risk Factors

- Chronic Iodine deficiency ↑ risk for Follicular carcinoma.
- Gender:
  - Female > Males.
- Age:
  - More common at young adults.
  - MTC usually diagnosed after 60.
- Race:
  - White race > Black race.


Thyroid Neoplasm
Benign
Malignant
Primary
Secondary
Follicular Cells
Parafollicular Cells
Lymphoid Cells
Medullary
Lymphoma
Differentiated
Undifferentiated
Follicular
Papillary
Hurthle Cell
Anaplastic

Presentation

- Solitary or Multiple thyroid nodules
- Neck Nodes
- Hoarse voice of recent onset
- Mediastinal adenopathy
- Bone or lung metastasis

Important History

- Radiation to neck / chest
- MEN syndrome
  - Family history
  - Diarrhoea
  - Adrenal tumour
- Recent change in a pre-existing goitre
  - Size change/nodularity
  - Vocal cord palsy

Evaluation

- Thyroid profile
- Serum Thyroglobulin
- Serum Calcitonin
- Thyroid scan
  - Hot/warm/**cold nodule 20% malignant**
- Serum Ca^{++}

Diagnosis

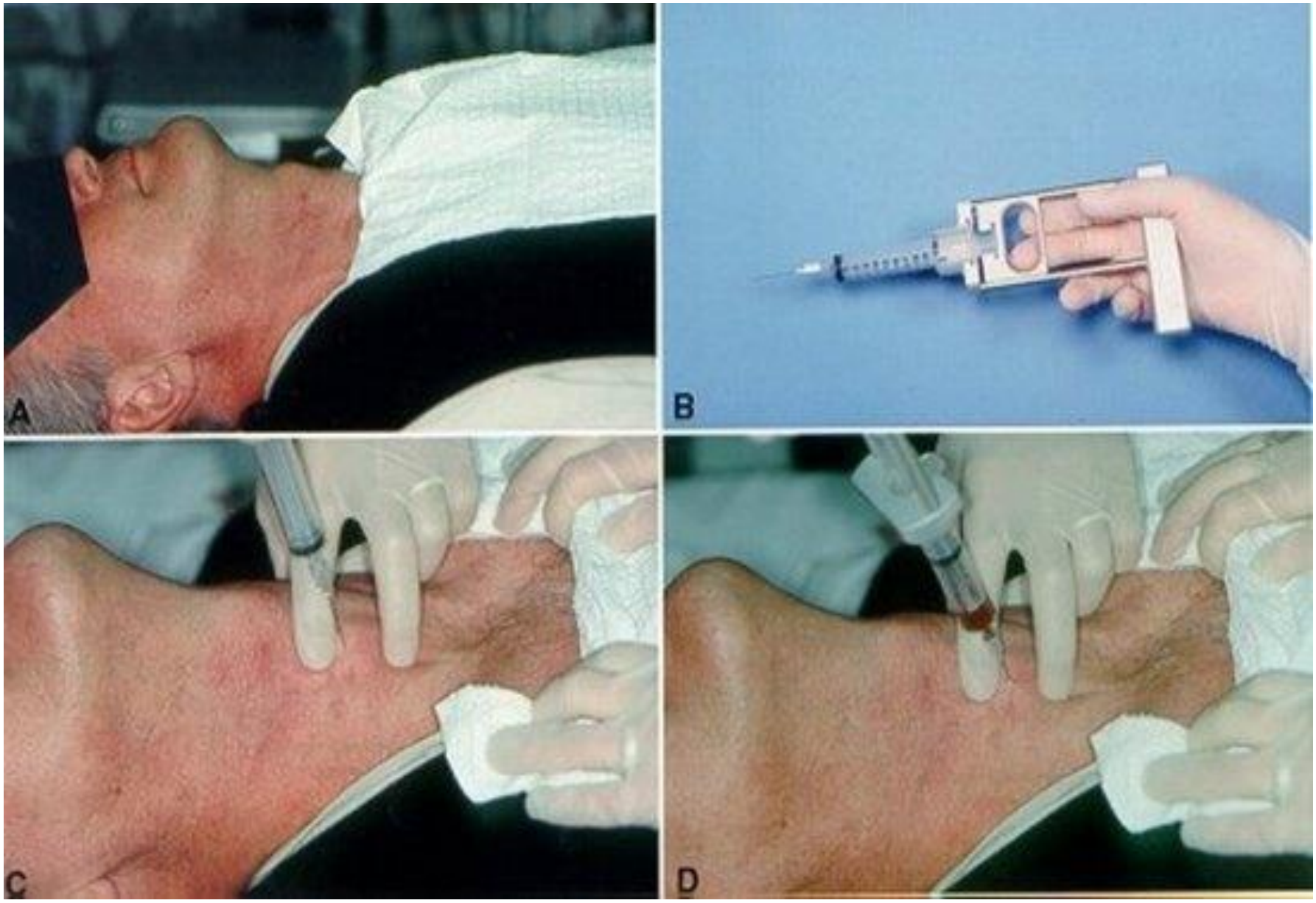
- Imaging
  - U/S
  - C.T
  - MRI
  - Scintigraphy
- Laboratory:
  - TSH
  - T3, T4
  - Serum Thyroglobulin
  - Serum Thyroid Antibodies
  - FNA

Laboratory

- Most patients are Euthyroid.
- Hyperfunctioning nodule → 1% chance of malignancy.
- Serum Tg cannot differentiate between benign and Malignant nodules
- Tg is used for:
  - F/U after total thyroidectomy
  - Serial F/U for non-operative treatment
- Serum Calcitonin → patients with MTC, or with family hx of MTC (MEN2)

FNA Cytology

- Single most important test.
- U/S guidance improve the sensitivity.
- Accuracy ranges from 70 – 95%.
- Nodules
- FNAC cannot differentiate between Benign and Malignant Follicular Neoplasia


A
B
C
D

Imaging

- U/S is the investigation of choice.
- C.T → Regional and distant metastases
- MRI → Limited role in the diagnosis

  Useful in detecting cervical LN metastases
- Scintigraphy (I-123)
  - Characterizing funtioning nodules
  - Staging of follicular and papillary Ca

2. Ultrasonography

- Solid vs cystic
- Can help in USG guided FNAC
- Evaluation of recurrent thyroid cancer in the thyroid bed and in regional lymph nodes

  features s/o malignancy.

  - Hypoechogenicity
  - Micro calcification
  - Thick, irregular or absent halo
  - Irregular margins
  - Invasive growth
  - regional lymphadenopathy, and
  - higher intranodular flow

Prognostic Indicators

- AGES score:
  - *A*ge
  - Hisological *G*rade
  - *E*xtrathyroidal invasion
  - *M*etastasis
- MACIS score (post-operative):
  - Distant *M*etastasis
  - *A*ge
  - *C*ompleteness of original surgical resection
  - Extrathyroidal *I*nvasion
  - *S*ize of original lesion

Table 53.10 TNM staging of thyroid cancer

Tumour

TX	Primary cannot be assessed
T0	No evidence of primary
T1	Limited to thyroid, 1 cm or less
T2	Limited to thyroid, > 1 cm but < 4 cm
T3	Limited to thyroid, > 4 cm
T4	Extending beyond capsule, any size

Nodes

NX	Cannot be assessed
N0	No regional node metastases
N1	Regional node metastases

Metastases

MX	Cannot be assessed
M0	No metastases
M1	Metastases present

Stage	Under 45 years	Over 45 years
I	Any T, any N, M0	T1, N0, M0
II	Any T, any N, M1	T2, N0, M0 or T3, N0, M0
III		T4, N0, M0 or any T, N1, M0
IV		Any T, any N, M1

Note the effect of age on stage; only patients older than 45 years can have stage III or IV disease.

Table 53.9 Differentiated thyroid carcinoma: risk group definitions

Low-risk group

Men of 40 years and younger, women of 50 years and younger, without distant metastases

All older patients with intrathyroid papillary carcinoma or follicular carcinoma with minor capsular involvement with tumours < 5 cm in diameter, no distant metastases

High-risk group

All patients with distant metastases

All older patients with extrathyroid papillary carcinoma or follicular carcinoma with major capsular involvement with tumours 5 cm in diameter or larger, regardless of extent of disease

Management

- Medical
  - Radioactive Iodine ablation therapy.
  - Chemotherapy (Adriamycin, Cisplatin).
  - Post-operative Thyroid hormone.
    - Replacement therapy.
    - Suppression of TSH release. (↓ recurrence)
- Surgical
    - Treatment of choice.
    - Extent of resection is still controversial.

Thyroid Surgeries

- Relates to the management of contralateral lobe.

- Types
  - Ipsilateral lobectomy
  - Subtotal Thyroidectomy
  - Near-total Thyroidectomy
  - Total Thyroidectomy

Papillary Carcinoma

- Most common Thyroid carcinoma (80%)
- Related to radiation exposure in I-sufficient areas.
- Female:male ratio is 2:1
- Mean age of presentation is 30 to 40 yrs.
- Slow growing painless mass. Euthyroid-status.
- LN metastases is common, may be the presenting symptom (Lateral Aberrant

Papillary Carcinoma

- FNA biopsy is diagnostic.
- Treatment
  - Ipsilateral Lobectomy + Isthmusectomy (No LN metastasis)
  - Near-total or Total Thyroidectomy + Modified-radical or Functional neck dissection (+ve LN metastasis).
  - Prophylactic LN dissection is unnecessary.

Follicular Carcinoma

- Account for 10% of all thyroid cancers.
- More common in I-deficient areas.
- Female:male ratio is 3:1
- Mean age at presentation is 50 yrs.
- Solitary thyroid nodule, rapid increase in size and long-standing goiter.
- Cervical LN metastasis is uncommon at presentation (5%), distant metastasis may be present.

Follicular Carcinoma

- FNA biopsy cannot differentiate between benign and malignant follicular tumors.
  - Pre-operative diagnosis of malignancy is difficult unless there is distant metastasis.
  - Large follicular tumor > 4 cm in old individual → CA.

- Treatment:
  - Thyroid Lobectomy (at least 80% are benign adenomas)
  - Total-Thyroidectomy in older individual with tumor > 4cm (50% chance of malignancy).

Table 53.8 Major differences between papillary and follicular carcinoma (after Cady)

	Papillary (%)	Follicular (%)
Male incidence	22	35
Lymph node metastases	35	13
Blood vessel invasion	40	60
Recurrence rate	19	29
Overall mortality rate	11	24
Location of recurrent carcinoma		
Distant metastases	45	75
Nodal metastases	34	12
Local recurrence	20	12

Post-operative Management

- Thyroid hormone
  - Replacement therapy
  - Suppression of TSH release
    - At 0.1 µU/L in Low-risk group
    - < 0.1 µU/L in High-risk group

- Thyroglobulin measurement
  - At 6-months interval then annually when disease-free
  - < 2ng/mL in total or near-total + Hormones
  - < 5ng/mL in hypothyroid patients.

Post-operative Management

- Radioiodine Therapy:
  - Controversial (No prospective RCTs).
  - Long-term cohort studies by Mazzaferri and Jhiang and DeGroot:
    - Small improvement in survival rate and less recurrence when RAI is used, even with Low-risk group.
  - RAI is less sensitive than Tg in detecting metastatic disease.
  - I-131 detect and treat 75% of metastatic differentiated thyroid tumors.

Medullary Carcinoma

- 5% of all thyroid malignancies.
- Arise from Parafollicular cells, concentrated in superolateral aspect of thyroid lobes.
- Most cases are sporadic, 25% are inherited (Germline mutation in *RET* oncogene).
- Female:Male ratio is 1.5:1
- Most patients present between 50 and 60 yrs.

Medullary Carcinoma

- MTC secrets a range of compounds:
  - Calcitonin, CEA, CGRP, PG A_2 and $F_{2\alpha}$, Seritonin.
  - May develop flushing and diarrhoea, Cushing's syndome (ectopic ACTH).
- Diagnosis
  - Hx and P/E (Family hx of similar tumors).
  - ↑ Serum Calcitonin, ↑ CEA
  - FNAC
- Screen patient for:
  - *RET* point mutation.

Syndrome	Manifestations
MEN2A	MTC, pheochromocytoma, primary hyperparathyroidism, lichen planus, amyloidosis
MEN2B	MTC, pheochromocytoma, marfanoid habitus, mucocutaneous ganglioneuromatosis
Familial MTC	MTC
MEN2A and Hirschsprung's disease	MTC, pheochromocytoma, primary hyperparathyroidism, Hirschsprung's disease

Medullary Carcinoma

- Treatment:
  - > 50% are bilateral, ↑ Multicentricity.
  - Total Thyroidectomy + :
    - Bilateral central node dissection as routine (No LN involvement)
    - Bilateral Modified-Radical Neck dissection (palpable LN)
    - Ipsilateral Prophylactic nodal dissection in tumor size > 1.5cm.
  - External Beam radiation for unresectable residual or recurrent tumor.
  - No effective Chemotherapy.

Medullary Carcinoma

- Prophylactic Thyroidectomy in *RET* mutation detection
  - Before age of 6 yrs for MEN2A
  - Before age of 1 yr for MEN2B

Anaplastic Carcinoma

- 1% of all thyroid malignancies.
- Women > Men.
- Majority present at 7^{th} - 8^{th} decade of life.
- Long-standing neck mass, rapidly enlarging in size.
- May be painful, with dyphonia, dyspnea, dysphagia.
- LN are usually involved at presentation.

Anaplastic Carcinoma

- FNAC is diagnostic.
- Treatment:
  - Most aggressive thyroid tumor.
  - Total Thyroidectomy if resectable.
  - Adjuvant Chemotherapy + Radiotherapy slightly improve long-term survival.

Other Types

- Thyroid Lymphoma:
  - 1% of all Thyroid Ca.
  - Most are Non-Hodgkin B-cell Lymphoma.
  - Underlying chronic lymphocytic thyroiditis.
  - FNAC is
- Hurthle-Cell Carcinoma:
  - 3% of all Thyroid Ca.
  - Subtype of Follicular Ca.
  - More multicenteric and bilateral (30%).
  - FNAC is not conclusive.
  - Lobectomy +

Prognosis

Tumor	Prognosis
Papillary Ca.	74-93% long-term survival rate
Follicular Ca.	43-94% long-term survival rate
Hurthle Cell Ca.	20% mortality rate at 10 years
Medullary Ca.	80% 10-year survival rate 45% with LN involvement
Anaplastic Tumor	Median survival of 4 to 5 months at time of diagnosis

Clinical presentation

- Palpable nodule (including self palpation)
- Rapidly progressive nodule
- Local compression including voice changes
- Neck lymph nodes
- Incidentaloma (CT-scan, PET-scan, carotid US,…)
- Incidentaloma at surgery for benign disease
- Rarely metastases as first presentation
- Rare familial cases (screening)
- Treatment: total thyroidectomy & 131I in some cases

MANAGEMENT OF THYROID CANCER

Thyroid cancer – Diagnosis (Surgeon/Endocrinologist, U/S and pathologist)

Total or near total thyroidectomy (Surgeon)

Post op whole body scan (Nuclear Medicine)

Na I-131 treatment (Nuclear Medicine)

7-10 days post therapy scan(Nuclear Medicine)

Na I-131 Whole body scan for follow up

FDG PET/CT (Nuclear Medicine)

Thyroxine suppressive therapy (Endocrinologist)

Thyroglobulin (Endocrinologist/Surgeon)

Ultrasound (Endocrinologist/Surgeon)

TKI and other MKI (Med Onc)

NEED FOR RAI ABLATION

Post total / near-total Thyroidectomy:

- Ablation of functional residual thyroid tissue (without an explicit
- commitment to specific benign or malignant target)
- Ablation of gross or microscopic residual disease
- Ablation of neck nodal disease (gross or microscopic)
- Ablation of distant metastatic disease
- Remnant Thyroid Ablation:
- Eliminate Tg & facilitate follow-up
- Potential reduction of recurrence risk

In general:
Remnant Thyroid Ablation: 75 - 100 mCi*
Positive lymph nodes: 125 - 150 mCi*
Metastases to lungs, bones: 175 - 200 mCi
Recurrent disease: consider >200 mCi with dosimetry
*: Consider risk stratification based on histopathology
➢ More aggressive histologic sub-types: poorly differentiated, tall cell, Hurthle cell, hobnail, insular, columnar and diffuse sclerosing variants
➢ Vascular Invasion
➢ Extrathyroidal extension
➢ No. & size of nodal involvement
➢ Mutational status (BRAF via ThyroSeq… done on FNA at Emory)
Consider steroids for uptake >5% on pre-Rx I-123 scan
If uptake on diagnostic scan is >10%, consider 30 mCi ablation first and reschedule full therapy 3-6 months later or consider surgical consult for reoperation.

Questions to be answered

- The incidence of DTC has been tripled over the last 40 yr
- The mortality rate remains unchanged
- Most patients have limited disease
- Maybe we overtreat some patients, maybe not…
- Radiation protection issues (eg. secondary cancer) are raised and relevant

Pathological classification of DTC
Staging (AJCC 7th edition)

Pathological classification of DTC Staging (AJCC 7th edition)

Additional ‘Staging’ information

- More aggressive sub-types
- Vascular and lymphatic invasion
- Number of LN in N+ patients
- Extracapsular spread in LN
- Size of LN invasion in affected LN
- BRAF V600E mutation and other genetic abnormalities
- Age and potential risk factors

Risk Stratification of DTC

Need for radioiodine treatment (ATA 2009)

TABLE 5. MAJOR FACTORS IMPACTING DECISION MAKING IN RADIOIODINE REMNANT ABLATION

		Expected benefit				
Factors	*Description*	*Decreased risk of death*	*Decreased risk of recurrence*	*May facilitate initial staging and follow-up*	*RAI ablation usually recommended*	*Strength of evidence*
T1	1 cm or less, intrathyroidal or microscopic multifocal	No	No	Yes	No	E
	1–2 cm, intrathyroidal	No	Conflicting data[a]	Yes	Selective use[a]	I
T2	>2–4 cm, intrathyroidal	No	Conflicting data[a]	Yes	Selective use[a]	C
T3	>4 cm					
	<45 years old	No	Conflicting data[a]	Yes	Yes	B
	≥45 years old	Yes	Yes	Yes	Yes	B
	Any size, any age, minimal extrathyroidal extension	No	Inadequate data[a]	Yes	Selective use[a]	I
T4	Any size with gross extrathyroidal extension	Yes	Yes	Yes	Yes	B
Nx,N0	No metastatic nodes documented	No	No	Yes	No	I
N1	<45 years old	No	Conflicting data[a]	Yes	Selective use[a]	C
	>45 years old	Conflicting data	Conflicting data[a]	Yes	Selective use[a]	C
M1	Distant metastasis present	Yes	Yes	Yes	Yes	A

- Very low risk patients: T1<1cm, unifocal and intra-thyroid; and N0 (no capsular invasion, no previous irradiation, no unfavourable histology, [tall, columnar and sclerosing]): No benefits, no indication for I131
- High risk patients: T3-4, N1, M1, persistent disease: treatment with a high activity (3.7 GBq or more) following withdrawal until remission
- Low risk patients: the other patients: Benefits of I131 controversial.
- Ablation may be performed with a low/high activity and following rhTSH/withdrawal

Risk of Structural Disease Recurrence

(In patients without structurally identifiable disease after initial therapy)

High Risk (>20%)

pT4
M1-R1, R2
Inappropriate post-op Tg

Intermediate Risk (5%-20%)

pT3 N0 Nx
pT1-3, N1a-N1b
Aggressive histology or vascular invasion
RAI uptake outside the thyroid bed

Low Risk (<5%)

pT1-T2 N0/Nx
No aggressive histology, no vascular invasion

FTC, extensive vascular invasion (≈ 30-55%)
pT4a gross ETE (≈ 30-40%)
pN1 with extranodal extension, >3 LN involved (38%)
pN1, any LN > 3 cm (≈ 30%)
BRAF mutated, not intrathyroidal (≈ 10-40%)
PTC, vascular invasion (≈ 15-30%)
Clinical N1 (≈20%)
pN1, > 5 LN involved (≈20%)
BRAF mutated, intrathyroidal, < 4 cm (≈10%)
pT3 minor ETE (≈ 3-8%)
pN1, all LN < 0.2 cm (≈5%)
pN1, < 5 LN involved (≈5%)
Intrathyroidal 2-4 cm PTC (≈ 5%)
Multifocal PMC (≈ 4-6%)
pN1 with extranodal extension, ≤ 3 LN involved (2%)
Minimally invasive FTC (≈ 2-3%)
BRAF wild type, intrathyroidal, < 4 cm (≈ 1-2%)
BRAF mutated, intrathyroidal unifocal PMC (≈ 1-2%)
Intrathyroidal, encapsulated, FV-PTC (≈ 1-2%)
Unifocal PMC (≈ 1-2%)

General recommendations

- Treatment should be given shortly after surgery (<3mo)
- Usual activity: 100 mCi for ablation
- No evidence of usefulness of pre Th 131I imaging (stunning)
- Higher activities for residual disease, metastases
- Preparation with rh-TSH (2 im) or L-T4 withdrawal (4 weeks)
- Always followed by WBS and suppressive L-T4 (TSH < 0.1 for 12-24 mo, than < 1)
- Radiation protection issues

Radiation protection issues for the patient

- Well-balanced indications (justification)
- Prevention of acute side effects (deterministic)
- Local pain (swelling) – symptomatic R/
- Nausea – vomiting: Avoid absolutely! – R/ domperidone
- Sialadenitis: 5-10d, mainly females, dose-dependent
- Hematologic complications very rare
- Delayed side effects (mainly stochastic)
- Negligeable: leukemia for high doses, solid cancer unclear, earlier menopause even for low dose (1-2 yr), no effect on fertility and offspring, xerostomia, xerophtalmia, lung fibrosis

Radiation protection for the family, relatives and public

- External irradiation (gamma 364 keV)
- Contact restrictions (1m / 30'/d) for 100 mCi - separate bed rooms - refrain from sexual activity, no kiss, hugging OK - no unnecessary travel by car and public transport
- Distance x 2, dose /4!!!
- 2 days: adults, children > 6y
- 1w: children <6y, pregnant women, public and work places

What is a RAI refractory patient?*

- No RAI uptake
- Disproportionate RAI uptake by comparison with Tg
- No clinical/radiological response in spite of RAI uptake
- PET+/RAI- numerous lesions
- Risks of 131I Rx outweighs benefits (eg. lung fibrosis)

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THANK YOU FOR YOUR ATTENTION