بسم الله الرحمن الرحيم

((قَالوا سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم))

صدق الله العظيم

Thyroid Cancer

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Publications

Bio

Classes

Images

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Bio

Biography | *Curriculum Vitae*

M.D.
in Radiation Oncology

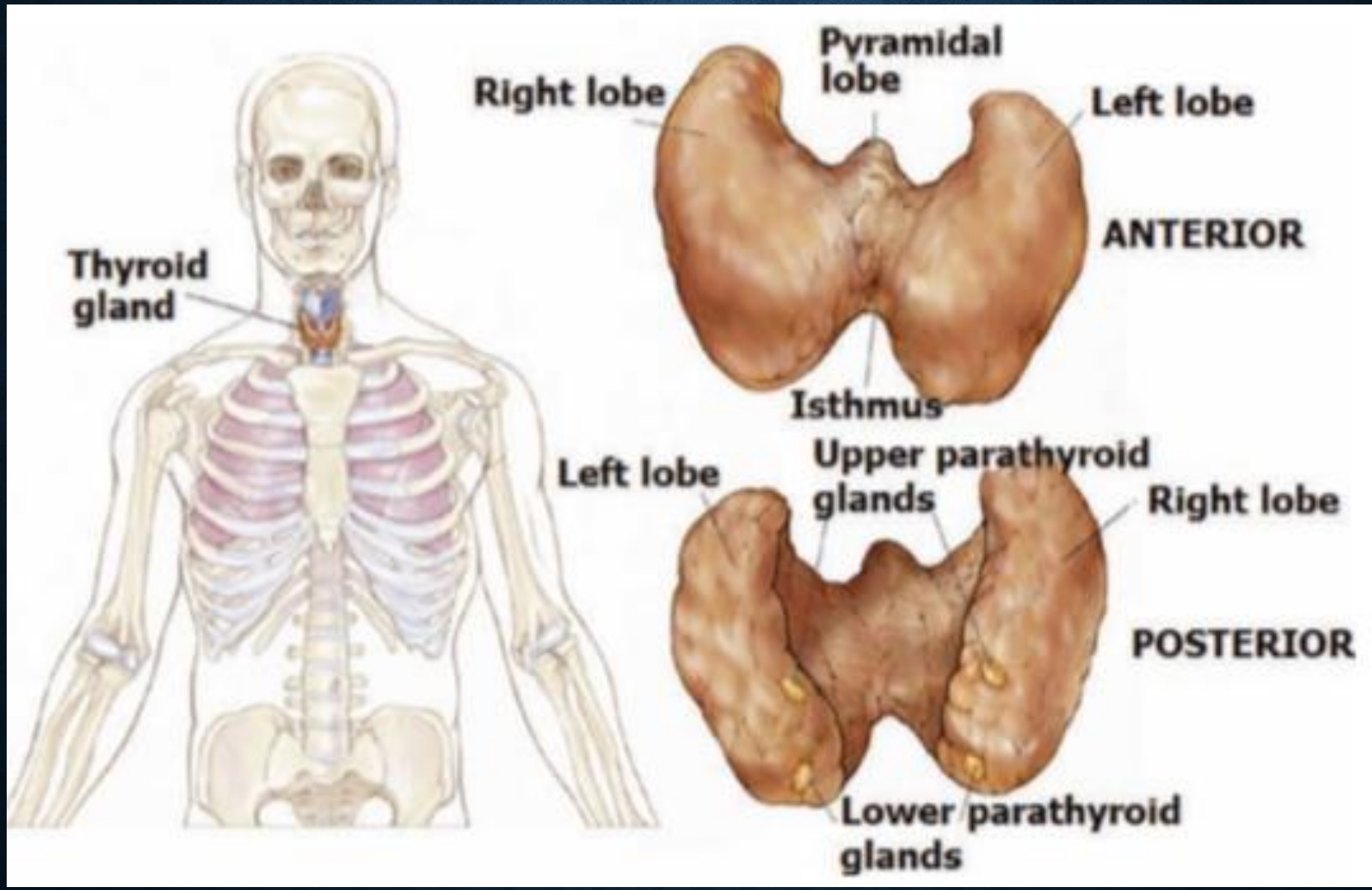
NCI, Cairo University,

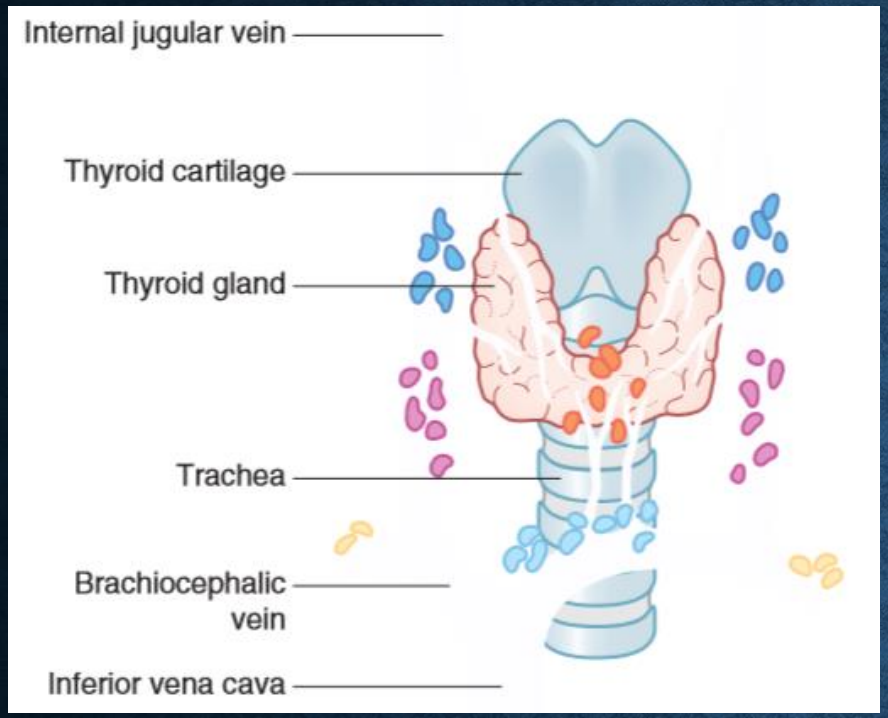
You Can Get This Presentation …. and… More

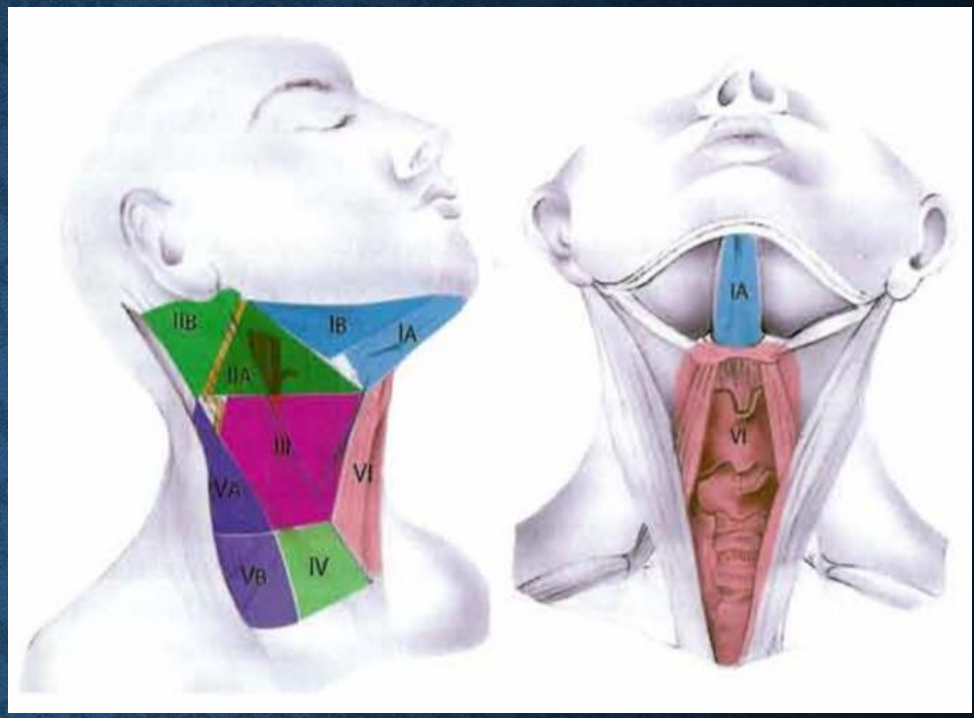
Anatomy

&

Physiology


Thyroid gland
Right lobe
Pyramidal lobe
Left lobe
ANTERIOR
Isthmus
Left lobe
Upper parathyroid glands
Right lobe
POSTERIOR
Lower parathyroid glands

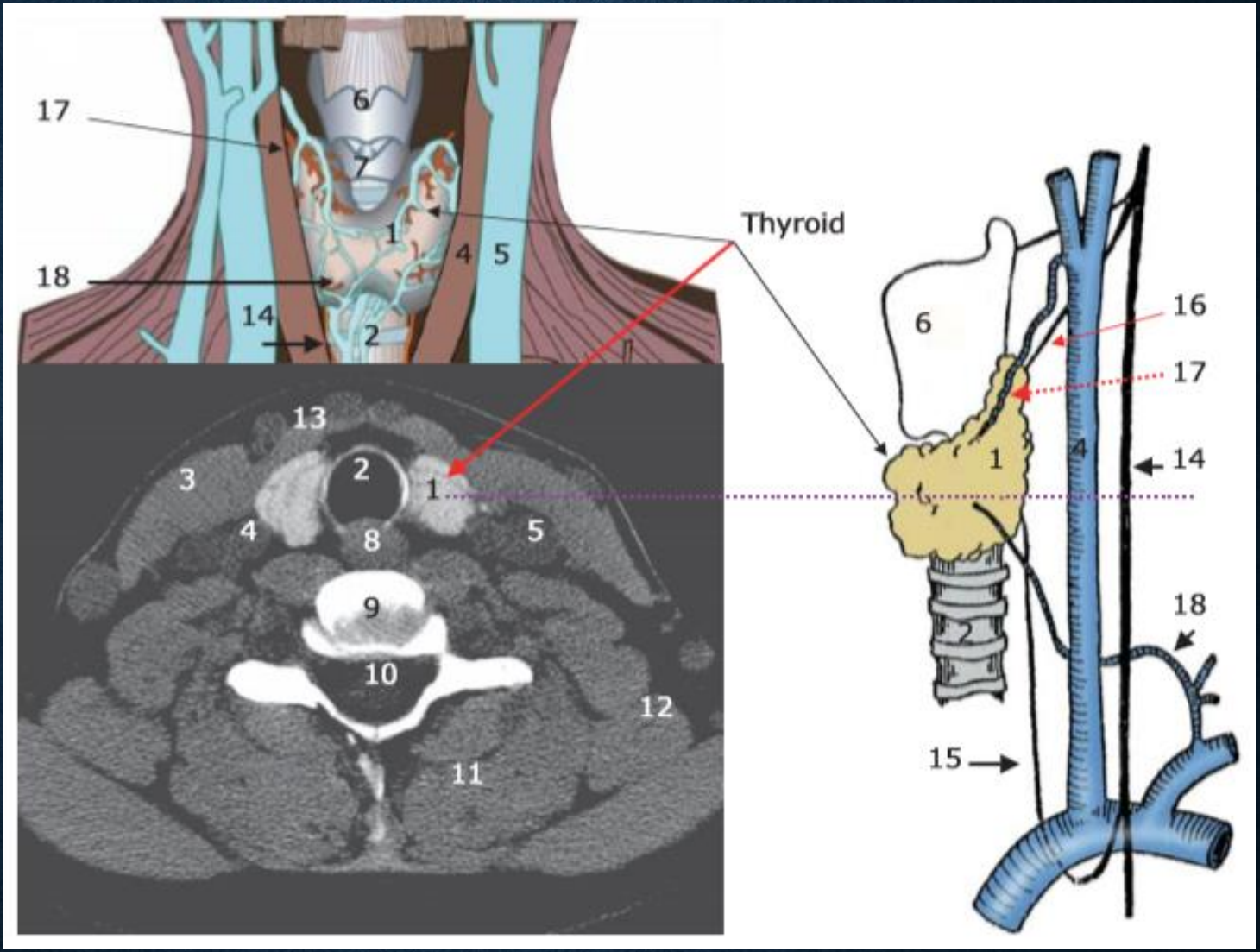




- Lymphatic drainage to level VI (extend from the hyoid to the suprasternal notch).
- Subsequent drainage to levels III–V and then to the SC nodes, or inferiorly to nodes in the tracheo-oesophageal groove or superior mediastinum (level VII and extends from the suprasternal notch to the brachiocephalic veins).

Close proximity of the external laryngeal nerve and the superior thyroidal artery.

Close proximity of the recurrent laryngeal nerve to the inferior aspect of the thyroid.



(1) thyroid gland (2) trachea (3) sternocleidomastoid muscles (4) common carotid artery (5) internal jugular vein (6) thyroid cartilage (7) Cricoid cartilage (8) esophagus (9) body of a cervical vertebra (10) the spinal canal and cord (11) erector spinae muscle 12) levator scapulae muscle (13) sternohyoid,sternothyroid muscles (14) vagus nerve (15) recurrent laryngeal nerve (16) external laryngeal nerve (17) superior thyroidal artery (18) inferior thyroidal artery.

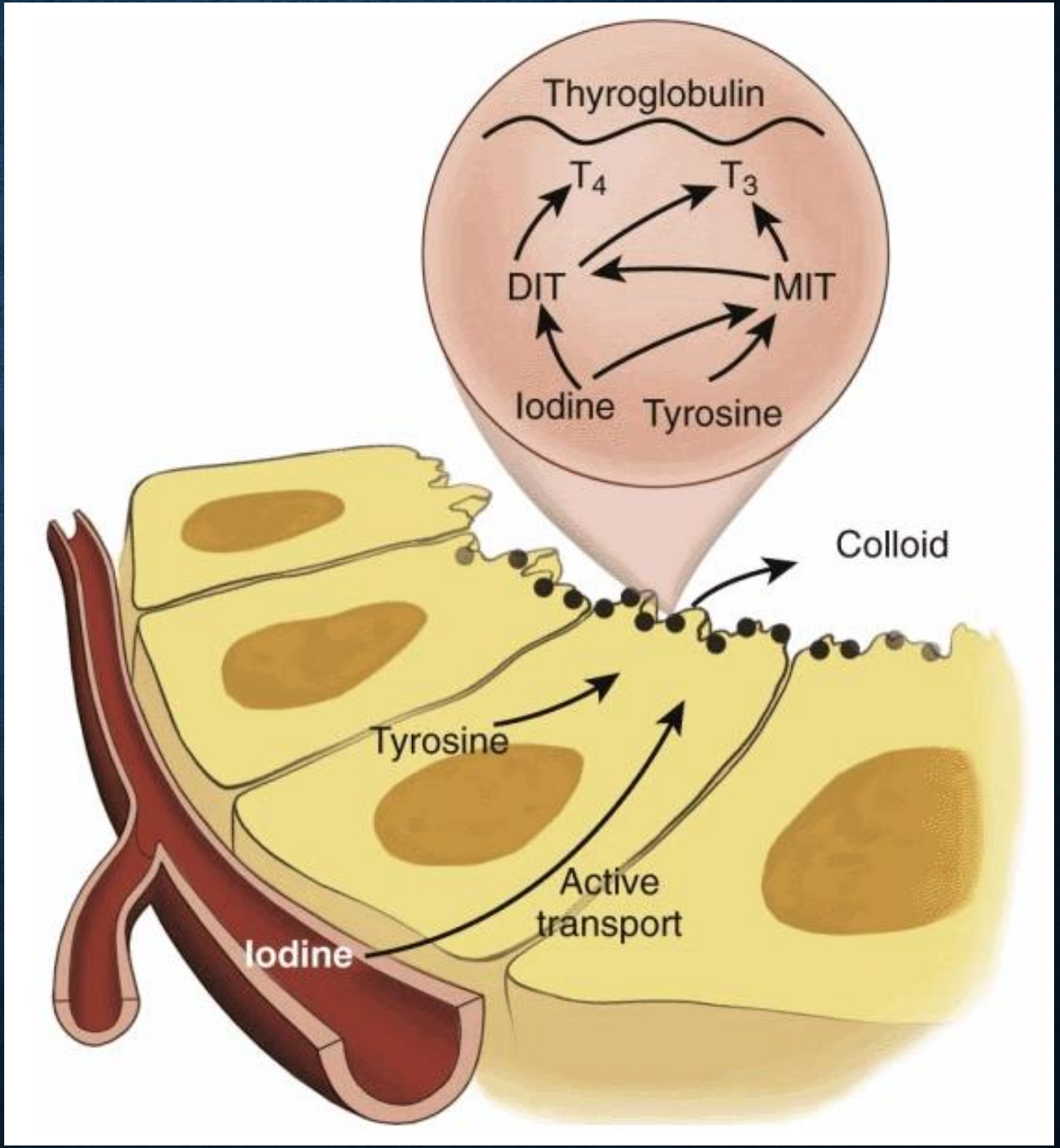
Thyroid hormone synthesis in the follicular cell, iodide uptake by active transport, with subsequent iodide oxidation, tyrosine oxidation, tyrosine oxidation, tyrosine iodination, and iodotyrosine coupling occurring in the apical membrane, catalyzed by thyroid peroxidase.

MIT Monoiodotyrosine

DIT Diiodotyrosine

T3 Triiodothyronine

T4 Thyroxine



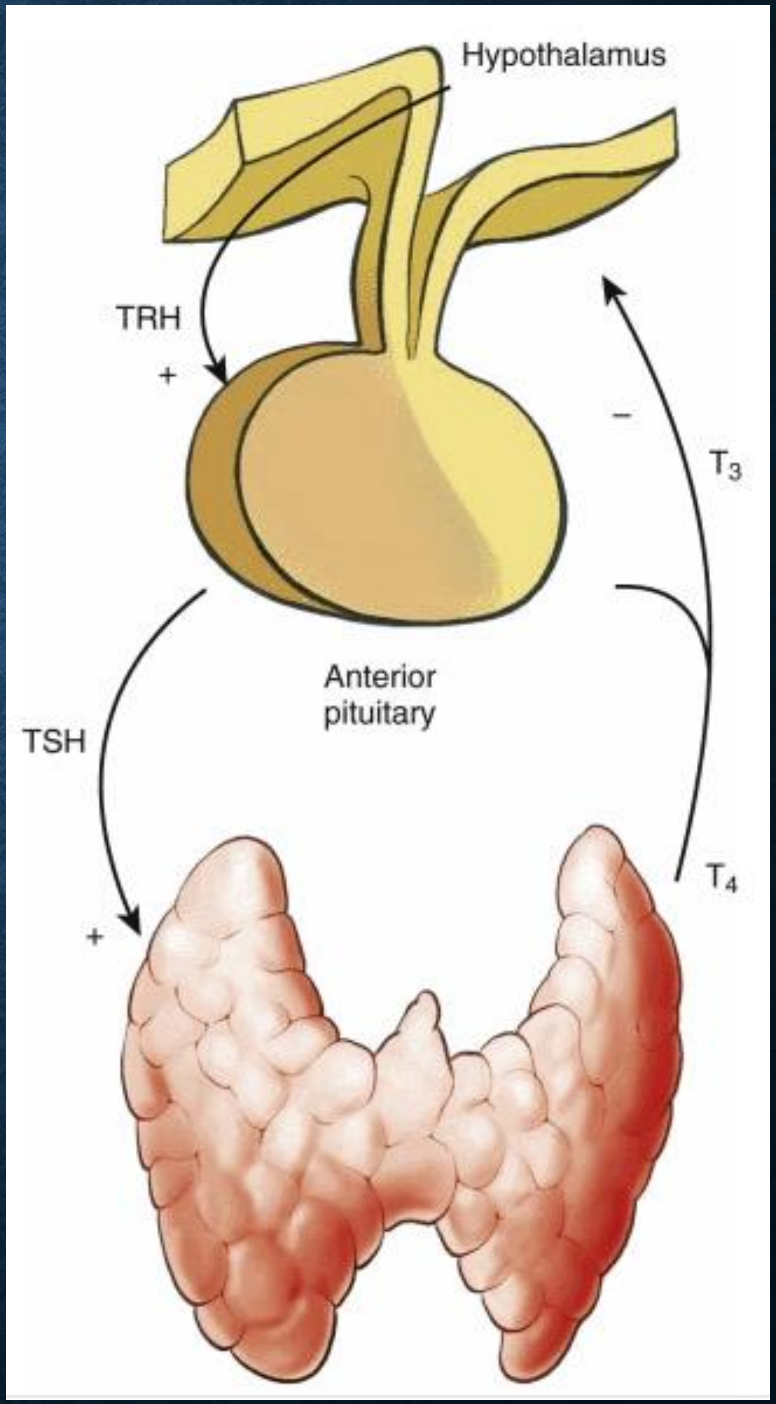
Negative-feedback regulation of thyroid hormone production in the hypothalamic-pituitary-thyroid axis.

TRH Thyrotropin-releasing hormone

TSH Thyroid stimulating hormone

T3 Triiodothyronine

T4 Thyroxine



Epidemiology

&

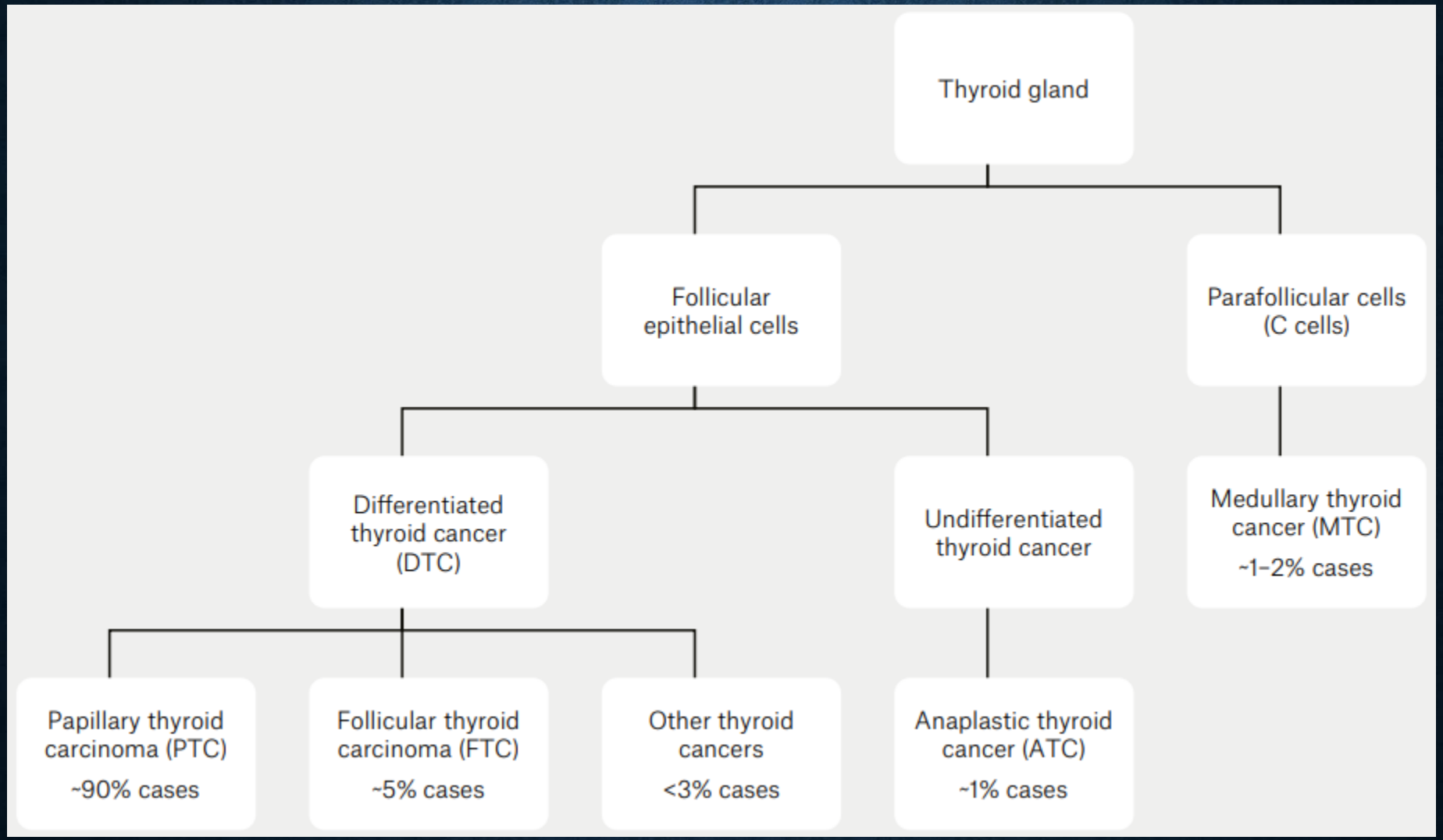
Etiology

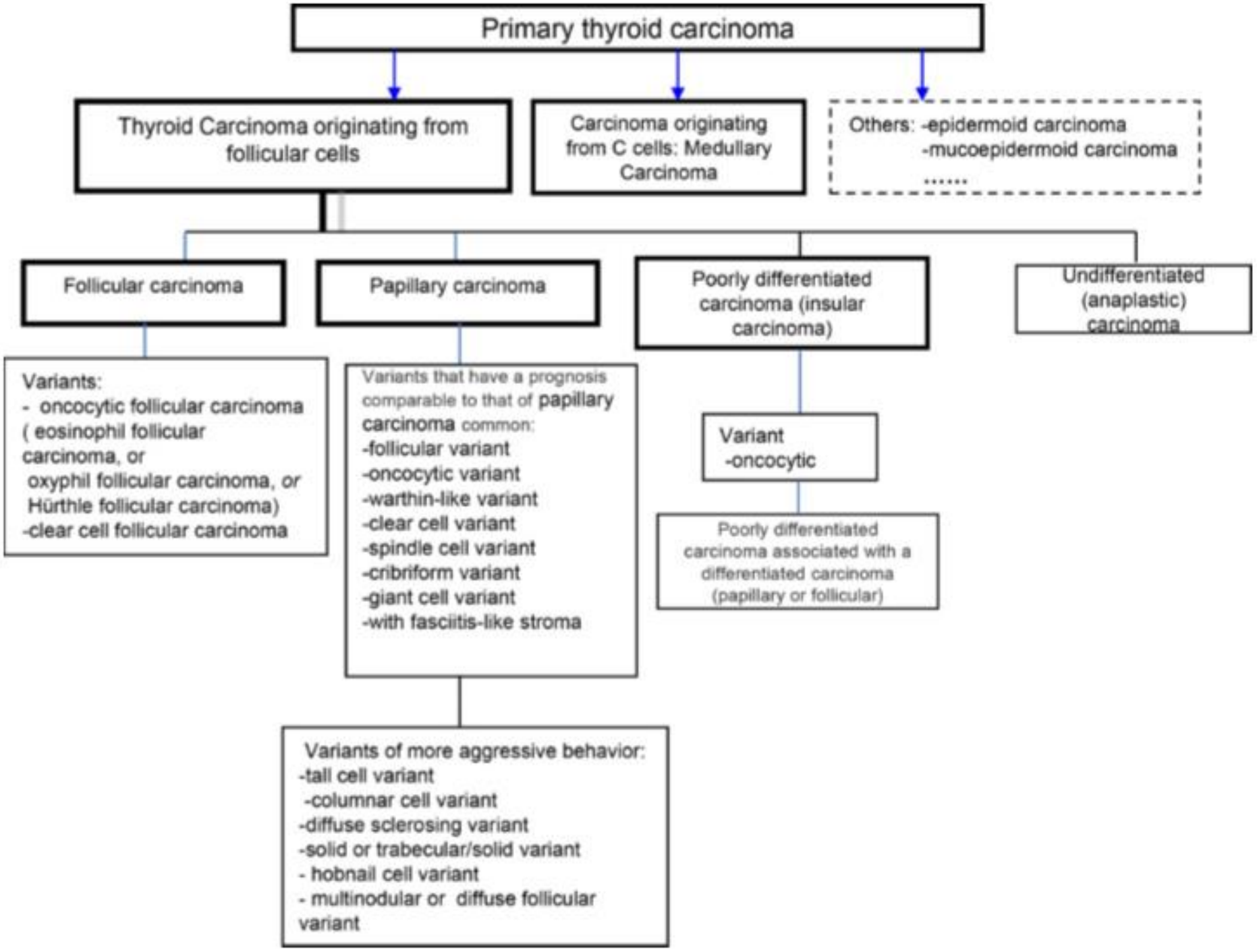
- Benign thyroid nodules are quite prevalent, found in 50% of the population.
- Thyroid malignancy is relatively uncommon, only 2% of human cancers.
- The most common endocrine neoplasms.
- Carcinomas are of follicular or parafollicular cell (C cell) origin, and 95% are well differentiated.

- Exposure to ionizing radiation is the most firmly established risk factor, particularly to the H&N region during childhood.
- Anaplastic (ATC) and follicular carcinoma (FTC) are relatively more common in areas endemic for goiter, and dietary iodine deficiency is responsible for the increased incidence rates in these areas.
- Role of female sex hormones as a risk factor still unresolved.

- Medullary thyroid carcinoma (MTC) is a rare malignant tumor originating from thyroid parafollicular C cells.
- 3-4% of thyroid neoplasias.
- MTC: sporadic (75%), or as part of MEN type 2 which includes:
  - FMTC (familial medullary thyroid carcinoma).
  - MEN 2A (75% of MEN 2): MTC, pheochromocytoma and hyperparathyroidism.
  - MEN 2B: MTC, pheochromocytoma, ganglioneuromatosis, and Marfanoid habitus.

Pathology


Thyroid gland
Follicular epithelial cells
Parafollicular cells (C cells)
Differentiated thyroid cancer (DTC)
Undifferentiated thyroid cancer
Medullary thyroid cancer (MTC)
~1–2% cases
Papillary thyroid carcinoma (PTC)
~90% cases
Follicular thyroid carcinoma (FTC)
~5% cases
Other thyroid cancers
<3% cases
Anaplastic thyroid cancer (ATC)
~1% cases


Primary thyroid carcinoma
Thyroid Carcinoma originating from follicular cells
Carcinoma originating from C cells: Medullary Carcinoma
Others: -epidermoid carcinoma
-mucoepidermoid carcinoma
.....
Follicular carcinoma
Papillary carcinoma
Poorly differentiated carcinoma (insular carcinoma)
Undifferentiated (anaplastic) carcinoma
Variants:
- oncocytic follicular carcinoma (eosinophil follicular carcinoma, or oxyphil follicular carcinoma, or Hürthle follicular carcinoma)
-clear cell follicular carcinoma
Variants that have a prognosis comparable to that of papillary carcinoma common:
-follicular variant
-oncocytic variant
-warthin-like variant
-clear cell variant
-spindle cell variant
-cribriform variant
-giant cell variant
-with fasciitis-like stroma
Variant
-oncocytic
Poorly differentiated carcinoma associated with a differentiated carcinoma (papillary or follicular)
Variants of more aggressive behavior:
-tall cell variant
-columnar cell variant
-diffuse sclerosing variant
-solid or trabecular/solid variant
- hobnail cell variant
- multinodular or diffuse follicular variant

- ATC Does not take up iodine or produce thyroglobulin.

- For differentiated thyroid cancers, avoid iodinated contrast with CT as this may preclude treatment with RAI for up to 6 months. If the patient received iodinated contrast, can check urine iodine level prior to RAI administration.

Prevention & Early Detection

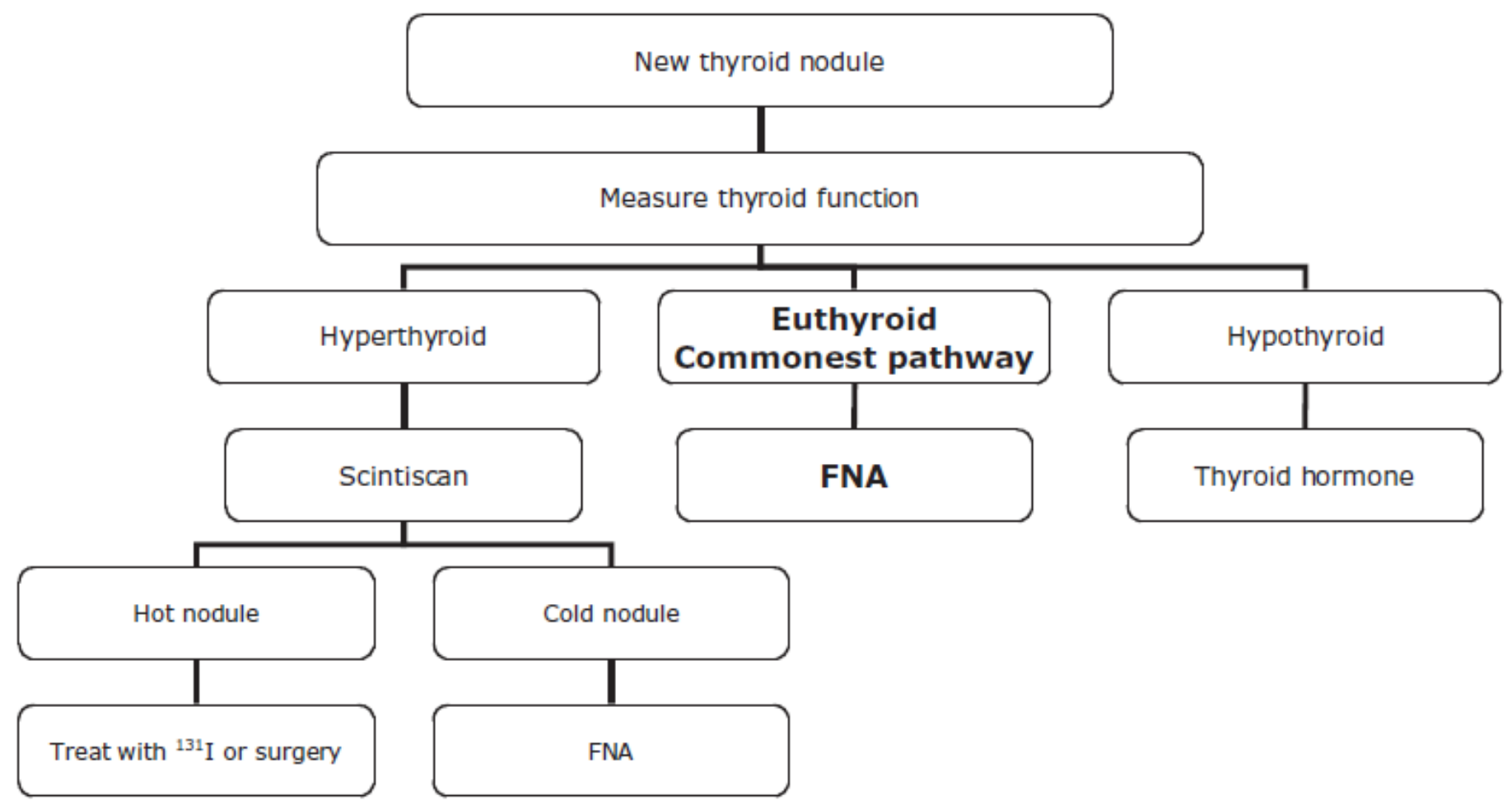
- Most thyroid cancers are sporadic and not caused by an avoidable environmental agent. Prevention of thyroid ca usually is impossible.
- In contrast, early detection of familial MTC is possible when there is evidence of RET proto-oncogene inherited mutation within the family.
- Prophylactic total thyroidectomy is recommended for persons shown to harbor the mutation, which completely prevents the development of MTC. If such a mutation is found in infancy, the current practice is to perform a total thyroidectomy when the child is 3-5 years old.

Spread & Clinical Manifestations

- PTC: About 35-50% of excised neck nodes were histologically +ve. Distant metastases are diagnosed in only 1-7%.
- FTC: rarely (5%) have clinically evident lymphadenopathy at presentation. 5-20% have distant metastases at presentation, and the most common sites of distant spread are lung and bone.
- ATC: highly malignant, rapidly invading adjacent structures and metastasizing throughout the body.

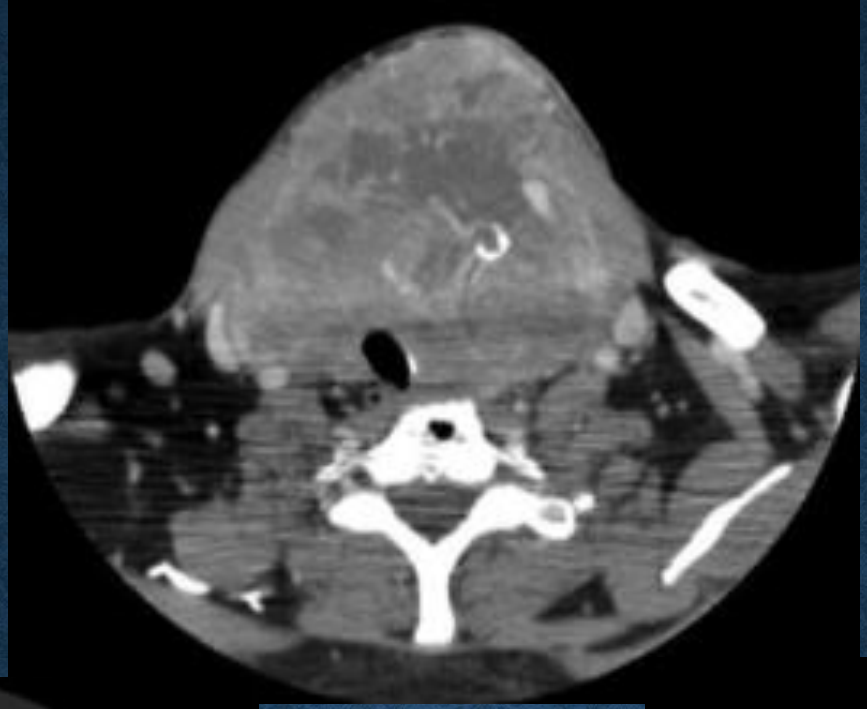
- MTC
  - LN metastases in ≥50%, while distant metastases in 20%. Minority of patients present systemic manifestations as diarrhea, flushing, or painful bone metastases.
  - Calcitonin: specific and highly sensitive marker for C-cell disease and frequently associated with one or more paraendocrine manifestations.
  - CEA is produced by neoplastic C cells.
  - Calcitonin and CEA are used as markers during FU of MTC.

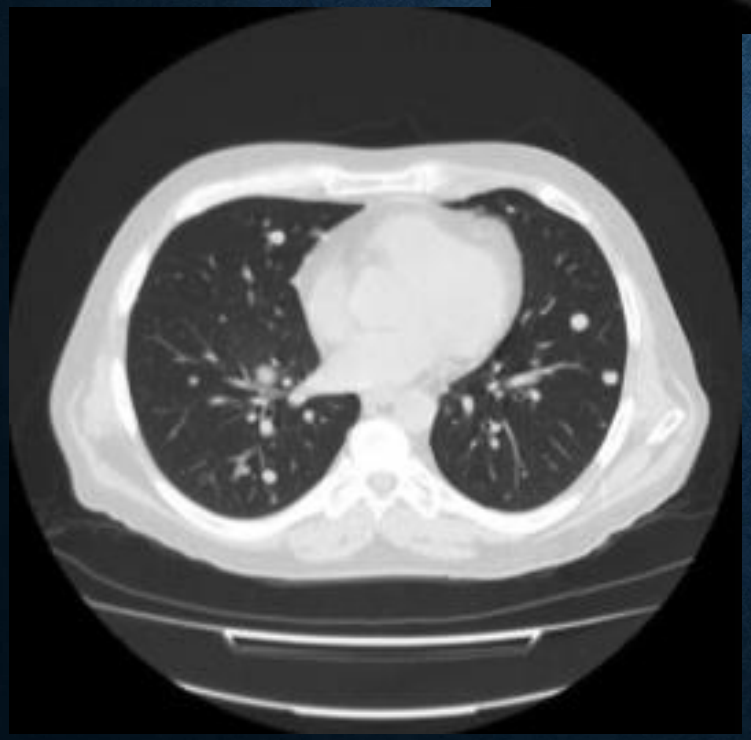
Management of New Thyroid Nodule

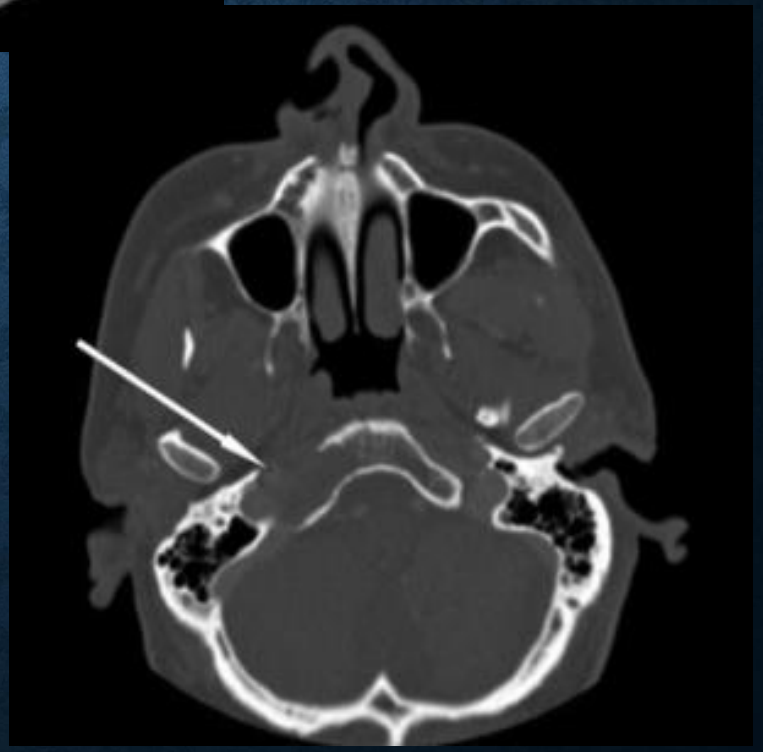


Patient Evaluation

- History
- Physical examination
- FNAC
- Neck Ultrasound
- Chest X-ray
- Others: vocal cord examination, chest CT, skeletal MRI, PET/CT.



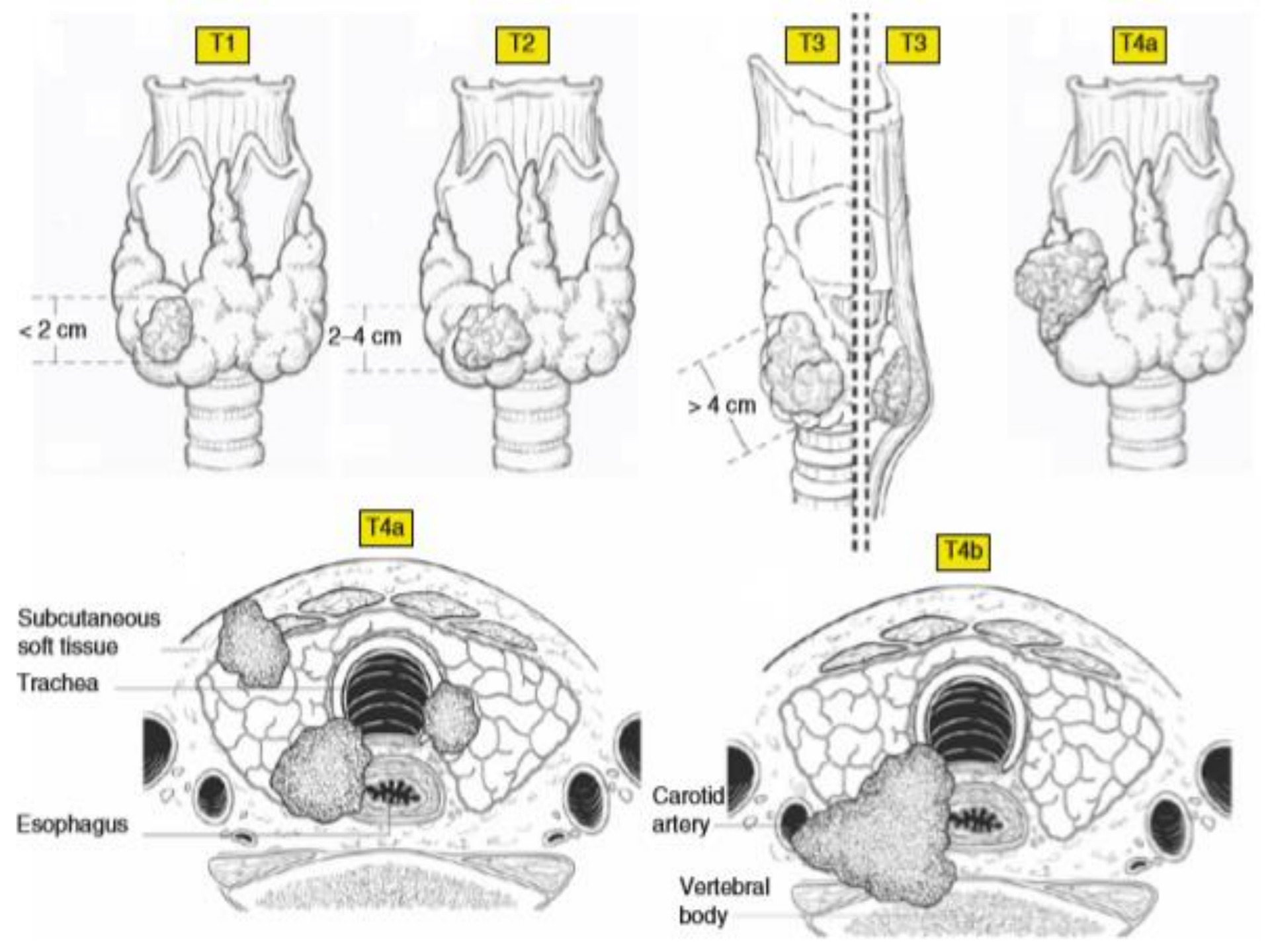




- FNA biopsy can provide a confident diagnosis of PTC, MTC, and ATC. FTC diagnosis still a problem because capsule or vascular invasion cannot be shown in cytology.
- Baseline serum thyroglobulin, Calcitonin and CEA.
- RAI Scan has little role in preoperative evaluation. However, a postoperative whole body scan has become the gold standard.

Staging

Although HNC is staged on the basis of anatomic extent, thyroid cancer staging is unique in that the histologic diagnosis and the age are included because of their prognostic importance.


T1
T2
T3
T3
T4a
< 2 cm
2–4 cm
> 4 cm
T4a
Subcutaneous soft tissue
Trachea
Esophagus
T4b
Carotid artery
Vertebral body

T1 Greatest dimension ≤2 cm, limited to the thyroid

T2 >2 cm but ≤4 cm, limited to the thyroid

T3a >4 cm, limited to the thyroid

T3b Gross extrathyroidal extension invading only strap muscles

T4a Tumor of any size extending beyond 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

Prognostic Factors

- Age
- Histology
- Grade
- Tumor size
- Tumor extent
- Completeness of resection

AJCC Stage Grouping

	DTC or PDTC	DTC or PDTC	MTC	ATC
Category	Age <55 years	Age ≥55 years	Any age	Any age
I	Any T Any N M0	T1 N0/NX M0 T2 N0/NX M0	T1 N0 M0	_____
II	Any T Any N M1	T1 N1 M0 T2 N1M0 T3a/T3b Any N M0	T2 N0 M0 T3 N0 M0	_____
III	_____	T4a Any N M0	T1-3 N1a M0	_____
IVA	_____	T4b Any N M0	T4a Any N M0 T1-3 N1b M0	T1-T3a N0/NX M0
IVB	_____	Any T Any N M1	T4b Any N M0	T1-T3a N1 M0 T3b Any N M0 T4 Any N M0
IVC	_____	_____	Any T Any N M1	Any T Any N M1

Scoring Systems

Scoring System	Prognostic Factors Used
EORTC	Gender, tumor histology type, extrathyroidal invasion, distant metastases
AGES	Age, tumor grade, extrathyroidal invasion, tumor size
MACIS	Age, extrathyroidal invasion, distant metastases, completeness of resection, tumor size
AMES	Age, extrathyroidal invasion, distant metastases, tumor size
TNM	Primary tumor size, lymph node status, distant metastases
DeGroot class	Cervical node metastasis, distant metastasis, extrathyroidal invasion
SAG	Sex, age, grade
Mazzaferri system	Tumor size, cervical nose status, multiple tumors (>3), extrathyroidal invasion, distant metastases

Primary Therapy

Surgery

- Is the standard treatment.
- Near-total or total thyroidectomy is the recommended operative procedure for FCDC and total thyroidectomy for MTC.
- Level VI LN removal should be routinely done and may not add morbidity. Modified radical neck dissection is indicated for gross nodal metastases found before or during surgery.
- Hemithyroidectomy, is appropriate only for a selected low-risk patients, such as papillary microcarcinoma.

Adjuvant Therapy

Adjuvant Therapy: Summary

- Thyroxine-suppressive therapy of TSH: standard postoperative management of FCDCs.
- Radioiodine remnant ablation (RRA): used in high-risk FCDCs but may not benefit low-risk patients.
- Radioactive iodine (RAI) therapy: used for distant metastasis, residual or unresectable PTC, and FTC or Hürthle cell carcinoma (HCC) cases.
- EBRT: reserved for locally advanced disease with high-risk surgical pathologic features and patients with recurrent or metastatic disease nonresponsive to RAI therapy.

Treatment Algorithm

Step 1

- Initial neck exploration/thyroid resection
- FCDC: usually near-total or total thyroidectomy
- MTC: total thyroidectomy
- ATC: open biopsy or subtotal thyroidectomy
- Lymphoma: FNA or open biopsy
- Lymph nodes: removal of central compartment nodes in FCDC and MTC; modified radical neck dissection for involved lateral nodes

Step 2

- Thyroid hormone therapy
- Replacement doses for MTC, ATC, lymphoma
- TSH-suppressive doses for FCDC except microcarcinoma

Step 3

- Outcome prediction by risk-group classification
- According to age, stage, histologic type, and cancer type-specific scoring systems (e.g., AMES, MACIS)

Risk Stratification
The American Thyroid Association (ATA)

Risk of recurrence	Definition	Initial TSH target*
Low (<5%)	PTC with **all** of the following: • Intrathyroidal tumour, size <4 cm, absence of gross extrathyroidal extension/vascular invasion/aggressive histology subtypes • Complete macroscopic tumour resection • No macroscopic locoregional or distant metastases FTC with **all** of the following: • Well-differentiated and minimal vascular invasion (<4 foci)	Hemithyroidectomy or initial Tg <0.2 µg/L: TSH target 0.5–2 mU/mL Total thyroidectomy and initial Tg ≥0.2 µg/L: TSH target 0.1–0.5 mU/L
Intermediate (5–20%)	PTC with **at least one** of the following: • Size >4 cm, microscopic tumour invasion into perithyroidal tissues, vascular invasion, aggressive histology subtypes • Macroscopic regional lymph node metastases FTC with: • Locoregional lymph node metastases	TSH target: 0.1–0.5 mU/L
High (>20%)	PTC with **at least one** of the following: • Macroscopic tumour invasion of perithyroidal tissues, poorly differentiated subtype • Large locoregional metastases or lymph nodes with extranodal extension • Distant metastases • Incomplete tumour resection FTC with **at least one** of the following: • Widely invasive or extensive vascular invasion • Incomplete resection • Distant metastases	TSH target: <0.1 mU/L

Step 4

- RAI therapy, EBRT, CT, or combinations.
- FCDC: RAI therapy indicated for distant spread, unresectable or residual neck tumor, possibly invasive disease in PTC and most cases of FTC or HCC; EBRT for local or metastatic tumor nonresponsive to RAI therapy; almost no role for CT in differentiated FCDC.
- MTC: residual or recurrent neck disease considered for EBRT; octreotide or CT considered for palliation only.
- ATC: Surgery + EBRT and concurrent CT.
- Lymphoma: CHOP + RT.

Thyroid Hormone

- Supra-physiologic oral doses of levothyroxine.
- High risk: TSH < 0.1 mU/L
- Low risk: TSH 0.1 - 0.5 mU/L

Radioactive Iodine

- Radioiodine Remnant Ablation (RRA):

  Destruction of residual macroscopically normal thyroid tissue after thyroidectomy.

- Radioactive Iodine (RAI) Therapy:

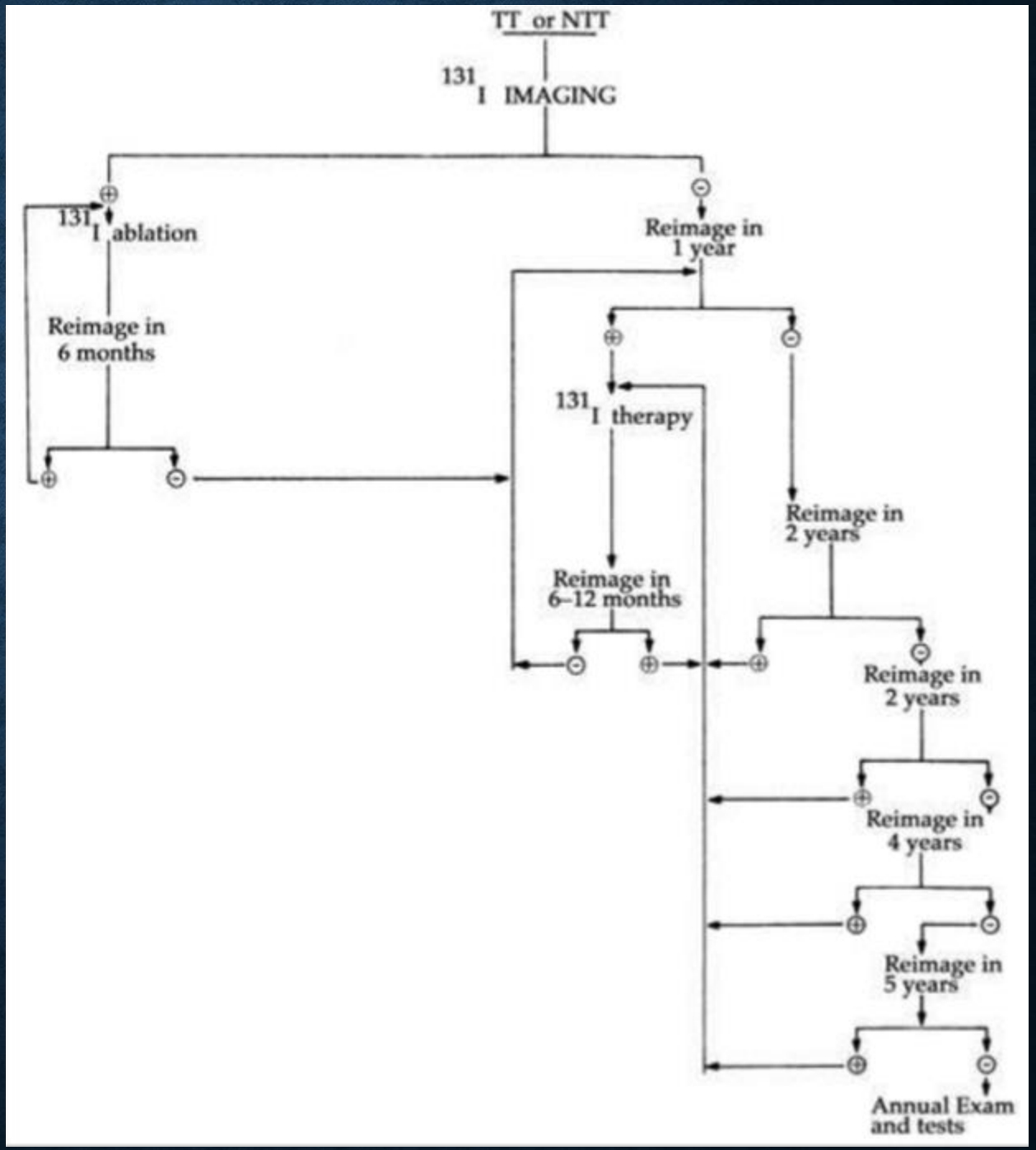
  Larger doses of ^{131}I are used in an attempt to destroy persistent neck disease or distant metastasis.

Advantages of RRA:

- Destroy occult microscopic cancer cells within the thyroid remnant.
- Facilitates later detection of residual or recurrent disease, particularly in the neck by RAI scanning.
- Increase the value of serum thyroglobulin measurement during FU.

- RRA Recommended for:
  - Carcinoma > 1.5 cm
  - +ve lymph node
  - Extrathyroidal extension
  - Multicentricity
- Low-dose (<30 mCi) have been used for small residual thyroid tissue. Higher doses (75-150 mCi) may be appropriate when microscopic residual cancer is present or when the initial scan suggests an unsuspected metastatic site.

Radioactive Iodine



Treatment Sequelae

- Acute radiation sickness (fatigue, headache, nausea, vomiting).
- Sialadenitis (swelling and pain in salivary glands).
- Transient hyperthyroidism (may occur after massive thyroid tissue destruction).
- Radiation pneumonitis and pulmonary fibrosis (especially if there were diffuse functioning lung metastases).
- Leukemia is rare (<2%).

External Beam Irradiation

- Historically, used for: residual disease, extrathyroidal extension, multiple LN involvement, Hürthle cell histology, older age, large tumor size, and residual disease that does not take up RAI.
- Several investigators have retrospectively reviewed their experience with EBRT and suggested improved LC or survival or both. Populations in these studies are not uniform with respect to other treatments that also effect LC, making interpretation difficult.
- EBRT in PTC and FTC is still controversial (is not uniformly used).

- The only randomized trial evaluating the role of EBRT was initiated in 2000 in pathologic $T_4N_{0-1}M_0$ after surgical resection and ablative ^{131}I. The study closed because of inadequate accrual in March 2003 despite acceptable toxicity.
- The study authors indicated that at early FU, there are lower than expected relapse rates in the nontreatment arm.
- Improvement in surgical management and the appropriate application of RAI may have accounted for the decreased relapse and mortality rates compared with historical studies.

- EBRT for differentiated thyroid cancer needs to be carefully tailored to the specific patient and applied after use of RAI.
- Although efforts to improve outcome have focused mainly on RAI treatment in high risk patients, there seems to be an evolving role for EBRT.

Rationale for EBRT:

- Treat tissues known to take less RAI (areas of extrathyroidal or extranodal extension, which are known poor prognostic indicators).
- Treat carcinomas that fail to concentrate and retain RAI (20% of differentiated thyroid cancer, Hürthle cell tumors, and >40 years old).
- Spare RAI toxicity (when adequate treatment of residual disease needs excessive RAI or when repeated treatment are likely to be necessary).
- Spare morbidity of uncontrolled locoregional cancer (obstruction of esophagus or trachea or both, neurovascular compromise, pain, hemorrhage, need for laryngectomy, and need for repeated excision).

- Multiple retrospective studies report good long-term LRC with EBRT for patients with gross residual or unresectable DTC.

- A study from the Royal Marsden Hospital showed CR in 37% and PR in additional 25%.

Hong Kong (Chow *Endocrine-Related Cancer* 2006):

- Retrospective study of 1297 patients with PTC treated with surgery ± RAI ± EBRT.
- Mean FU 9.9 years.
- Among 217 pts with gross residual disease, EBRT improved 10-year LC (24 → 64%) and CSS (50 → 74%).
- If pT4, EBRT and RAI together improved 10-year LC (41 → 88%).

MSKCC (Romesser, J Surg Oncol 2014):

- 66 patients with gross residual/unresectable non-anaplastic thyroid cancer treated with EBRT +/− concurrent CT.
- 3-year LRC overall 77%; adding CT improved LRC for poorly differentiated (89% vs. 66%).

Princess Margaret (Brierley Clin Endocrinol 2005):

- Retrospective of 729 patients treated with surgery and/or RAI and/or EBRT.
- Median FU 11 years.
- EBRT significantly improved LRC (66% → 86%) and CSS (65% → 81%) among patients age > 60 with extrathyroid extension and no gross residual disease (n = 70).

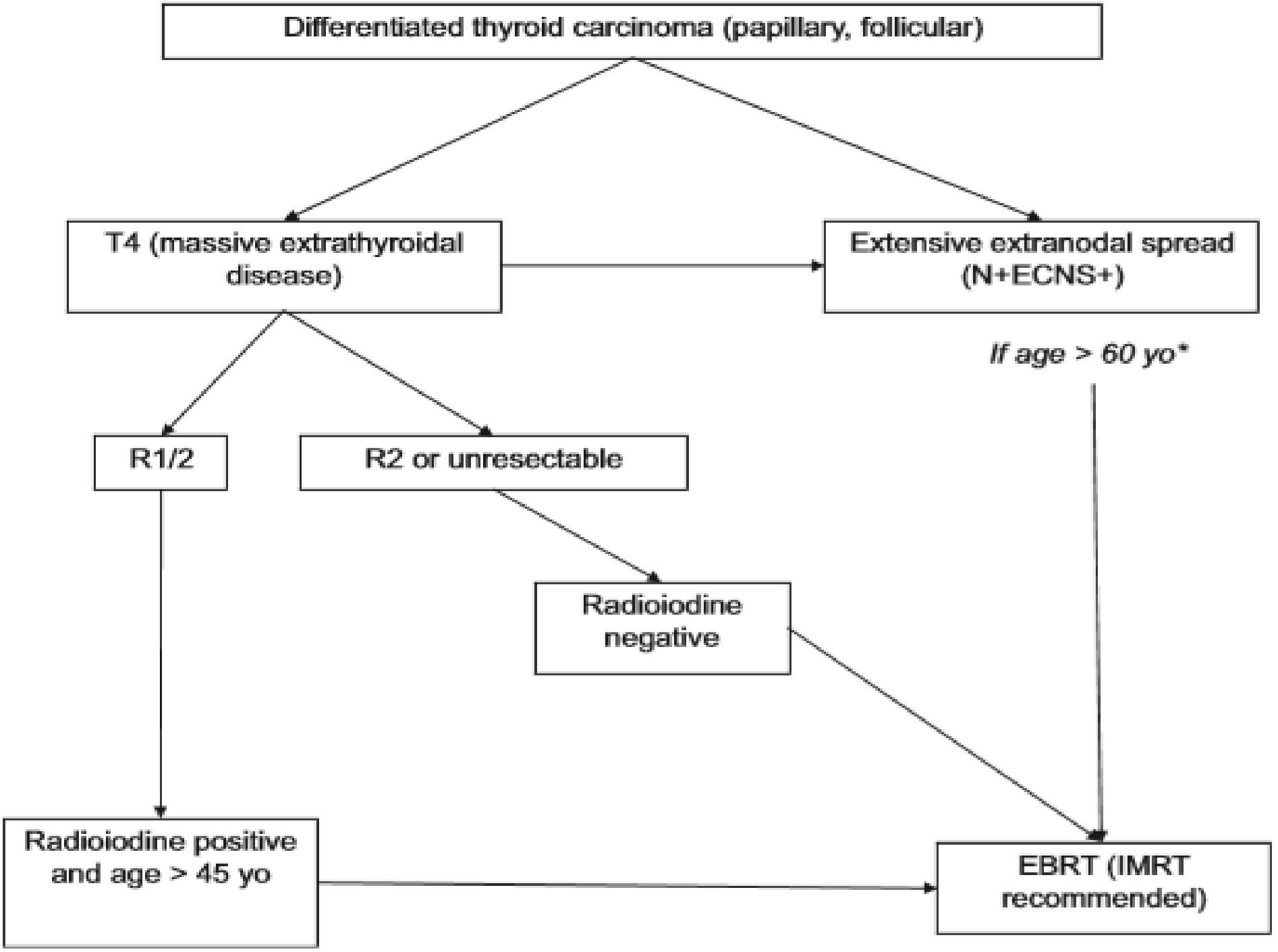
Systematic review (Fussey et al)

The available evidence suggests an improvement in LRC when EBRT is used in patients >45 years at high risk for locoregional recurrence.

Guidelines For Adjuvant EBRT In DTC

American Thyroid Association (ATA) & British Thyroid Association (BTA)

ATA	Over age of 45 years with grossly visible extrathyroidal extension at the time of surgery and a high likelihood of microscopic residual disease
	Gross residual tumour for whom further surgery or RAI would probably be ineffective
BTA	Gross evidence of local tumour invasion at surgery, presumed to have significant macro-or microscopic residual disease, particularly if the residual tumour fails to concentrate sufficient amounts of RAI
	Extensive pT4 disease in patients >60 years of age, with extensive extranodal spread after optimal surgery, even in the absence of evident residual disease

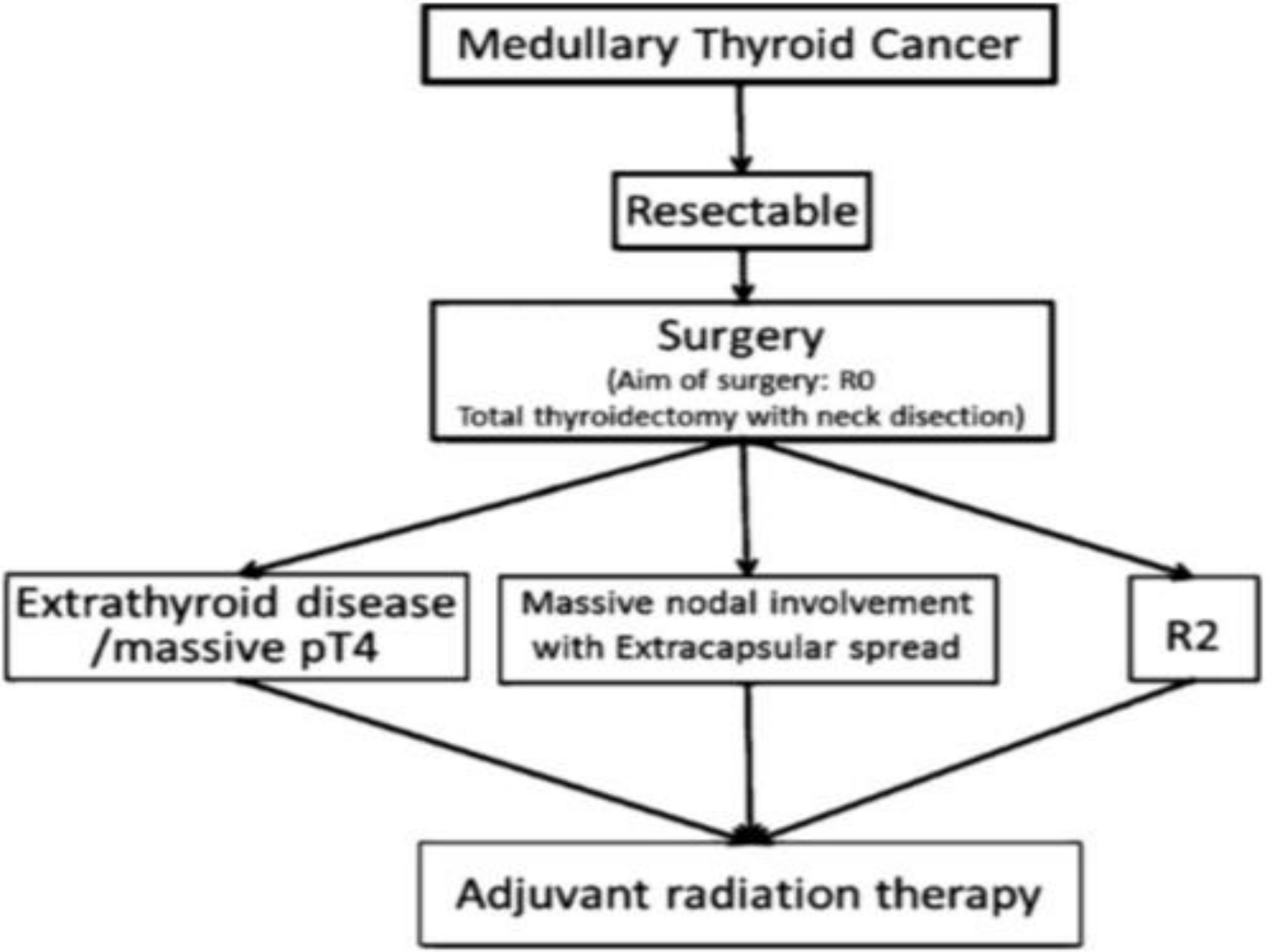

Differentiated thyroid carcinoma (papillary, follicular)
T4 (massive extrathyroidal disease)
Extensive extranodal spread (N+ECNS+)
If age > 60 yo*
R1/2
R2 or unresectable
Radioiodine negative
Radioiodine positive and age > 45 yo
EBRT (IMRT recommended)

The Endocrine Surgery Committee of the American Head and Neck Society has published recommendations regarding EBRT for DTC (Kiess, Head Neck 2016).

- Recommended for gross residual or nonresectable locoregional disease, except for patients >45 years with limited gross disease that is RAI avid.
- Should not be routinely used as adjuvant therapy after complete resection of gross disease.
- After complete resection, EBRT may be considered in select patients >45 years with a likelihood of microscopic residual and low likelihood of responding to RAI.
- Cervical LN involvement alone should not be an indication for adjuvant EBRT.

Adjuvant EBRT ……. Conclusion

- Benefit from adjuvant EBRT remains controversial in DTC.
- EBRT has a potential role in older patients with non-iodine-avid residual disease or for extensive pT4 disease with extensive extranodal spread, even in the absence of evident post-surgical residual disease.
- However, the benefits of EBRT need to be weighed against its acute and long-term toxicities.


Medullary Thyroid Cancer
Resectable
Surgery
(Aim of surgery: R0
Total thyroidectomy with neck disection)
Extrathyroid disease
/massive pT4
Massive nodal involvement
with Extracapsular spread
R2
Adjuvant radiation therapy

Technology

- EBRT is challenging because of the body contour in this area; the potential extension of disease in the upper mediastinum; involvement of LNs in the central and lateral neck and mediastinum; and the close proximity of the lungs, spinal cord, esophagus, larynx, pharyngeal constrictors, and brachial plexus.

Adverse Events

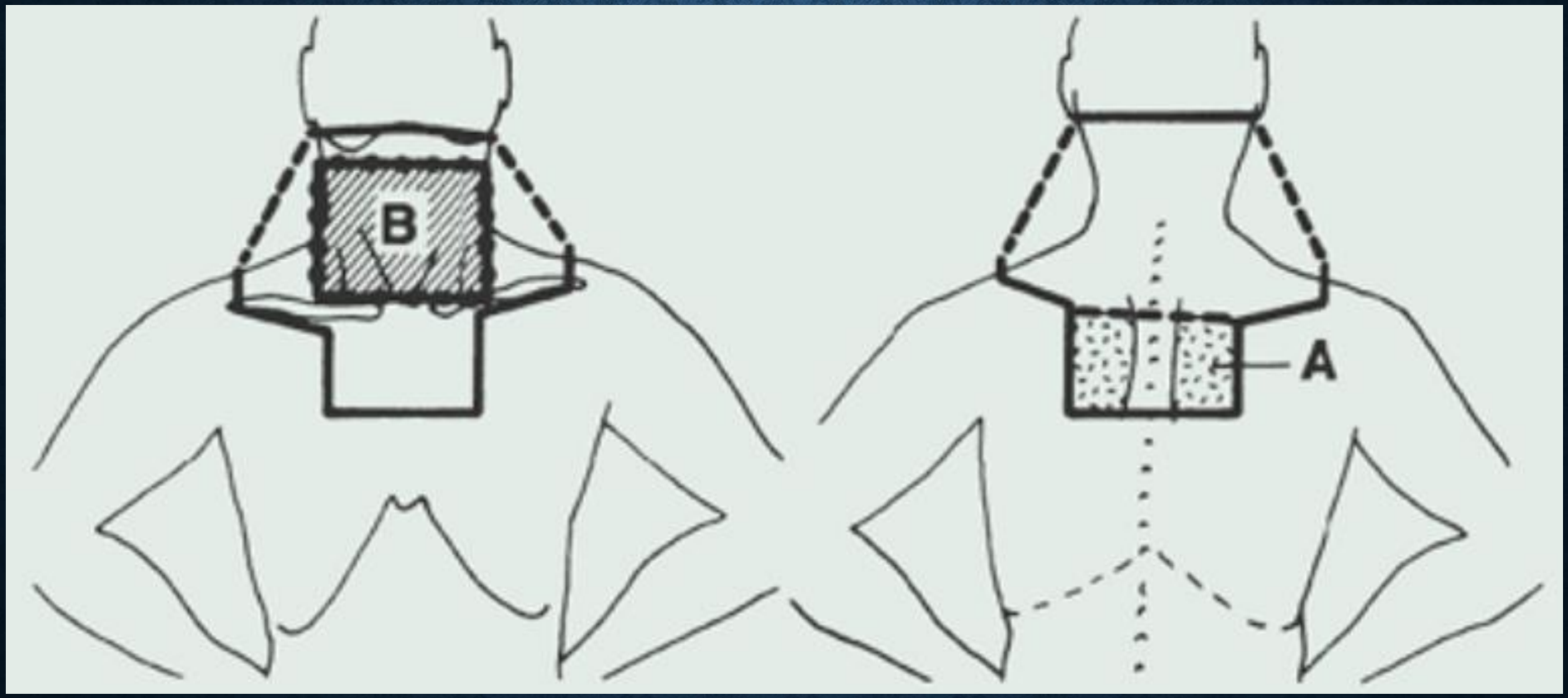
Acute: dermatitis, esophagitis, mucositis, dysphagia, changes in taste, xerostomia, laryngitis.

Late: neck fibrosis and lymphedema, xerostomia, dental caries, esophageal stenosis, chronic feeding tube dependence.

- For adjuvant treatment or for locoregionally advanced or recurrent disease with curative intent, CTV should include the thyroid bed, neck LNs (from hyoid bone to carina, levels II-VI), and upper mediastinum.

- For palliation, it is reasonable to consider treating only the gross tumor + margin.

- 50-60 Gy / 5-6 weeks for microscopic disease (adjuvant treatment).
- 60-70 Gy / 6-7 weeks for gross residual.
- Several approaches have been reported for the initial extended fields, including a single anterior electron field, an anterior field with a posterior supplemental field for the mediastinum, and lateral fields.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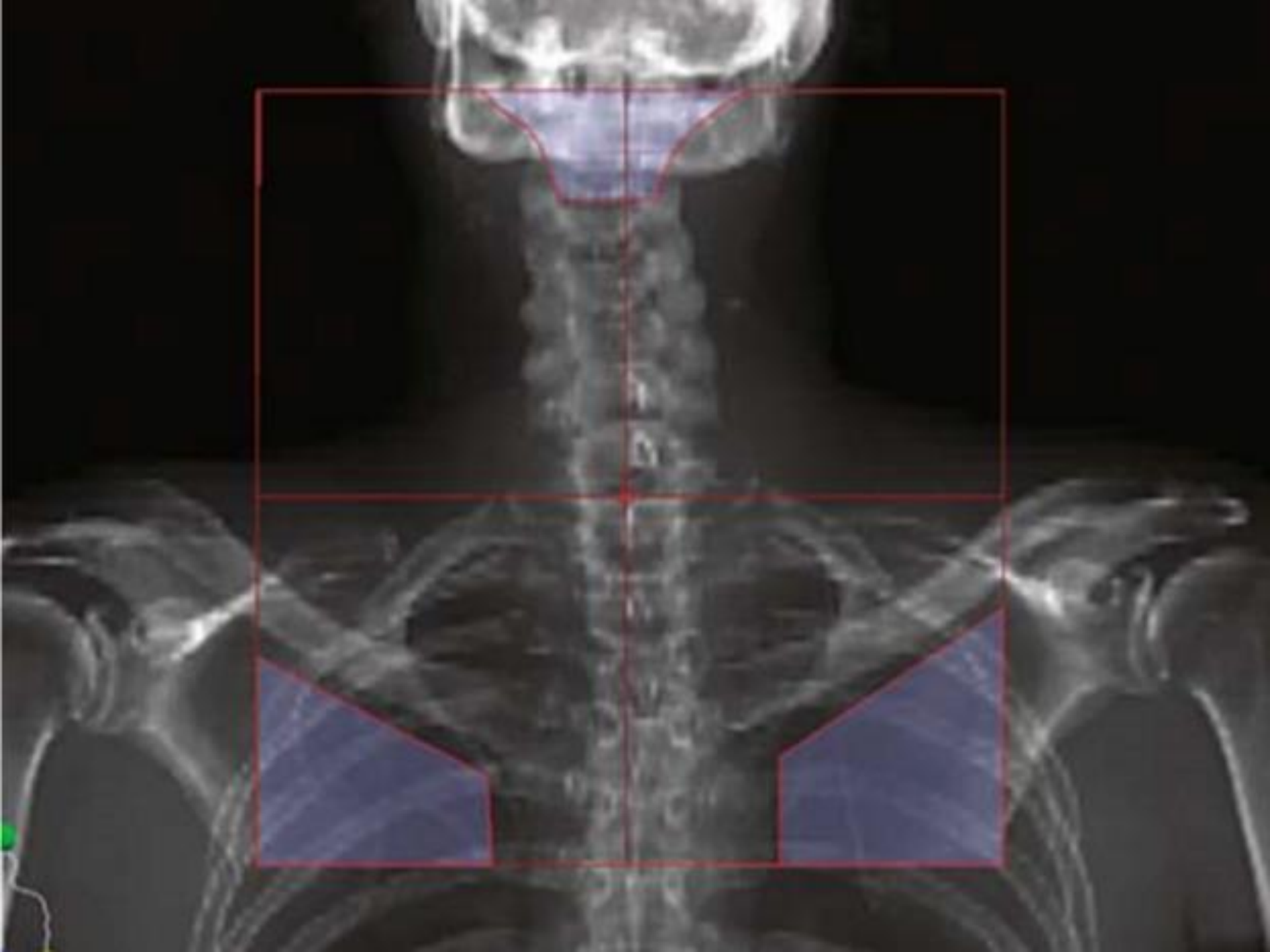
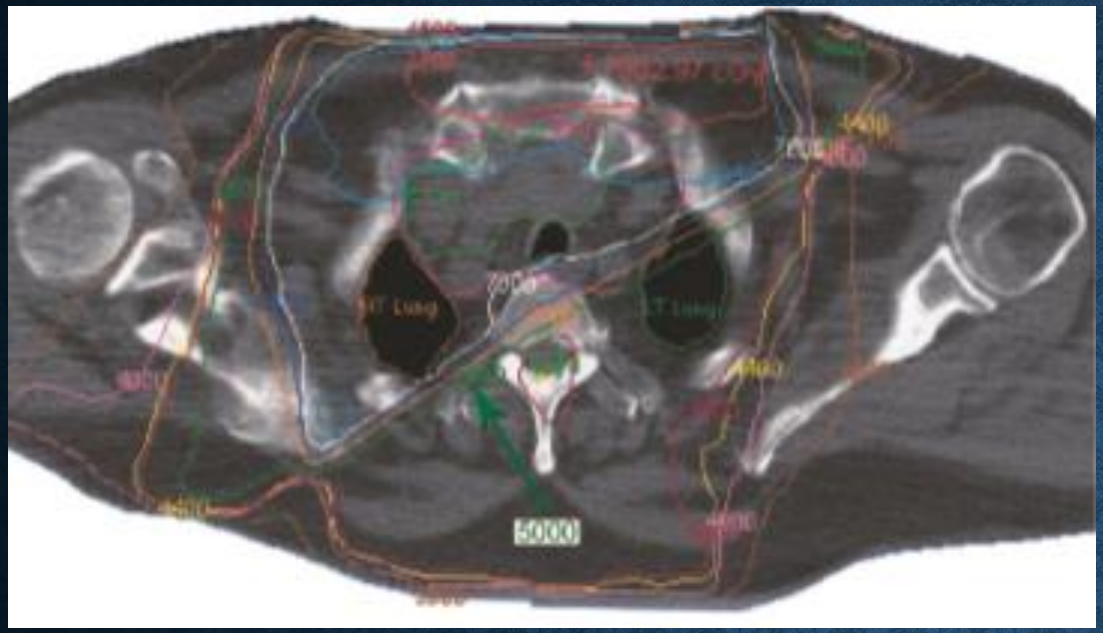
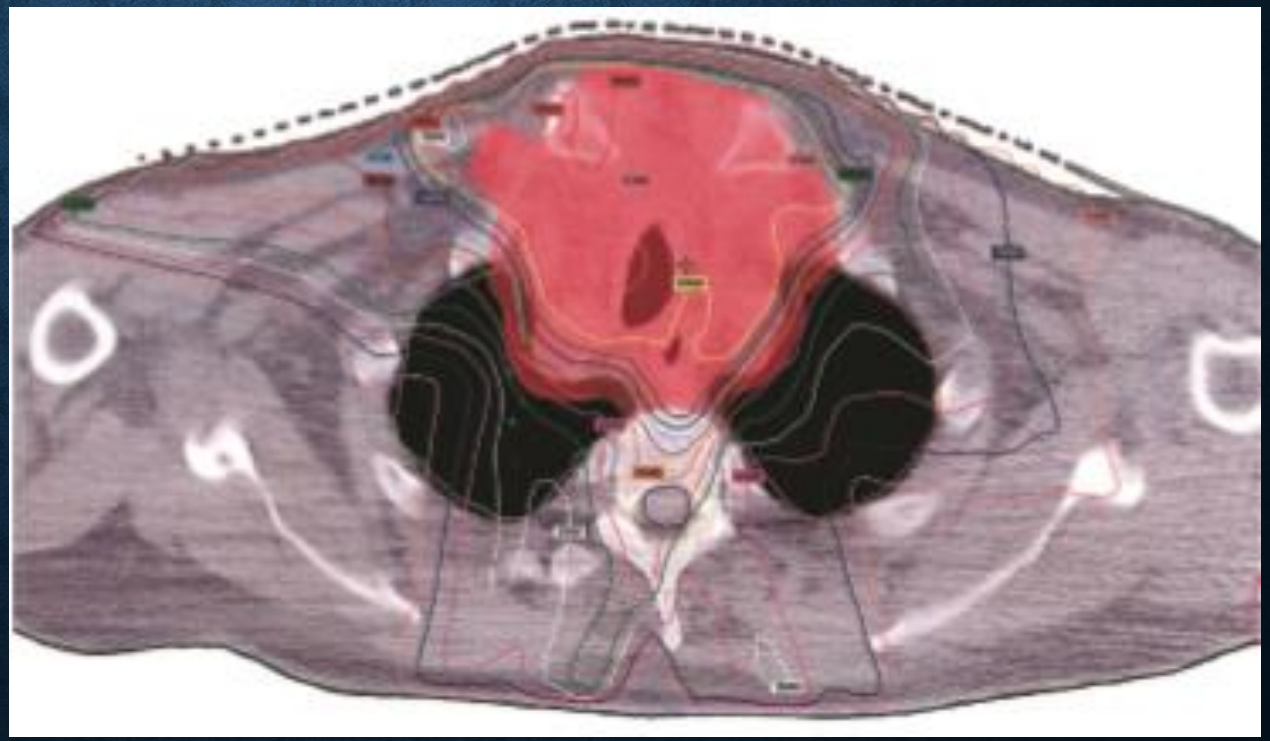




3D & IMRT

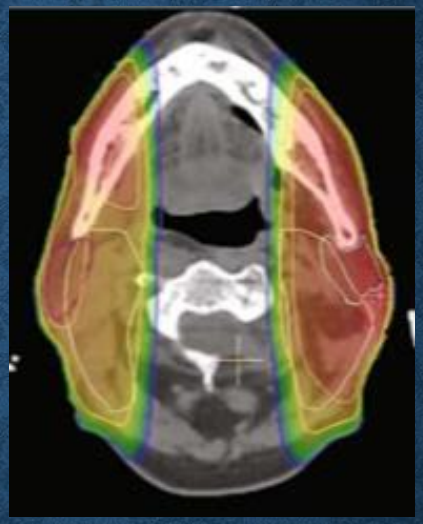


IMRT allows better parotid and spinal cord sparing, better conformation of dose over portions of the body of different thickness (neck and chest)

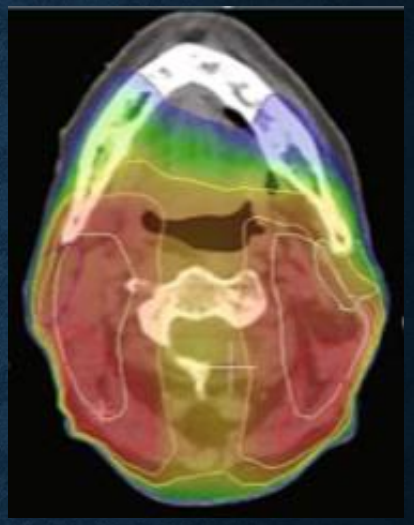
With conventional therapy the hotspots overlap the parotid glands, while with IMRT these are spared.

With IMRT target coverage is improved, at the expense of large volumes of the head and neck that receive a low dose, regions that may receive no dose with conventional therapy.

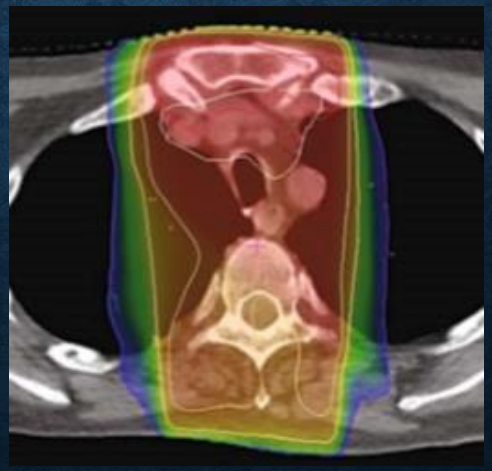
IMRT Improved conformality of the high dose region and it is further from the spinal cord, reducing the risk of cord complications due to set-up errors.

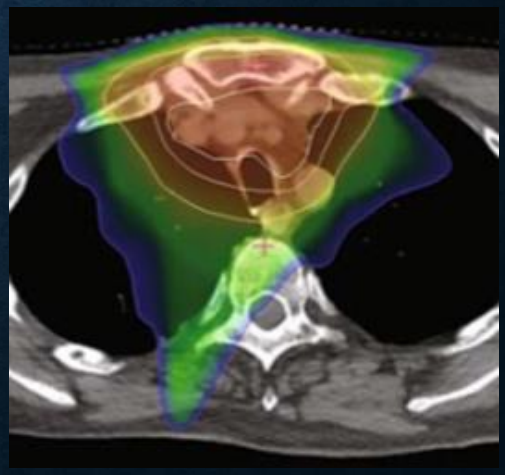


AP-PA



IMRT





Early experiences with IMRT suggest that dose escalation is technically feasible without increasing toxicity.

- Gross disease (70 Gy)
- Margin-positive regions (66 Gy)
- Margin-negative thyroid bed (60 Gy)
- Nodal regions outside the thyroid bed (54 Gy)

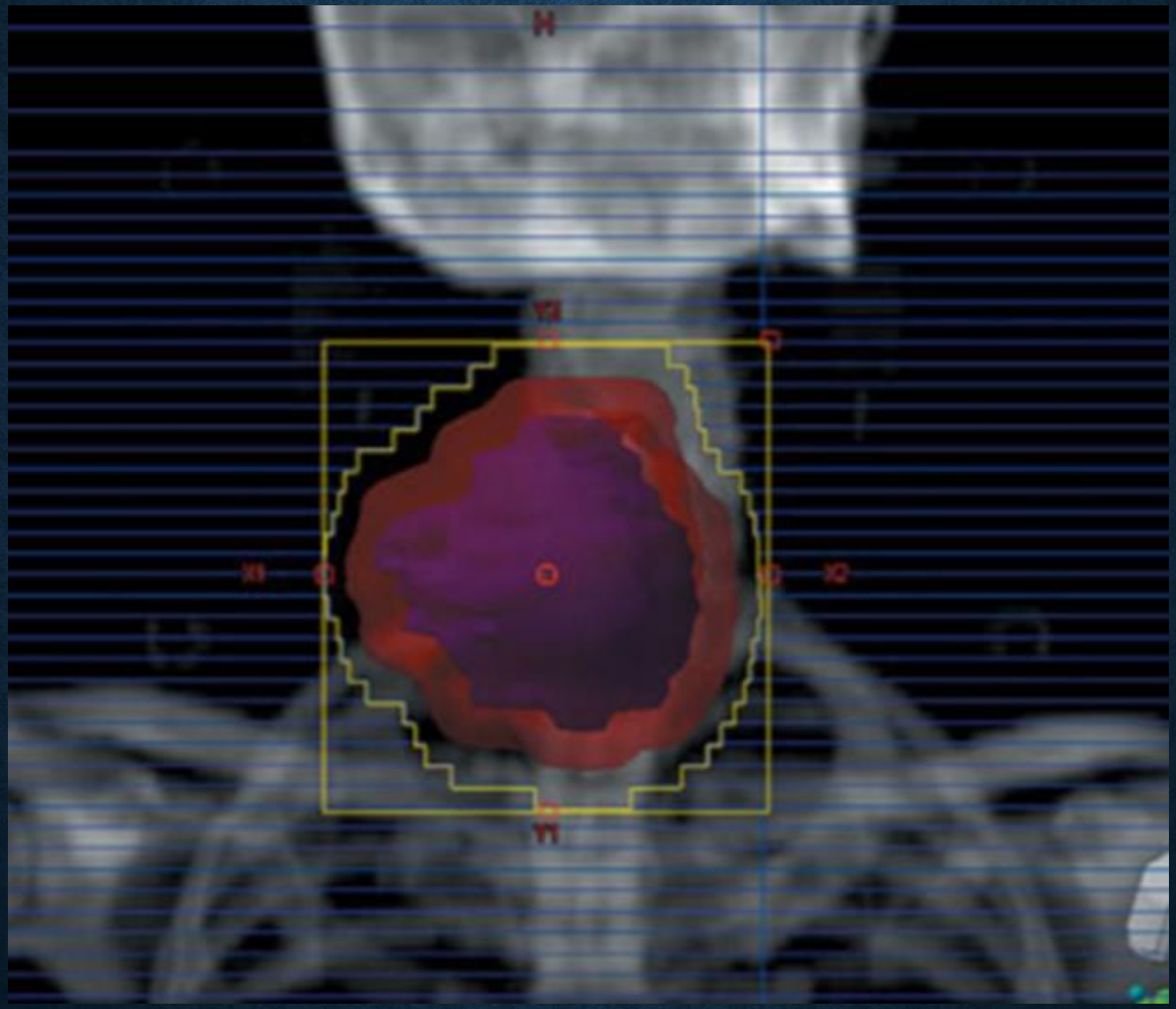
IMRT is recommended to improve sparing these OARs.

SBRT has been proposed as a highly targeted technique that is efficient (1-3 fractions) and effective in controlling cervical LN recurrence of nonanaplastic thyroid cancer (100% tumor control) with no serious adverse events.

Other Indications for EBRT

- Primary therapy if irresectable, particularly if ^{131}I does not concentrate in tumor.
- Bulky tumor (e.g., mediastinal disease) large enough that it is uncontrollable by ^{131}I alone.
- Residual bulky tumor in the neck that may not be controlled by ^{131}I alone.
- Brain metastases.

- Skeletal metastases
  - Small or absent concentration of ^{131}I.
  - Concern about a pathologic fracture, regardless of the degree of ^{131}I concentration.
- Relief of pressure symptoms caused by soft-tissue masses.
- Superior vena cava syndrome.
- Continually recurring tumor regardless of ^{131}I accumulation.
- Recurrent or metastatic disease occurring after maximal ^{131}I.
- In sequence or conjunction with CT, particularly in ATC .
- Preoperative therapy.



Palliative RT for ATC

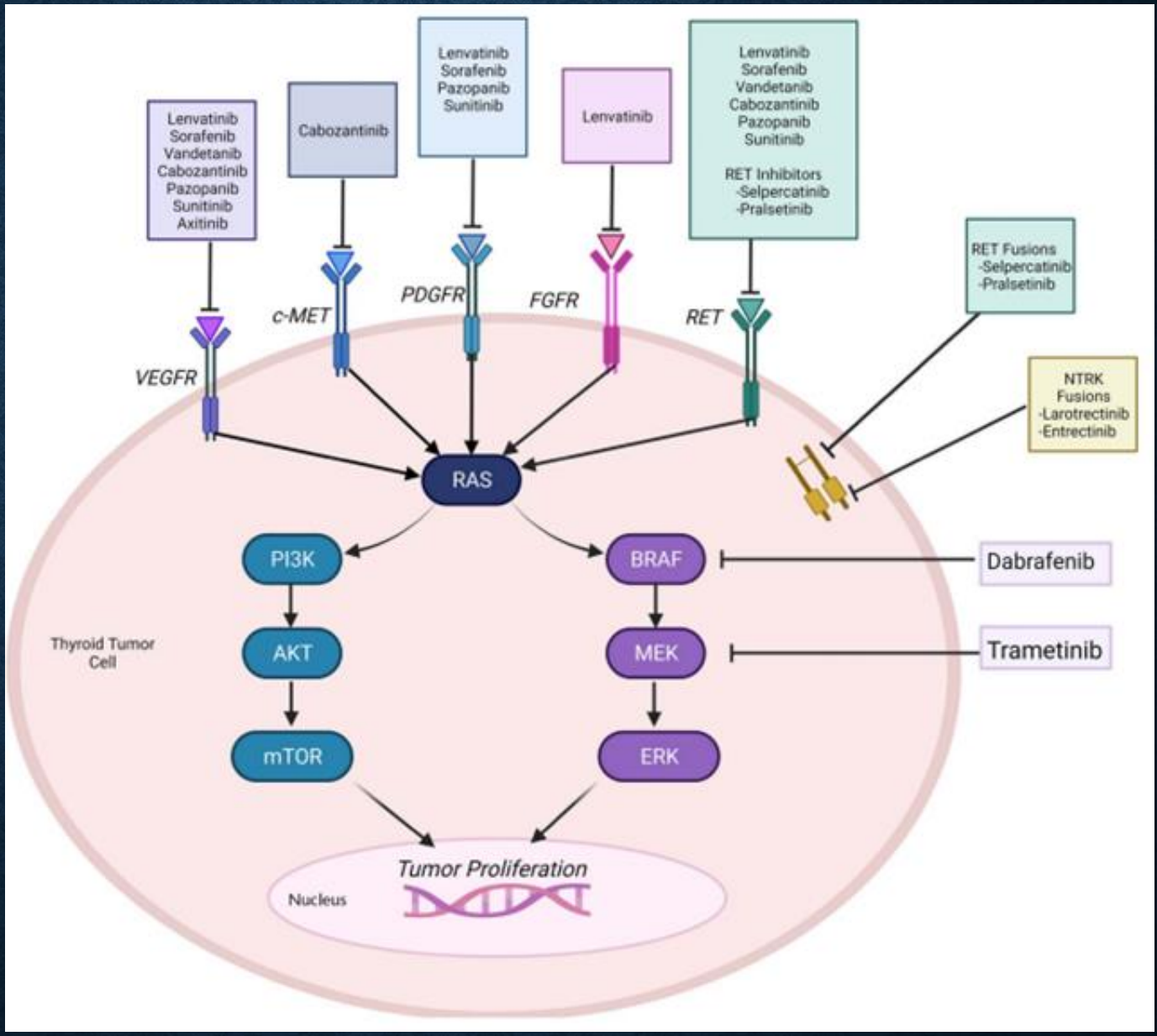
AP/PA fields with MLC shielding

Chemotherapy

- Its role in the treatment of differentiated thyroid carcinoma is limited. Most agents have low RR. The most active single agent is Adriamycin.
- ECOG reported the only randomized study using CT in locally advanced or metastatic thyroid cancer. CR was 6% and PR was 15%. No advantage to the combination-drug regimen over doxorubicin alone.

- The main challenge in the management of MTC is patients with advanced and progressive disease, because conventional therapies have poor results.
- No effective therapy for distant metastases, since CT and EBRT for metastatic or recurrent disease have limited RR.

Targeted Therapy



ERK, extracellular-regulated kinase; FGFR, fibroblast growth factor; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor α; PI3K, phosphatidylinositol 3-kinase; RET, rearranged during transfection; VEGFR, vascular epithelial growth factor receptor.

Targeted Therapy	Tumor Target	Response
Multikinase inhibitors-DTC		
Sorafenib	VEGFR, PDGFR, RET	PFS, 10.8 months ORR, 12%
Lenvatinib	VEGFR, PDGFR, RET, FGFR	PFS, 18.3 months ORR, 64.8%
Multikinase inhibitors-MTC		
Vandetanib	RET, VEGFR, EGFR	ORR, 45%
Cabozantinib	RET, VEGFR, c-MET	
BRAF/MEK inhibitors		
Dabrafenib and trametinib	BRAF V600E	DTC: dabrafenib alone ORR, 42% *v* dabrafenib plus trametinib ORR, 48% ATC: ORR, 61%
RET inhibitors		
Selpercatinib	RET	*RET* fusion-TC (previously treated) ORR, 79% *RET*-mutant MTC (no previous treatment) ORR, 73% *RET*-mutant MTC (previously treated) ORR, 69%
Pralsetinib	RET	*RET* fusion-TC ORR, 85.7% *RET*-mutant MTC (no previous treatment) ORR, 71% *RET*-mutant MTC (previously treated) ORR, 60%
NTRK inhibitors		
Larotrectinib	NTRK	*NTRK* fusion-TC ORR, 71%

	Tumor Type	Target	Partial Response (%)	Progression-Free Survival (Months)
FDA APPROVED				
Sorafenib	PTC	BRAF, RET, other TKRs	13-41	10-18
Vandetanib	MTC	RET, other TKRs	16-45	20-27
Cabozantinib	MTC	RET, other TKRs	28	11.2
NON-FDA APPROVED				
Axitinib	PTC, FTC	Other TKRs	26-40	NA
Pazopanib	PTC, FTC	RET, other TKRs	49	11.7
Sunitinib	PTC, FTC	RET, other TKRs	28	10-21

Systemic Therapy Or Not ?

- Even in the presence of radioiodine-refractory disease, advanced thyroid cancer does not always progress to cause symptoms or result in decreased QoL.
- Therefore, it is important to offer these treatments to those patients where the benefits may outweigh the harm.
- A potential subgroup are patients with RAI refractory, previously irradiated disease and nonsurgical, non-EBRT candidates with progressive or threatening symptoms.

- Patients with metastatic RAIR-DTC and MTC with asymptomatic disease and small tumors with slow indolent progression are amenable to close active surveillance with serial imaging.
- For RAIR-DTC and MTC, targeted therapy is recommended for:
  - Rapidly progressive tumors not amenable or failure to alternative localized therapies
  - Symptomatic disease
  - Tumors in a threatening location.

Medullary Ca

Calcitonin and CEA should be measured 2:3 months after surgery:

- Normal calcitonin and CEA: considered biochemically cured and continue surveillance.
- Calcitonin levels detectable but <150: neck imaging (US ± CT or MRI) to identify persistent locoregional disease.
- Calcitonin levels ≥150: additional imaging (CT or MRI neck, C/A/P, bone scan) to identify possible DM.

Anaplastic Thyroid Carcinoma

- The only long-term survivors were patients who had undergone surgical resection. So, surgery should be considered. Surgery has been performed before or after RT, CT, or both.
- Because of the high metastatic rate and high rate of local failure with RT alone, the use of CT in addition to RT is warranted.
- Most studies use doxorubicin-based CT concurrent with RT.
- The optimal EBRT fractionation has not yet been determined.
- Multimodality therapy (surgery, RT, and CT) offers the best option.

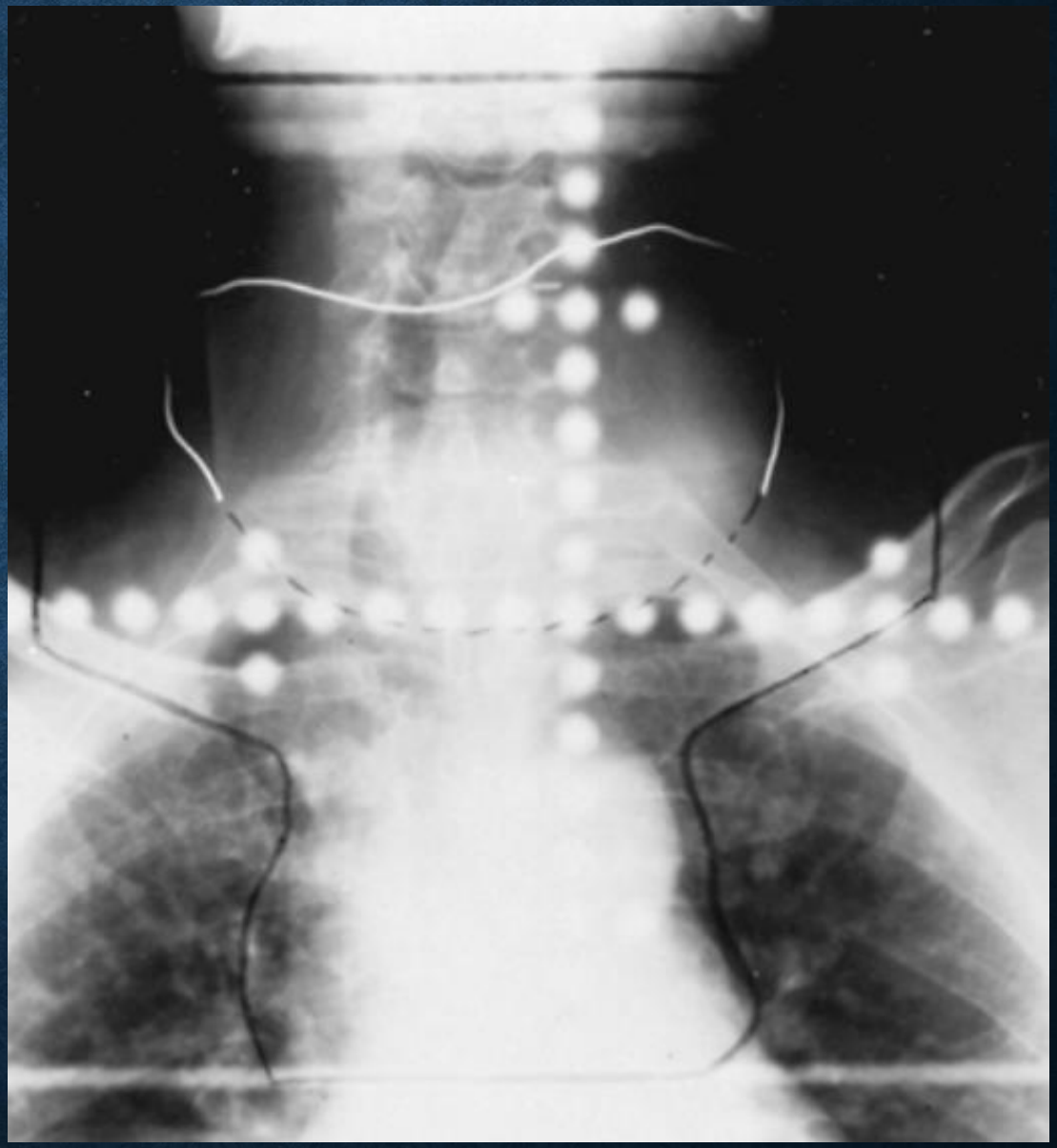
Primary Thyroid Lymphoma

- MALT lymphoma have a more indolent natural history, whereas DLBCL is more aggressive.
- Surgery has a diagnostic role only, and this role is diminishing with the increasing accuracy of FNA.
- Early stage, indolent, low grade (including MALT) lymphoma is treated with EBRT alone, 24 Gy/12 f to IF.
- Stage III-IV disease (indolent follicular lymphoma, marginal zone lymphoma) is treated with RT alone to 24 Gy/12f to IF. For palliation, 4Gy/2f may be sufficient.

- Stage I & II DLBCL: treatment is R-CHOP followed by EBRT 30 Gy/15f to IF if there is CR to CT. CT+EBRT improve DFS or PFS and OS when compared to CT alone by randomized clinical data.
- EBRT alone should be given only when CT is not feasible or tolerated.
- Stage III-IV DLBCL involving the thyroid gland, the treatment would generally be R-CHOP alone.

- Two large prospective randomized studies have evaluated the use of combined-modality therapy in thyroid lymphomas. Studies by ECOG and Southwestern Oncology Group (SWOG) evaluated the use of CHOP ± IF-RT for stage I or II NHL, including thyroid lymphomas.
- The number of thyroid lymphoma patients enrolled in these studies is not published, but 18% of the patients in the ECOG study had stage IE.
- Both studies indicated a survival benefit for combined-modality therapy.
- 30 Gy was used in the ECOG study after 8 X CHOP except when there was only a PR. In that circumstance, 40 Gy was delivered using standard fractionation.
- In the SWOG study, the combined-modality arm received 3 X CHOP along with 40 to 55 Gy.
- The OS at 6 years in the ECOG study was 84% for combined-modality therapy compared with 70% with CT alone ($p<0.05$). The SWOG report estimated an 82% OAS compared with 72% for CHOP alone ($p=0.02$).
- Based on these randomized studies, it seems that the use of combined-modality therapy offers the most appropriate management.

Initial large field, including the neck and mediastinum, in a patient with a large thyroid lymphoma.



Salama, et al., J Cytol Histol 2014, 5:5
http://dx.doi.org/10.4172/2157-7099.1000257

Cytology & Histology

Case Report

Myxofibrosarcoma of the Thyroid: Second Case in Africa

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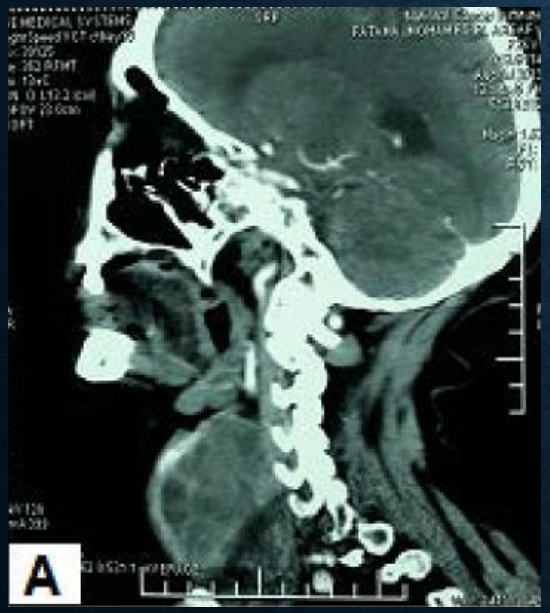

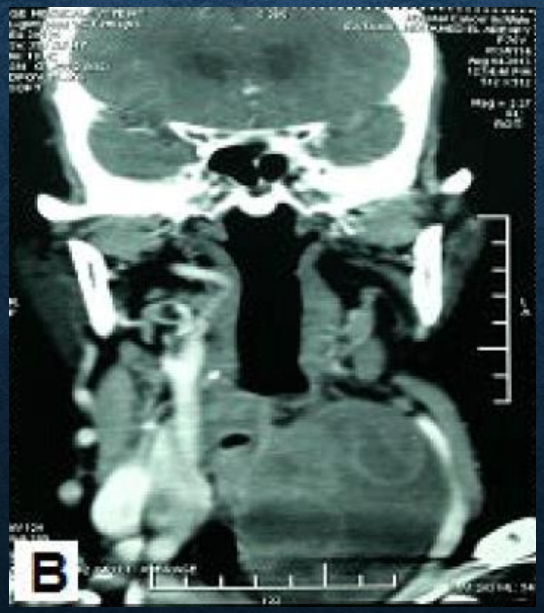

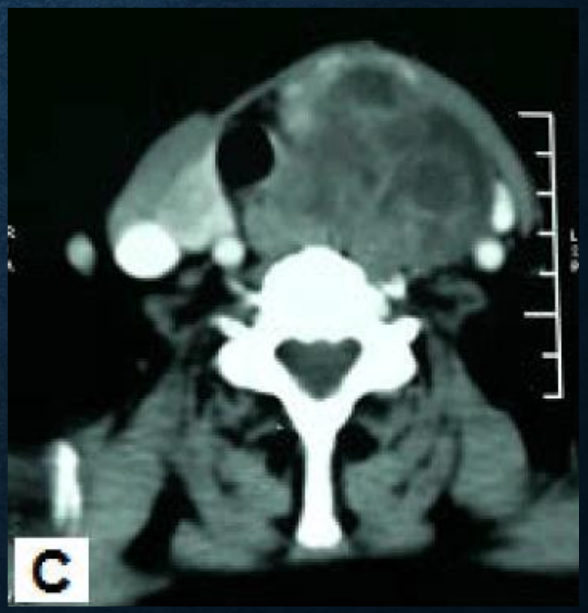

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Nuclear Medicine Notes

- Incidence of malignancy in solitary cold nodule is 15%.
- Thyroid scan done by technetium not iodine.
- No I^{131} imaging done after surgery.
- I^{131} ablation dose (adjusted according to the risk category) not less than 100 MCI will be given. Lower doses as 30MCI is no more used because it did not ablate the residual thyroid tissue in most of cases.
- Post-ablative dose imaging done and detect any residual malignancy or distant metastasis.
- Thyroxin therapy started 24 hours (maximum period for I uptake) after I therapy. 200 mg single dose in the morning on empty stomach. Evaluated at least after 1 month by Free T3 and Free T4 and TSH. If there is symptoms of toxicity, check the pulse rate.

- 6 months after ablative dose, management according to post-ablative dose imaging.
- No treatment if –ve.
- 2^{nd} ablative dose if residual normal thyroid tissue (can be repeated 2-3 times only, if residual persist after that just FU).
- I^{131} therapy for metastatic disease (150 mCI for bone mets, 200 mCI for lung mets).
- If metastatic, evaluate I^{131} therapy every 6 months by re-I therapy and post imaging.
- Maximum single I dose is 200 mCI and maximum cumulative dose is 1000 mCI. After maximum dose, therapy dose can be given but every year.
- No risk of lung fibrosis except if there is diffuse lung metastasis.
- Follow up every 6 months by (CT neck and chest with contrast or neck US and CT chest without contrast) and serum thyroglobulin.

- Thyroglobulin <2 is good for cancer free patient.
- Thyroglobulin should be checked in 2 points (at high and at low TSH level). Its ½ life is 2-3 days, so check postoperatively after >3 weeks.
- 1 mCI give 1 cGy to total body and every 1µCI reaching the thyroid or cancer cells give 1cGy. Thyroid and cancer cells uptake 10% of the given I dose.
- PET-CT is useful in anaplastic and non RAI avid tumors.
- ½ life of T4 is 2-3 weeks and for T3 is 1 day. TSH should reach 30 to let I^{131} imaging and treatment optimal. Stop T4 therapy 1 month or stop T4 for 3 weeks during it give T3 and then stop it and image 1 day later. Another method is to give IM TSH (Thyrogen) and image.
- Stunning: thyroiditis due to RAI or EBRT. Decrease RAI uptake. So, imaging and EBRT is not preferable before ablation or RAI therapy.