Taipei Veterans General Hospital Oncology Practice Guidelines:

Thyroid Cancer

Version 1: 2013.11.14
Version 2: 2014.11.27
Version 3: 2015.10.08
Version 4: 2016.11.10
Version 5: 2017.09.14
Version 6: 2018.09.13
Version 7: 2019.09.12
Version 8: 2020.09.24
Version 9: 2021.10.14
Version10:2022.10.06

Taipei VGH Breast Cancer Panel Members (2017)

- **Surgical Oncology**
  - 李建賢; 曾令民; 陳瑞裕; 蔡宜芳; 郭栢仲
  - 朱本元; 戴世光; 李宗倫; 張嘉帆
- **Medical Oncology**
  - 陳涵栩; 郭錦松 ; 黃君睿
- **Nuclear Medicine Oncology**
  - 姚珊汎*
- **Diagnostic Radiology**
  - 邱宏仁; 王信凱
- **Pathology**
  - 杭仁釩
- **Specialized Nursing & Social Worker:** 史書華

***Writing Committee Member**

Thyroid Nodules are a Common Clinical Problem

- **The prevalence of palpable thyroid nodules is 5% in women and 1% in men**
- **High-resolution ultrasound can detect thyroid nodules in 19 to 67% with higher frequencies in women and elderly.**
- **The clinical importance of thyroid nodules is the need to exclude thyroid cancer**

Kloos RT, et al. *Thyroid*. 2009; 19: 565-612.
Cooper DS, et al. Thyroid 2009; 19: 1167-1214

Identify Malignant Nodules

- **History and physical examination**
- **Laboratory testing**
- **Imaging studies**
- **Fine needle aspiration biopsy**
- **Assess the likelihood of malignancy**

Hegedüs L et al. *Endocr Rev*. 2003;24:102-132.[1]

History in Favor of Malignancy

- **Young age (<15 yr) or older age (>45 yr)**
- **Male gender**
- **Neck irradiation during childhood or adolescence**
- **Rapid growth**
- **Recent changes in speaking, breathing, or swallowing**
- **Family history of thyroid malignancy or MEN2**

[1] Hegedüs L et al. *Endocr Rev*. 2003;24:102-132.

Manifestations of Malignancy on Physical Examination

- **Firm consistency of nodule**
- **Irregular shape**
- **Fixation to underlying or overlying tissues**
- **Vocal cord paralysis**
- **Regional lymph adenopathy**

Hegedüs L et al. *Endocr Rev*. 2003;24:102-132.[1]

What is The First-line Screening Test?

- **Measure serum TSH in the initial evaluation**
- **If serum TSH is subnormal, a radionuclide thyroid scan should be performed**
- **Hyperfunctioning nodules rarely malignancy**

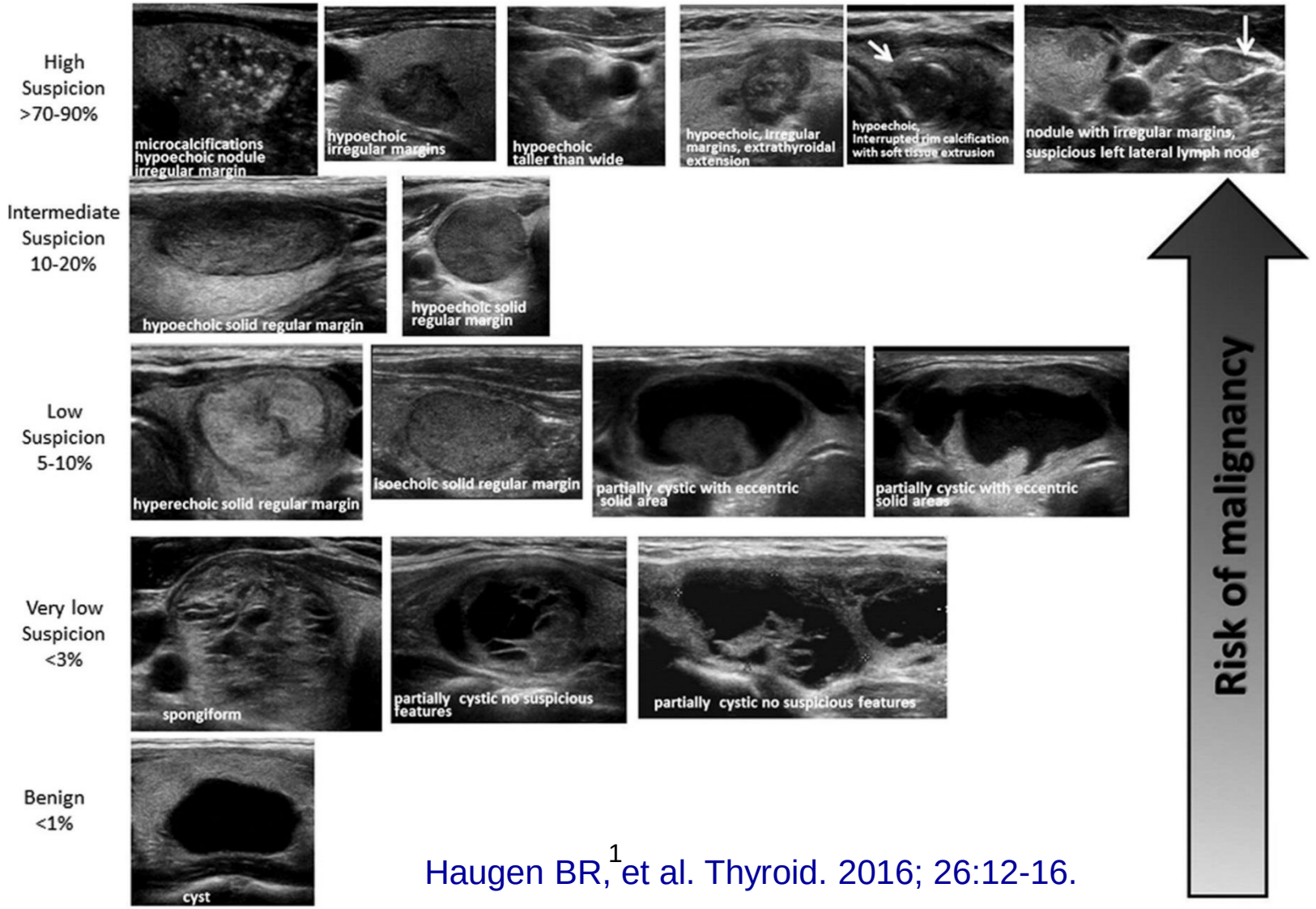
Boelaert K et al. JCEM 2006; 91:4295–4301.

What Imaging Studies are Indicated?

- **Thyroid ultrasonography should be performed in all patients with thyroid nodules.**
- **Ultrasonography can represent the most useful thyroid image**
- **Assess the morphology and the size**
  Assist in FNA and follow-up

[1] Cooper DS, et al. Thyroid 2009; 19: 1167-1214

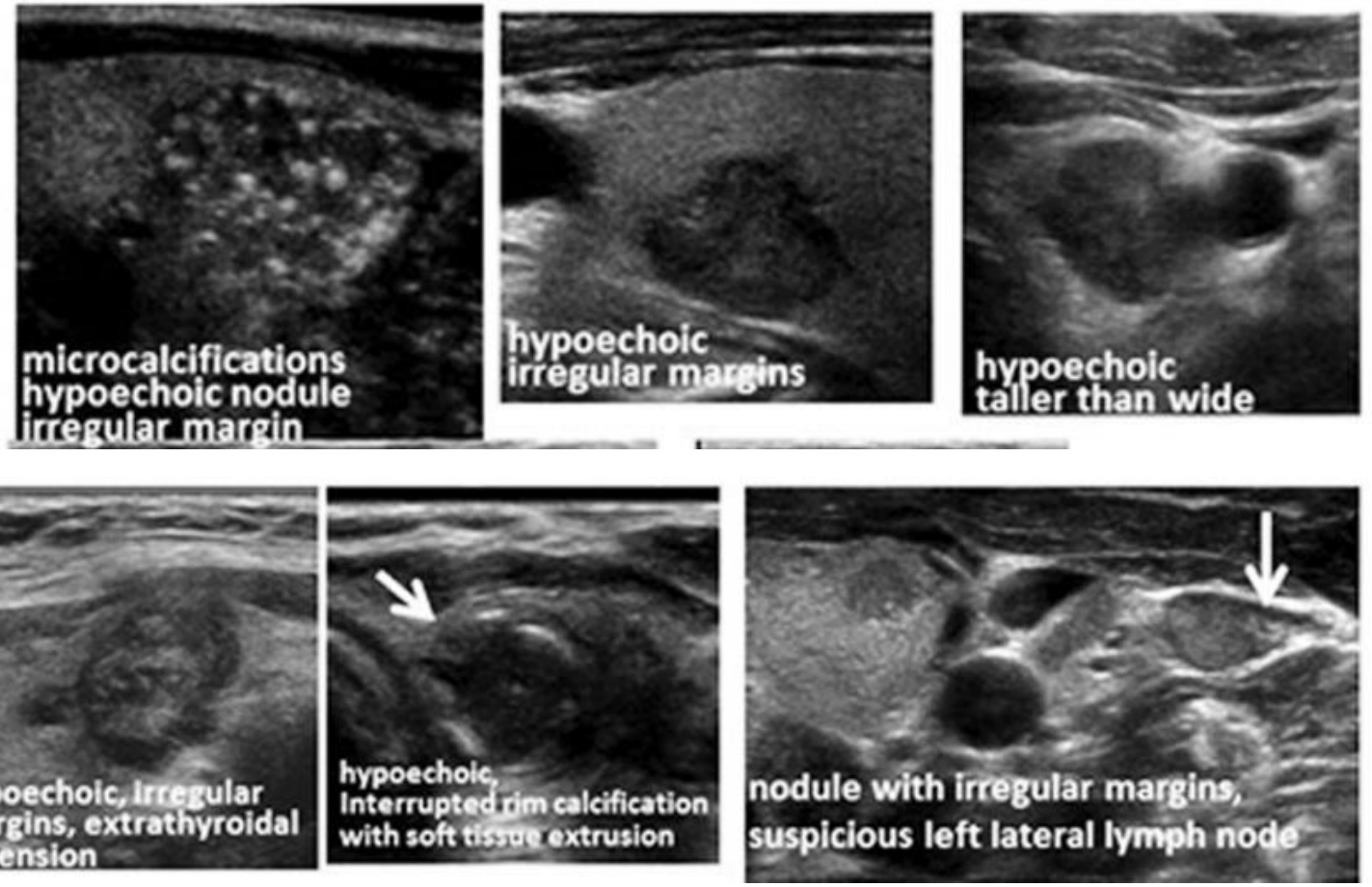
Sonographic Patterns and Risk of Malignancy



Haugen BR,[1] et al. Thyroid. 2016; 26:12-16.

Ultrasound Findings
High Suspicion of Malignancy

High Suspicion >70-90%



[1] Haugen BR, et al. Thyroid. 2016; 26:12-16.

Sonographic Features of Thyroid Nodules and Recommended Threshold Size for FNA (2016)

Sonographic features	*Estimated risk of malignancy*	*Consider biopsy FNA size cutoff (largest dimension)*
High suspicion	>70-90 %	FNA at nodule >1 cm
Intermediate suspicion	10-20%	FNA at nodule >1 cm
Low suspicion	5-10%	FNA at nodule >1.5 cm
Very low suspicion	<3%	FNA at nodule >2 cm Observation without FNA is also a reasonable option
Benign	<1%	No biopsy Aspirate the cyst may be considered for symptomatic or cosmetic drainage

1

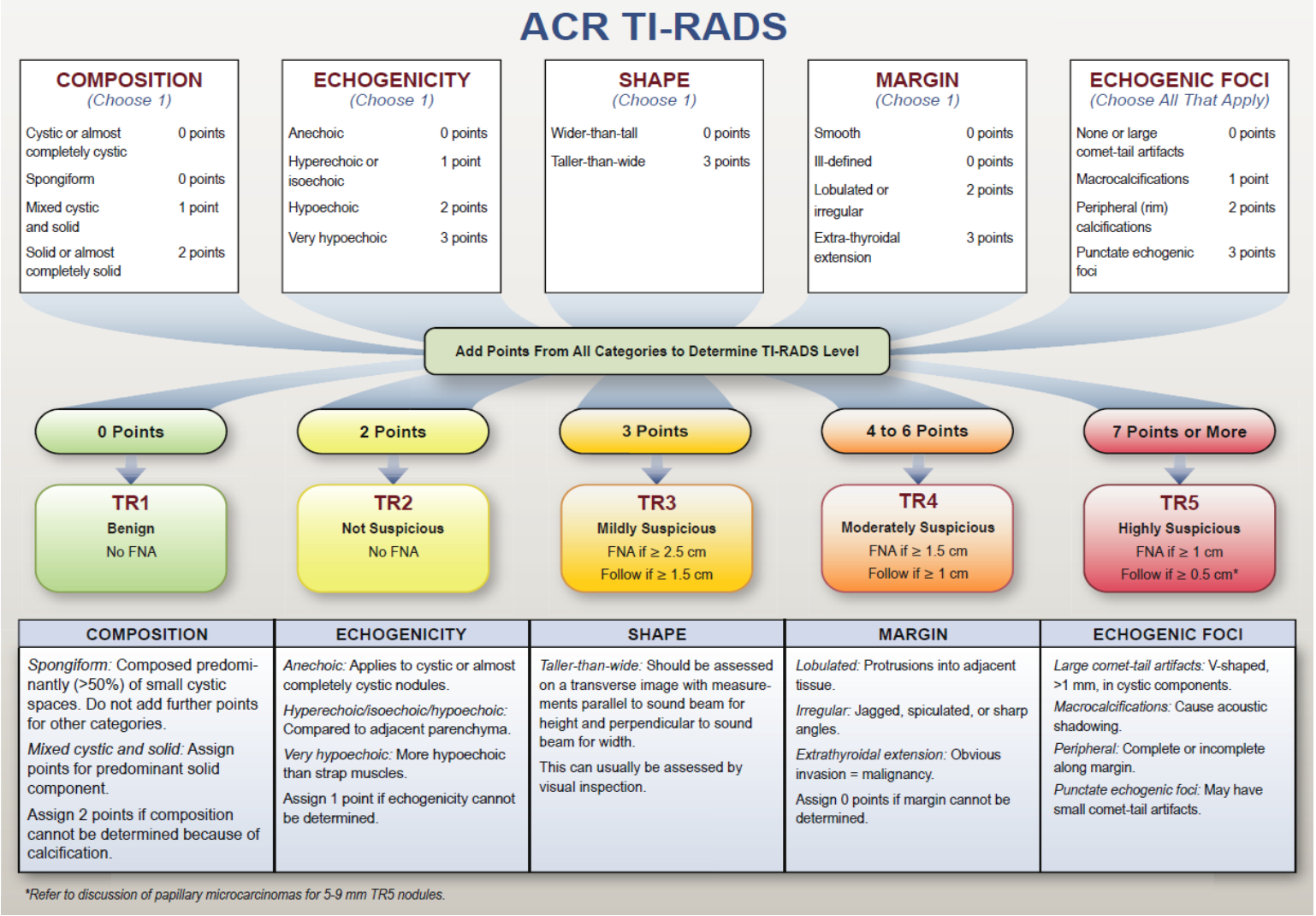
Haugen BR, et al. Thyroid. 2016; 26:12-16.

Sonographic Features of Thyroid Nodules and Recommended Threshold Size for FNA

Sonographic features	*Estimated risk of malignancy*	*Consider biopsy FNA size cutoff (largest dimension)*
High suspicion	>70-90 %	FNA at nodule >0.5 cm
Intermediate suspicion	10-20%	FNA at nodule >1 cm
Low suspicion	5-10%	FNA at nodule >1.5 cm
Very low suspicion	<3%	FNA at nodule >2 cm
Benign	<1%	Aspirate the cyst may be considered for symptomatic or cosmetic drainage

1

ACR Thyroid Imaging, Reporting and Data System (TI-RADS)



J Am Coll Radiol. 2017 May;14(5):587-595.
http://tiradscalculator.com/

What is the role of FNA biopsy?

- **FNA is the most accurate and cost-effective method**
- **FNA may be performed via palpation**
- **US guidance for FNA for difficult cases and previous nondiagnostic cytology.**

[1] Cooper DS, et al. Thyroid 2009; 19: 1167-1214

The Major Limitation of FNA

- **Limited utility in the evaluation of follicular neoplasms.**
- **Inadequate sampling or nondiagnostic specimens.**

Adequate Sampling (2016)

- **A satisfactory specimen contains at least five or six groups of 10 to 15 well-preserved cells.**
- **Some authors recommend between three and six aspirations per nodule.**
- **Use of ultrasound-guided biopsy combined with on-site cytologic examination improves the accuracy of sampling**

1

Haugen BR, et al. Thyroid. 2016; 26:12-16.

FNA cytology: Bethesda system

TABLE 8. THE BETHESDA SYSTEM FOR REPORTING THYROID CYTOPATHOLOGY: DIAGNOSTIC CATEGORIES AND RISK OF MALIGNANCY[a]

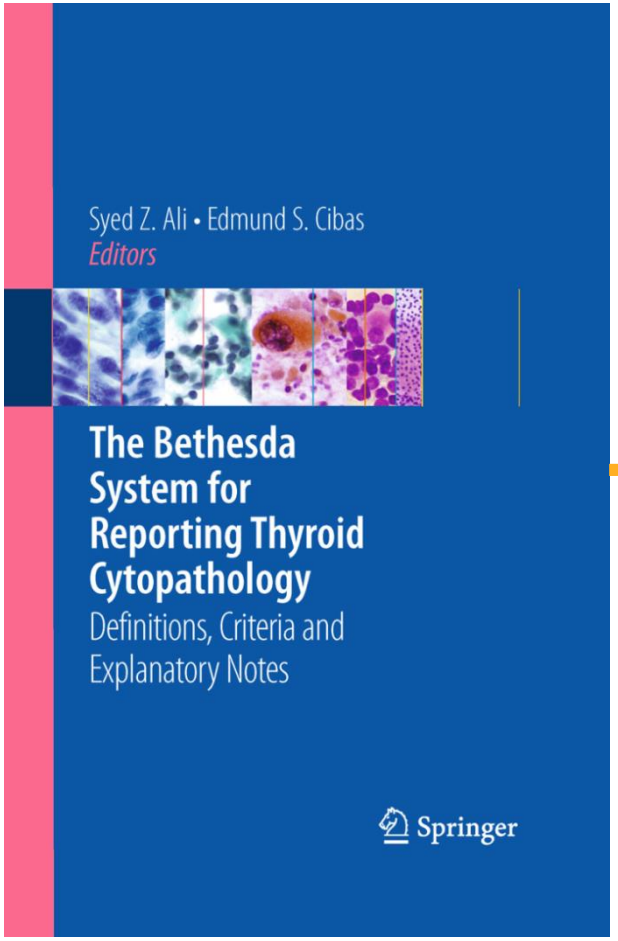
Diagnostic category	*Estimated/predicted risk of malignancy by the Bethesda system, %*[a]	*Actual risk of malignancy in nodules surgically excised, % median (range)*[b]
Nondiagnostic or unsatisfactory	1–4	20 (9–32)
Benign	0–3	2.5 (1–10)
Atypia of undetermined significance or follicular lesion of undetermined significance	5–15	14 (6–48)
Follicular neoplasm or suspicious for a follicular neoplasm	15–30	25 (14–34)
Suspicious for malignancy	60–75	70 (53–97)
Malignant	97–99	99 (94–100)

[a]As reported in The Bethesda System by Cibas and Ali (1076).
[b]Based on the meta-analysis of eight studies reported by Bongiovanni *et al.* (103). The risk was calculated based on the portion of nodules in each diagnostic category that underwent surgical excision and likely is not representative of the entire population, particularly of nondiagnostic and benign diagnostic categories.

Haugen BR, et al. Thyroid. 2016; 26:12-16.[16]

The Bethesda System for Reporting Thyroid Cytopathology

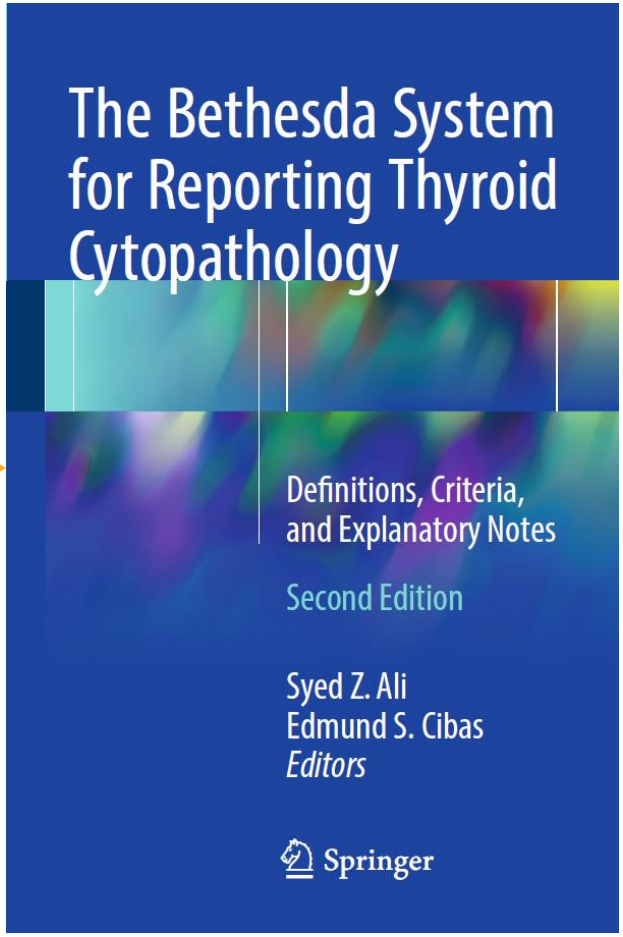
1st Ed, 2010



1. Updated literature
2. Introduce of molecular testing

3. Revised ATA guidelines
4. Reclassification of NIFTP

2nd Ed, 2017



The 2017 Bethesda System for Reporting Thyroid Cytopathology

- **TBS I: Nondiagnostic or Unsatisfactory**
  - should use only one of these for reporting results
- **TBS II: Benign**
- **TBS III: Atypia of Undetermined Significance**
  - Subcategorization based on types of atypia
- **TBS IV: Suspicious for a Follicular Neoplasm**
  - Cases that demonstrate mild nuclear changes associated with PTC are now included
- **TBS V: Suspicious for Malignancy**
- **TBS VI: Malignant**
  - Limited in cases with classical PTC features

Risk of Malignancy and Management

Diagnostic category	ROM (%) NIFTP = CA	ROM (%) NIFTP ≠ CA	Usual management
Nondiagnostic or unsatisfactory	5-10	5-10	Repeat FNA with ultrasound guidance
Benign	0-3	0-3	Clinical and sonographic follow-up
AUS	10-30	6-18	Repeat FNA, molecular testing, or lobectomy
SFN	25-40	10-40	Molecular testing, lobectomy
Suspicious for malignancy	50-75	45-60	Near-total thyroidectomy or lobectomy
Malignant	97-99	94-96	Near-total thyroidectomy or lobectomy

Discussion for Re-Classification of Class I and II

I. Nondiagnostic or Unsatisfactory

1. Cyst fluid only
2. Virtually acellular specimen
3. Other (obscuring blood, clotting artifact, drying artifact, etc.)

II. Benign

1. Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)
2. Consistent with chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical context
3. Consistent with granulomatous (subacute) thyroiditis

After Voting:

Class 0: Cyst fluid only

Class I. Unsatisfactory

1. Virtually acellular specimen
2. Other (obscuring blood, clotting artifact, drying artifact, etc.)

Class II. Benign

1. Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)
2. Consistent with chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical context
3. Consistent with granulomatous (subacute) thyroiditis

2019 VGHTPE Thyroid FNA Statistics

	n	%	excision	op rate %
TBS I	370	13.8	13	3.5
TBS II	2030	75.9	97	4.8
TBS III	107	4	34	31.8
TBS IV	32	1.2	21	65.6
TBS V	24	0.9	17	70.8
TBS VI	111	4.2	79	71.2
total	2674	100	261	/

2019 VGHTPE Thyroid FNA Correlation

	malignancy	ROM	overall ROM	neoplasm	RON
TBS I	3	23.1	0.8	3	23.1
TBS II	14	14.4	0.7	18	18.6
TBS III	16	47.1	15	21	61.8
TBS IV	1	4.8	3.1	15	71.4
TBS V	16	94.1	66.7	16	94.1
TBS VI	79	100	71.2	79	100
total	129	/	/	152	/

2019 VGHTPE Thyroid FNA AUS Subtypes

	n	%	excision	op rate %
AUS-C	59	55.1	19	32.2
AUS-A	24	22.4	7	29.2
AUS-H	16	15	7	43.8
AUS-C/A	3	2.8	1	33.3
AUS-NOS	5	4.7	0	0
total	107	100	34	/

2019 VGHTPE Thyroid FNA AUS Subtypes

	malignancy	ROM	overall ROM	neoplasm	RON
AUS-C	14	73.7	23.7	15	78.9
AUS-A	1	14.3	4.2	3	42.9
AUS-H	0	0	0	2	28.6
AUS-C/A	1	100	33.3	1	100
AUS-NOS	0	NA	NA	0	NA
total	16			21	

Benign Cytology

- The management of patients with benign lesions is more variable.
- Thyroid nodule size should be monitored by serial ultrasound about every 6-12 months.
- A second biopsy should be performed within 2 years to confirm the benign status.
- Repeat FNA is indicated if a nodule enlarges

[1] Cooper DS, et al. Thyroid 2009; 19: 1167-1214

Follow-up of nodules

Sonographic features	*Recommended follow-up*
High suspicion	Repeat US + FNA within 12 months
Low to intermediate suspicion	Repeat US at 12-24 months Consider FNA if nodules growth
Very low suspicion	Repeat US at 2-5 years Consider FNA if nodules growth

Modified from Haugen BR, et al. Thyroid. 2016; 26:12-16.[1]

Nodule Growth Detected by Sonography

- More than a 50% increase in volume

or

- 20% increase in at least two dimensions with a minimal increase of 2 mm in solid nodules or in the solid portion of mixed cystic–solid nodules

[1] Cooper DS, et al. Thyroid 2009; 19: 1167-1214

Large Tumors

- Surgery should also be considered for large tumors (>3 cm)
- Especially in young subjects
- Composed of various cell populations, results of FNA are less reliable.

McCoy KL, et al. *Surgery*. 2007;142:837-844.

Pathology

HISTOPATHOLOGIC TYPE

Differentiated follicular thyroid carcinoma

- Papillary thyroid carcinoma
- Follicular thyroid carcinoma
- Follicular neoplasm of uncertain malignant potential
- Poor differentiated thyroid carcinoma

Anaplastic (undifferentiated) thyroid carcinoma

Non-follicular thyroid carcinoma

Medullary thyroid carcinoma

Others

Lymphoma

Metastasis to thyroid

Carcinoma, type cannot be determined

Papillary Thyroid Carcinoma (PTC)

- **Papillary thyroid carcinoma: (PTC)**
- Variants:

1. Classical (usual)
2. Microcarcinoma (occult, latent, small, papillary microtumor)
3. Clear cell variant
4. Columnar cell variant
5. Cribriform-morular variant
6. Diffuse sclerosing variant
7. Follicular variant
8. Macrofollicular variant
9. Oncocytic or oxyphilic variant (follicular variant, non-follicular variant)
10. Solid variant
11. Tall cell variant
12. Warthin-like variant

Follicular Thyroid Carcinoma (FTC)

- **Follicular thyroid carcinoma (FTC)**

1. Minimal invasive
2. Widely invasive

- Subtype variant:

➢ Oncocytic (Hürthle) cell type
➢ Clear cell variant

2017 WHO Classification for Encapsulated Follicular-patterned Tumors

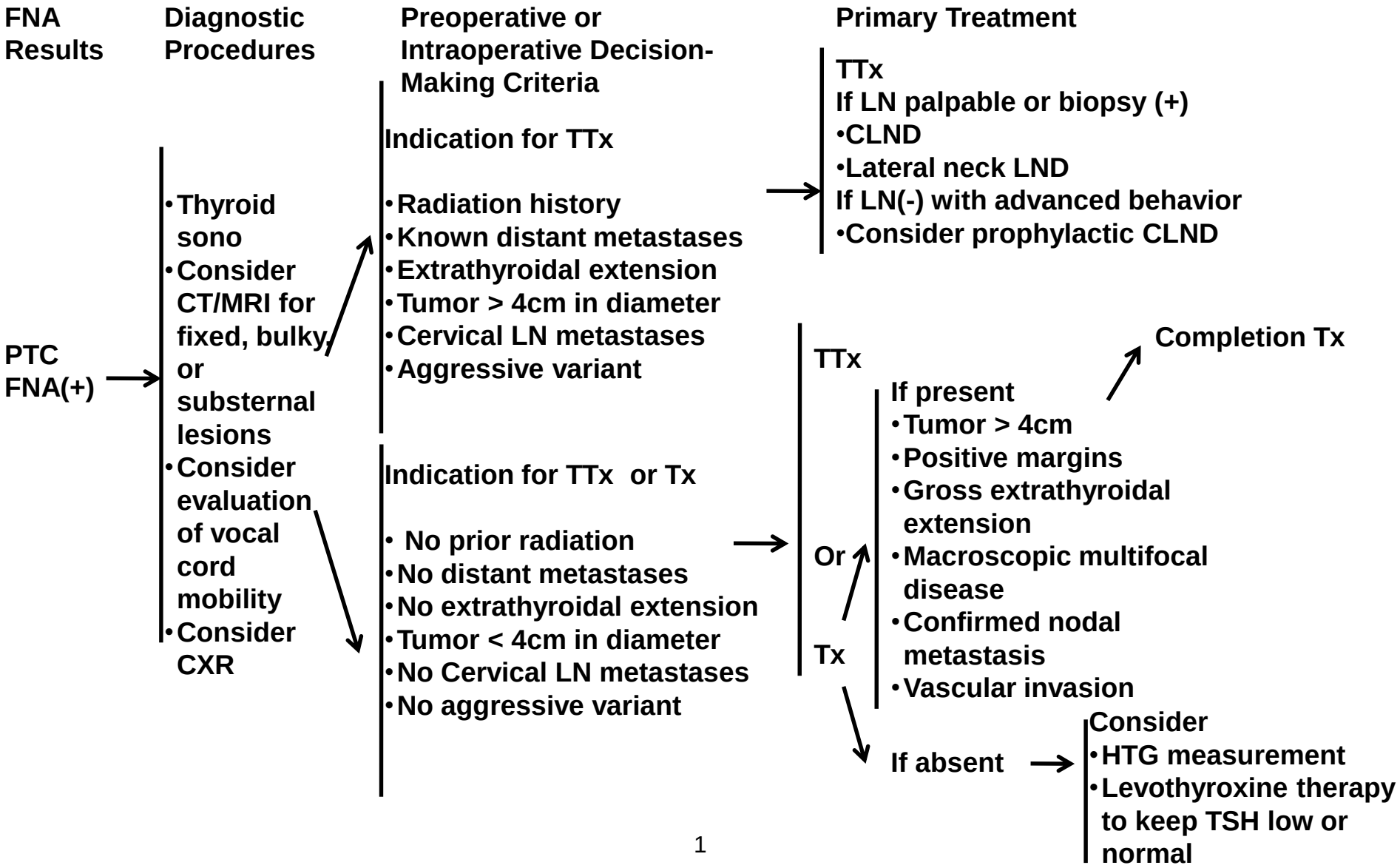
		Capsular/Vascular Invasion		
		Yes	?	No
Nuclear Features of PTC	Yes	Invasive EFVPTC	WDT-UMP	NIFTP
	?	WDC-NOS		
	No	FTC	FT-UMP	FA

1

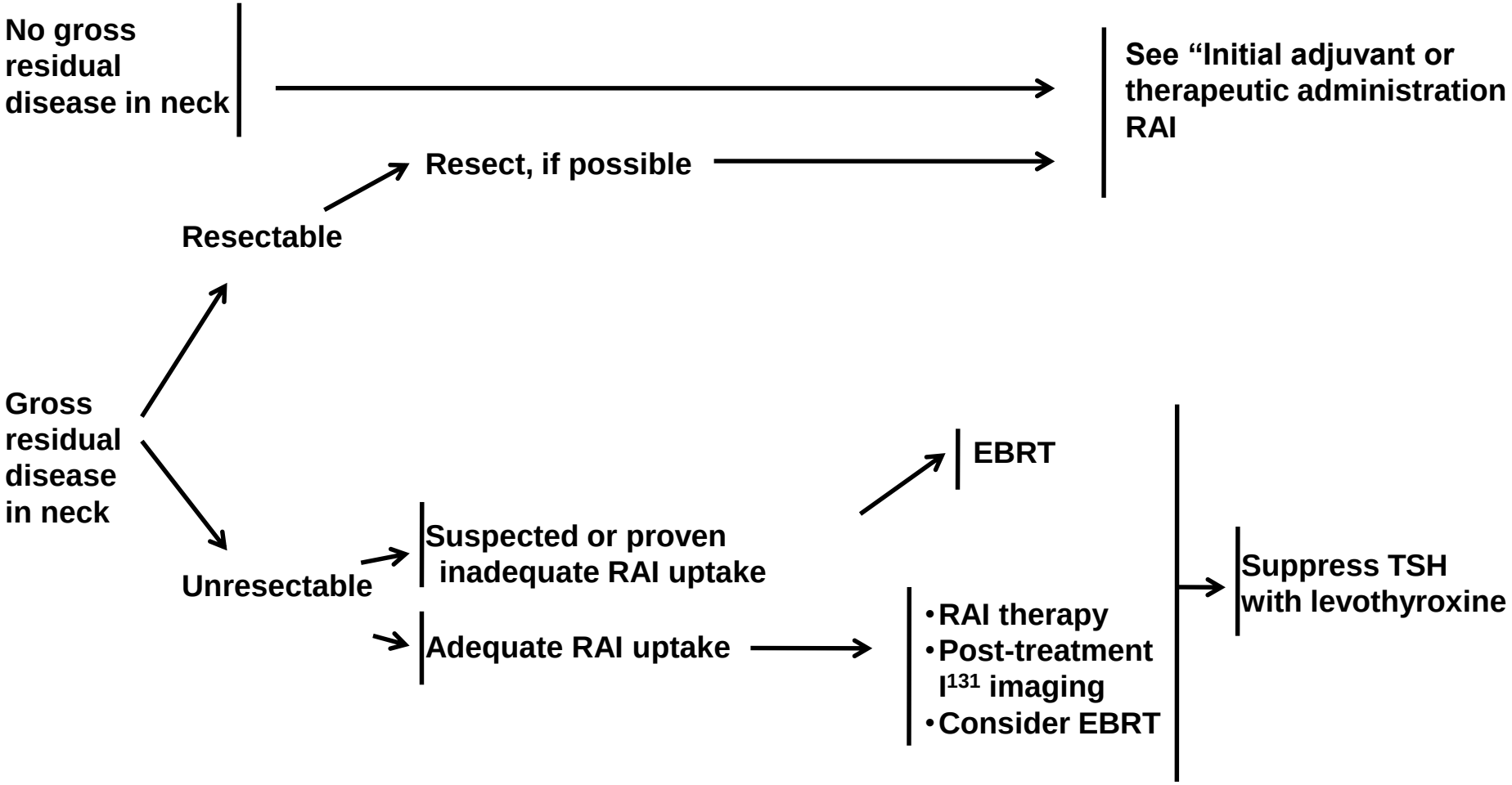
Treatment Related Terminology

- **Human thyroglobulin: hTG**
- **Operation procedures:**
  - **Thyroidectomy: Tx**
  - **Subtotal thyroidectomy: sTx**
  - **Total thyroidectomy: TTx**
  - **Central lymph node dissection: CLND**
  - **Modified radical lymph node dissection: MRLND**
- **Radioiodine: RAI**
- **External-beam radiation therapy: EBRT**
- **Parathyroidectomy: PTX**

Treatment of Papillary Thyroid Carcinoma (PTC)



Treatment of Residual Disease (PTC)



Initial Adjuvant or Therapeutic Administration of RAI (PTC)

➢ **RAI recommended:**

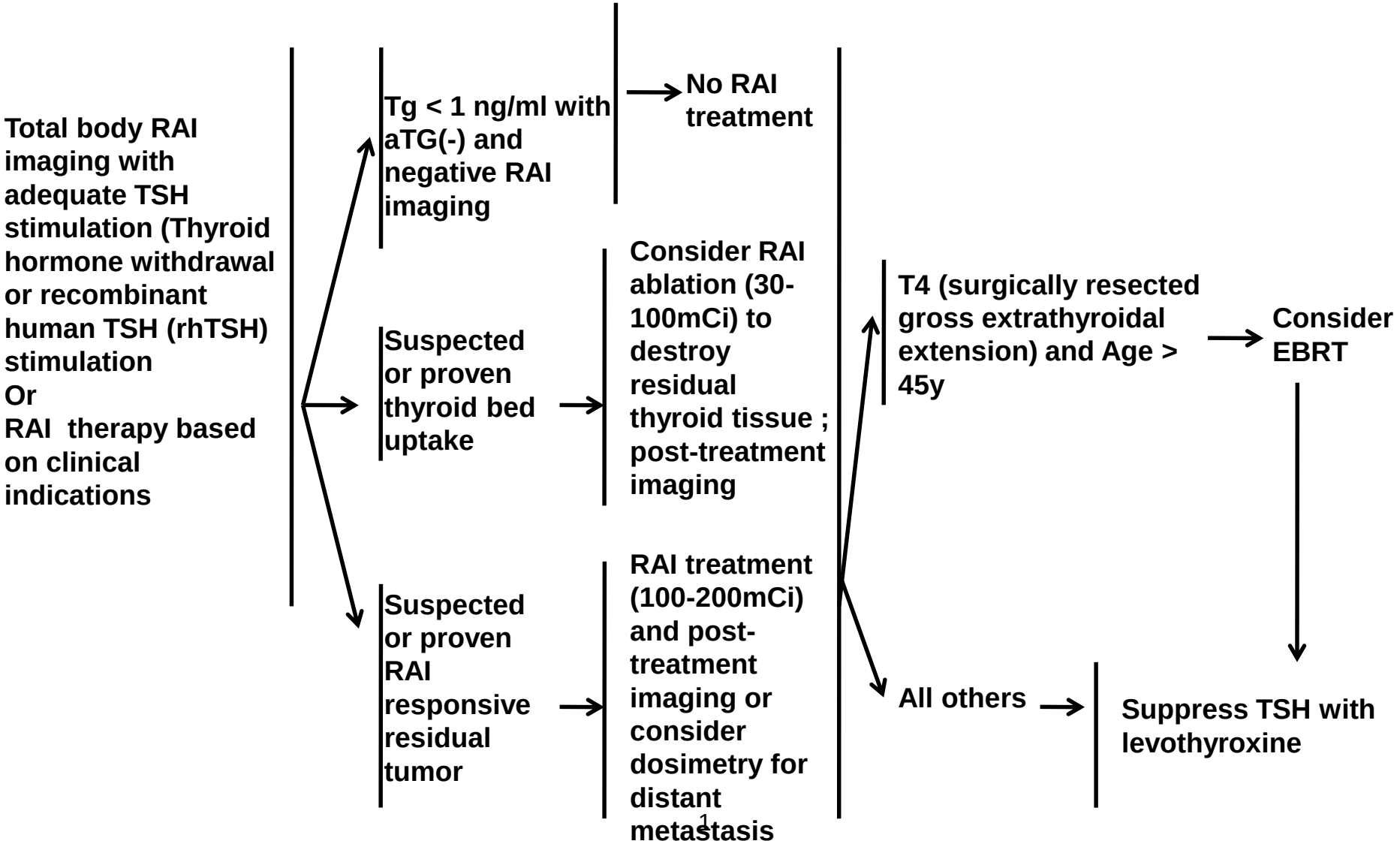
- **Gross extrathyroidal extension**
- **Primary tumor > 4cm**
- **Known or suspected distant metastases**

➢ **RAI selectively recommended:**

- **Residual thyroid tissue suspected**
- **High-risk histology**
- **Vascular invasion** Lymphatic invasion
- **Cervical LN metastases**
- **Minor extrathyroidal extension**
- **Inappropriate post-op Tg**

  Detectable TgAb

Post-op for Patients Considered for RAI Therapy (PTC)



Surveillance, Maintenance and Recurrence (PTC)

Surveillance and Maintenence

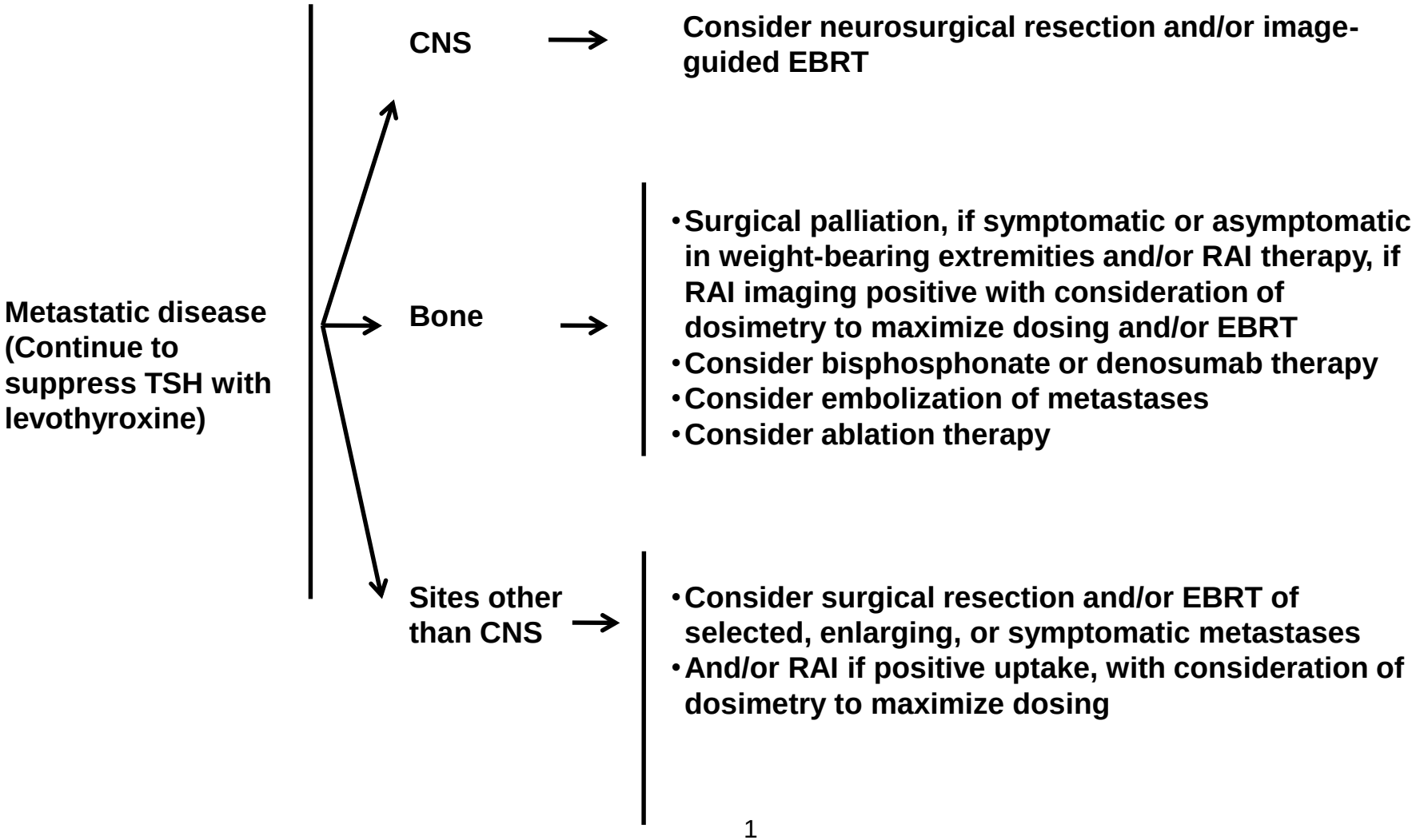
- **Physical examination, TSH and Tg measurement + aTG**
- **Neck ultrasound**
- **Consider TSH-stimulated RAI imaging in high-risk patients, patients with previous RAI avid metastases, or patients with abnormal Tg levels, stable or rising aTG, or abnormal ultrasound during surveillance**
- **If RAI imaging negative and elevated hTg, consider additional non-RAI imaging (eg, neck ultrasound, neck CT, chest CT, FDG-PET/CT)**

Recurrent Disease

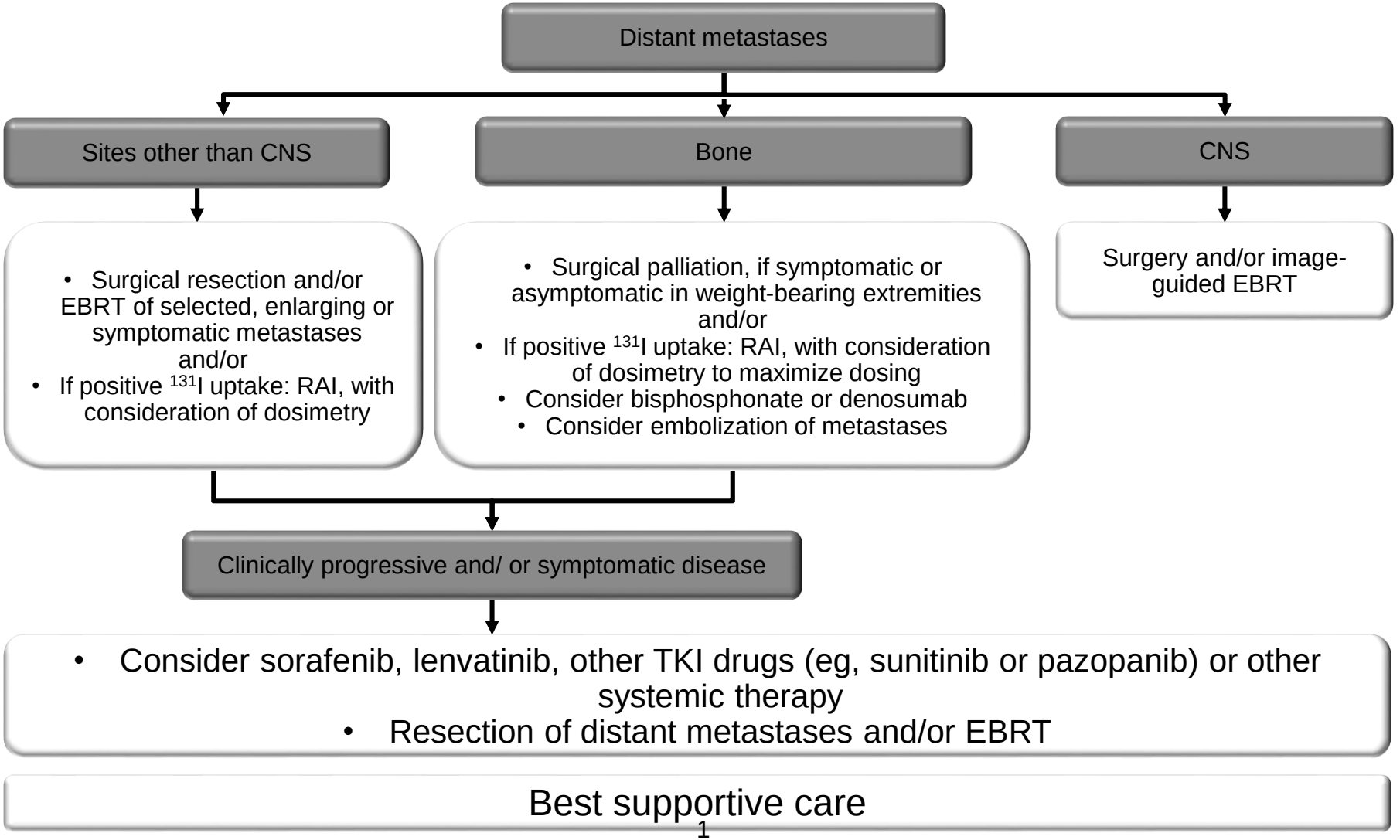
Local regional recurrence → **Surgery if resectable And/or RAI treatment if RAI imaging positive And/or EBRT, if radioiodine imaging negative**

Metastatic disease → **See treatment of metastases**

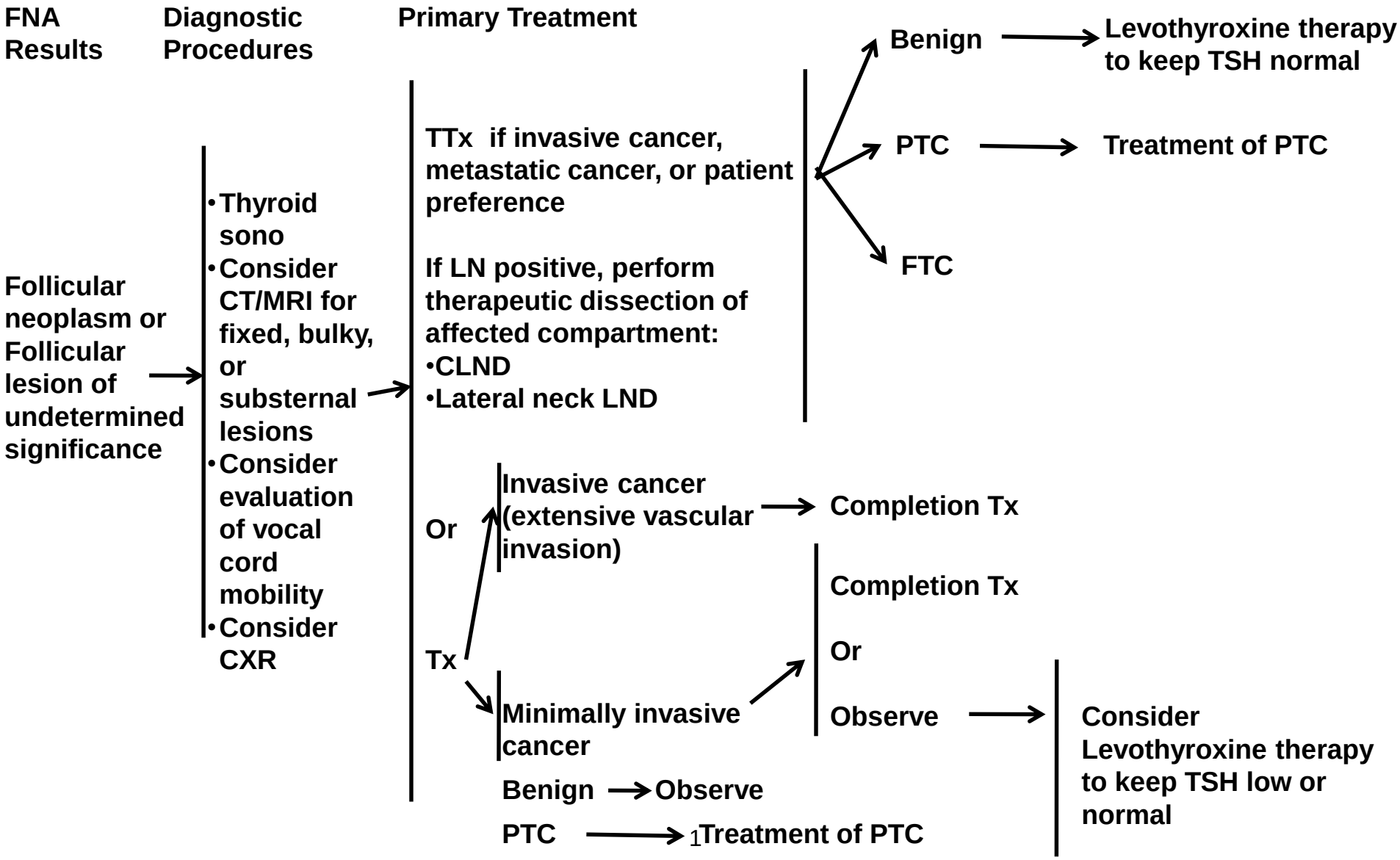
Treatment of Metastases (PTC)



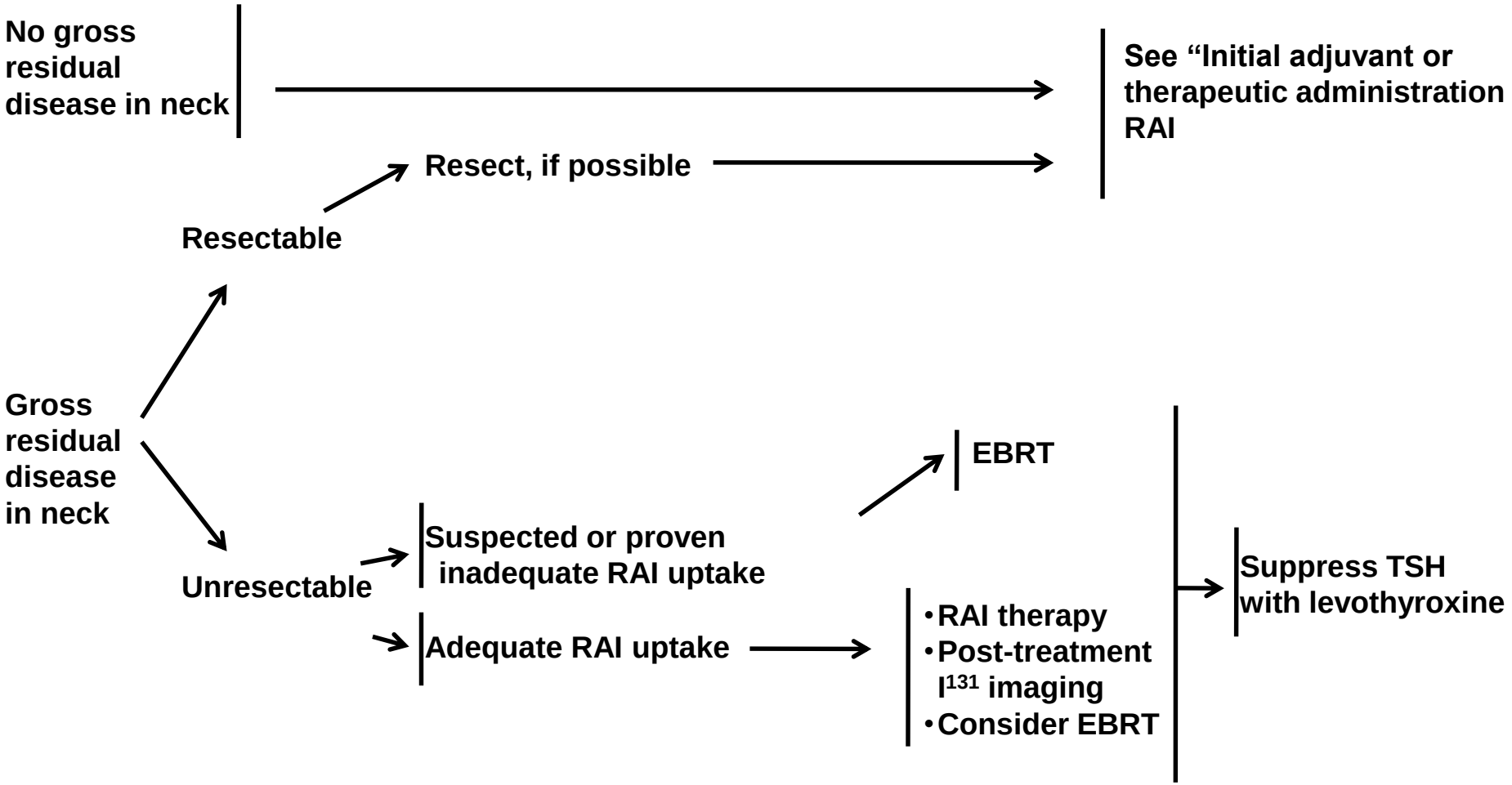
Treatment of Metastases (PTC)



Treatment of Follicular Thyroid Carcinoma (FTC)



Treatment of Residual Disease (FTC)



Initial Adjuvant or Therapeutic Administration of RAI (FTC)

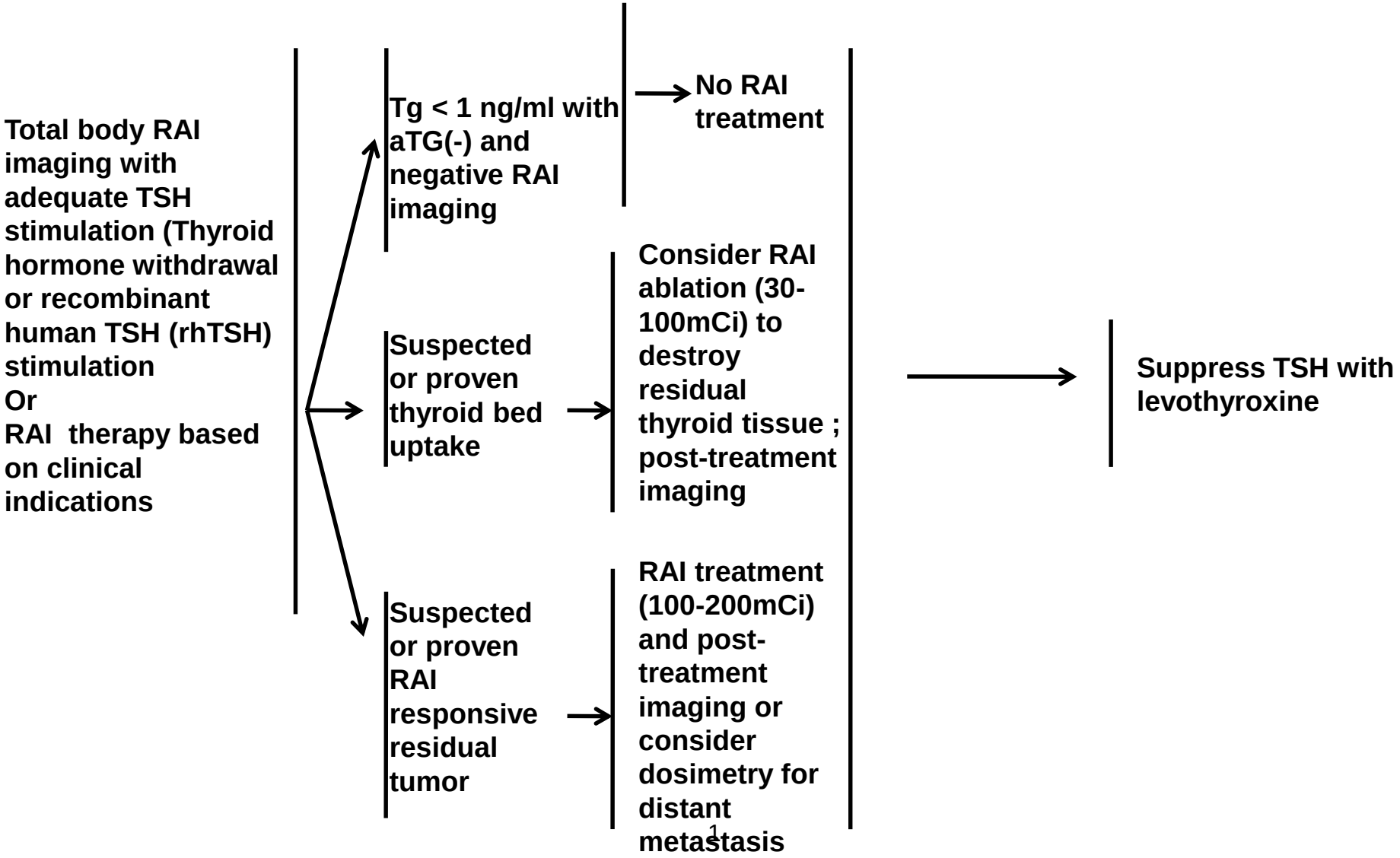
➢ **RAI recommended:**

- **Gross extrathyroidal extension**
- **Primary tumor > 4cm**
- **Known or suspected distant metastases**
- **Extensive vascular invasion**

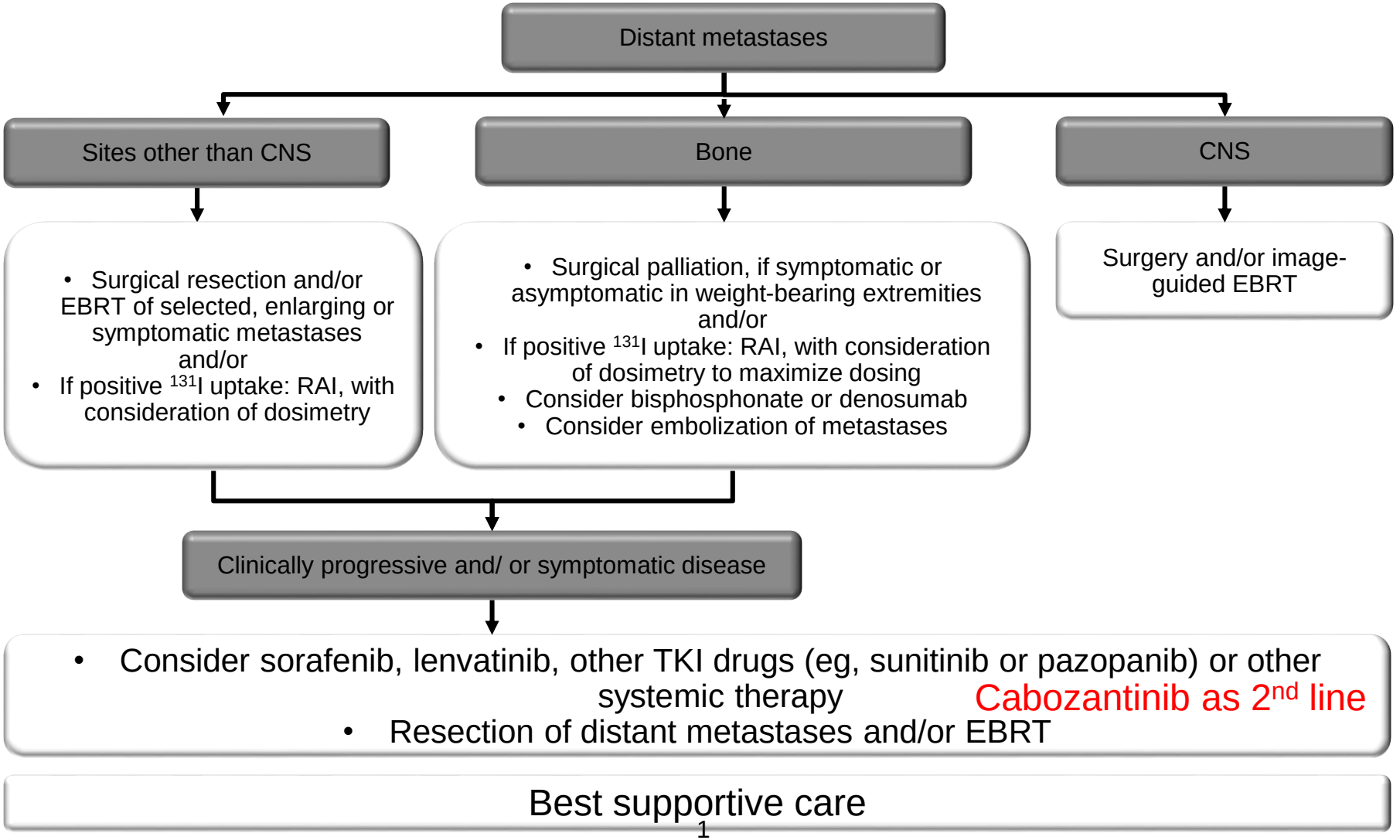
➢ **RAI selectively recommended:**

- **Residual thyroid tissue suspected**
- **High-risk histology**
- **Minor vascular invasion**
- **Cervical LN metastases**
- **Minor extrathyroidal extension**
- **Inappropriate post-op Tg**

Post-op for Patients Considered for RAI Therapy (FTC)



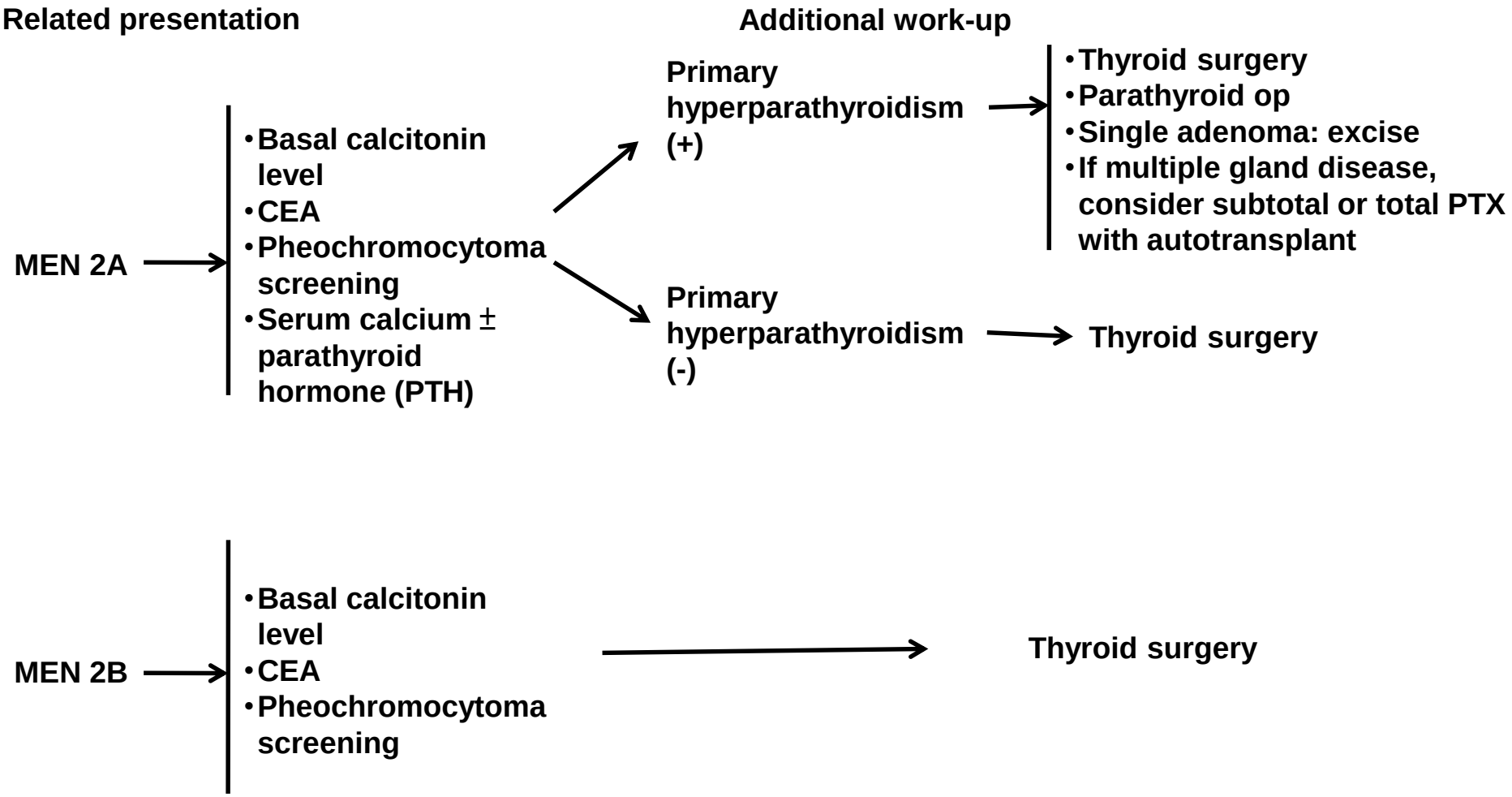
Treatment of Metastases (FTC)



Treatment of Medullary Thyroid carcinoma (MTC)

Clinical presentation	Additional work up	Primary Treatment
MTC on FNA →	• Basal calcitonin level • CEA • Pheochromocytoma screening • Serum calcium • Neck ultrasound • Consider CT/MRI if N1 disease or clacitonin > 400 pg/ml • Consider test of RET proto-oncogene mutations if available (utility and cost)	→ • TTx with CLND • Therapeutic lat. ipsilateral or bil. MRLND for clinically or radiologically identifiable disease • Consider prophylactic ipsilateral MRLND for high volume or gross disease in the adjacent central neck • Consider therapeutic EBRT for grossly incomplete tumor resection • Consider adjuvant EBRT for gross extrathyroidal extension (T4a or T4b) with positive margins after resection of all gross disease and following resection of moderate –to high-volume disease in the central or lat. Neck LN with extranodal soft tissue extension • Postoperative levothyroixine supply to normalize TSH

MTC and Multiple Endocrine Neoplasia (MEN)



Recurrence or Persistent Disease (MTC)

Locoregional →
- Surgical resection ± postop EBRT
- Consider EBRT
- Consider target therapy for unresectable disease

Symptomatic distant metastases →
- Consider palliative resection, ablation, embolization, or other regional treatment
- Consider target therapy for unresectable disease

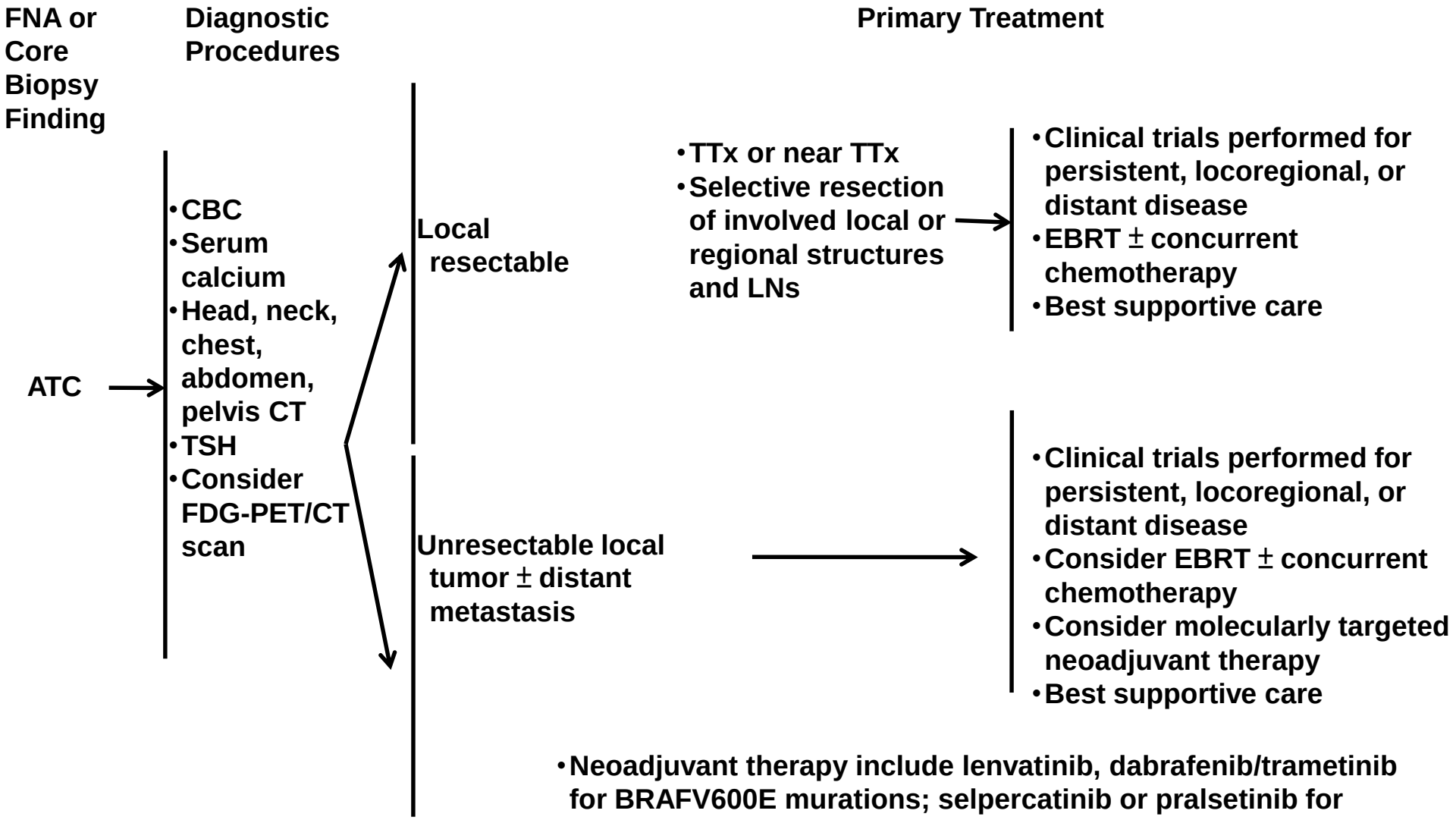
Asymptomatic distant metastases →
- Observe
- Or
- Consider resection, ablation, embolization, or other regional treatment
- Consider target therapy for unresectable disease

→ **Disseminated symptomatic disease** →
- Consider target therapy
  Vandetanib (approved in NHI-Taiwan)
  Cabozantinib, Selpercatinib, Pralsetinib, Pembrolizumab
- Consider clinical trial or chemotherapy
- EBRT for focal symptoms
- Consider bisphosphonate or denosumab therapy for bone metastases
- Best supportive care

NHI: National Health Insurance

1

Anaplastic Thyroid Carcinoma (ATC)



- Neoadjuvant therapy include lenvatinib, dabrafenib/trametinib for BRAFV600E murations; selpercatinib or pralsetinib for RET-fusion positive tumors; and larotrectinib or entrectinib with NTRK[1] gene fusion-positive tumors

Precision Medicine in Thyroid Cancer

- **Molecular testing should be considered for actionable mutations**
- **Well-differentiated thyroid carcinoma**
  - Pan-TKI: lenvatinib & sorafenib Cabozantinib as 2nd line
  - *NTRK* TKI: larotrectinib & entrectinib (2018)
  - *RET* TKI: selpercatinib (2020)
  - TMB-high: pembrolizumab (2020)
  - *BRAF* inhibitor: vemurafenib & dabrafenib (off-label/on-going trial)
- **Medullary thyroid carcinoma**
  - Pan-TKI: vandetanib
  - *RET* TKI: selpercatinib (2020)
  - TMB-high: pembrolizumab (2020)
- **Anaplastic thyroid carcinoma**
  - *BRAF, NTRK, ALK, RET*, and tumor mutation burden (TMB)

Pembrolizumab for patients with tumor mutational burdenhigh (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors

How to Choose the Right TKIs and Use Optimally

1.NCCN guideline:

- Lenvatinib 的反應率優於sorafenib (65% vs. 12% 因此NCCN列Lenvatinib 為preferred)
- age>65 yrs: Lenvatinib有整體存活率的好處
- 在brain mets的病人，兩藥皆無data

2. ESMO:

- Higher response rate with lenvatinib and it may delay progression for longer
- lenvatinib and sorafenib are recommended as treatment options for differentiated thyroid cancer after radioactive iodine. However, they are recommended only for patients who have not had TKI before, or who have to stop them early because of tolerability (specifically, toxicity that cannot be managed by dose delay or dose modification). This is because there is not enough clinical evidence and no cost-effectiveness evidence to determine whether the treatments are effective when used sequentially.

3. lenvatinib is the optimally cost-effective treatment for RR-DTC, although both lenvatinib and sorafenib are cost-effective compared to placebo.

Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial

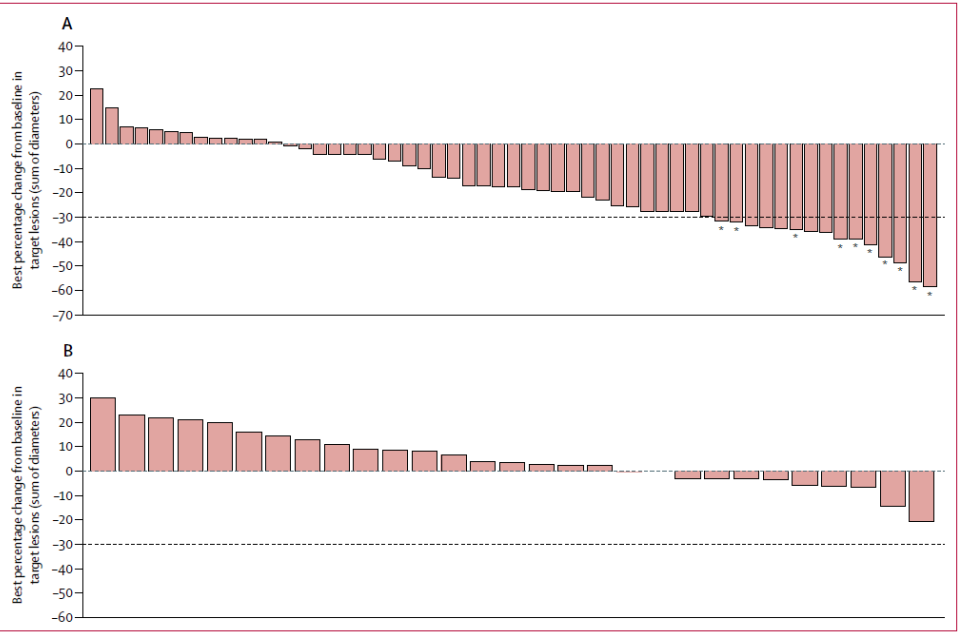


Figure 2: **Waterfall plot for maximum percentage tumour reduction from baseline in target lesions for individual patients (objective response rate intention-to-treat population)**
(A) Cabozantinib group. (B) Placebo group. Tumour response was assessed with Response Evaluation Criteria in Solid Tumours version 1.1 by blinded independent radiology committee. The waterfall plots show the maximum percentage reduction or minimum increase from baseline in sum of diameters of target lesions before progressive disease or initiation of any non-protocol anti-cancer medication. Only patients with at least one baseline and post-baseline assessment are shown. Of the 58 patients in the cabozantinib group and 31 in the placebo group with at least one-post baseline assessment, one patient in the cabozantinib group and two patients in the placebo group did not have a qualifying sum of diameter for inclusion in the waterfall plot. *Confirmed partial response.

	ITT	Placebo
Radioiodine therapy status†		
Refractory	65 (97%)	33 (100%)
Ineligible	3 (4%)	0
Previous sorafenib or lenvatinib		
Sorafenib but no lenvatinib	26 (39%)	12 (36%)
Lenvatinib but no sorafenib	22 (33%)	13 (39%)
Sorafenib and lenvatinib	19 (28%)	8 (24%)

ORR 15%
PR 15%
SD: 69%
PD:6%

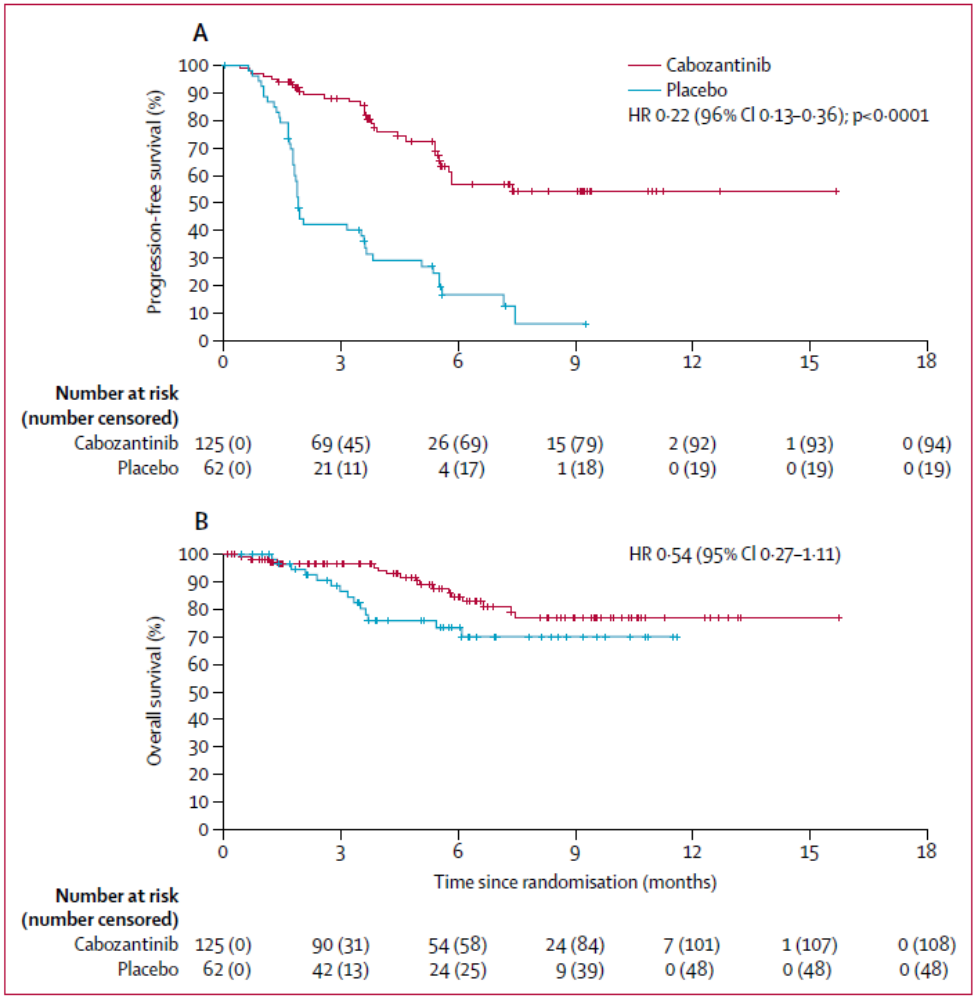


Figure 3: **Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) in the intention-to-treat population**
Disease progression was assessed with the use of Response Criteria in Solid Tumours, version 1.1 by blinded independent radiology committee. NE=not estimable. NR=not reached.

ITT PFS: not reached (5.7-)
PFs: 57% vs 17 % over 6 mo

Placebo PFS: 1.9 mo (5.8 in SELECT Trial)

References: Pathology(1)

- Patel S, Shah JP. Part II: Head and neck sites. In: Edge SB, Byrd DR, Carducci MA, Compton CA, eds. *AJCC Cancer Staging Manual. 7th ed. New York, NY:* Springer; 2009.
- DeLellis RA, Lloyd RV, Heitz PU, Eng C, eds. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Endocrine Organs. Lyon: IARC Press; 2004.*
- Sobin LH, Wittekind C. *UICC TNM Classification of Malignant Tumours. 6th ed.* New York: Wiley-Liss; 2002.
- Rosai J, Carcangiu ML, DeLellis RA. *Atlas of Tumor Pathology. Tumors of the Thyroid Gland. 3rd series. Fascicle 5. Washington, DC: Armed Forces Institute of* Pathology; 1992.
- Chan JKC. The thyroid gland. In: Fletcher CDM, ed. *Diagnostic Histopathology of Tumours. 3rd ed. Edinburgh; Churchill Livingstone Elsevier; 2007:1018.*
- Komorowski RA, Hanson GA. Occult thyroid pathology in the young adult: an autopsy study of 138 patients without clinical thyroid disease. *Hum Pathol.* 1988;19:689-696.
- Ghossein RA, Hiltzik RA, Carlson DL, et al. Prognostic factors of recurrence in encapsulated Hürthle cell carcinoma of the thyroid gland: a clinicopathologic study of 50 cases. *Cancer. 2006;106:1669-76.*
- Stojadinovic A, Ghossein RA, Hoos A, et al. Hürthle cell carcinoma: a critical histopathologic appraisal. *J Clin Oncol. 2001;19:2616-25.*
- Collini P, Sampietro G, Pilotti S. Extensive vascular invasion is a marker of risk of relapse in encapsulated non-Hürthle cell follicular carcinoma of the thyroid gland: a clinicopathological study of 18 consecutive cases from a single institution with a 11-year median follow-up. *Histopathology. 2004;44:35-9.*
- Standring S. Thyroid gland. In: Standring S, ed. *Gray's Anatomy: The Anatomical Basis of Clinical Practice. 39th ed. Edinburgh: Elsevier Churchill Livingstone;* 2005:560-564.
- Rosai J, Carcangiu ML, DeLellis RA. The normal thyroid gland. In: Rosai J, ed. *Tumors of the Thyroid. Atlas of Tumor Pathology. Facicle 5. Third series.* Washington, DC: Armed Forces Institute of Pathology; 1992: 1-17.
- Gnepp DR, Ogorzalek JM, Heffess CS. Fat-containing lesions of the thyroid gland. *Am J Surg Pathol. 1989;13;605-612.*
- Carcangiu ML. Thyroid. In: Mills SE, ed. *Histology for Pathologists. Third ed.* Philadelphia; Lippincott Williams & Wilkins; 2007: 1129-1148.

References: Pathology (2)

- Robbins KT et al. Neck dissection classification update. *Arch Otolaryngol Head Neck Surg. 2002;128:751-758.*
- Robbins TK et al. Consensus statement on the classification and terminology of neck dissection. *Arch Otolaryngol Head Neck Surg. 2008;134:536-538.*
- Robbins T, Medina JE, Wolfe GT, Levine PA, Sessions RB, Pruet CW. Standardizing neck dissection terminology: official report of the academy's committee for head and neck surgery and oncology. *Arch Otolaryngol Head Neck Surg. 1991;117:601-605.*
- Yamashita H, Noguchi S, Murakami N et al. Extracapsular invasion of lymph node metastasis is an indicator of distant metastasis and poor prognosis in patients with thyroid papillary carcinoma*. Cancer. 1997;80:2268-72.*
- From: Cummings, CW. *Cummings: Otolaryngology: Head and Neck Surgery. 4th* ed. Philadelphia; Mosby, Inc: 2005. (Electronic Textbook)
- Kondo T, Ezzat S, Asa SL. Pathogenetic mechanisms in thyroid follicular-cell neoplasia. *Nat Rev Cancer. 2006;6:292-306.*
- Cheung CC, Carydis B, Ezzat S, Bedard YC, Asa SL. Molecular genetic analysis refines the fine needle aspiration diagnosis of thyroid cancer. *J Clin Endocrinol Metab. 2001;86:2187-2190.*
- Sapio MR, Posca D, Raggioli A, et al. Detection of RET/PTC, TRK and BRAF mutations in preoperative diagnosis of thyroid nodules with indeterminate cytological findings. *Clin Endocrinol. 2007;66:678-683.*
- Kim SK, Kim DL, Han HS, et al. Pyrosequencing analysis for detection of BRAFV600E mutation in an FNAB specimen of thyroid nodules. *Diagn Mol Pathol.* 2008;17:118-125.
- Marchetti I, Lessi F, Mazzanti CM, et al. A morpho-molecular diagnosis of papillary thyroid carcinoma: BRAF V600E detection as an important tool in preoperative evaluation of fine-needle aspirates. *Thyroid. 2009;19:837-842.*
- Nikiforov YE, Steward DL, Robinson-Smith TM, et al. Molecular testing for mutations in improving fine-needle aspiration diagnosis of thyroid nodules. *J Clin Endocrinol Metab. 2009;94:2092-2098.*
- Altanerova V. Cancers connected with mutations in RET proto-oncogene. *Neoplasma. 2001;48:325-31.*
- Stoler MH. Prophylactic surgical pathology. *Am J Surg Pathol. 2002;26:257-259.*

References: Nodule Evaluation

- American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009 Nov;19(11):1167-214
- Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, Moley JF, Pacini F, Ringel MD, Schlumberger M, Wells SA Jr. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid. 2009 Jun;19(6):565-612.
- Hegedüs L, Bonnema SJ, Bennedbaek FN. Management of simple nodular goiter: current status and future perspectives. Endocr Rev. 2003 Feb;24(1):102-32
- Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. J Clin Endocrinol Metab. 2006 Nov;91(11):4295-301.
- Frates MC, Benson CB, Charboneau JW, Cibas ES, Clark OH, Coleman BG, Cronan JJ, Doubilet PM, Evans DB, Goellner JR, Hay ID, Hertzberg BS, Intenzo CM, Jeffrey RB, Langer JE, Larsen PR, Mandel SJ, Middleton WD, Reading CC, Sherman SI, Tessler FN; Society of Radiologists in Ultrasound. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology. 2005 Dec;237(3):794-800.
- Baloch ZW, LiVolsi VA, Asa SL, Rosai J, Merino MJ, Randolph G, Vielh P, DeMay RM, Sidawy MK, Frable WJ. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. Diagn Cytopathol. 2008 Jun;36(6):425-37.
- Mehta RS, Carty SE, Ohori NP, Hodak SP, Coyne C, Lebeau SO, Tublin ME, Stang MT, Johnson JT, McCoy KL, Nikiforova MN, Nikiforov YE, Yip L. Nodule size is an independent predictor of malignancy in mutation-negative nodules with follicular lesion of undetermined significance cytology. Surgery. 2013 Oct;154(4):730-8.
- Edge SB, Byrd DR, Compton CC, et al, eds. AJCC Cancer Staging Manual, 7th ed. New York, NY: Springer; 2010.
- Tuttle RM, Ball DW, Byrd D, Dilawari RA, Doherty GM, Duh QY, Ehya H, Farrar WB, Haddad RI, Kandeel F, Kloos RT, Kopp P, Lamonica DM, Loree TR, Lydiatt WM, McCaffrey JC, Olson JA Jr, Parks L, Ridge JA, Shah JP, Sherman SI, Sturgeon C, Waguespack SG, Wang TN, Wirth LJ; National Comprehensive Cancer Network. Thyroid carcinoma. J Natl Compr Canc Netw. 2010; 8: 1228-74.
- Hiroshi Takami, Yasuhiro Ito, et al. Treatment of thyroid tumor : Japanese clinical guidelines. New York : Springer, 2013.

References: Treatment(1)

- Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006;16:109–142.
- Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 1995;141:259–277.
- Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418–428.
- Ito Y, Tomoda C, Uruno T, et al. Papillary microcarcinoma of the thyroid: how should it be treated? World J Surg 2004;28:1115– 1121.
- Sherman SI. Thyroid carcinoma. Lancet 2003;361:501–511.
- Ito Y, Uruno T, Nakano K, et al. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. Thyroid 2003;13:381–387.
- Henry JF, Denizot A, Puccini M, et al. [Early diagnosis of sporadic medullary cancers of the thyroid: value of systematic assay of calcitonin]. Presse Med 1996;25:1583–1588 [in French].
- Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167–1214.
- Cheung K, Roman SA, Wang TS, et al. Calcitonin measurement in the evaluation of thyroid nodules in the United States: a cost-effectiveness and decision analysis. J Clin Endocrinol Metab 2008;93:2173–2180.
- Newman KD, Black T, Heller G, et al. Differentiated thyroid cancer: determinants of disease progression in patients <21 years of age at diagnosis: a report from the Surgical Discipline Committee of the Children's Cancer Group. Ann Surg 1998;227:533–541.
- Robie DK, Dinauer CW, Tuttle RM, et al. The impact of initial surgical management on outcome in young patients with differentiated thyroid cancer. J Pediatr Surg 1998;33:1134–1138; discussion 1139–1140. Sherman SI, Brierley JD, Sperling M, et al. Prospective multicenter study of thyroid carcinoma treatment: initial analysis of staging and outcome. National Thyroid Cancer Treatment Cooperative Study Registry Group. Cancer 1998;83:1012–1021.
- Tsang RW, Brierley JD, Simpson WJ, et al. The effects of surgery, radioiodine, and external radiation therapy on the clinical outcome of patients with differentiated thyroid carcinoma. Cancer 1998;82:375–388.
- Dottorini ME, Vignati A, Mazzucchelli L, et al. Differentiated thyroid carcinoma in children and adolescents: a 37-year experience in 85 patients. J Nucl Med 1997;38:669–675.

References: Treatment(2)

- Samuel AM, Rajashekharrao B, Shah DH. Pulmonary metastases in children and adolescents with well-differentiated thyroid cancer. J Nucl Med 1998;39:1531–1536.
- Hay ID, Bergstralh EJ, Goellner JR, et al. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 1993;114:1050–1057; discussion 1057–1058.
- Shaha AR, Loree TR, Shah JP. Prognostic factors and risk group analysis in follicular carcinoma of the thyroid. Surgery 1995;118:1131–1136; discussion 1136–1138.
- DeGroot LJ, Kaplan EL, Straus FH, Shukla MS. Does the method of management of papillary thyroid carcinoma make a difference in outcome? World J Surg 1994;18:123–130.
- Miccoli P, Antonelli A, Spinelli C, et al. Completion total thyroidectomy in children with thyroid cancer secondary to the Chernobyl accident. Arch Surg 1998;133:89–93.
- Palme CE, Waseem Z, Raza SN, et al. Management and outcome of recurrent well-differentiated thyroid carcinoma. Arch Otolaryngol Head Neck Surg 2004;130:819–824.
- Frankenthaler RA, Sellin RV, Cangir A, Goepfert H. Lymph node metastasis from papillary-follicular thyroid carcinoma in young patients. Am J Surg 1990;160:341–343. 65. LiVolsi VA. Follicular lesions of the thyroid. In: LiVolsi VA, ed. Surgical Pathology of the Thyroid. Philadelphia, PA: WB Saunders; 1990:173–212.
- Brennan MD, Bergstralh EJ, van Heerden JA, McConahey WM. Follicular thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome. Mayo Clin Proc 1991;66:11–22.
- Belchetz G, Cheung CC, Freeman J, et al. Hurthle cell tumors: using molecular techniques to define a novel classification system. Arch Otolaryngol Head Neck Surg 2002;128:237–240.
- Chen H, Nicol TL, Zeiger MA, et al. Hurthle cell neoplasms of the thyroid: are there factors predictive of malignancy? Ann Surg 1998;227:542–546.
- Thompson NW, Dunn EL, Batsakis JG, Nishiyama RH. Hurthle cell lesions of the thyroid gland. Surg Gynecol Obstet 1974;139:555–560.
- Lopez-Penabad L, Chiu AC, Hoff AO, et al. Prognostic factors in patients with Hurthle cell neoplasms of the thyroid. Cancer 2003;97:1186–1194.
- Khafif A, Khafif RA, Attie JN. Hurthle cell carcinoma: a malignancy of low-grade potential. Head Neck 1999;21:506–511.

References: Treatment(3)

- Samaan NA, Schultz PN, Hickey RC, et al. The results of various modalities of treatment of well differentiated thyroid carcinomas: a retrospective review of 1599 patients. J Clin Endocrinol Metab 1992;75:714–720.
- Samaan NA, Schultz PN, Haynie TP, Ordonez NG. Pulmonary metastasis of differentiated thyroid carcinoma: treatment results in 101 patients. J Clin Endocrinol Metab 1985;60:376–380.
- Sugino K, Ito K Jr, Ozaki O, et al. Papillary microcarcinoma of the thyroid. J Endocrinol Invest 1998;21:445–448.
- Hay ID. Papillary thyroid carcinoma. Endocrinol Metab Clin North Am 1990;19:545–576.
- Emerick GT, Duh QY, Siperstein AE, et al. Diagnosis, treatment, and outcome of follicular thyroid carcinoma. Cancer 1993;72:3287–3295.
- Yamashita H, Noguchi S, Murakami N, et al. Extracapsular invasion of lymph node metastasis is an indicator of distant metastasis and poor prognosis in patients with thyroid papillary carcinoma. Cancer 1997;80:2268–2272.
- Sellers M, Beenken S, Blankenship A, et al. Prognostic significance of cervical lymph node metastases in differentiated thyroid cancer. Am J Surg 1992;164:578–581.
- Lindegaard MW, Paus E, Hoie J, et al. Thyroglobulin radioimmunoassay and 131I scintigraphy in patients with differentiated thyroid carcinoma. Acta Chir Scand 1988;154:141– 145.
- Schlumberger M, Challeton C, De Vathaire F, Parmentier C. Treatment of distant metastases of differentiated thyroid carcinoma. J Endocrinol Invest 1995;18:170–172.
- Sisson JC, Giordano TJ, Jamadar DA, et al. 131-I treatment of micronodular pulmonary metastases from papillary thyroid carcinoma. Cancer 1996;78:2184–2192.
- Brown AP, Greening WP, McCready VR, et al. Radioiodine treatment of metastatic thyroid carcinoma: the Royal Marsden Hospital experience. Br J Radiol 1984;57:323–327.
- Casara D, Rubello D, Saladini G, et al. Different features of pulmonary metastases in differentiated thyroid cancer: natural history and multivariate statistical analysis of prognostic variables. J Nucl Med 1993;34:1626–1631.
- Lin JD, Kao PF, Weng HF, et al. Relative value of thallium-201 and iodine-131 scans in the detection of recurrence or distant metastasis of well differentiated thyroid carcinoma. Eur J Nucl Med 1998;25:695–700.

References: Treatment(4)

- Hay ID, Grant CS, Taylor WF, McConahey WM. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. Surgery 1987;102:1088–1095.
- Hay ID, Grant CS, Bergstralh EJ, et al. Unilateral total lobectomy: is it sufficient surgical treatment for patients with AMES low-risk papillary thyroid carcinoma? Surgery 1998;124:958–964.
- Dackiw AP, Zeiger M. Extent of surgery for differentiated thyroid cancer. Surg Clin North Am 2004;84:817–832.
- Shaha AR. Implications of prognostic factors and risk groups in the management of differentiated thyroid cancer. Laryngoscope 2004;114:393–402.
- DeGroot LJ, Kaplan EL. Second operations for “completion” of thyroidectomy in treatment of differentiated thyroid cancer. Surgery 1991;110:936–939; discussion 939–940.
- Scheumann GF, Seeliger H, Musholt TJ, et al. Completion thyroidectomy in 131 patients with differentiated thyroid carcinoma. Eur J Surg 1996;162:677–684.
- Chao TC, Jeng LB, Lin JD, Chen MF. Completion thyroidectomy for differentiated thyroid carcinoma. Otolaryngol Head Neck Surg 1998;118:896–899.
- Pacini F, Elisei R, Capezzone M, et al. Contralateral papillary thyroid cancer is frequent at completion thyroidectomy with no difference in low- and high-risk patients. Thyroid 2001;11:877– 881.
- Burge MR, Zeise TM, Johnsen MW, et al. Risks of complication following thyroidectomy. J Gen Intern Med 1998;13:24–31.
- Udelsman R, Lakatos E, Ladenson P. Optimal surgery for papillary thyroid carcinoma. World J Surg 1996;20:88–93.
- Pattou F, Combemale F, Fabre S, et al. Hypocalcemia following thyroid surgery: incidence and prediction of outcome. World J Surg 1998;22:718–724.
- Mazzaferri EL, Kloos RT. Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001;86:1447–1463.
- Mazzaferri EL. Thyroid remnant 131I ablation for papillary and follicular thyroid carcinoma. Thyroid 1997;7:265–271.
- Taylor T, Specker B, Robbins J, et al. Outcome after treatment of high-risk papillary and non-Hurthle-cell follicular thyroid carcinoma. Ann Intern Med 1998;129:622–627.

References: Treatment(5)

- Leger FA, Izembart M, Dagousset F, et al. Decreased uptake of therapeutic doses of iodine-131 after 185-MBq iodine-131 diagnostic imaging for thyroid remnants in differentiated thyroid carcinoma. Eur J Nucl Med 1998;25:242–246.
- Muratet JP, Giraud P, Daver A, et al. Predicting the efficacy of first iodine-131 treatment in differentiated thyroid carcinoma. J Nucl Med 1997;38:1362–1368.
- Mazzaferri EL. Carcinoma of follicular epithelium: Radioiodine and other treatment outcomes. In: Braverman LE, Utiger RD, eds. The Thyroid: A Fundamental and Clinical Text. Philadelphia, PA: Lippincott-Raven; 1996:922–945.
- Brierley J, Maxon HR. Radioiodine and external radiation therapy in the treatment of thyroid cancer. In: Fagin JA, ed. Thyroid Cancer. Boston, MA: Kluwer Academic; 1998:285–317.
- Tuttle RM, Leboeuf R, Robbins RJ, et al. Empiric radioactive iodine dosing regimens frequently exceed maximum tolerated activity levels in elderly patients with thyroid cancer. J Nucl Med 2006;47:1587–1591.
- Van Nostrand D, Wartofsky L. Radioiodine in the treatment of thyroid cancer. Endocrinol Metab Clin North Am 2007;36:807– 822, vii–viii.
- Maxon HR III, Englaro EE, Thomas SR, et al. Radioiodine-131 therapy for well-differentiated thyroid cancer—a quantitative radiation dosimetric approach: outcome and validation in 85 patients. J Nucl Med 1992;33:1132–1136.
- Benua RS, Cicale NR, Sonenberg M, Rawson RW. The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. Am J Roentgenol Radium Ther Nucl Med 1962;87:171–182.
- Sherman SI, Tielens ET, Sostre S, et al. Clinical utility of posttreatment radioiodine scans in the management of patients with thyroid carcinoma. J Clin Endocrinol Metab 1994;78:629– 634.
- Pacini F, Molinaro E, Castagna MG, et al. Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. J Clin Endocrinol Metab 2003;88:3668–3673.
- Haugen BR, Pacini F, Reiners C, et al. A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. J Clin Endocrinol Metab 1999;84:3877–3885.
- Kloos RT, Mazzaferri EL. A single recombinant human thyrotropin-stimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. J Clin Endocrinol Metab 2005;90:5047–5057.
- Ladenson PW, Braverman LE, Mazzaferri EL, et al. Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. N Engl J Med 1997;337:888–896.