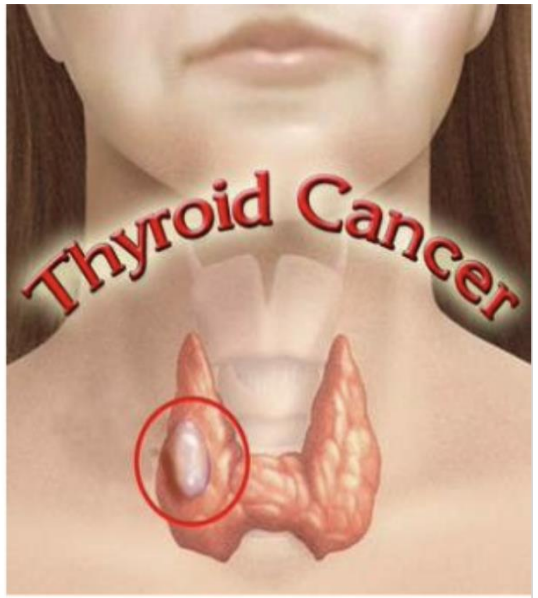


# Case Approach to Thyroid carcinoma

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**Department of Endocrinology**

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# Thyroid nodules and Thyroid Carcinomas

- Prevalence of palpable thyroid nodules **– 5% in women and 1 % in men** in iodine sufficient part of the world (ATA 2015)

- Thyroid cancers – **7 -15 %** of cases on age, sex, radiation exposure history, family history and other factors

- Differentiated thyroid cancer (DTC), which includes papillary and follicular cancer, comprises the vast majority (>90%) of all thyroid cancers and < 3 % are poorly differentiated tumors

# Risk factors for Malignancy

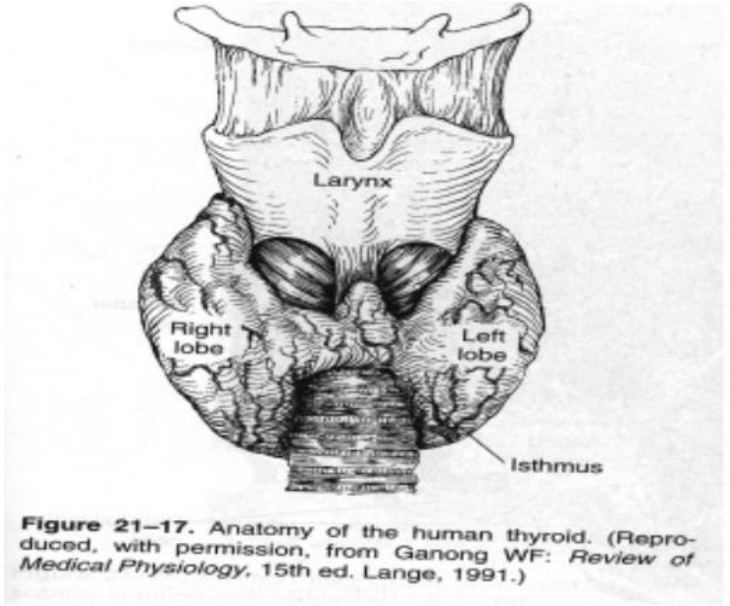
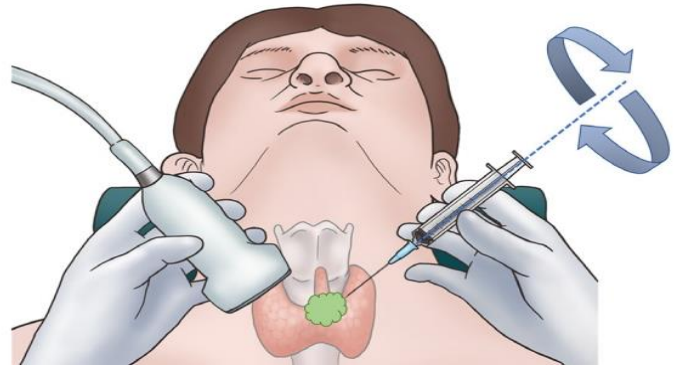


**Figure 21–17.** Anatomy of the human thyroid. (Reproduced, with permission, from Ganong WF: *Review of Medical Physiology*, 15th ed. Lange, 1991.)

1. Prior irradiation
2. Family history
3. Male sex
4. Nodules in individuals < 15 yr , > 45 yr
5. Symptoms of invasiveness: development of hoarseness, progressive dysphagia or dyspnea

# Case 1

- A 35 year-old female with hypothyroidism
- CT head after recent MVA showed a 2.5 cm thyroid nodule
- No history of neck or mantle radiation
- No family history of thyroid cancer
- USG guided FNA report- Malignant cells

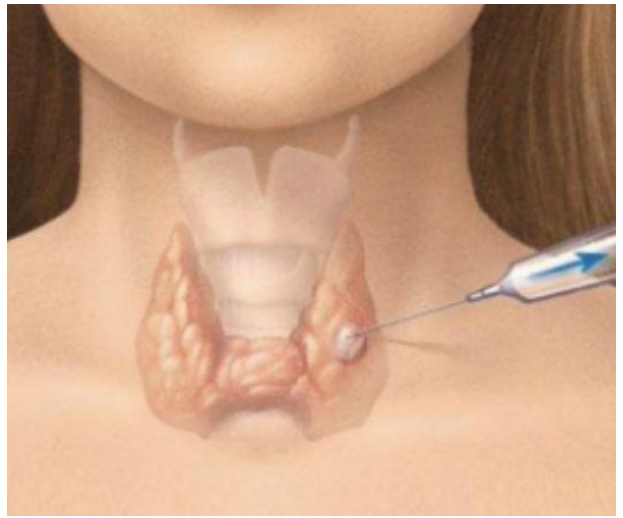


What is the plan of management?

# How can we get diagnosis of thyroid carcinoma?

From findings on USG or USG guided FNA

- Follicular neoplasm- 80% of these nodules-benign & 20 %- thyroid carcinoma
- Papillary carcinoma- accuracy of FNA approaches 100 %



# 2019 ESMO guidelines / 2017 WHO classification

Cytological analysis of FNAB specimens is used to estimate malignancy risk.

Bethesda system for thyroid cytopathology, which comprises the following categories

1. Malignant (risk 97-99%) 
2. Suspicious for malignancy (risk 60-75%)
3. Follicular neoplasm or suspicious for follicular neoplasm (risk 15-30%)
4. Atypia of undetermined significance or follicular lesion of undetermined significance (risk 5-15% based on repeated atypicals)
5. Non-diagnostic or unsatisfactory (risk 1-4%)
6. Benign (risk 0-3%)

# WHO classification for differentiated follicular-derived Thyroid carcinomas

**Table 1. WHO classification for differentiated follicular-derived thyroid carcinomas: morphological parameters and molecular markers**

| Tumour type | Morphology | Molecular markers |
|---|---|---|
| NIFTP | Encapsulated, clear nuclei, no papillae | *RAS, BRAF K601E* |
| Papillary carcinoma | | |
| Classical | Papillae and clear nuclei | *BRAF V600E, RET/PTC fus, NTRK fus, ALK fus,* 1q amp |
| Follicular variant | Follicles and clear nuclei | *BRAF K601E, RAS, PAX8/PPARγ, EIF1AX, THADA fus,* 22q del |
| Tall, columnar, solid, hobnail variants | Special structural and cell features | *BRAF V600E,* 1q amp, *TERT* promoter, *TP53, PIK3CA, CTNNB1* |
| Follicular carcinoma | Capsular invasion (MI), vascular invasion >4 blood vessels (angioinvasive), extrathyroidal invasion (WI) | *RAS, PAX8/PPARγ, PTEN, PIK3CA, TSHR, TERT* promoter, *CNA* |
| Hürthle cell carcinoma | Capsular invasion (MI), vascular invasion >4 blood vessels (WI) | *RAS, EIF1AX, PTEN, TP53, CNA, mtDNA* |
| Poorly differentiated carcinoma | Invasion, mitoses >3, necrosis, convoluted nuclei | *RAS*, *TERT* promoter, *TP53, PIK3CA, PTEN, CTNNB1, AKT1, EIF1AX, ALK* fus, histone methyltransferases, SWI/SNF chromatin remodelling complex |

amp, amplification; CNA, copy number alteration; del, deletion; fus, fusion; MI, minimally invasive; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; SWI/SNF, switch/sucrose non-fermentable; WHO, World Health Organization; WI, widely invasive.

Management plan for Case 1 ???

Pre-op assessment ?

# What is the role of preoperative staging with diagnostic imaging and laboratory tests?

1. USG ( Neck)
2. CT/ MRI/ PET
3. serum Tg or anti-Tg

# Role of preoperative staging with diagnostic imaging (USG – NECK)

- (A) Preoperative **neck US** for cervical lymph nodes - **all patients** undergoing thyroidectomy for malignant or suspicious for malignancy

*(Strong recommendation, Moderate-quality evidence)*

- (B) US-guided FNA - lymph node ≥ 8–10 mm

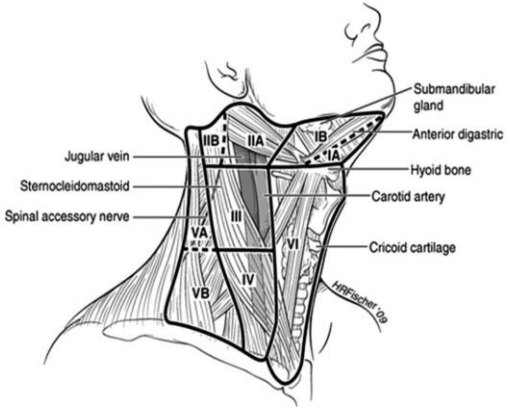
*(Strong recommendation, Moderate-quality evidence)*

- (C) FNA-Tg washout - suspicious cervical lymph nodes in selected patients

*(Weak recommendation, Low-quality evidence)*

# Role of preoperative staging with diagnostic imaging (USG-Neck)

- Differentiated thyroid carcinoma ( PTC)- cervical lymph node metastases in 20%–50%




- preoperative US - positive **only half** of lymph nodes at surgery
- USG features suggestive of abnormal metastatic lymph nodes

**include enlargement, loss of the fatty hilum, a rounded rather than oval shape, hyperechogenicity, cystic change, calcifications, and peripheral vascularity**

- Malignant lymph nodes are much more likely to occur in **levels III, IV, and VI than in level II**

# Role of preoperative staging with diagnostic imaging (CT/ MRI / PET)

(A) Preoperative (CT, MRI) (IV) contrast - an adjunct to US for patients with clinical suspicion for **advanced disease, including invasive primary tumor, or clinically apparent multiple or bulky lymph node involvement.** *(Strong recommendation, Low-quality evidence)*

(B) Routine preoperative 18FDG-PET scanning is not recommended.

# Role of preoperative staging with laboratory tests

- Routine preoperative measurement of serum Thyroglobulin (Tg) or anti-Tg antibodies is not recommended.

# Treatment of Thyroid carcinoma (DTC)

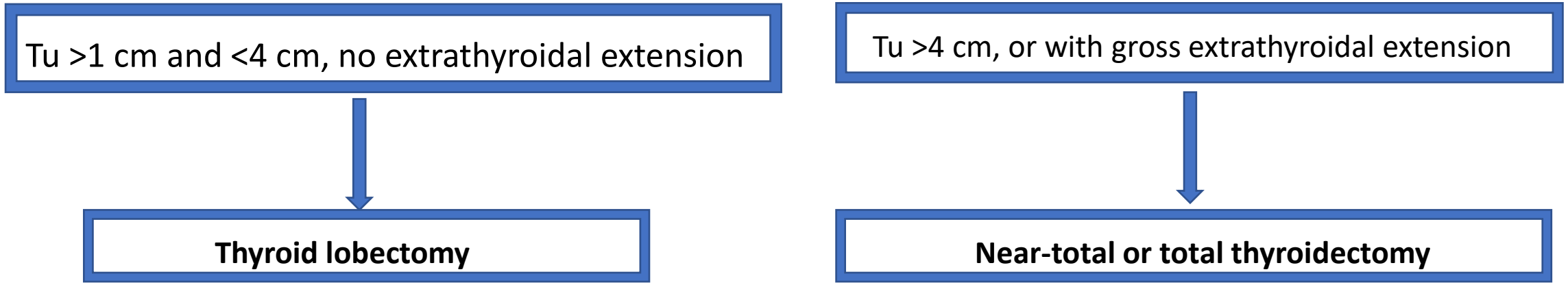
**Surgery**

- For cytology “diagnostic of” or “suspicious for” papillary thyroid cancer, **surgery is** recommended.

- If FNAB cytology is indeterminate, use of **molecular markers** such as **BRAF, RAS, RET/PTC, Pax8-PPARɣ, or galectin-3** may be considered to guide management

- **Iodine-123 ($^{123}$I)** thyroid scan - considered if the cytology report documents a **follicular neoplasm**, especially TSH -in the low-normal range

# Surgery




An alternative active surveillance management approach can be considered in:

A) patients with very low risk tumors
B) patients at high surgical risk because of co-morbid conditions,
C) patients expected to have a relatively short remaining life span

# Management after Surgery

Patients on thyroid replacement therapy to suppress TSH for approximately 4-6 weeks

**Radioiodine Therapy**

T4 stopped to induce high TSH

4- 6 weeks after surgery

To detect and destroy any metastasis and residual tissue in the thyroid

Any normal thyroid remnant or metastatic disease -Therapeutic dose of $^{131}I$

- Therapy is administered until radioiodine uptake is completely absent.
- Radioiodine treatment may be used again 6-12 months after initial treatment of metastatic disease

Patients with low-risk differentiated papillary thyroid cancer have shown excellent responses to total thyroidectomy without radioiodine remnant ablation.

# How should initial risk estimates be modified over time?

Risk of structural disease recurrence is a continuum of risk that ranges from <1% in very low-risk patients to >50% in high-risk patients

Initial recurrence risk estimates should be continually modified during follow-up,

because the risk of recurrence and disease-specific mortality can change over time

*(Strong recommendation, Low-quality evidence) (ATA 2015)*

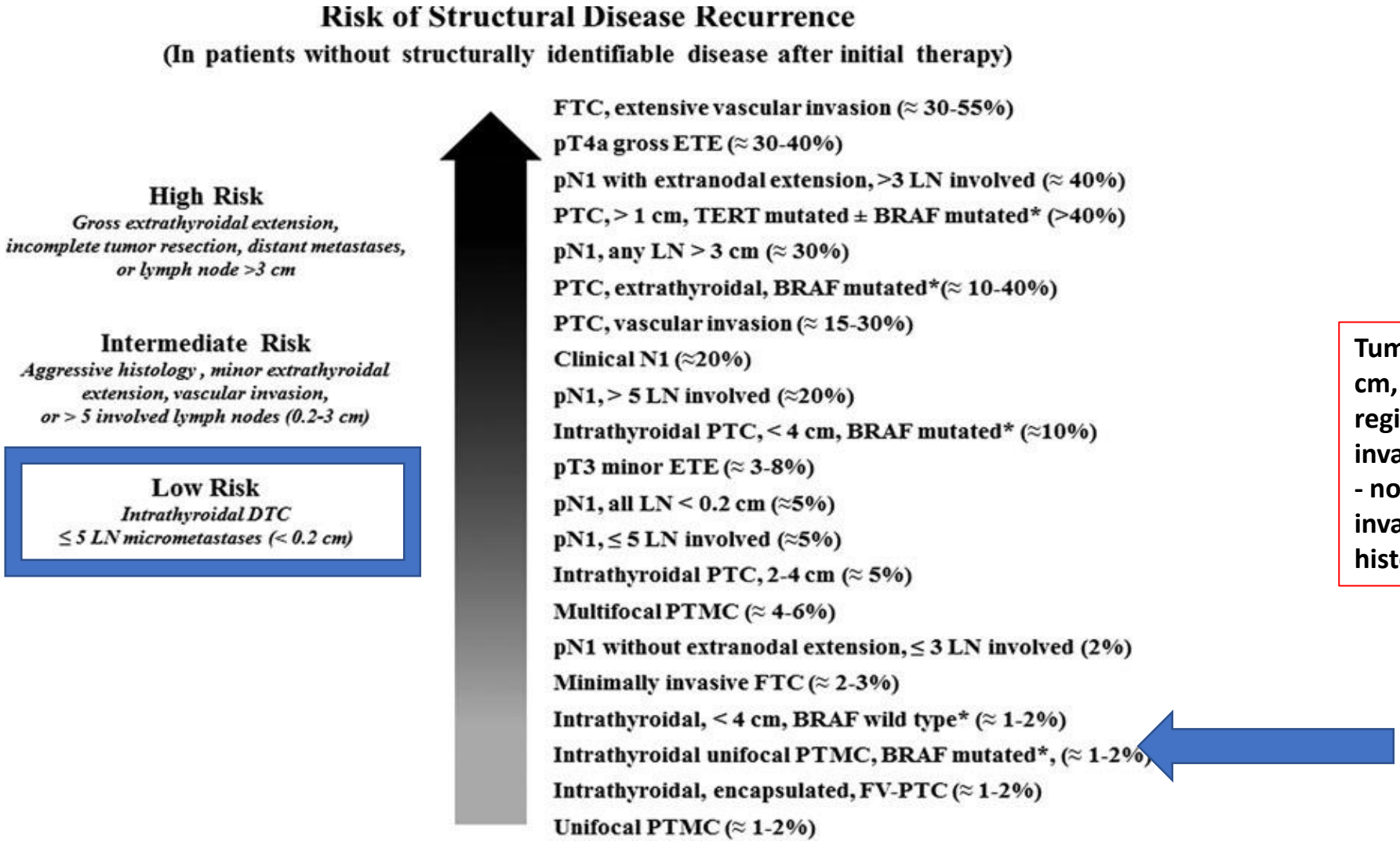
# How can we do follow-up for this patient? (case 1)

Biopsy reports- Tumor size 2.5 cm ,no loco-regional invasions

- no vascular invasion
- histology – well differentiated papillary cell type

**What are risks of recurrence for the patients with thyroid carcinoma who undergoes Surgery ?**

# Modified Initial Risk Stratification System



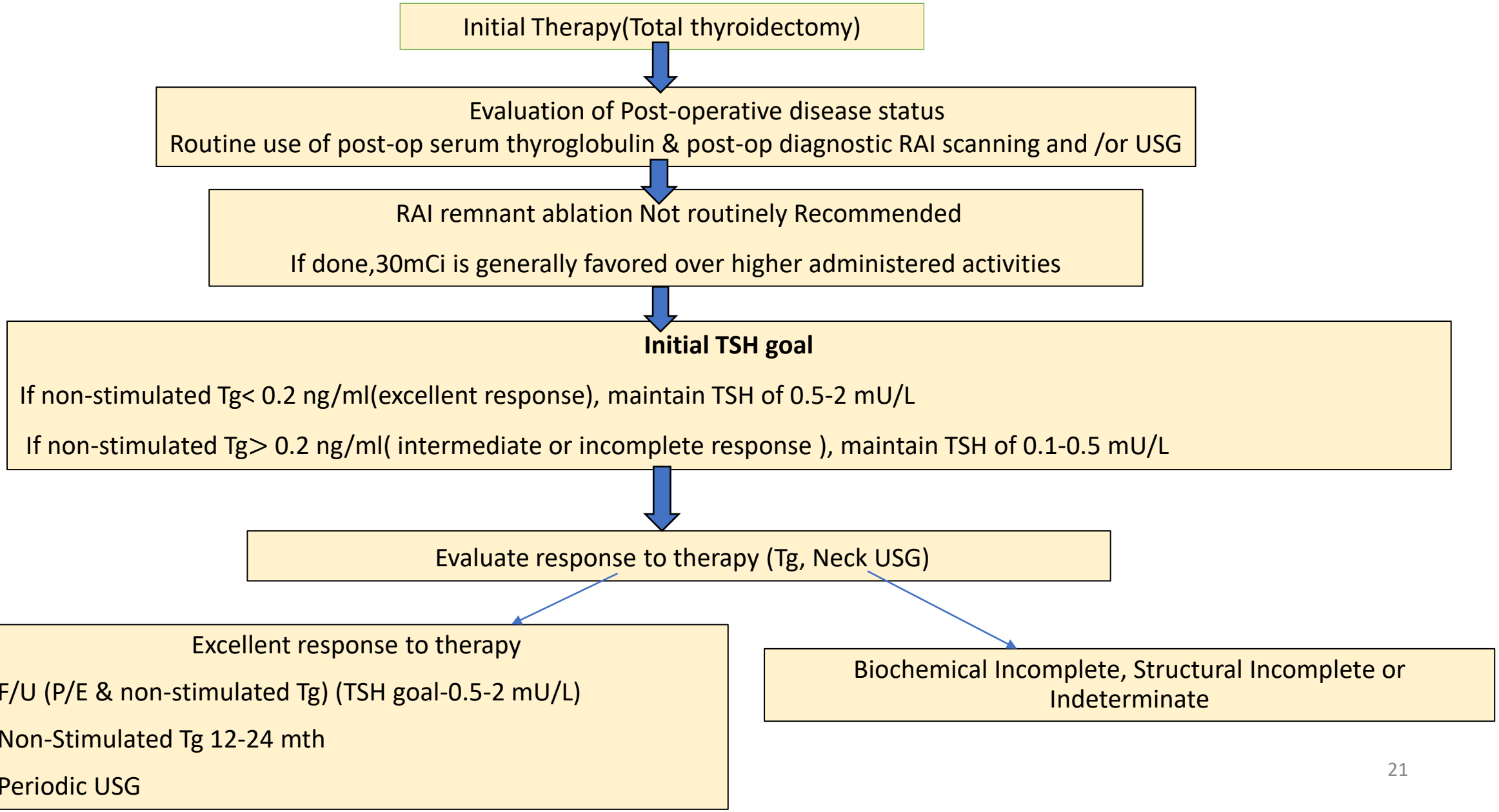

**Tumor size 2.5 cm, no loco-regional invasions**
**- no vascular invasion**
**histology – PTC**

# ATA 2009 Risk Stratification System

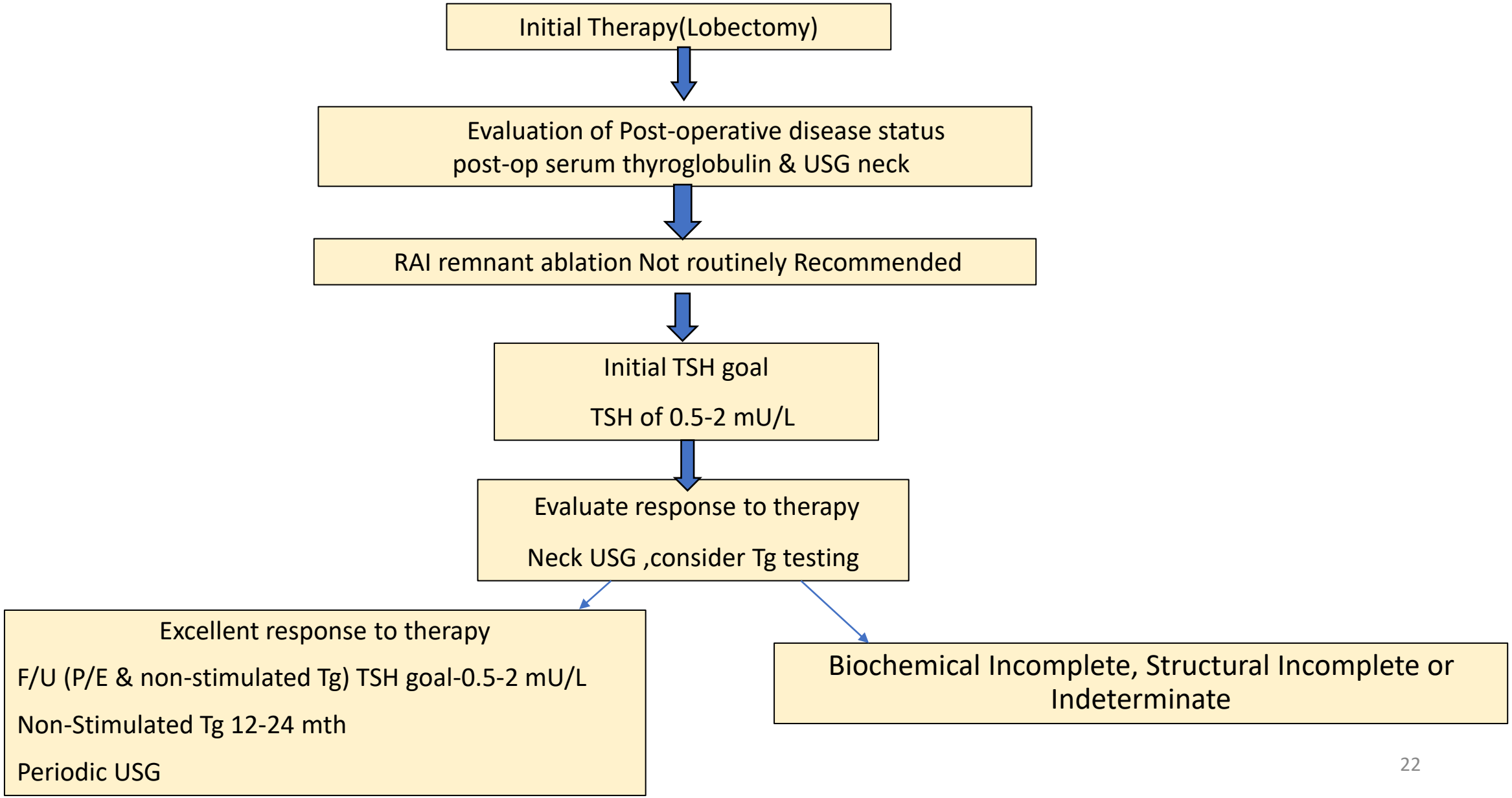
**ATA low risk**

- Papillary thyroid cancer (with **all of the following**):
- No local or distant metastases;
- All macroscopic tumor has been resected
- No tumor invasion of loco-regional tissues or structures
- No aggressive histology (e.g., tall cell, hobnail variant, columnar cell)
- If $^{131}I$ is given, no RAI-avid metastatic foci outside thyroid bed
- No vascular invasion
- Clinical N0 or $\leq$ 5 pathologic N1 micro-metastases (<0.2 cm in largest dimension)
- Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer.
- Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasions

# Follow up- low-risk DTC



# Follow up- low-risk DTC (less than total thyroidectomy )(lobectomy or lobectomy with isthmusectomy)

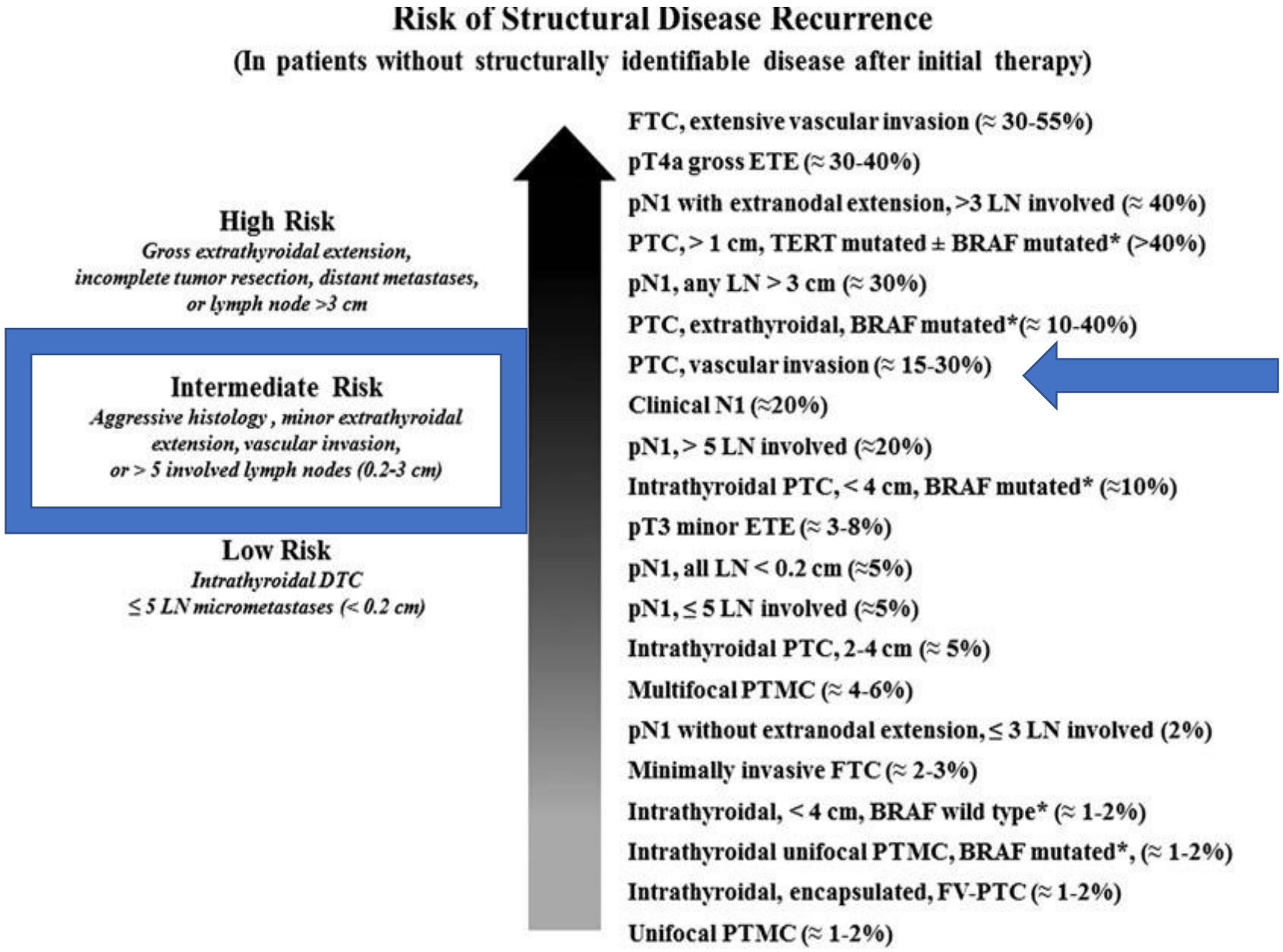


# Case 2

- Patient is a 38 year-old female who presents after finding a “lump in my neck”
- TSH- normal , USG (Thyroid) -TIRADS- 5
- USG guided FNAC reports - Malignant risk cells
- Patient undergoes Thyroidectomy
- Histology report- **Papillary thyroid cancer with vascular invasion** , **Microscopic invasion of tumor into the perithyroidal soft tissues**
  Clinical N1 or >5 pathologic N1 with all involved lymph nodes

**What is risk of recurrence for this patient ??**

# Case 2



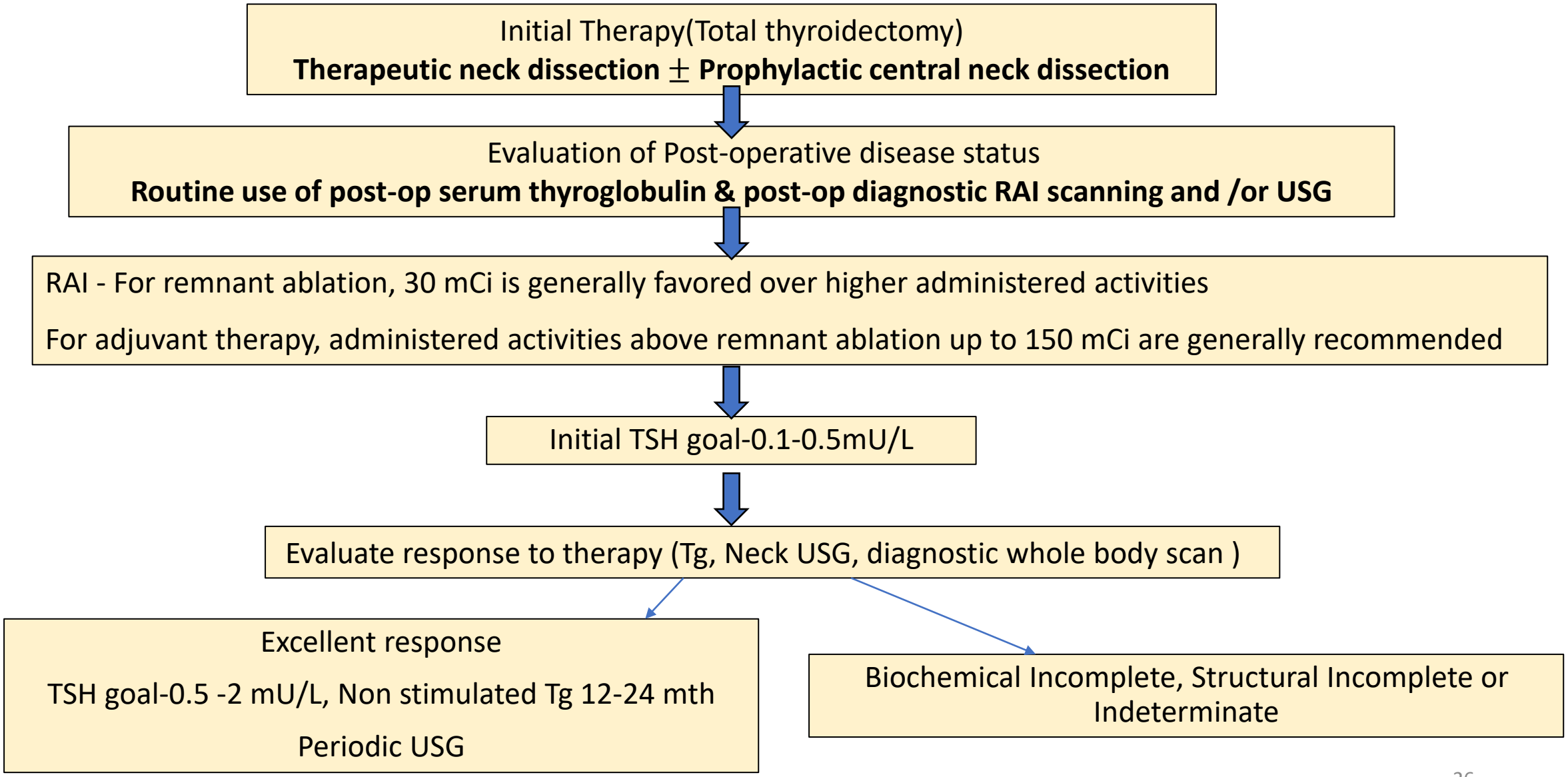

vascular invasion ,microscopic invasion to perithyroidal soft t/s

# ATA 2009 Risk Stratification System

**ATA intermediate risk**

- Microscopic invasion (**perithyroidal soft tissues)**
- RAI-avid metastatic foci in neck on the first posttreatment whole-body RAI scan
- Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma)
- Papillary thyroid cancer with vascular invasion
- Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension
- Multifocal papillary microcarcinoma with ETE and BRAFV600E mutated

# Follow up- Intermediate risk DTC

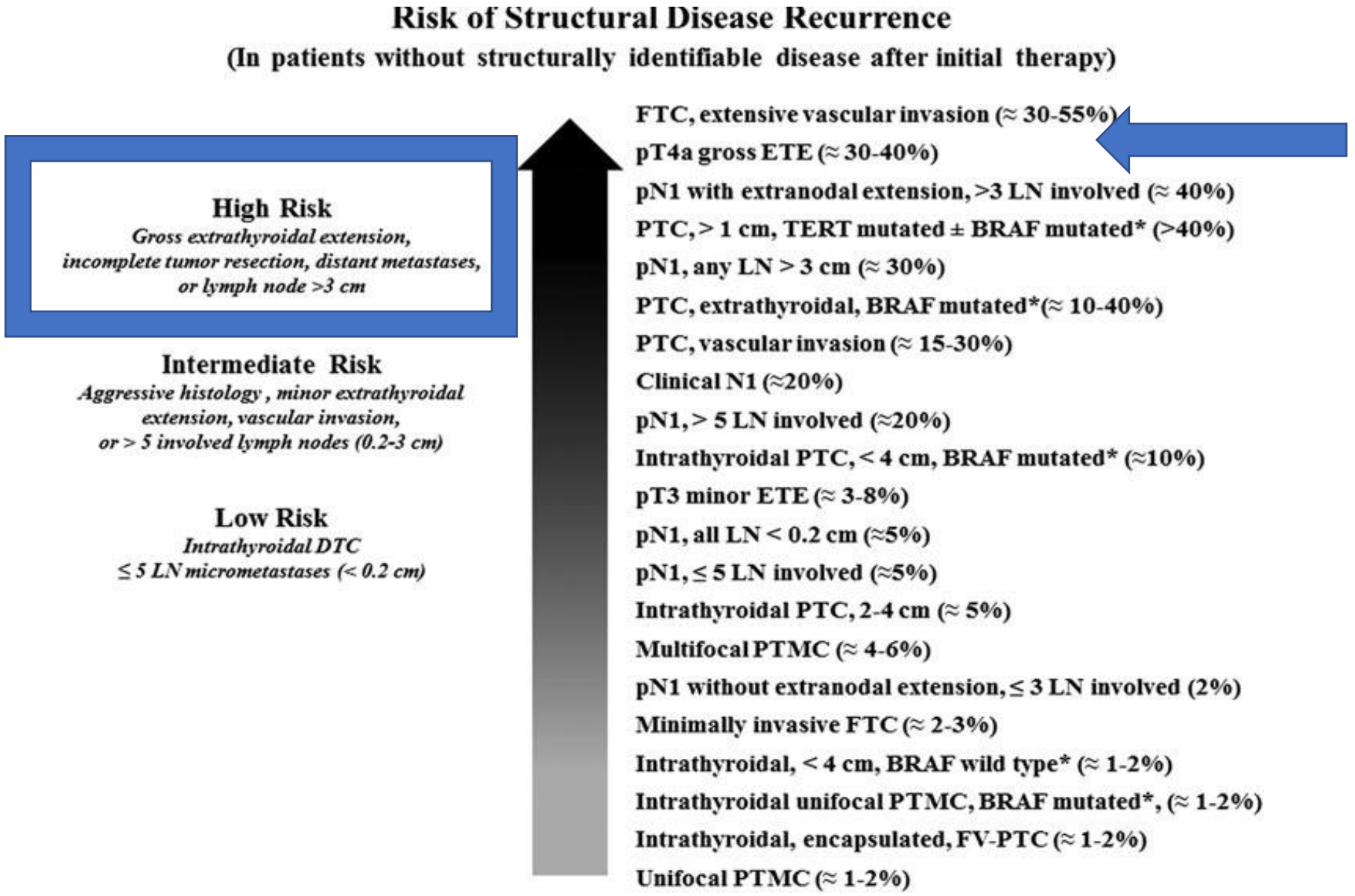


# Case 3

- A 45 year-old  gentleman with an enlarging neck mass
- Mother has thyroid cancer
- USG- 4 nodules on the right all > 2.8 cm and 3 nodules on the left all > 2.0 cm, Multiple nodules on both sides have increased internal blood flow and calcifications
- Significant bilateral lymphadenopathy
- FNAC- malignant cell (FTC)
- Total Thyroidectomy and central neck dissection -done
- Histology reports- **Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE), Incomplete tumor resection, metastatic cervical lymph node**

**What is risk of recurrence for this patient ??**

# Case 3



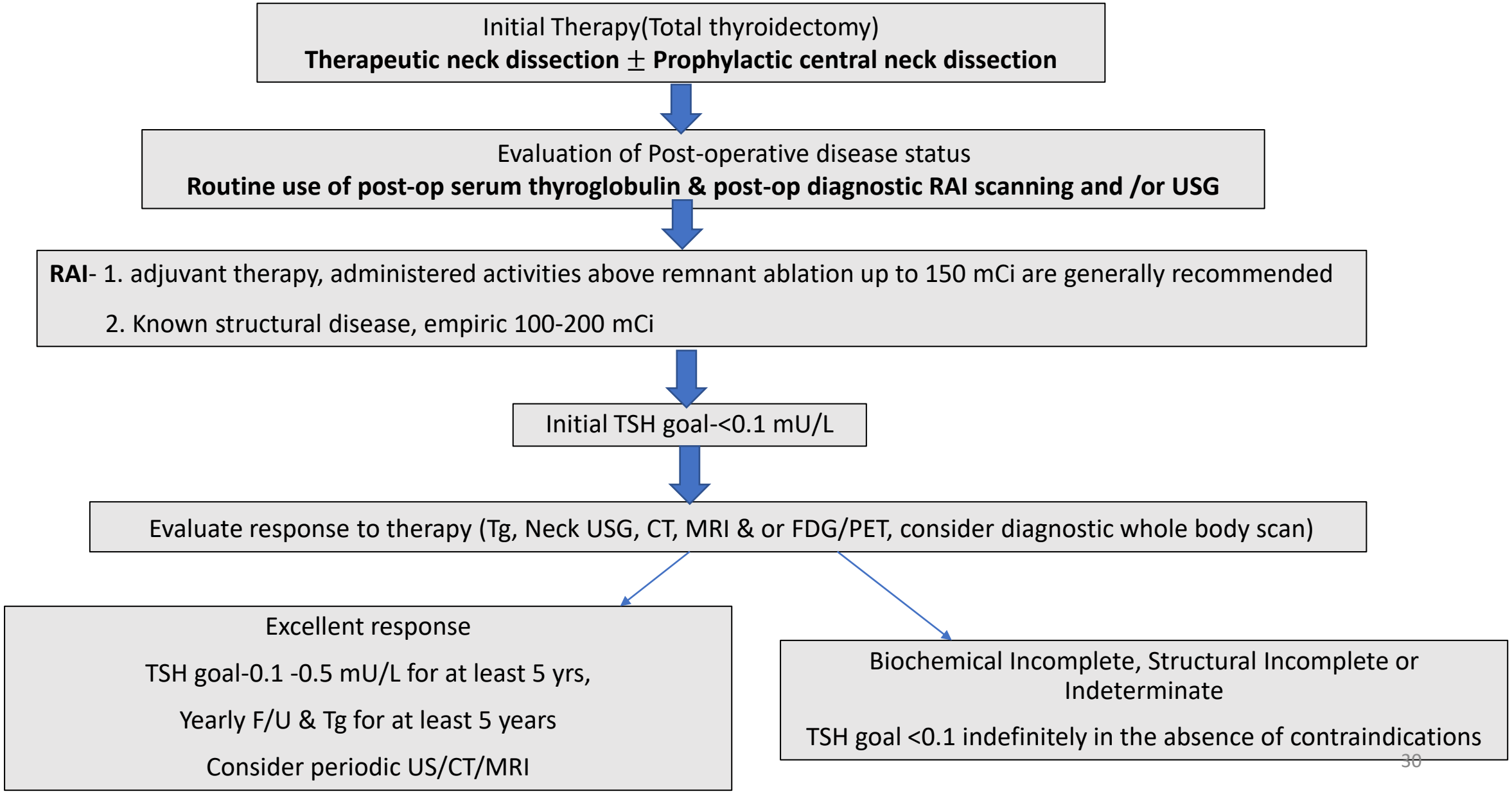

ETE,Cx L/N(+)
Histology- FTC

# ATA 2009 Risk Stratification System

**ATA high risk**

- Macroscopic invasion of tumor into the perithyroidal soft tissue(gross ETE)
- Incomplete tumor resection
- Distant metastases
- Postoperative serum thyroglobulin suggestive of distant metastases
- Pathologic N1 with any metastatic lymph node ‡3 cm in largest dimension
- Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)

# Follow up for High Risk DTC



# Definition of response to therapy

- **Excellent response:** no clinical, biochemical, or structural evidence of disease
- **Biochemical incomplete response**: abnormal Tg values in the absence of localizable disease
- **Structural incomplete response**: persistent or newly identified loco-regional or distant metastases / structural or functional (RAI scan, 18FDG-PET) evidence of loco-regional or distant metastases .
- **Indeterminate response**: biochemical or structural findings that cannot be classified as either benign or malignant (acceptable response)

# Follow up plan

| Response | Management plan |
|---|---|
| Biochemical incomplete response | 1. If associated stable or declining Tg values -continued observation with ongoing TSH suppression in most patients.<br>2. Rising Tg or anti-Tg antibody -prompt additional investigations & potentially additional therapies. |
| Structural incomplete response | Additional treatments or ongoing observation d/p on multiple clinico-pathologic factors (size, location, rate of growth, RAI avidity, 18FDG avidity, and specific pathology) |
| Indeterminate response | 1.continued observation (serial imaging of the nonspecific lesions & Tg monitoring.<br>2. Nonspecific findings that become suspicious over time can be further evaluated with additional imaging or biopsy. |

# Treatment of Advanced Disease

- USG-guided percutaneous ethanol injections - excellent alternative to surgery
- Stage T4 disease- external beam radiation therapy (EBRT)
- Chemotherapy- in symptomatic patients with recurrent or advancing disease, and it may improve the quality of life in patients with bone metastases
- Novel agents are under active investigation as options for systemic therapy (multitargeted kinase inhibitors) (eg, levatinib, sorafenib, sunitinib, axitinib, vandetanib, pazopanib)
- BRAF V600E mutation inhibitors (eg, vemurafinib, dabarafenib)

What is long term follow-up plan for patients with thyroid CA?

# Long-term Management

1. Repeat  RAI scan 6-12 months after ablation & every 2 years thereafter

2. Tg- every 6-12 months for at least 5 years

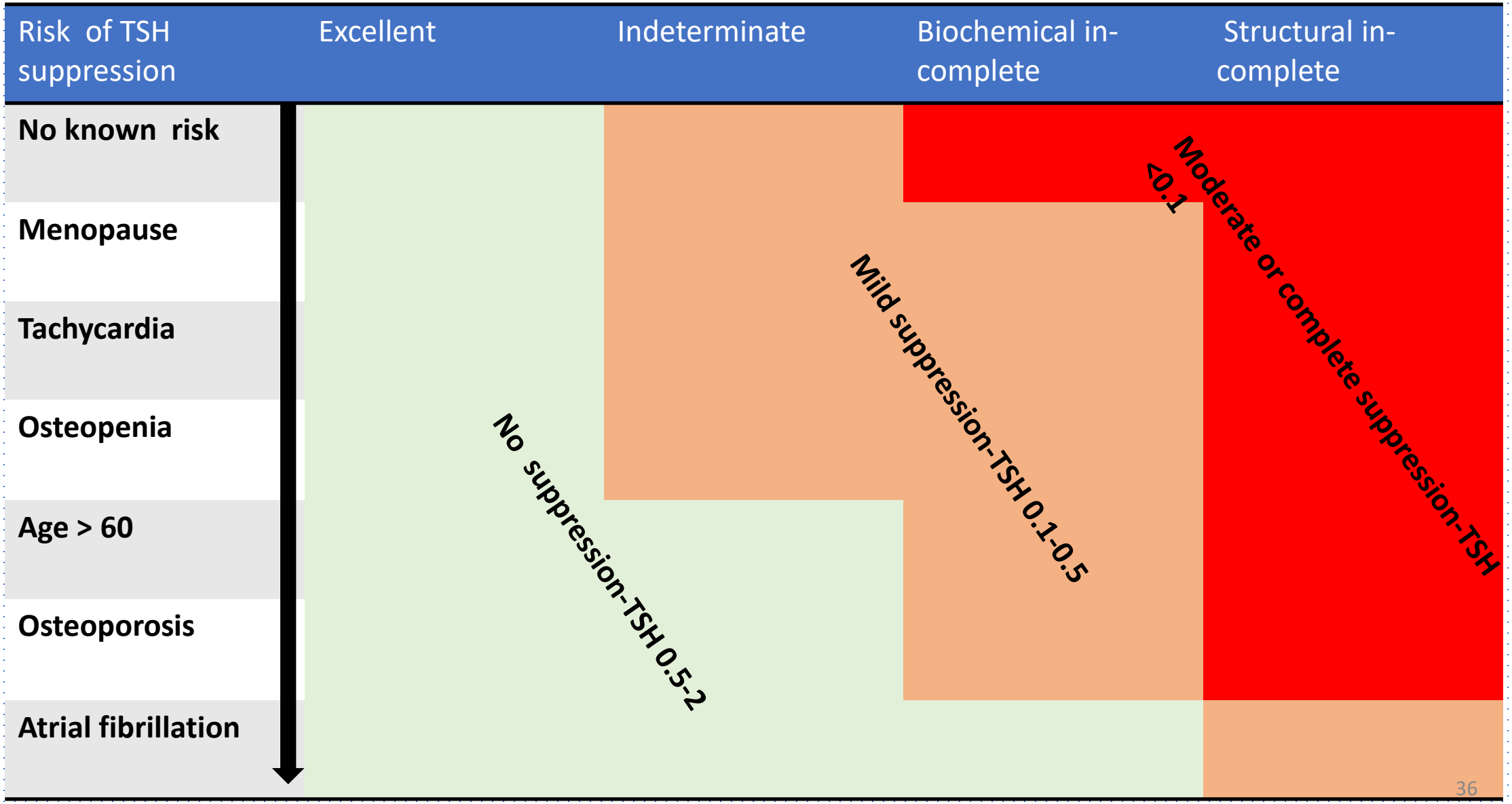
3.Annual measurement of unstimulated  Tg and periodic neck  USG

4**.** A patient who has had a thyroidectomy without parathyroid preservation requires **vitamin D and calcium** supplementation for life.

5. Patients require lifelong thyroid hormone replacement therapy, especially after total thyroidectomy (**levothyroxine** in a dosage of **2.5-3.5 mcg/kg/d)**

- What are the risks of thyroid hormone replacement???

# Thyrotropin Targets for Long-Term Thyroid Hormone Therapy



# Case 4

- 52 year of gentleman present with 4 cm irregular palpable nodule in neck
- He has h/o – operated pheochromocytoma 8 years ago
- Family h/o- malignancy (+)
- USG guided FNA- suspicious for malignancy (Medullary cell) type)

- What is management plan for this patient???

# Management plan for Medullary Thyroid Ca

**Clinically apparent MTC**

1. Tu $\leq 1cm$
2. No Suspicious L/N on US

Total thyroidectomy with bilateral Central Neck dissection

1. Tu $\geq 1cm$
2. Suspicious L/N on US
3. Positive central neck nodes

Total thyroidectomy with bilateral Central Neck dissection & Ipsilateral Lateral Neck Dissection

1. (+) contra lateral nodes US
2. Extensive L/N ipsilaterally
3. Bilateral tu $\geq 1cm$

Add contralateral lateral Neck Dissection

Pre-operative Work up

1.Calcitonin & CEA

2. RET genetic testing

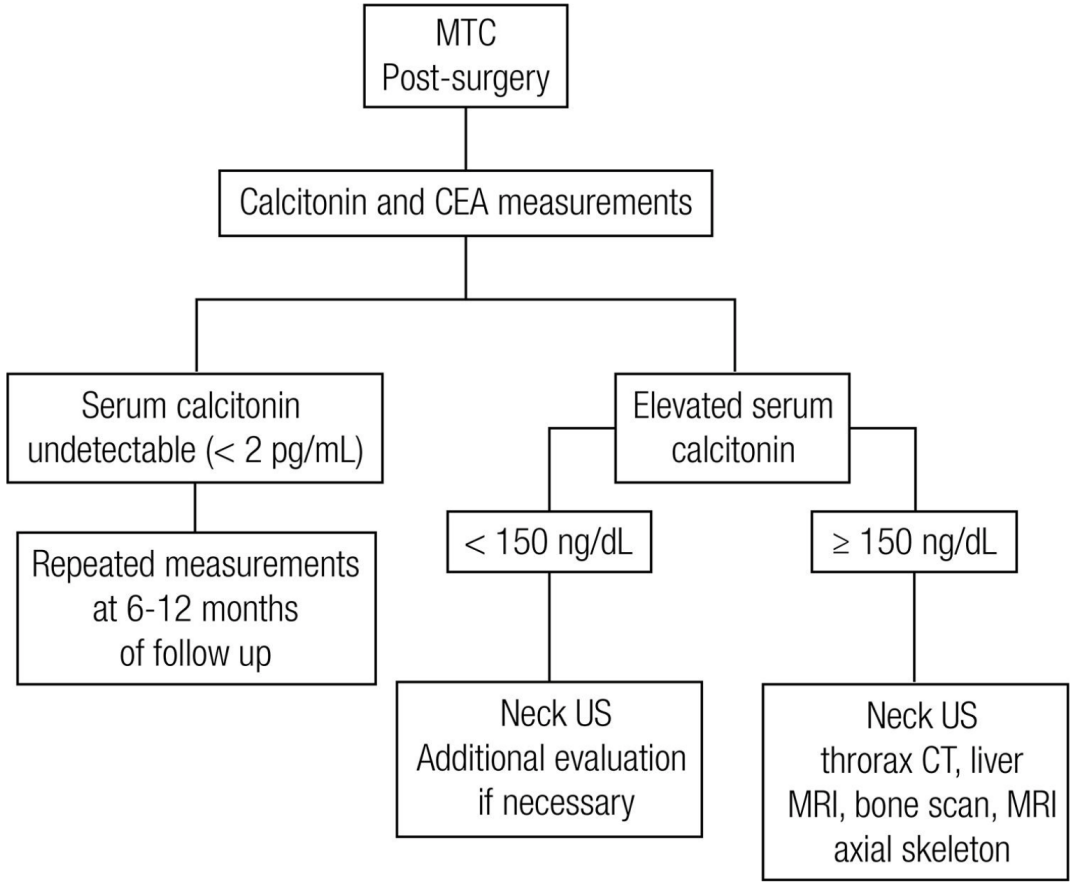
3. Serum Ca, PTH

4. Urinary or Plasma Metanephrines

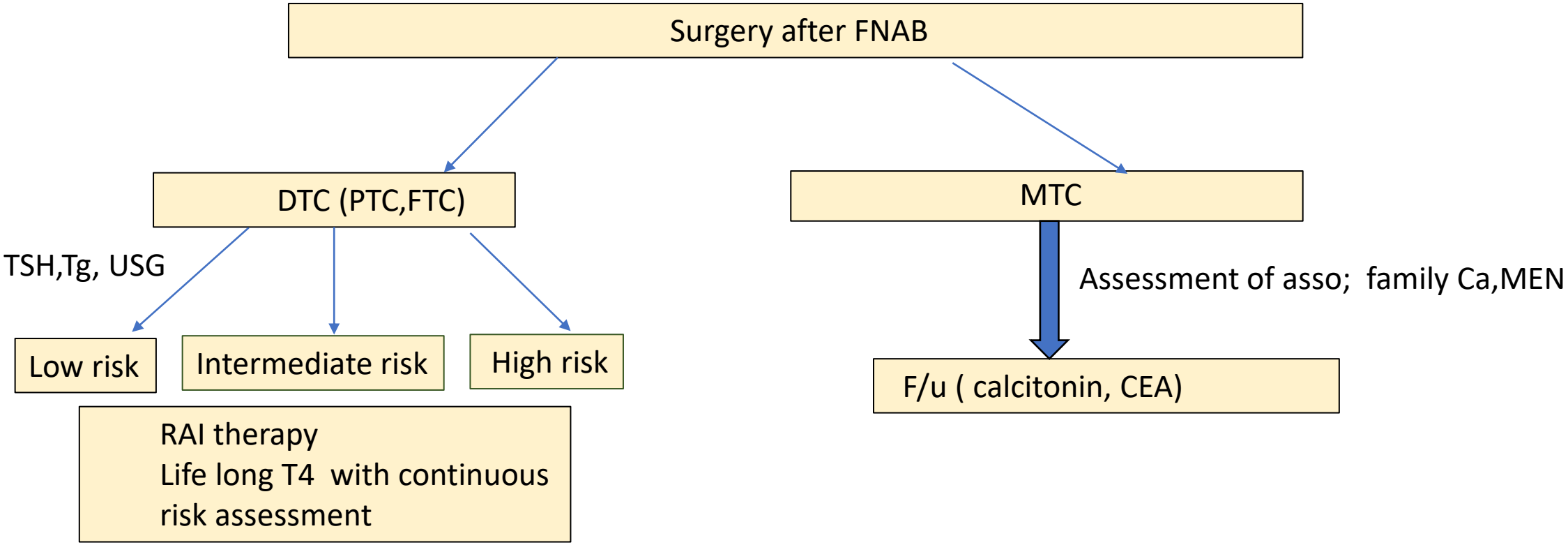
5. Neck USG

6.CT( chest & Mediastinum)

# Post op management for MTC



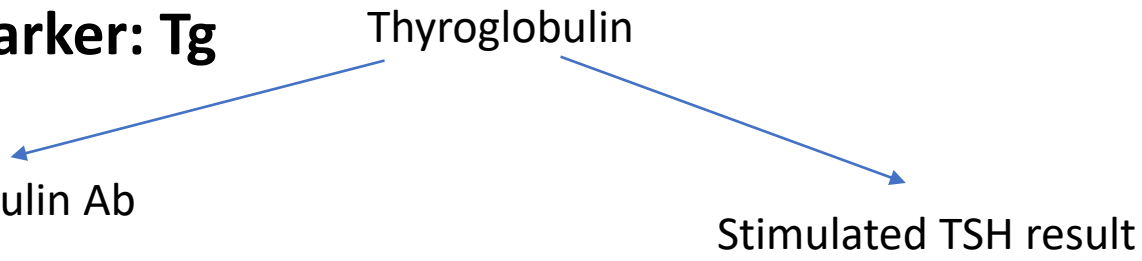
# Summary




**DTC** –curable disease with long term high survival rates
Surgery- main stay of treatment
DTC treatment – multi-disciplinary team ( Thyroid surgeon, nuclear medicine specialist, endocrinologist, medical oncologist and radiation oncologist)
RAI- available and highly effective treatment
Serum Calcitonin- mainly in MTC mx & F/U

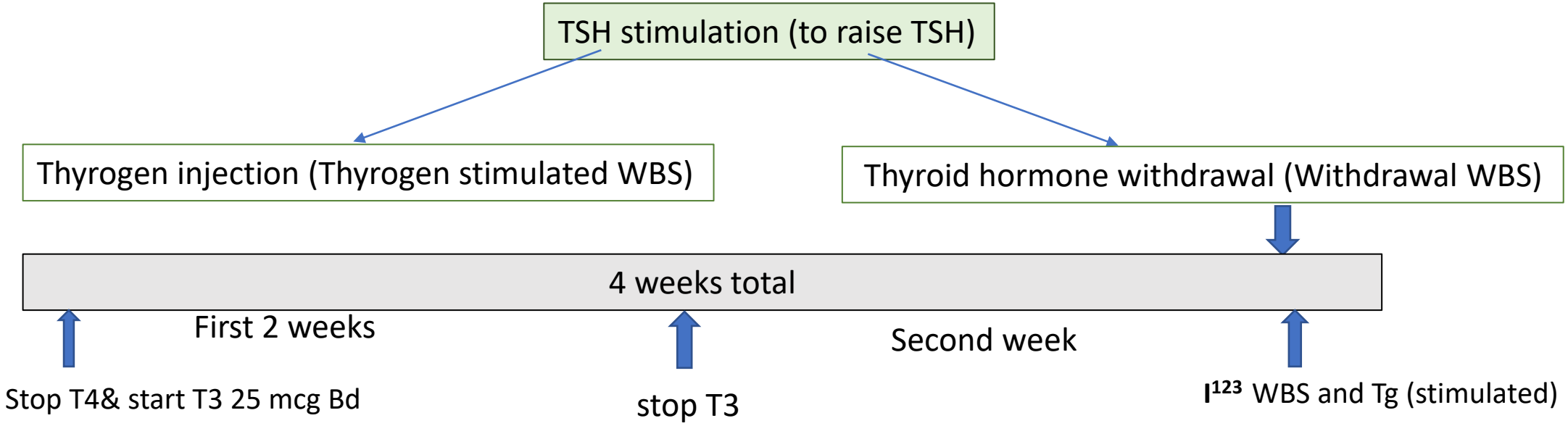
# Monitoring thyroid carcinoma recurrence (Thyroid Ca Clinic, UCS, Fresno)

- 1. **Thyroid ca marker: Tg**




-suppressed Tg (TSH <0.1)
-Non-stimulated Tg(TSH-0.1-<30)
-stimulated Tg (TSH > 30 )

- 2. **Thyroid US**
- 3. **$I^{123}$ WBS (thyrogen stimulated WBS) and stimulated Tg measurement**



# References


- American Thyroid Association (ATA) (2015)
- National Comprehensive Cancer Network (NCCN) (2014)
- European Society for Medical Oncology (ESMO)
- American Association of Clinical Endocrinologists/Association of Medicine Endocrinologist /European Thyroid Association (AACE/AME/ETA)

# “Thank You”

# Anti-Tg antibodies

- Anti-Tg antibodies, which occur in approximately 25% of thyroid cancer patients (797) and 10% of the general population
- Anti-Tg antibodies should be measured in a different assay if the routine anti-Tg antibody assay is negative in a patient with surgically proven Hashimoto thyroiditis
- It may be useful to measure anti-Tg antibodies shortly after thyroidectomy and prior to ablation because high levels may herald the likelihood of recurrence in patients without Hashimoto thyroiditis
- Serial serum anti-Tg antibody quantification using the same methodology may serve as an imprecise surrogate marker of residual normal thyroid tissue, Hashimoto thyroiditis, or tumor
- Following total thyroidectomy and RAI remnant ablation, anti-Tg antibodies usually disappear over a median of about 3 years in patients without evidence of persistent disease

- No curative treatment currently exists for anaplastic thyroid cancer (ATC). The majority of patients present with unresectable or metastatic disease.  NCCN guidelines recommend attempting total thyroidectomy in patients with resectable disease. [5]
- ESMO guidelines note that incomplete palliative resection (R2) or ‘debulking‘ does not affect prognosis and is not recommended. Complete or near-complete (R0 or R1) resection followed by high-dose EBRT, with or without concomitant chemotherapy, provides optimal local disease control. For best outcomes, postoperative radiotherapy must be delivered as soon as possible after surgery. IMRT is the recommended approach. [6]
- ATA guidelines recommend total lobectomy or total or near-total thyroidectomy with a therapeutic lymph node dissection for patients with intrathyroidal ATC. In patients with extrathyroidal invasion, an en bloc resection should be considered if grossly negative margins (R1 resection) can be achieved. [3] Both the NCCN and ATA guidelines recommend adjuvant radiation therapy, chemotherapy, or both. [3, 5]

- In all three cases, RAI administration must be followed by an iodine-131 ($^{131}$I) whole-body scan (WBS) to stage the disease and document the $^{131}$I avidity of any structural lesion.
- The estimated level of risk for persistent/recurrent disease will determine whether and how much RAI is given. Low activities are usually given for remnant ablation (30 mCi, 1.1 GBq); high activities (≥100 mCi, 3.7 GBq) are used for treatment purposes.
- To optimise isotope uptake, RAI should be given after thyroid-stimulating hormone (TSH) stimulation, which can be achieved by withdrawing levothyroxine for 4–5 weeks, ideally until serum TSH levels reach ≥30 µIU/ml
- Alternatively, recombinant human TSH (rhTSH) can be given (two daily injections of 0.9 mg of rhTSH followed by RAI on day 3)
- The resulting TSH level is not usually measured (unless doubts arise as to whether the injections have been properly administered). Levothyroxine withdrawal is preferred if distant metastases are present.
- The use of rhTSH is associated with superior short-term QoL

- amount of residual thyroid cancer and/or normal thyroid tissue, the TSH level at the time of Tg measurement, the functional sensitivity of the Tg assay,
- the Tg cutoff used for analysis, the individual risk of having RAI-avid loco-regional or distant metastasis, the time elapsed since total thyroidectomy, and/or the sensitivity of the post- therapy scanning technique (SPECT/CT vs. planar imaging).
- a postop- erative Tg threshold of >5 ng/mL was suggested as an in- dication for RAI treatment
- an unstimulated Tg of ‡2 ng/mL with a concomitant median TSH level of 0.48 mIU/L was reported to detect all patients with disease recurrenc