ATA Guidelines for Medullary Thyroid Cancer: approach to initial management of sporadic and inherited disease

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AMERICAN THYROID ASSOCIATION
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Disclosures related to MTC

- OSU Thyroid Cancer Unit MTC Research:
  - Exelixis: XL184
  - Esai: E7080
  - NCI funded study of Sorafenib in MTC (Bayer Pharmaceuticals and Onyx Pharmaceuticals)
- Consulting (without honorarium)
  - Bayer and Onyx Pharmaceuticals
  - Eli Lilly
  - Exelixis
  - Novo Nordisk

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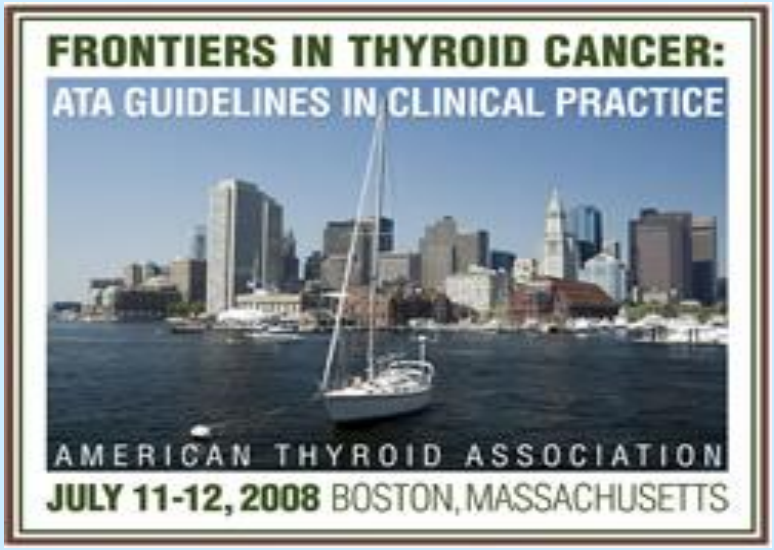

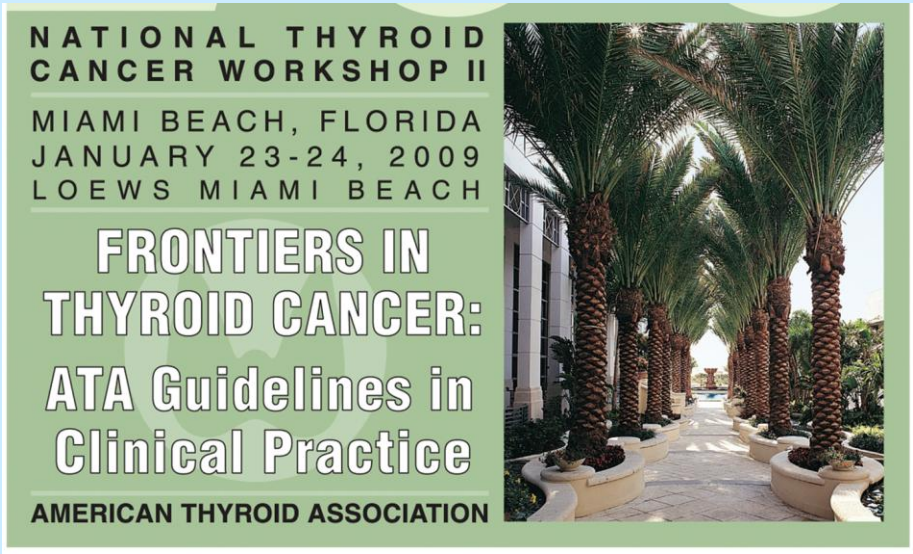

Guideline Development

- Background: The ATA chose to create specific MTC clinical guidelines that would bring together, and update, the diverse MTC literature and combine it with evidence-based medicine and a panel of expert clinicians.
- Methods: The Task Force considered how patients with MTC or a genetic disposition to MTC were encountered, diagnosed, and treated.
- A series of flow diagrams were created and a list of questions were answered using the published literature and expert opinion.
- Relevant articles were identified using a systematic PubMed search and supplemented by additional published materials.
- Evidence-based recommendations were created then categorized using criteria adapted from the United States Preventive Services Task Force, Agency for Healthcare Research and Quality.

Guideline Development

- **Guideline Development**
  - First face-to-face meeting October 2006. Subsequent meetings, multiple teleconferences, and numerous electronic communications.
- **Document published**
  - Thyroid 2009 June 19(6):565-612.
- **The document consists of:**
  - 47 pages
  - 6 tables (including 1 as a table of contents plus searchable Location Keys)
  - 5 figures
  - 122 recommendations
  - 398 references
  - Endorsement by 15 societies

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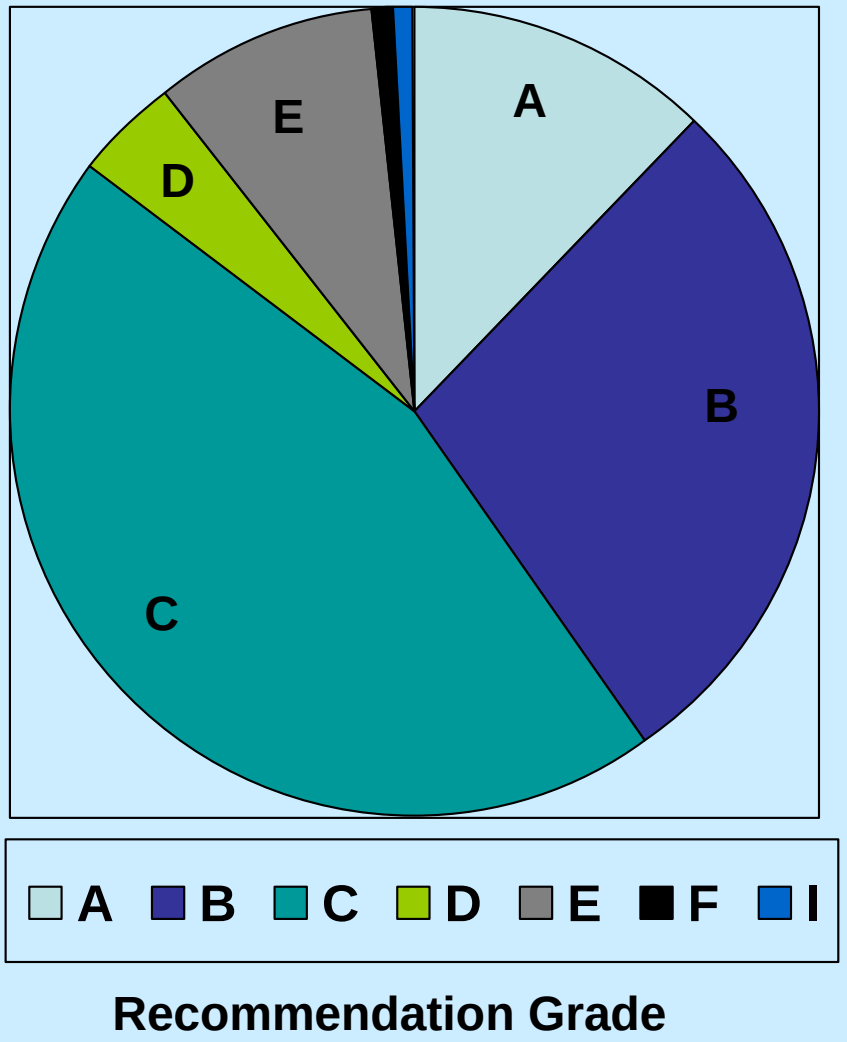

Guideline major subdivisions

- **Initial Diagnosis and Therapy of Pre-clinical Disease** (including RET oncogene testing, and the timing of prophylactic thyroidectomy)
- **Initial Diagnosis and Therapy of Clinically Apparent Disease** (including pre-operative testing and imaging, extent of surgery, and management of devascularized parathyroid glands)
- **Initial Evaluation and Treatment of Post-operative Patients** (including the role of completion thyroidectomy)
- **Management of Persistent or recurrent Metastatic Disease** (including the role of tumor marker doubling times, and treatment of patients with distant metastases, and hormonally active metastases)
- **Long-term Follow-up and Management** (including the frequency of follow-up and imaging)
- **Directions for future research**

Initial Diagnosis and Therapy of Pre-clinical Disease

ATA Risk levels A-D guide prophylactic thyroidectomy: genotype-phenotype

- **ATA Level D mutations:** carry the highest risk for MTC. These mutations include codons 883 and 918, and are associated with the youngest age of onset and highest risk of metastases and disease specific mortality. (MEN 2B)
- **ATA Level C mutations:** carry a lower yet still high risk of aggressive MTC and include mutations in codon 634.
- **ATA Level B mutations:** carry a lower risk for aggressive MTC mutations and include mutations in *RET* codons 609, 611, 618, 620, and 630.
- **ATA Level A mutations:** carry the "least high" risk. The most common ATA Level A mutations are found in codons 768, 790, 791, 804, and 891.

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Prophylactic Thyroidectomy

- Goal
  - To remove the thyroid prior to spread of MTC outside of the thyroid gland and at a time when the risk of central lymph node dissection can be avoided (if possible).

Table 6. ATA Risk Level and prophylactic thyroidectomy testing and therapy

ATA Risk Level	Age of *RET* testing	Age of required 1st US	Age of required 1st Serum Ct	Age of prophylactic surgery
D	ASAP[1] and within the 1st year of life	ASAP and within the 1st year of life	6 months, if surgery not already done	ASAP and within the 1st year of life
C	<3-5 years	>3-5 years	>3-5 years	Before age 5 years
B	<3-5 years	>3-5 years	>3-5 years	Consider surgery before age 5. May delay surgery beyond age 5 years if stringent criteria are met[2].
A	<3-5 years	>3-5 years	>3-5 years	May delay surgery beyond age 5 years if stringent criteria are met[2].

[1]As soon as possible

[2]A normal annual basal +/- stimulated* serum Ct, normal annual neck US, less aggressive MTC family history, and family preference.

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Prophylactic Central Neck Dissection

- Potential Goals
  - Accurately stage patients as N0 or N1.
    - Unclear immediate impact of this distinction (unless N1 would mandate lateral neck dissection [controversial]).
  - Remove microscopic N1 disease that, if left alone, would likely require subsequent, higher risk, therapeutic surgery
  - Curative removal of metastatic disease before it spreads elsewhere.
    - This appears to be a small group of patients/narrow point in time as many/most N1 patients appear to have persistent disease post-operatively.

Summary of size and Ct cut-offs for central neck dissetion (CND)

- When the basal Ct is normal **and** the thyroid US is normal it is **very unlikely** to have N1 or persistent disease. Any cases reported?
- When the basal Ct is <40 ng/L **and** all thyroid nodules are ≤5 mm it is **uncommon** to have N1 or persistent disease. Of those that are N1, the minority are cured with CND. Thus, prophylactic CND is not recommended given the greater risk of harm as opposed to benefit.
- No convincing evidence that accuracy of timing thyroidectomy or CND can be improved using stimulated Ct cut-off levels, and pentagastrin is simply not an option in the US and many other countries.

Initial Diagnosis and Therapy of Pre-clinical Disease

- **RECOMMENDATION 35:** MEN 2A or FMTC patients undergoing prophylactic thyroidectomy within the first 3-5 years should not undergo prophylactic level VI compartmental dissection unless there is clinical or radiological evidence of lymph node metastases, or thyroid nodules > 5 mm in size at any age, or a basal serum Ct > 40 pg/ml (see figure 2). Recommendation E

- **RECOMMENDATION 36:** In MEN 2A or FMTC, the clinical or radiological evidence of lymph node metastases or thyroid nodules ≥ 5mm in size at any age, or a serum basal serum Ct is > 40 pg/ml when > 6 months old, suggest the possibility of more extensive disease that requires further evaluation and treatment (see Figure 2). Recommendation B

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Initial Diagnosis and Therapy of Clinically Apparent Disease

Summary of screening Ct in nodular goiter

- Rationale for screening
  - MTC has frequently metastasized at clinical diagnosis: 50% have lymph node metastases, and 10–20% have distant metastases.
  - Once metastatic, few patients are cured with surgery and data regarding new systemic therapies are encouraging, but favorable data regarding improved PFS is just emerging while no data exists regarding OS.
- Rationale against screening
  - The incidence of MTC found by Ct screening is low and only slightly higher than the incidence of MTC at autopsy, and most detected tumors are small and of unknown significance.
  - No RCT has demonstrated improved outcome by screening.
  - Depending on the Ct cut-off, most operated patients will not have MTC.
  - Since most nodular goiter patients do not have MTC, cost-effectiveness studies are additionally influenced by the cost of Ct test, and the number of times it is repeated in follow-up.

Ct measurement in nodular goiter

- **RECOMMENDATION 52:** This Guideline defers the recommended approach to thyroid nodules, including FNA and serum Ct testing, to the ATA Guideline that addresses thyroid nodules (5). However, if obtained, a basal or stimulated* serum Ct level ≥100 pg/mL should be interpreted as suspicious for MTC and further evaluation and treatment should ensue (Fig. 2). Grade: A Recommendation. **Kloos et al. 2009 Thyroid 19;6:565**
- **Cooper et al. 2009 DTC Guideline 19;11:1167**
  - **R4 The panel cannot recommend either for or against the routine measurement of serum calcitonin. Recommendation I**

Initial diagnosis and therapy of clinically apparent disease

FNA or calcitonin diagnostic or suspicious for MTC

- Mandatory skilled neck US to include the superior mediastinum, central and bilateral lateral neck compartments
- serum calcitonin, CEA, and calcium [1]
- RET mutation analysis[2]
- Treat PHEO before MTC.[3] PHEO excluded if negative: 1) RET and family history, or 2) plasma free metanephrines and normetanephrines, or 24-hour urine metanephrines and normetanephrines, or 3) adrenal CT or MRI

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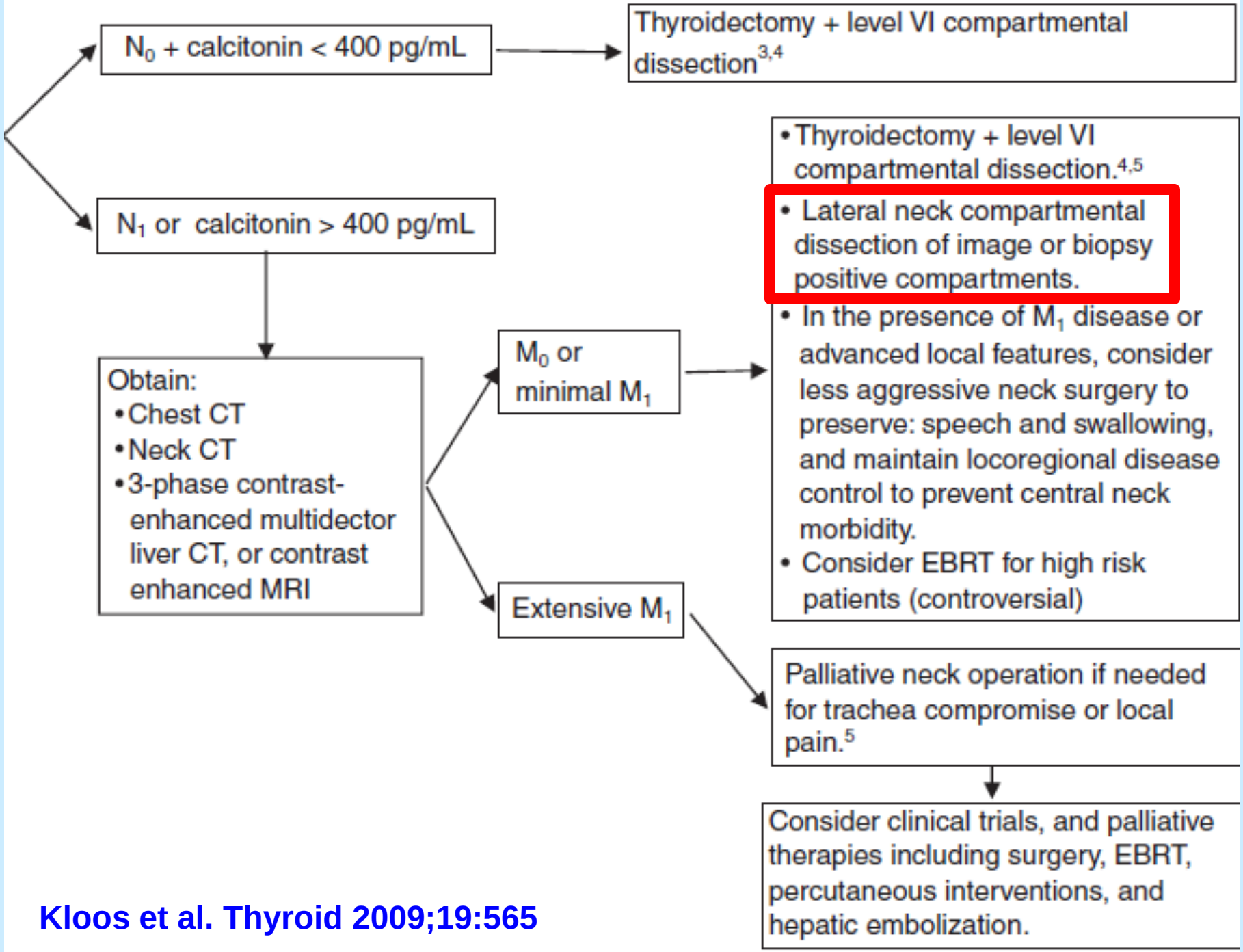

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Prospect of biochemical cure

- Institutional series of 224 consecutive patients with MTC and elevated preoperative basal calcitonin levels, only **10%** of N1 patients achieved postoperative basal and pentagastrin stimulated serum Ct levels <10 pg/mL.
- This did not happen when the preoperative basal Ct level was **>3000** pg/mL or the tumor was **>40mm** in diameter.

Machens et al. JCEM 2005;90:2029

bCt and PGT sCt levels <10 pg/mL

Postoperative Serum Calcitonin and M Classification Grouped by Quantitative Lymph Node Analysis

	Positive lymph nodes excised				
	0	1–9	10–19	≥ 20	
n[a]	17	26	8	4	*P* value
Postoperative calcitonin					
Basal (pg/mL)	4 (2–12)	11 (2–71)	288 (86–1114)	843 (168–2499)	< 0.001
Peak (pg/mL)	6 (2–27)	86 (7–646)	1759 (1072–5769)	2548 (304–7682)	< 0.001
Incremental factor[b]	1.3 (1.0–1.8)	2.9 (1.9–10.1)	6.5 (2.4–35)	2.7 (1.4–3.2)	0.002
M1 (%)	0	4	13	50	0.013
Calcitonin normalization (%)	65	31	0	0	0.003
All lymph nodes excised	59 (22–69)	52 (40–72)	55 (43–74)	63 (52–81)	0.68

- **When > 9 metastatic lymph nodes are present the chance of biochemical cure is very low.**

Machens et al. Cancer 2000;88:1909

Summary of prophylactic lateral neck dissection

- Aggressive prophylactic surgery in the ipsilateral lateral neck compartment +/- contralateral neck compartment may biochemically cure a relatively small percentage of patients who happen to have <10 metastatic lymph nodes, which is unlikely to happen when the contralateral lateral neck is involved.
- It is unknown how these results would apply to patients that are N0 by modern pre-operative US.
- There is no evidence that the extent of lymph node surgery improves survival.

Initial Diagnosis and Therapy of Clinically Apparent Disease

- **RECOMMENDATION 62:** MTC patients with suspected limited local metastatic disease to regional lymph nodes in the central compartment (with a normal US examination of the lateral neck compartments) in the setting of no distant (extra-cervical) metastases, or limited distant metastases should typically undergo a total thyroidectomy and level VI compartmental dissection. A minority of the Task Force favored prophylactic lateral neck dissection when lymph node metastases were present in the adjacent paratracheal central compartment. Recommendation B

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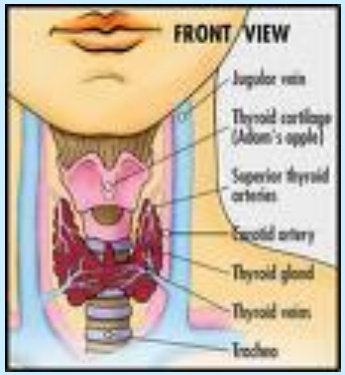
Initial Evaluation and Treatment of Post-Operative Patients



Initial Evaluation and Treatment of Post-Operative Patients

- **RECOMMENDATION 69:** Postoperatively, the TNM classification (Table 4) and other factors, such as the post-operative Ct level and the Ct and CEA DTs, should be used to predict outcome and to help plan long-term follow-up of patients with MTC (Figures 3 and 5). Recommendation C

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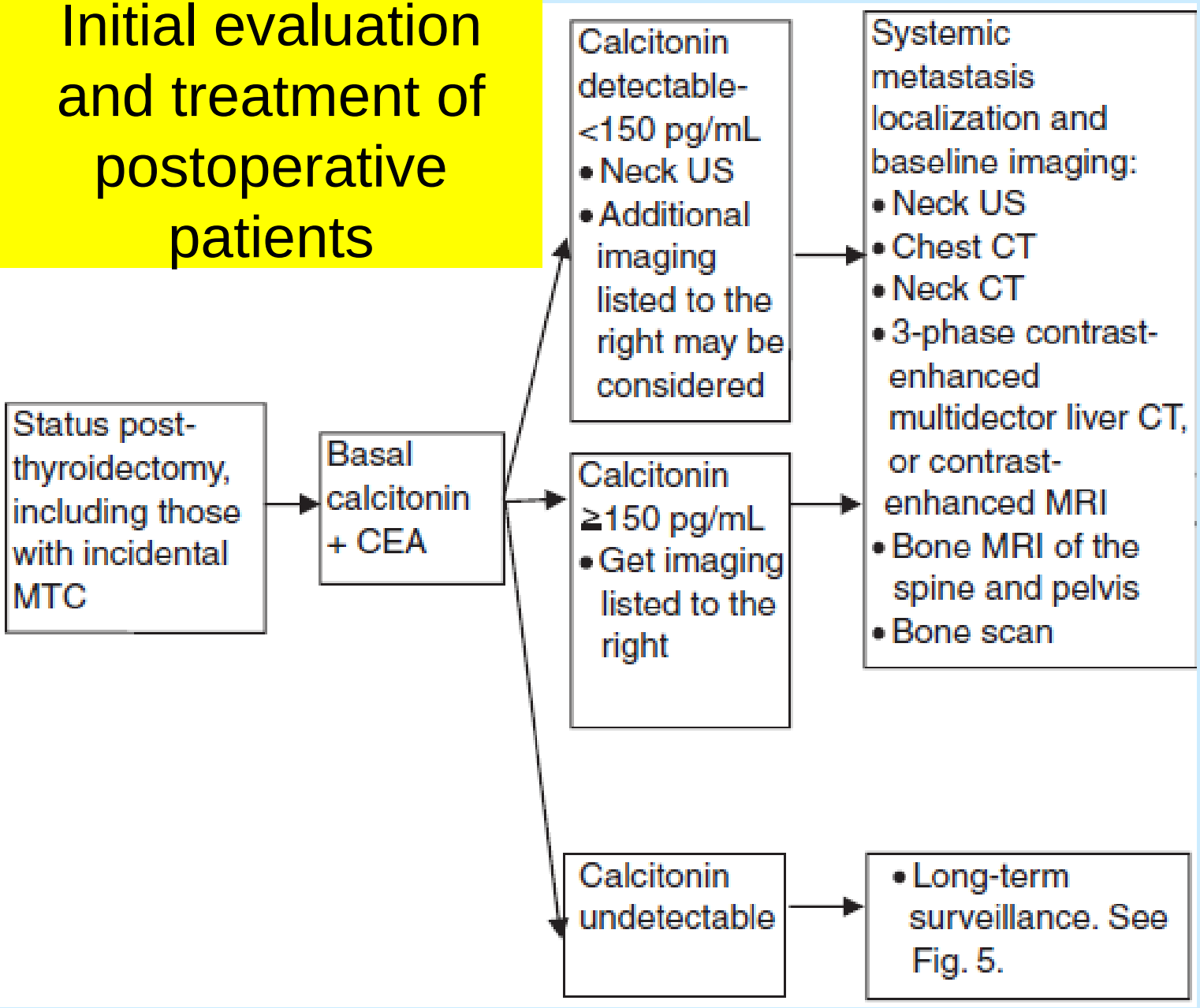
Initial evaluation and treatment of postoperative patients



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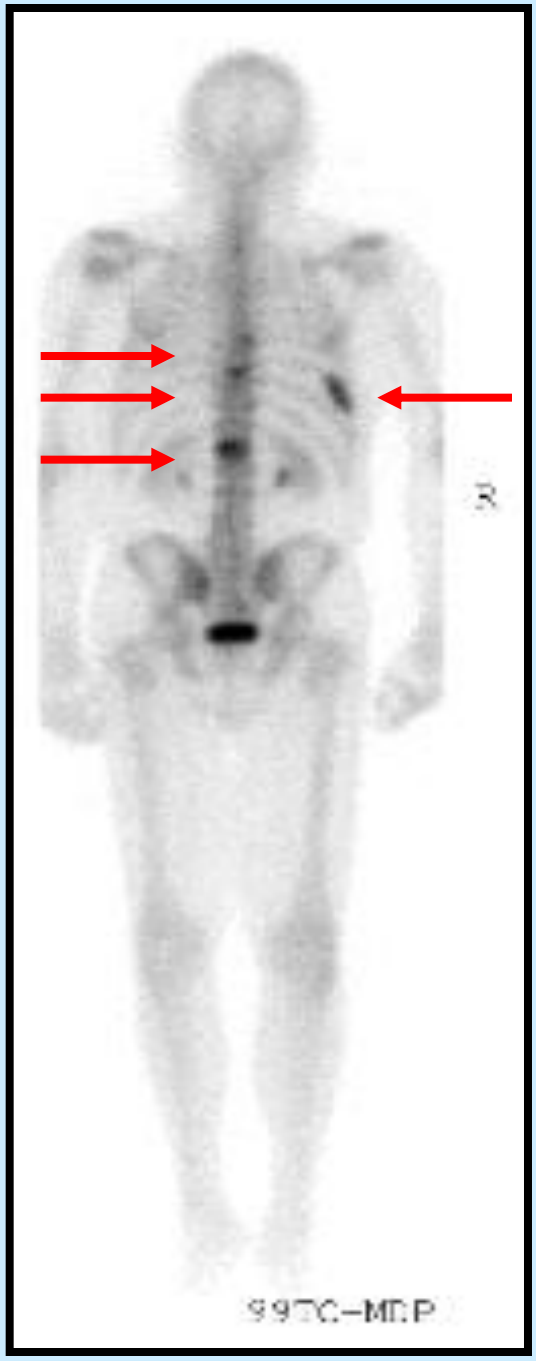

- Compartmental dissection of image or biopsy positive compartments.[1,2,3]
- Consider empiric level VI compartmental dissection if not previously done[1] (controversial).
- In the presence of M_1 disease or advanced local features, consider less aggressive neck surgery to preserve speech and swallowing, and maintain locoregional disease control to prevent central neck morbidity.
- Consider EBRT for high risk patients (controversial).

M_0 or minimal M_1

Extensive M_1

Palliative neck operation if needed for trachea compromise or local pain.[1,2]

Consider clinical trials, and palliative therapies including surgery, EBRT, percutaneous interventions, and hepatic embolization.

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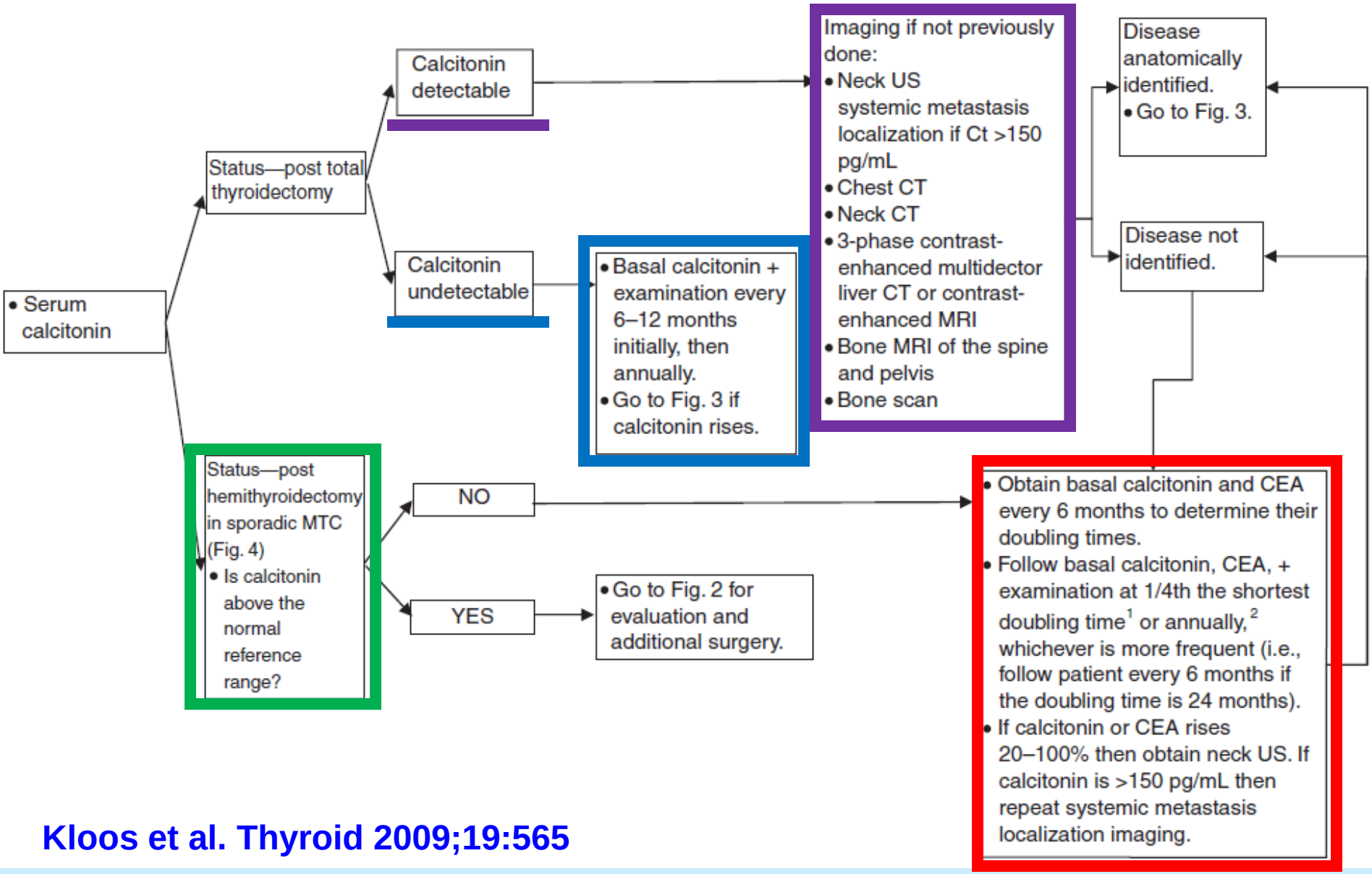
Long-Term surveillance



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Long-Term surveillance

- **Obtain basal calcitonin and CEA every 6 months to determine their doubling times.**
- **Follow basal calcitonin, CEA, + examination at 1/4th the shortest doubling time[1] or annually[2], whichever is more frequent (i.e. follow patient every 6 months if the doubling time is 24 months).**
- **If calcitonin or CEA rises 20%-100% then obtain neck U/S. If calcitonin is > 150 pg/ml then repeat Systemic Metastasis Localization imaging.**

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Predicting Survival

	5-yr survival	10-yr survival
Calcitonin DT		
>2 yrs	100%	100%
0.5-2.0 yrs	94%	64%
<0.5 yrs	23%	15%

- Barbet et al reported that only the Ct DT remained an independent predictor of survival by multivariate analysis. Barbet et al. J Clin Endocrinol Metab. 2005 90:6077-6084
- Giraudet et al reported that the Ct DT and CEA DT were strongly correlated in 80% of patients. When they were both ≤ or > 24 months then progressive disease at 1 year was seen in 94% and 14%, respectively. Giraudet et al. European journal of endocrinology / European Federation of Endocrine Societies. 2008 158:239-246

Ct and CEA doubling time calculator

- **Initial surgery 01/26/01**
- **Death due to MTC 2 years later**

Date of Test (mm/dd/yyyy)	Calcitonin (must be number)	CEA (must be number)
04/26/2001	4000	27.3
07/24/2001	3980	53.4
11/01/2001	8580	160.3
07/02/2002	54600	443.7
Days:	107.14	107.75
Months:	3.52	3.54
Years:	0.29	0.29

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Persistent or recurrent MTC: when metastases require treatment

RECOMMENDATION 87: Active treatment is most often indicated in patients with lesions in critical locations such as brain metastases, impending or active central nervous system compression, airway compromise, symptomatic lesions, hormonal secretion, and impending or active fracture of a weight bearing bone. Grade: A Recommendation

RECOMMENDATION 88: Asymptomatic patients with small volume metastatic disease that is stable to slowly progressive as determined by anatomic imaging, or Ct and CEA DT > 2 years, typically do not require systemic therapy, and the decision to initiate such treatment should be made with the patient only after a thorough discussion. Grade: E Recommendation

RECOMMENDATION 89: Patients with rapidly progressive disease by anatomic imaging or biochemical DT < 2 years should be considered for treatment, ideally in the context of a well-designed clinical trial. Grade: B Recommendation

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