Medullary Thyroid Carcinoma: Diagnosis and Treatment of Sporadic and Hereditary Tumors

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Contents

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Cases

Case 1

62-year-old female
Palpable nodule, left thyroid lobe

US: solitary nodule in the left thyroid lobe, size – 30 mm; ovoid, hypoechogenic, regular sharp margins, no macro–/microcalcification
Scintigraphy: "non-functioning" nodule on right side

Thyroid-stimulating hormone (TSH): 0.9 (0.4–4.0 u/L); free triiodothyronine (FT3), free thyroxine (FT4) normal – normal thyroid metabolism

Ca: 2.3; parathyroid hormone (PTH): 29, calcifediol (25(OH)D3) n.d.

Ct: 4 pg/mL (Immulite 2000; Diagnostic Products Corporation [ICMA] reference range: F: –6.4 pg/mL)

Creatinine (Cr): 0.9 mg/dL

FNAB: follicular neoplasm/suspicious for follicular neoplasm (Bethesda 4)

Surgery: left hemithyroidectomy, left CND

Frozen section: no signs of malignancy

Histology: microfollicular adenoma; medullary thyroid microcarinoma (near the upper left pole: multifocal [three lesions], each measuring 1 mm), pN0 (0/5)

(1) Follow-up only
(2) Completion of thyroidectomy en principe? With/without CND/LND?
(3) Completion of thyroidectomy after specific "testing"? With/without CND/LND?

If (1) Follow-up
(1a) US, every 6 months
(1b) Biochemistry (Ct), every 6 months
(1c) 1a + 1b
If (2) Right lobectomy en principe
(2a) Without CND
(2b) With CND
If 3
(3a) Biochemistry (Ct) with Ca stimulation
(3b) Biochemistry (Ct), plasma metanephrine, plasma normetanephrine, genetic testing (RET proto-oncogene)

Case 2

66-year-old female
Palpable nodule, right thyroid lobe

US: solitary nodule in the right thyroid lobe, 39 mm – mild hypoechogenic, regular sharp margin, no macro–/microcalcification

Scintigraphy: "non-functioning" nodule on the right side

TSH: 1.2 (0.4–4.0 u/L); FT3, FT4 normal

Ca: 2.4 PTH 26, 25(OH)D3 42

Ct: 1549 pg/mL (Immulite 2000; Diagnostic Products Corporation [ICMA] reference range: F: –6.4 pg/mL)

Cr: 1.0 mg/dL

CEA: 1690 ng/mL (Elecsys System 2010 (Roche-Diagnostics, Germany) (reference range – 3.8 µg/L)

plasma metanephrines/plasma normetanephrines: normal catecholamines/metanephrines and normetanephrines (24-h urine): normal

(1) Follow-up
(2) Surgery

(2a) Thyroidectomy
(2b) Thyroidectomy with unilateral CND
(2c) Thyroidectomy with bilateral CND, bilateral LND
(2d) Thyroidectomy with bilateral CND, frozen section

Case 3

60-year-old male

No palpable nodules in both thyroid lobes

US: small thyroid gland, inhomogeneous echogenicity, nodules less than 3 mm

Appearance as in autoimmune thyroiditis

Scintigraphy: not performed

TSH: 85 (0.4–4.0 u/L); FT3 1.2 (1.8–4.2 ng/mL), FT4 0.7 (0.8–1.9 ng/mL) – hypothyroidism.

Microsomal antibodies: 1403 (normal range <80 U/mL)

Ca: 2.34 PTH 31, 25(OH)D3 n.d.

Ct: 685 pg/mL (Immulite 2000; Diagnostic Products Corporation [ICMA] reference range: M: – 9.5 pg/mL)

Cr: 0.7 mg/dL

Plasma metanephrines/plasma normetanephrines: normal catecholamines/metanephrines and normetanephrines (24-h urine): normal

(1) Follow-up
(2) Further diagnostic tests (stimulation tests)
(3) Surgery – MTC suspected: thyroidectomy, bilateral CND, if tumor DSR-negative: bilateral LND

Case 4

63-year-old male
Palpable nodule in the right thyroid lobe

US: right thyroid lobe nodule – 49 mm, ovoid, hypoechogenic, regular sharp margins; left lobe is inhomogeneous

TSH: 0.03 (0.4–4.0 u/L); FT3, FT4 – normal

Scintigraphy: "non-functioning" nodule on the right side – multifocal thyroid autonomy in both thyroid lobes

Ca: 2.23 PTH 40, 25(OH)D3–24, reduced vitamin D uptake

Ct < 2 pg/mL (Immulite 2000; Diagnostic Products Corporation [ICMA] reference range: M: –9.5 pg/mL)

Cr: 0.9 mg/dL

FNAB: follicular neoplasm/suspicious for follicular neoplasm (Bethesda 4)

Surgery: thyroidectomy, frozen section: inconclusive – follicular neoplasia

Histology: encapsulated follicular variant of papillary thyroid carcinoma, pT2–36 mm, pNx

medullary thyroid microcarcinoma with DSR, left lobe – pT1a – <1 mm pNx

(1) Ct
(2) Completion surgery with left CND
(3) Molecular genetic analysis
(4) Ct, molecular genetic analysis

Case 5

42-year-old male
No palpable thyroid nodule

Prophylactic health examination

Carotid US: incidentally – left lobe: solitary nodule, 9 mm – mild hypoechogenic, regular shape, no macro-/microcalcification

TSH: 1.67 (0.4–4.0 u/L); FT3, FT4 – normal

Scintigraphy: not performed

Ca: 2.54 PTH 43, 25(OH)D3: 40

Ct: 10 pg/mL, follow-up 13 pg/mL (Immulite 2000; Diagnostic Products Corporation [ICMA] reference range: M: –9.5 pg/mL)

Cr: 0.85 mg/dL

(1) Ct follow-up in 1 year
(2) Stimulation test to select patient for surgery
(3) Hemithyroidectomy with left CND
(4) Molecular genetic analysis

8.1 Introduction

Medullary thyroid cancer (MTC) is a rare ("orphan") disease. MTC accounts for approximately 3% of all thyroid cancers in unselected American and European series (USA: 177/5583; Germany: 79/2537) [1, 2]. The overall prevalence of occult MTC was 0.14% among 7897 autopsies from 24 published series [3], increasing to 0.85% in North American and European clinical series routinely applying calcitonin (Ct) measurements in the biochemical workup of thyroid nodules (0.13–0.85%; 238 [0.34%] of 70,286 patients; 13 authors) [4].

In contrast to well-differentiated, follicular-cell-derived thyroid cancer, MTC originates from the parafollicular (neuroendocrine) C cells (CCs) of the thyroid. CCs comprise a minor population of the thyroid, representing approximately 2–4% of

the organ's cells, and secrete Ct in the low normal range. The CC belongs to the group of neuroendocrine cells. Therefore, it may to a lesser degree secrete smaller quantities of several other neuroendocrine peptides, such as somatostatin, Ct gene–related peptide, and serotonin.

8.2 Clinical Presentation

In former clinical studies, patients with MTC (sporadic or hereditary index patients) presented clinically in 45–94% with a palpable thyroid mass [5, 6]. Less symptomatic patients are dominant in current surveys [7].

Neck masses may provoke symptoms reported in up to 30%, such as dysphagia, shortness of breath, hoarseness, or diarrhea. In patients with a palpable primary, MTC has already metastasized clinically to the cervical lymph nodes (LN; 42–52%). Spread is most frequent to the central compartment (Robbins level VI [8]); Dralle central neck = C1a/C1b [9]), followed by the ipsilateral jugular chain of nodes and the contralateral cervical nodes (levels II–V; C2 and C3), but it is also seen to the upper and anterior mediastinum (level VII; C4) [9–11] – ◘ Table 8.1.

Distant metastasis may occur in the lungs, liver, bones, brain, and soft tissues (documented in 12–28%). Metastatic spread may be difficult to assess by cross-sectional imaging because of the fine, miliary pattern of these lesions. Laparoscopy with direct imaging of the liver may identify small metastatic deposits not visible by conventional imaging in 25% of patients with elevated Ct levels following therapeutic surgery [12].

Computed tomography (CT) or magnetic resonance imaging (MRI) studies for distant disease are done preoperatively if Ct levels are higher than 500 pg/mL. Neither fluorodeoxyglucose- (FDG-) positron emission tomography (PET)/CT nor fluorodopa- (F-DOPA-) PET/CT is used routinely for preoperative staging but may contribute information in doubtful individual cases.

◘ **Table 8.1** Correlation between Robbins LN levels [8] and Dralle compartments [9]

Robbins (level)	Dralle (compartment)		Neck dissection
VI	C1	1a – central right 1b – central left	Central
(I), II–V	C2/3	C2 – right lateral C3 – left lateral	Lateral
VII	C4	Upper/lower mediastinal	Mediastinal

8.3 Ultrasonography

Ultrasound (US) examination is a valuable diagnostic tool to diagnose MTC. Typical MTC appears as a solid, (often markedly) hypoechogenic lesion without a halo and quite commonly containing micro- or macrocalcifications. However, the first three features are known to be very unspecific and the other two are less sensitive.

The presence of a lesion with the appearance described above should lead to suspicion of MTC and be considered as an argument for further diagnostic steps such as Ct measurements [13]. However, most MTCs do not present all of the mentioned features, and some of them can have a relatively benign US appearance [14].

Neck US revealed an overall sensitivity of only 90% in detecting MTC with a mean tumor size of 20 mm and larger. In the subgroup of patients with tumors ≤10 mm, the sensitivity was even lower (71%) [15].

The sensitivity of US to diagnose LN metastasis was overall only 6% and 56% in the central and lateral neck, respectively [15].

8.4 FNAB

A meta-analysis demonstrated that fine-needle aspiration biopsy (FNAB) is able to detect approximately one half of MTC lesions [16]. These low diagnostic rates suggest that other techniques are needed in combination with FNAB to improve the diagnosis of MTC and to avoid false-negative results. The majority of small nodules are difficult or are even impossible to examine by FNAB. Small MTC size (≤10 mm) and a smooth margin may be factors predicting false-negative FNAB results [17].

Routine basal Ct (bCt) measurements have been documented to show a higher sensitivity to diagnose MTC compared with FNAB cytology, especially in diagnosing small (≤10 mm) MTCs [18].

Desmoplastic stromal reaction (DSR) appears to be an excellent (intraoperative) marker to predict LN involvement with a high specificity. Initial lateral neck dissection (LND) may be avoided in MTC patients without DSR, because these tumors never metastasize, independent of tumor size and bCt levels [19–21].

Therefore, FNAB should be avoided as a first-step diagnostic procedure, as traumatizing the tumor capsule may trigger the development of scar tissue in the tumor, leading to be misinterpreted as DSR positivity [22].

8.5 FNAB and Evaluation of Ct in the Fine-Needle Aspirate

Boi et al. [23] were the first to recommend Ct measurements in wash-out fluids from fine-needle aspiration to improve the diagnosis in primary (and metastatic) MTC in the workup of thyroid nodules to avoid false-negative or inconclusive results from cytology [24].

Almost all MTC lesions >10 mm were correctly diagnosed. However, even this modification of FNAB may be inconclusive or hardly possible in small (≤10 mm) tumors [25].

8.6 Carcinoembryonic Antigen

Besides Ct, carcinoembryonic antigen (CEA) is a widely used tumor marker for the diagnosis and postoperative follow-up of patients with MTC. However, not all patients with MTC are characterized by elevated CEA levels.

8.7 Procalcitonin

It was suggested that procalcitonin (PCT) may be an accurate biomarker in the diagnosis and follow-up of MTC. In the first systematic review to analyze the value of PCT, a total of 15 out of 184 articles were retrieved and analyzed [26]. Of these 15 studies, 3 were case reports. In these studies, the values of Ct and PCT were assessed in a group of patients with MTC versus another consisting of healthy volunteers and patients with benign/malignant thyroid nodular disease or bacterial infection. *The authors suggested that PCT would seem to be a useful biomarker for the diagnosis and follow-up of MTC when used in conjunction with Ct, particularly in a small proportion of tumors that are Ct-negative or secrete low levels of Ct.* So far, the data have not been sufficient to suggest a specific threshold for normal PCT. However, most studies indicate a value of 0.1 μg/mL as an acceptable cut-off in everyday clinical practice. The authors concluded that Ct should continue to be the primary biomarker in MTC, with the addition of PCT in some patient groups (e.g., Ct-negative MTC). Nevertheless, larger patient series were suggested in order to provide safer and more accurate results.

In a prospective study [27] among 2705 patients, 9 with positive serum PCT (i.e., above 0.1 μg/L) and 370 with negative PCT underwent thyroid surgery. MTC was histologically confirmed in all patients with positive PCT but not found in patients with negative PCT. The serum PCT levels were significantly higher in patients with MTC (median 0.64 μg/L, range 0.16–12.9 μg/L) than in those without (median 0.075 μg/L,

range 0.075–0.16 μg/L; P < 0.0001). ROC curves were plotted to calculate the optimal PCT value separating patients with MTC from those without. The best cut-off was 0.155 μg/L with sensitivity, specificity, positive, and negative predictive values as well as accuracy of 100%, 99.7%, 91.7%, 100%, and 99.7%, respectively. Positive and negative likelihood ratios were 329 and 0, respectively. *It was concluded that the measurement of PCT may be a sensitive and accurate method for detecting MTC in patients with thyroid nodules and thus could be a reliable alternative to, but not completely replace, Ct measurement.*

8.8 Ct

Ct is a polypeptide hormone consisting of 32 amino acids with a disulfide bridge between position 1 and 7 and is involved in calcium (Ca)-phosphorus metabolism.

Elevations in serum Ca trigger release of Ct from CCs. Ct release from CCs in response to elevated serum Ca provides the basis for the Ca stimulation test. Other hormones such as gastrin have been reported to stimulate Ct release as well. The sensitivity of CC to gastrin led to the application of pentagastrin (Pg) to increase the Ct secretion in CC disease. However, widely used previously, Pg is no longer available [28].

CCs become clinically relevant when they change their normal "morphology." Oncogenic transformation of the thyroid CC is thought to progress through a hyperplastic process prior to malignancy with increasing levels of serum Ct serving as a biomarker for tumor burden [29]. Repeatable elevated bCt levels may indicate CC disease [30].

Ct is the established gold-standard biomarker for the diagnosis and follow-up of MTC. Reliable and sensitive Ct assays applied to screen sporadic and hereditary MTC are important for health and economic reasons, as they facilitate early diagnosis [31, 32]. However, the normal ranges and cut-offs of bCt levels differ in the literature because Ct is measured by different assays, resulting in difficulties in interpreting and comparing the results.

Over the past decade, commercial assays for measuring Ct have progressed to the newest immunochemiluminometric assays (ICMAs) that are highly sensitive and specific for monomeric Ct. With ICMAs, cross-reactivity with other Ct-related peptides is largely eliminated. Ultrasensitive Ct assays have mostly eliminated false-negative rates of bCt measurements when diagnosing CC disease [33].

The growth of MTC is relatively slow, but if metastasized to the LNs or distant organs, or if it persists or recurs after surgery, it may become very aggressive, causing more than 13% of all thyroid-cancer-related deaths.

Lacking alternative treatment (e.g., radioiodine, chemo–/radiotherapy), stage-adapted (= adequate) surgery is the only curative therapeutic modality with a high chance for cure if surgery is performed as long as MTC is limited to the thyroid. Since surgical treatment for even small MTCs must be more radical compared to other types of thyroid cancer, the preoperatively definitive (early) diagnosis of MTC significantly influences management. Delayed diagnosis and inadequate initial treatment deteriorate the prognosis. In two retrospective North American cohort studies of patients with MTC, 15–41% of patients did not receive appropriate surgical therapy because the malignant disease was unknown preoperatively [34, 35]. Adherence rates to the American Thyroid Association (ATA) recommendations for the treatment of MTC increased modestly following the publication of guidelines in 2009. However, only 66.8% of patients treated between 2009 and 2013 received care in accordance with the recommendations, compared to 61.4% of patients treated between 2004 and 2008 [36]. In another report, only half of the MTC patients in California underwent central LN dissection (CLND) at the time of thyroidectomy, which may suggest a lack of appropriate care across a range of healthcare systems [37].

Overall, poor prognosis is linked with late diagnosis. It is well documented that early diagnosis based on preoperatively established Ct levels followed by adequate surgery improves prognosis [38, 39].

Although Cheung et al. [40] concluded that routine Ct screening in patients undergoing evaluation for thyroid nodules appears to be cost-effective in the United States, comparable to the measurement of thyroid-stimulating hormone, colonoscopy, and mammography screening, there is still an ongoing discussion concerning the benefits of early diagnosis [41].

Proponents of Ct evaluation during the diagnostic workup of thyroid nodule(s), regardless of their sizes and function, clearly state the benefits of early diagnosis of MTC, which facilitate one-step (adequate) surgery and therefore a greater potential for cure.

While European guidelines recommend this procedure [42], Anglo-American guidelines are more restricted [13, 33, 43].

Because expert opinions vary regarding the usefulness of routinely measuring serum Ct levels in patients with nodular thyroid disease, the members of the ATA Guidelines Task Force suggested that covering physicians should decide whether Ct determinations are useful in establishing a management strategy in any particular situation [33].

8.9 Interpretation of bCt Levels

Adequate interpretation of Ct results during the diagnostic workup of thyroid nodules allows the supervising team of specialists to appropriately select patients for surgery.

Tumor volume correlates with bCt levels [44–46]. Therefore, it is very important to correlate bCt and the results of ultrasonography, documenting the size of the lesion(s) in the thyroid gland and LN status. A careful interrelation of these findings guides subsequent diagnostic procedures such as the application of further diagnostic tests (e.g., stimulation test) and finally the indication to surgery and surgical decision-making [47, 48]. Elevated bCt levels must always be questioned and reasons for non-CC-derived Ct elevations or the rare cases of false-positive results due to heterophilic antibodies have to be considered [49].

Especially in the absence of thyroid nodules in US (no indication per se to determine Ct), or *if there is a discrepancy between the size of a thyroid nodule and bCt level (a small nodule and an inadequately high bCt level), stimulation tests may help to differentiate thyroid from non-thyroid sources of Ct production* [50–52]. Ectopic Ct production by neuroendocrine tumors has to be taken into account, characterized by no or a less than twofold increase in Ct levels after stimulation. *When stimulation exceeds bCt by more than twofold, MTC is found exclusively* [50].

Up to now, there are no generally accepted Ct cut-off levels to predict MTC, as different Ct assays are used in different laboratories.

In a recently published paper, four different assays based on three assay types were used for Ct measurements [53]. Each assay has its specific gender-dependent cut-off value for positivity. In this chapter, the most precise bCt thresholds for the identification of MTC were ≥46 pg/mL for males and ≥35 pg/mL for females. Using these cut-offs, only 6% of the male patients were not identified as having MTC, whereas 5% were false-positive, having CC hyperplasia (CCH) instead. In females, the discrepancy was higher, since 13% of the female MTC patients were false-negative by using the cut-off of ≥35 pg/mL missing MTC, and 13% had false-positive results (suffering from CCH), which retrospectively led to "unnecessary" surgery. Therefore, "cut-off levels" recommended for decision-making should be applied with caution. Based on various publications and respecting conversion factors [31, 32, 54], ◘ Table 8.2 shows the three most frequently used assay variants in the literature and their gender-specific cut-off values, which definitively predict MTC.

Table 8.2 bCt "cut-off levels" for the most commonly used Ct assays – predicting MTC in 100%

Gender	CIS (Cisbio)	Immulite DPC (Siemens)	DiaSorin (Liaison)	Cobas (Roche)	Mean
	IRMA	ICMA	ICMA	ECLIA	
	bCt pg/mL	bCt pg/mL	bCt pg/mL	bCt pg/mL	bCt pg/mL
Female	>28	>23	>33	>29	>28
Male	>53	>43	>58	>52	>51

IRMA immunoradiometric assay, *ICMA* immunochemiluminescent assay, *ECLIA* electrochemiluminescence immunoassay, *DPC* Diagnostic Products Corporation, *bCt* basal calcitonin
Conversion formula [31, 32, 54]
Immulite 2000 DPC (Siemens) = 0.8 × DiaSorin(Liaison) – 3.4
DiaSorin (Liaison) = 1.24 × (Immulite 2000 DPC /Siemens) + 4.24
Cobas (Roche) = Immulite 2000 DPC × 1.17 + 1,2
Immulite 2000 DPC (Siemens) = (Cobas −1.2)/1.17
Immulite 2000 DPC (Siemens) = CIS × 0.8
Cis (Cisbio) = Immulite 2000 DPC (Siemens): 0.8

The gender-specific mean upper limits for bCt concentrations that led to a recommendation to operate a suspected thyroid nodule as MTC were around 30 pg/mL in women and 50 pg/mL in men.

As a rule, males have higher bCt values than females. Without specifying the characteristics of the Ct assay and without respecting gender differences, concentrations between 60 and 100 pg/mL have been assessed as highly suggestive/pathognomonic of MTC in recently published guidelines [43]. After excluding non-CC-derived Ct elevations [49] and considering the assay and gender, patients may be subdivided into those with "mildly" elevated and others with "highly" elevated bCt levels.

8.10 Surgery

Surgery is the most effective option for curative therapy, reduction in tumor burden, or effective palliation in sporadic and hereditary (index) patients and also for prophylactic and early surgery for those with hereditary MTC.

Surgical decision-making is based on bCt values in sporadic and hereditary patients [47, 55, 56].

8.11 Clinically Occult MTC – "Mildly" Elevated bCt Levels

By definition, in patients with "mildly" elevated bCt levels (= gray zone), the Ct values are documented below assay and gender-specific cut-off Ct values for MTC. In these patients, there is an indistinct overlap between CCH and micro-MTC (mMTC).

If treated surgically, mMTC (≤10 mm; pT1, pN0 or exceptionally pN1a) is expected. mMTC is clinically "silent" and predominantly found beside a clinically dominant benign or a follicular-cell-derived malignant tumor [57].

As shown recently, the bCt levels were documented in the "gray zone" in 41/70 (58.6%) females and 58/79 (73.4%) males [48]. The final histological examination of the thyroid glands and the central LNs revealed MTC in more males (19/58 [32.8%]) than in females (7/41 [17.1%]). All MTCs in the male and female patients in this group were classified as pT1. While all tumors in the 19 males were staged pN0, central LN metastases (pN1a) were documented in 1/7 females. Independent of gender, unilateral or bilateral multifocality was documented in hereditary (89%) but also in sporadic mMTCs (23%) [48].

The goal of surgical treatment is to perform thyroidectomy as long as the malignancy is still confined to the thyroid gland and, if the tumors have early spread locally, to remove micrometastasis in the central LNs. While a more liberal indication for surgery may be considered in men, a restricted indication for surgery may theoretically exist in women, as MTC was found in fewer females than males. However, CLND should be an integral strategy in females. Because bCt levels did not sufficiently specify the possible causes of mildly elevated Ct values, stimulation tests have been recommended in the literature [13, 58, 59].

Ct stimulations either with Ca or Pg have failed to improve diagnostic quality. Neither bCt nor stimulated Ct (sCt) levels (or the combination of both) were able to discriminate between CCH and MTC in either gender within the "gray zone" [28].

The Ca stimulation test may be helpful to theoretically subclassify patients with "mildly" elevated bCt, who are definitively not candidates for surgery. In a previous investigation (cited by many following studies), surgery was recommended in all subjects with an abnormal Ct response to stimulation above 100 pg/mL. This was because peak Ct levels exceeding 100 pg/mL were considered to be indicative of MTC, and MTC was definitively documented in many patients [60].

Costante et al. [61] reported that sCt values after Pg infusion of above 100 pg/mL predicted MTC in at least 40%. However, CCH was revealed in the majority of females (83%) and less frequently in males (66%) [48].

Frank-Raue et al. [62] recommended to re-evaluate patients with "mildly" elevated bCt values in intervals of 3 to 6 months and advise surgery in patients only with rising Ct levels, which may indicate MTC. However, the clinical experience with this concept is marginal. There is only one series of 171 patients who were followed for 2 to 4 years and in 170 of those basal levels remained stable. Only one man experienced an increase after 2 years of follow-up. He underwent a stimulation test (with Pg) with positive results and a peak level above 100 pg/mL. Surgery demonstrated the presence of CCH only [61].

Many patients are aware that Ct is a sensitive tumor marker for MTC. Reproducible "mildly" elevated bCt levels may be the first sign of MTC in those presenting with thyroid nodules ≤10 mm. With regard to the psychological burden accompanying such awareness, keeping some patients in persistent anxiety and uncertainty, many call for surgery even after having been informed about the minor long-term consequences of "mildly" elevated bCt. Potential morbidity must be carefully discussed with the patients and be balanced against unnecessary thyroid surgery and continuous follow-up.

In experienced surgical teams, patients with "mildly" elevated Ct values who decide for surgery may be treated early by (total) thyroidectomy and bilateral CLND, which seems mandatory, because LN micrometastasis may also be present in patients with "mildly" elevated bCt levels (at least in females). "First-step CLND" is recommended to keep permanent morbidity low [63].

Initial (total) thyroidectomy and bilateral CLND is recommended if patients and their supervising physicians decide upon surgical treatment in the presence of "mildly" elevated Ct levels and suspected clinically occult MTC.

In all patients with documented sporadic hypercalcitoninemia, rearranged during transfection (*RET*) proto-oncogene mutation analysis by screening exons 8, 10, 11, 13, 14, 15, and 16 to establish the possible genetic basis for the disease within an individual is mandatory, even in the absence of a positive family history.

In a prospective study in approximately 13% of patients with presumed sporadic CCH or MTC, a germline *RET* mutation was verified. Consequently, pheochromocytoma and primary hyperparathyroidism as part of multiple endocrine neoplasia (MEN) type 2A have to be excluded [56].

If pheochromocytoma is diagnosed biochemically and confirmed by imaging, it is to be treated surgically before treating MTC.

8.12 Biochemically and Clinically Apparent MTC – "Highly" Elevated bCt Levels

By definition, patients with bCt values above the assay and gender-specific cut-off levels suffer from MTC (no false-positive patients!) and therefore are definitive candidates for surgery [48]. "Biochemically apparent MTCs" (= T1a, ≤10 mm, (N0) N1, M0) and "clinically apparent (=palpable) tumors," staged as pT1b-4 (>10 mm, N0 or N1; M0 or M1), are included in this patient group.

In a recently published series of patients with various thyroid nodules prospectively screened for MTC, fulfilling the criteria of biochemically or clinically apparent MTC, overall LN metastases were revealed in 12/21 (57.1%) males and in 8/29 (27.6%) females. Radiologically distant metastasis were found in 3/21 (14.3%) males and in 1/29 (3.5%) females, respectively [48].

In a subanalysis, "biochemically apparent pT1a tumors" were documented in 7/21 (33.3%) males and 15/29 (51.7%) females, with positive LNs in 2/7 (28.6%) males and 2/15 (13.3%) females, respectively [48].

The aim of initial surgery is to control locoregional disease with the prevention of locoregional persistence/recurrence and long-term disease-free survival with biochemical as well as clinical cure [47, 64]. The special biology of MTC is to be respected in selecting the adequate surgical strategy to reach this aim.

8.13 Surgical Strategy – Central Neck

Independent of the genetic background, up to 15% of sporadic MTCs are multifocal and 5% bilateral, with higher rates in patients with germline *RET* mutations because of widespread CCH resulting in multiple foci of MTC [65].

LN metastases occur early in the course of MTC. The pattern of LN metastatic distribution in the neck areas varies between patients and is not related to tumor size [66].

Accidental horizontal (central to lateral) and vertical (central to paratracheal [prelaryngeal/pretracheal] to mediastinal or contralateral central/lateral) lymphatic flows are the cause of formation of LN metastasis. Reviewing the literature, LN involvement was identified in 10–30% of tumors ≤10 mm [11, 57, 67]. Overall, at the time of initial surgery, the involvement of central LNs has been documented in 50–100% in the literature [10, 11, 66].

In terms of diagnosing central LN metastasis, neck US demonstrated a sensitivity of only 6%. In particular, micrometastasis may be hidden by the thyroid gland and may therefore be missed on US [15].

Therefore, (total) thyroidectomy and bilateral CLND (level VI) is recommended initially in all patients with biochemically and clinically apparent tumors [33, 43].

For completeness of CLND, Perros et al. [43] recommended to extend dissection down to the innominate artery (Robbins levels VI and VII).

8.14 Surgical Strategy – Lateral Neck

Independent of size, the occurrence of malignant ipsilateral nodes ranges from 48% to 81% [10, 11, 66]. Furthermore, contralateral LN metastases were found on histology in 44% of patients with palpable unilateral and in 49% with bilateral MTC [10, 11, 66].

Skip metastasis (= negative central but positive lateral or mediastinal LNs) may occur in 21.3% [68]. Mediastinal LN metastases were revealed in 32% [10].

The presence [7, 69] and the higher numbers of removed and affected LNs [70] predict a lower chance of biochemical cure and negatively influence disease-free survival.

The biochemical cure rate was 33% in node-positive patients; the latter was improved to 45% after four compartment lymphadenectomies [71].

Quantitative LN analysis of MTC improves prediction of Ct normalization. When more than two compartments are involved, normalization of serum Ct cannot be attained. Surgery should then be less extensive and directed rather at preventing local complications [50].

Individually, the extent of neck dissection did not alter disease-specific survival. But patients who underwent both central neck dissection (CND) and LND at the time of initial surgery were less likely to require reoperation for locoregional recurrence [70].

There is a general consensus to dissect central and lateral compartments with clinical or radiological evidence of involved LNs to prevent local recurrence and, if possible, persistence [33, 43].

However, as shown recently [15], the sensitivity of US to correctly document lateral LN metastasis was only 56% with a specificity of 97% (overall accuracy: 84%).

The prophylactic dissection of ipsilateral or bilateral lateral LNs in node-negative patients is part of an ongoing discussion. The oncological benefit of more extended (lateral) LN dissection is to be weighed against higher rates of surgical complications compared with total thyroidectomy and CLND alone.

Patients with tumor multiplicity based on preoperative imaging evaluations more frequently showed lateral node positivity based on pathological examination than those without tumor multiplicity. However, 28% of solitary MTCs based on preoperative findings were histopathologically positive for lat-

eral LN metastasis. Twenty-nine percent of the MTCs measuring 2 cm or less were lateral-node-positive [72].

Machens et al. [73] investigated the rates of occult lateral compartment metastases in patients with central compartment nodal disease, and identified a risk of ipsilateral lateral compartment metastasis of 77% if one to three central compartment nodes were involved, and the same risk of contralateral lateral compartment involvement if more than 10 central compartment nodes were involved.

Bilateral LND for thyroid cancers confers a significant amount of morbidity. Knowledge of the complications of this procedure, especially in the setting of questionable survival benefit, may assist in preoperative decision-making and patient counseling [74].

The morphology of the primary tumor (DSR – yes/no) and the involvement of central LNs (yes/no) influence the indication for a more extended lateral LN dissection (LLND).

An observational study [19] confirmed that the extent of LN surgery may be individualized based on intraoperative frozen sections documenting DSR negativity. DSR is defined as the presence of a newly formed fibrotic (collagenous) stroma surrounding the invasive epithelial tumor cells, which is not found in the non-neoplastic thyroid parenchyma. Patients with DSR-negative tumors are always LN-negative (pN0: negative predictive value 100%) and have an excellent long-term prognosis without persisting or recurrent disease, even without lateral LN surgery, regardless of tumor size, thus reducing the surgical trauma and possible complications [20]. FNAB should be avoided during the diagnostic workup of a thyroid nodule because a DSR may be triggered by inserting a needle into the nodule [22].

Perros et al. [43] recommended ipsilateral prophylactic LLND only after documenting histologically proven central compartment node metastasis because of the higher risk of lateral LN involvement [75]. However, this recommendation does not consider the phenomenon of skip lesions.

CLND and ipsilateral (or contralateral) LN dissection may be performed as a one-stage or a two-stage procedure (= delayed LLND in a second operation) [76].

Two-stage LLND has the advantage of providing the pathological nodal status of the central compartment, as well as postoperative Ct levels, both of which may influence the decision to follow a supplementary approach. If there is no histopathologic evidence of central LN metastasis and postoperative Ct is normal, then delayed LN dissection is unlikely to confer any benefit. The disadvantage of two-stage LN dissection is the requirement for a second hospital stay and general anesthesia.

While the classification of LN levels by Robbins [8] is used in the Anglo-American literature, the classification of LN com-

partments by Dralle [9] is applied in Central Europe. Table 8.1 shows the correlation of both nomenclatures.

There is a close correlation among Ct levels, tumor size, and tumor stage. Higher biomarker levels reflect larger primary tumors and/or more severely involved LNs and/or distant metastasis.

Therefore, Ct levels allow for a "tailored" surgical strategy [77].

Preoperative Ct levels may guide the extent of LN dissection. Disregarding gender-specific cut-off bCt levels, LN metastases were present in the ipsilateral central and lateral neck, contralateral central neck, contralateral lateral neck, and upper mediastinum, respectively, beyond bCt thresholds of 20, 50, 200, and 500 pg/mL applying an Immulite 2000 automated Ct assay (Diagnostic Products Corp., Los Angeles, CA) [47].

In most newly diagnosed MTC patients, that is, those with pretherapeutic bCt levels greater than 200 pg/mL, bilateral compartment-oriented neck surgery is recommended to reduce the number of reoperations [47].

Applying the same Ct assay and respecting gender [48], all male patients with LN metastases were diagnosed with bCt levels ≥100 pg/mL (sensitivity: 100%). The specificity for the diagnosis of any LN metastases (pN1a or pN1b) was 82% and 74% for the presence of lateral LN metastases (pN1b only).

Among the female patients, one woman was diagnosed with a single LN metastasis in the central compartment (N1a) with a bCt level of 23 pg/mL. Therefore, the cut-off of ≥23 pg/mL was used to diagnose any LN metastases (pN1a or pN1b) and specificity was only 22% with a sensitivity of 100%. However, all other women with LN metastases had bCt levels ≥85 pg/mL and metastases in the lateral compartment (specificity: 57%).

8.15 Locally Advanced MTC and Distant Metastasis

In patients with suspected locally advanced MTC, invasion of the aerodigestive tract or involvement of the mediastinum has to be ruled out using CT or MRI. These techniques clarify the technical resectability of the tumor from the neck or mediastinum.

Functional imaging with F-DOPA-PET (CT or MRT) may confirm LN metastases in the mediastinum, which are revealed in 32% [10]. When there is strong suspicion or evidence of mediastinal node involvement below the brachiocephalic vein, and no evidence of distant metastases, the patient should be considered for mediastinal dissection, which will require sternotomy [71, 78].

Functional imaging with F-DOPA-PET (CT or MRT) is able to ensure the diagnosis of distant metastasis [15]. Patients

with distant metastases at presentation often have prolonged survival. Even in the presence of disseminated disease, less aggressive surgery in the central and lateral neck may be appropriate to preserve speech, swallowing, parathyroid function, and shoulder mobility. External beam radiotherapy, systemic medical therapy, and other non-surgical therapies should be considered to achieve local tumor control [33, 43].

8.16 Special Situations

As shown previously [57] in systematically performed determinations of Ct levels during the diagnostic workup of unselected thyroid nodules, 153/159 (96.2%; pT1a: 91/159 [57.2%], pT1b-pT4: 62/159 [39%]) were screened positive and 6/159 (3.8%; pT1a: 6/159 [3.8%]) screened negative for MTC.

In these rare cases, incidentally discovered mMTCs with preoperatively normal bCt levels are revealed in final histological/immunohistochemical examinations. These tumors are predominantly ≤5 mm in diameter and show no LN metastasis.

Analysis of germline RET proto-oncogene mutations (hereditary or de novo) should be undertaken to identify hereditary cases. Completion thyroidectomy should be performed in genetically positive patients because of the high risk of a contralateral focus of MTC.

In sporadic patients, the necessity for reoperation (completion thyroidectomy, uni−/bilateral CND) depends on the results of bCt. Surgery is recommended if postoperative levels are elevated 3 months postoperatively or if there is radiological evidence of residual disease [57].

8.17 TNM Classification and Staging

The Union for International Cancer Control system is recommended for staging all MTC patients [79].

The eighth edition introduced important changes in the criteria used for staging MTC. In the absence of gross extracapsular extension, the primary will be staged solely on the basis of its size (pT1, pT2, or pT3a). Tumors of any size with gross extrathyroidal extension invading the strap muscles (sternohyoid, sternothyroid, or omohyoid muscles) are classified as pT3b (Table 8.3a, b).

Table 8.3 **a** TNM classification and staging of hereditary and sporadic MTC [79]. **b** TNM staging of hereditary and sporadic MTC [79]

Table 3a			
T – primary tumor			
Tx	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor 2 cm or less in greatest dimension, limited to the thyroid T1a		
T1b	Tumor >1 cm but ≤2 cm in greatest dimension, limited to the thyroid		
T2	Tumor >2 cm but ≤4 cm in greatest dimension, limited to the thyroid		
T3	Tumor >4 cm in greatest dimension, limited to the thyroid or with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, or omohyoid muscles)		
T3a	Tumor >4 cm in greatest dimension, limited to the thyroid		
T3b	Tumor of any size with gross extrathyroidal extension invading strap muscles (sternohyoid, sternothyroid, or omohyoid muscles)		
T4a	Tumor extends beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, esophagus, recurrent laryngeal nerve		
T4b	Tumor invades prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size		
N – Regional lymph nodes			
N0	No evidence of locoregional lymph node metastasis N		
N1a	Metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes) or upper/superior mediastinum		
N1b	Metastasis in other unilateral, bilateral, or contralateral cervical compartments (levels I, II, III, IV or V) or retropharyngeal		
M – Distant metastasis			
M0	No distant metastasis		
M	Distant metastasis		
Table 3b			
Stage	**T**	**N**	**M**
I	1a, 1b	0	0
II	2, 3	0	0
III	1–3	1a	0

(continued)

Table 8.3 (continued)

IVA	1–3	1b	0
	4a	Any N	0
IVB	4b	Any N	0
IVC	Any T	Any N	1

The pT and pN categories correspond to the T and N categories

pN0 histological examination of a selective neck dissection specimen will ordinarily include 6 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0

The eighth edition of the UICC TNM staging system introduced several changes compared with the seventh edition. The main changes are noted with superscript numbers and are described in detail as following:

Minor extrathyroidal extension was removed from the definition of T3 disease

Two new categories, T3a and T3b, were introduced

N1a was expanded to include the upper mediastinum (previously included in the N1b category)

8.18 Hereditary MTC

Approximately 3–7% of patients with presumed sporadic MTC actually have hereditary MTC, including about 2–9% with de novo germline mutations [80–85].

Approximately 98% of "index patients" with hereditary CC disease have identifiable mutations that are caused by several missense gain-of-function mutations of the RET proto-oncogene, which encodes the receptor tyrosine kinase on chromosome 10. RET encodes a receptor tyrosine kinase, which is expressed in neural-crest-deriving cells and involved in cell proliferation control.

In a prospective investigation [56], germline mutations in the RET proto-oncogene were documented in 22 (8.5%) of 260 patients with apparently sporadic CC diseases, in 4 (3.2%) of 126 patients with various types of CCH, and in 18 (13.4%) of 134 patients with MTC.

It is important to test for germline RET mutations in any patient with MTC, regardless of their family history [86].

The mutations can be distributed in several codons (including non-hot-spot). Codons are located in different exons of the RET gene. It is recommended that RET genetic screening should cover not only exons 10, 11, and 16 but also 5, 8, 13, 14, and 15 [33].

Hereditary MTC represents a progression from normal histopathology to preneoplastic CCH and to MTC [87]. Hereditary and sporadic MTCs do not differ morphologically. In pathological reports, however, the presence of CCH should always be mentioned. Still, its usefulness alone for indicating familial risk is limited.

Hereditary CC disease (CCH and/or MTC) may be part of one of the three autosomal-dominant hereditary cancer syndromes (Table 8.4). Familial MTC "only" is documented in

Table 8.4 Current classification of hereditary MTC tumor syndromes [33]

Classification	Definition
MEN 2A	Classic: MTC, PHEO, PHPT
	MEN 2A with lichen amyloidosis
	MEN 2A with Hirschsprung's disease
	FMTC
MEN 2B	MTC, PHEO

MEN multiple endocrine neoplasia, *MTC* medullary thyroid cancer, *PHEO* pheochromocytoma, *PHPT* primary hyperparathyroidism, *FMTC* familial medullary thyroid cancer "only"

approximately 15%, MEN 2A in 80%, and MEN 2B in 5% of affected patients [88].

Multifocal tumors are more often found in a genetic background.

Hereditary MTC is a potentially lethal disease. MTC remains confirmed to the thyroid gland for a distinct period of time. Once spread beyond the thyroid gland, it is incurable in the majority of patients, spreading on to the regional LNs and subsequently to the liver, lung, bone, and brain.

Thyroidectomy (without CLND) should be offered to mutation carriers before the development of MTC ("prophylactic surgery"; CCH is expected) or while the malignancy is still confirmed to the thyroid gland ("early surgery," surgery in a "preclinical stage"; mMTC without expected LN metastasis).

Ultrasonography is insufficient to identify MTC of any size or micrometastasis in LNs in hereditary CC disease [89].

Applying direct DNA analysis, mutation carriers (patients at risk to develop MTC) can be specified within a family. A given patient's genotype (specific *RET* mutation) predicts per se the aggressiveness of the clinical course.

Patients carrying the same mutation may show a heterogenic progression of disease. Even within the same family, the natural course of disease may vary. Neoplastic CCH is the precursor lesion of hereditary MTC. MTC develops over time. There is a well-documented age-related progression from neoplastic CCH to asymptomatic micro- and to clinically apparent macrocarcinoma (including LN and distant metastasis).

The current ATA risk levels stratify very well all known RET mutations into one of three risk levels (highest risk, high risk, moderate risk; Table 8.5).

Thyroid surgery is generally recommended based on the ATA risk levels (Table 8.6) [33].

There is also a positive correlation among bCt and sCt levels, tumor size, and stage of hereditary MTC.

Table 8.5 The current American Thyroid Association (ATA) risk levels: risk classification in correlation to (common) RET proto-oncogene mutations [33]

Risk classification	RET mutation
Moderate (ATA-MOD)	790, 791, 804, 609, 611, 618, 620
High (ATA-H)	634, 883
Highest (ATA-HST)	918

ATA American Thyroid Association, *MOD* moderate risk, *H* high risk, *HST* highest risk

Table 8.6 Risk classification of (common) RET proto-oncogene mutations – timing of surgery following the **G** (enetic) **A** (ge) **C** (alcitonin) concept [33]

Risk classification	RET mutation	Timing of surgery
Moderate (ATA-MOD)	790, 791, 804, 609, 611, 618, 620	Based on serum calcitonin levels
High (ATA-H)	634, 883	≤5 years (or earlier based on the elevated serum calcitonin levels)
Highest (ATA-HST)	918	<1 year (3 months)

ATA American Thyroid Association, *MOD* moderate, *H* high, *HST* highest

The moment of transition from CCH to MTC seems to occur when Ct levels rise upon stimulation. In patients with normal bCt but increased sCt levels, the chance of mMTC increases significantly (Table 8.7). In this situation, "early thyroidectomy" should definitively be performed (minimum total thyroidectomy). Elevated bCt and sCt levels may indicate MTC with LN metastasis. Therefore, CND (level VI) is mandatory for staging and to remove micrometastasis in patients with elevated bCt levels [90] (Table 8.8).

Postponing surgery and avoiding CND (level VI) in patients with moderate-risk levels are only justified in families with a less aggressive MTC history and in combination with the results of normal bCt and (Ca-) stimulated serum Ct levels.

Table 8.7 Pretherapeutic calcitonin levels and histology [90]

Calcitonin		*n* (%)	Normal CCH	MTC pN0	MTC pN1	Cured
Basal	**Stimulated**		**92**	**76**	**46**	
Normal	Normal	34 (16)	32	2	0	34 (100)
Normal	Increased	40 (19)	26	14	0	33 (100)
Increased	Increased	140 (65)	34	60	46	87 (69)
Cured		154 (79)	79 (100)	69 (100)	7 (15)	

MTC medullary thyroid cancer, *N* lymph node

Table 8.8 Indication for prophylactic and early thyroidectomy and central neck dissection [33]; see also Table 8.7

Calcitonin		Thyroidectomy		Central neck dissection
Basal	**Stimulated**			
Normal	Normal	Prophylactic	Yes	No
Normal	Increased	Early	Yes	No/Yes[a]
Increased	Increased		Yes	Yes

[a]If bCt is less than 40 pg/mL, a total thyroidectomy without central (level VI) neck dissection is adequate therapy

Thyroidectomy can be delayed in some children with MEN 2A if the serum Ct and neck ultrasonography results are normal [33].

bCt (and sCt) levels, determined in periodical intervals, may help to individually schedule timely surgery and to minimize the extent of the surgical procedure. This may satisfy parents who wish to postpone surgery in their children.

Although no data are as yet available, Ct measurements are recommended based on the ATA risk levels: every 6 months in the high and annually in the moderate levels [33].

Considering genotype, age, and bCt (and sCt) levels, the time of surgery may be postponed individually and the extent of the surgical intervention (CND [level VI]: yes/no) may be modified (Table 8.6).

If bCt is less than 40 pg/mL, total thyroidectomy without CND (level VI) may be an adequate therapy ([33] – Table 8.8).

The timing of surgery in asymptomatic disease requires a balance between the prevention of thyroid malignancy and the risks

of the operation (permanent hypoparathyroidism, permanent paralysis of the recurrent laryngeal nerve) [91].

"Prophylactic" and "early" thyroidectomy (with and without neck dissection) should be performed by high-volume endocrine neck surgeons to reduce morbidity to the lowest possible extent [92].

The surgical strategy to treat "hereditary, clinically apparent MTC" (index patients) follows the same guidelines as for sporadic disease.

8.19 MEN 2A

Besides premalignant or malignant thyroid lesions, tumors in the adrenal glands (pheochromocytoma) and/or the parathyroid glands may develop with variable penetrance and must be ruled out, first, by measuring 24-h urinary catecholamine or, preferably, metanephrine concentrations to exclude pheochromocytoma and, second, by determining serum Ca concentrations and the serum parathyroid hormone to exclude primary hyperparathyroidism before planning thyroid surgery [93].

Table 8.9 summarizes the recommendations when screening for pheochromocytoma, and primary hyperparathyroidism should start depending on the given RET proto-oncogene mutation.

8.20 MEN 2B

In the clinical setting of MEN 2B, MTC is highly aggressive and associated with a very early onset of metastasis (ATA risk level "D"). LN metastases are documented within the first year of life. Most frequently, MEN 2B arises as a result of a de novo mutation, with the child having unaffected parents. In the past, the diagnosis has often been delayed because

Table 8.9 Hereditary MTC – Recommendation: age of screening considering the (common) RET proto-oncogene mutation for screening pheochromocytoma and primary hyperparathyroidism [33]

Risk classification	Start for screening for Pheo/PHPT (a)
Moderate (ATA-MOD)	16
High (ATA-H)	11
Highest (ATA-HST)[a]	

Pheo pheochromocytoma, *PHPT* primary hyperparathyroidism, *a* age, *ATA* American Thyroid Association, *MOD* moderate, *H* high, *HST* highest

[a]No PHPT screening necessary

the typical phenotype is often not apparent in early childhood or the typical symptoms were not appreciated on time. Awareness of non-endocrine components (tearless crying, constipation) may help to diagnose this syndrome earlier. In the presence of genetically verified MEN 2B, children should undergo thyroidectomy as soon as possible within the first year of life (preferably within the first 6 months of life). CND (level VI) should be considered particularly when bCt (and more importantly, stimulated Ct) is elevated, and in children older than 6 months [94].

8.21 Prognosis and Postoperative Follow-Up

Early detection and adequate surgical treatment is followed by cure and disease-free survival (defined by normal or undetectable Ct values) in over 98% of patients.

At clinical presentation, about 50% of patients with MTC show LN metastasis. Distant metastases are detected in 10% of newly diagnosed patients, and more than 20% of patients will die from progressive metastatic disease.

The 10-year survival rates for all patients with MTC range from approximately 61–76% [7, 95–97].

The 5-year and 10-year survival rates for all patients with MTC in a Ct screening program were 96 +/− 2% (patients at risk: 43) and 93 +/− 3% (patients at risk: 6), respectively [56].

Patients with distant metastases at diagnosis have a poor prognosis, with a 10-year survival rate of merely 40% [97].

Prognosis is directly related to postoperative staging considering tumor size (in former studies, extrathyroidal invasion – however, not respected in the current TNM classification), nodal and distant metastasis. The quantities of involved LNs and compartments are also prognostically relevant.

Postoperative measurements of bCt (and CEA) are widely used as tumor markers also for postoperative follow-up. The bCt levels indicate cure and persisting or recurring disease [98].

Ct levels typically normalize within 1 week and within a fortnight in patients with node-positive MTC and preoperative Ct levels of 500–1000 pg/mL. Ct normalization takes longer with node-positive MTC and preoperative Ct levels exceeding 1000 pg/mL, and with more than ten nodal metastases [99]. In cases with very high preoperative bCt levels, a decrease in bCt might be delayed for 24 h to 12 weeks after surgery [100]. Therefore, 3 months following surgery appears to be the optimal time point for determining Ct levels [100, 101].

Postoperative, undetectable bCt levels (optimal documentation together with a negative provocative test) are strong predictors of complete remission [98].

Serum bCt determinations should be repeated every 3 to 6 months for the first 2 to 3 years. When bCt stays unmeasurable, it should be determined annually thereafter. Patients with biochemical remission after an initial treatment have a 3% chance of recurrence during long-term follow-up [102].

Patients with biochemically and clinically apparent MTC have tumors very frequently metastasized to regional LNs and to distant organs. This condition cannot be cured biochemically, despite aggressive surgery, including bilateral LLND [47, 103].

Despite meticulous surgical techniques, Ct levels remain detectable in 40–66% of patients after initial surgery, and the optimal surgical management for persistent or recurrent disease remains controversial.

Localized and limited locoregional disease can be treated with resections, with the intention to cure. However, in more advanced localized or in residual/recurrent disease, a multimodal approach is generally recommended to control local disease and to reduce tumor progression. The extent of surgery will depend on the types of surgical procedures performed previously and on the nature of the relapse and bCt level.

When the extent of initial surgery was incomplete, the preferred surgery protocol is always resection. Patients with residual LN metastases after initial thyroidectomy are likely to benefit from reoperation [103].

In 59 (44.4%) of 133 patients who had no LN metastases removed at the initial operation, systematic CLND, and LLND attained biochemical cure. Conversely, biochemical cure was reached in only 12 (18.5%) of 65 patients in whom 1 to 5 LN metastases had been previously cleared. If more than five LN metastases were dissected at prior surgery, the biochemical cure rate fell to 4.7% (2 of 43 patients). When preoperative serum Ct levels exceeded 1000 pg/mL, biochemical cure was exceptional (1 of 76 patients). Based on these data, systematic LN dissection in patients who had inadequate neck surgery is worthwhile as long as the preoperative serum Ct level is <1000 pg/mL and no more than five LN metastases were removed. Beyond these thresholds, the focus of surgical treatment shifts to the maintenance of local control in the neck [103].

The rate of Ct normalization after reoperation for MTC is enhanced by applying meticulous compartment-oriented LN dissection. Compartment-oriented LN dissection results in Ct normalization in 18.6% of reoperated MTC patients [104].

When patients have bCt levels less than 150 pg/mL following thyroidectomy, any persistent or recurrent disease is nearly always confined to LNs in the neck. When the postoperative Ct level exceeds 150 pg/mL, patients should be evaluated with imaging procedures, including CT of the neck and chest, contrast-enhanced MRI and US of the liver and bone, and PET-CT to exclude distant metastasis [47].

One can estimate the growth rate of MTC metastases by quantifying increases in tumor size over time from sequential imaging studies analyzed with the response evaluation criteria in solid tumors (RECIST).

The tumor burden and proliferation characteristics can be estimated from imaging studies and measurements of tumor marker doubling times.

In patients with elevated serum Ct and CEA, the tumor dynamics can be described by calculating the time to double the serum concentration (tumor doubling time).

bCt and CEA doubling times of less than 2 years are negative prognostic factors for MTC progression-free and total survival in patients with persistent or recurrent disease [105].

When the doubling time of bCt was less than 6 months, the 5- and 10-year survival rates were 25% and 8%, respectively; when the doubling time was longer than 2 years, all patients were alive at the end of follow-up [106].

Once metastases appear, clinicians must decide which patients require therapy. They must balance the often slow rate of tumor progression, which is associated with good quality of life, against the limited efficacy and potential toxicities of local and systemic therapies [33].

Only patients with significant tumor burden and those with symptomatic or progressive, measurable disease are candidates for systemic therapy.

Progression is defined as a ≥20% increase in the sum of the longest lesion diameters or the appearance of one or more new lesions within a given time interval (e.g., 12 months) [33].

8.22 Unresectable, Progressive, and Symptomatic Sporadic and Hereditary MTC

Unresectable and progressive MTC affects both patients' health-related quality of life and survival. A systematic review [107] identified two placebo-controlled trials. Schlumberger et al. [108] evaluated the efficacy and safety of cabozantinib, while the Zactima Efficacy in Thyroid Cancer Assessment (ZETA) trial evaluated the efficacy and safety of vandetanib [109, 110].

Both drugs significantly improved progression-free survival compared to placebo ($P < 0.001$). Within the symptomatic and progressive MTC population, the effects on progressive-free survival were similar (vandetanib vs. cabozantinib: hazard ratio 1.14, 95% credible interval 0.41–3.09). Neither trial demonstrated a significant overall survival benefit for cabozantinib or vandetanib versus placebo, although data from ZETA were subject to potential confounding.

Answers to the Questions

Case 1: (3)

Completion thyroidectomy, CND only if: bCt [and/or sCt] elevated – genetic background

Specific "testing" – Ca stimulation 2 (0 min) – 21 (3 min) pg/mL; plasma metanephrine, plasma normetanephrine normal range; exon 14 – codon V804L – [GTG > TTG: val – leu];

Right lobectomy with right CND – MTC 1 mm, pN0 (0/6) – hereditary MTC, pT1mpN0 (0/11) – no CCH.

Case 2: (2d)

Adequately high bCt level in correlation with the size of the nodule: thyroidectomy, bilateral CND – frozen section DSR: yes/no

MTC – pT2–39 mm; pN0 (0/8), DSR negative – no bilateral neck dissection – follow-up: 164 months, bCt <1 pg/mL; CEA: 1.0 µg/L.

Case 3: (2)

Inadequately high bCt level in correlation with the size of the nodules – other than thyroid CC disease

Ca stimulation test: 704 pg/mL (0 min) – 1219 pg/mL – sCt less than twofold bCt – lung X-ray: 36 mm lesion right intermediate lobe, enlarged paratracheal and infracarinal lymph nodes – paraneoplastic Ct secretion by a neuroendocrine neoplasia of the lungs.

Case 4: (3)

Incidentally discovered mMTCs with preoperatively normal bCt levels

Except for molecular genetic analysis (in this particular patient: no RET proto-oncogene mutation), no further treatment.

Case 5: (2)

Clinically asymptomatic/mildly elevated bCt – reproducible – anxious patient – to select patients for surgery – stimulation test: 21 pg/mL (0 min) – 1664 pg/mL (3 min) – MTC suspected - plasma metanephrines/plasma normetanephrines: normal catecholamines/metanephrines and normetanephrines (24-h urine): normal – RET proto-oncogene mutation (exon 10, codon C611Y – GTG>TTG; cys – tyr)

Thyroidectomy, bilateral CND (early thyroidectomy) – multifocal, bilateral mMTC (pT1am; L: 5 mm; R: 1 mm with DSR; neoplastic CCH – N: pN0 (0/15); M: M0

References

1. Holzer S, Reiners C, Mann K, Bamberg M, Rothmund M, Dudeck J, et al. Patterns of care for patients with primary differentiated carcinoma of the thyroid gland treated in Germany during 1996. U.S. and German Thyroid Cancer Group. Cancer. 2000;89(1):192–201. https://doi.org/10.1002/1097-0142(20000701)89:1<192::aid-cncr26>3.0.co;2-7.
2. Hundahl SA, Cady B, Cunningham MP, Mazzaferri E, McKee RF, Rosai J, et al. Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the United States during 1996.

U.S. and German Thyroid Cancer Study Group. An American College of Surgeons Commission on cancer patient care evaluation study. Cancer. 2000;89(1):202–17. https://doi.org/10.1002/1097-0142(20000701)89:1<202::aid-cncr27>3.0.co;2-a.
3. Valle LA, Kloos RT. The prevalence of occult medullary thyroid carcinoma at autopsy. J Clin Endocrinol Metab. 2011;96(1):E109–13. https://doi.org/10.1210/jc.2010-0959.
4. Daniels GH. Screening for medullary thyroid carcinoma with serum calcitonin measurements in patients with thyroid nodules in the United States and Canada. Thyroid. 2011;21(11):1199–207. https://doi.org/10.1089/thy.2010.0297.
5. Bergholm U, Adami HO, Bergstrom R, Johansson H, Lundell G, Telenius-Berg M, et al. Clinical characteristics in sporadic and familial medullary thyroid carcinoma. A nationwide study of 249 patients in Sweden from 1959 through 1981. Cancer. 1989;63(6):1196–204. https://doi.org/10.1002/1097-0142(19890315)63:6<1196::aid-cncr2820630626>3.0.co;2-o.
6. Kebebew E, Ituarte PH, Siperstein AE, Duh QY, Clark OH. Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. Cancer. 2000;88(5):1139–48. https://doi.org/10.1002/(sici)1097-0142(20000301)88:5<1139::aid-cncr26>3.0.co;2-z.
7. Torresan F, Cavedon E, Mian C, Iacobone M. Long-term outcome after surgery for medullary thyroid carcinoma: a single-center experience. World J Surg. 2018;42(2):367–75. https://doi.org/10.1007/s00268-017-4321-z.
8. Robbins KT, Clayman G, Levine PA, Medina J, Sessions R, Shaha A, et al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. Arch Otolaryngol Head Neck Surg. 2002;128(7):751–8. https://doi.org/10.1001/archotol.128.7.751.
9. Dralle H. Lymph node dissection and medullary thyroid carcinoma. Br J Surg. 2002;89(9):1073–5. https://doi.org/10.1046/j.1365-2168.2002.02160.x.
10. Machens A, Hinze R, Thomusch O, Dralle H. Pattern of nodal metastasis for primary and reoperative thyroid cancer. World J Surg. 2002;26(1):22–8. https://doi.org/10.1007/s00268-001-0176-3.
11. Moley JF, DeBenedetti MK. Patterns of nodal metastases in palpable medullary thyroid carcinoma: recommendations for extent of node dissection. Ann Surg. 1999;229(6):880–7; discussion 7-8. https://doi.org/10.1097/00000658-199906000-00016.
12. Tung WS, Vesely TM, Moley JF. Laparoscopic detection of hepatic metastases in patients with residual or recurrent medullary thyroid cancer. Surgery. 1995;118(6):1024–9; discussion 9-30. https://doi.org/10.1016/s0039-6060(05)80109-6.
13. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedus L, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules--2016 update. Endocr Pract. 2016;22(5):622–39. https://doi.org/10.4158/EP161208.GL.
14. Wolinski K, Rewaj-Losyk M, Ruchala M. Sonographic features of medullary thyroid carcinomas--a systematic review and meta-analysis. Endokrynol Pol. 2014;65(4):314–8. https://doi.org/10.5603/EP.2014.0043.
15. Brammen L, Niederle MB, Riss P, Scheuba C, Selberherr A, Karanikas G, et al. Medullary thyroid carcinoma: do ultrasonography and F-DOPA-PET-CT influence the initial surgical strategy? Ann Surg Oncol. 2018;25(13):3919–27. https://doi.org/10.1245/s10434-018-6829-3.

16. Trimboli P, Treglia G, Guidobaldi L, Romanelli F, Nigri G, Valabrega S, et al. Detection rate of FNA cytology in medullary thyroid carcinoma: a meta-analysis. Clin Endocrinol. 2015;82(2):280–5. https://doi.org/10.1111/cen.12563.
17. Choi N, Moon WJ, Lee JH, Baek JH, Kim DW, Park SW. Ultrasonographic findings of medullary thyroid cancer: differences according to tumor size and correlation with fine needle aspiration results. Acta Radiol. 2011;52(3):312–6. https://doi.org/10.1258/ar.2010.100247.
18. Essig GF Jr, Porter K, Schneider D, Debora A, Lindsey SC, Busonero G, et al. Fine needle aspiration and medullary thyroid carcinoma: the risk of inadequate preoperative evaluation and initial surgery when relying upon FNAB cytology alone. Endocr Pract. 2013;19(6):920–7. https://doi.org/10.4158/EP13143.OR.
19. Scheuba C, Kaserer K, Kaczirek K, Asari R, Niederle B. Desmoplastic stromal reaction in medullary thyroid cancer-an intraoperative "marker" for lymph node metastases. World J Surg. 2006;30(5):853–9. https://doi.org/10.1007/s00268-005-0391-4.
20. Niederle MB, Riss P, Selberherr A, Koperek O, Kaserer K, Niederle B et al. Omission of lateral lymph node dissection in medullary thyroid cancer without a desmoplastic stromal reaction. Br J Surg. 2021;108(2):174–181. https://doi.org/10.1093/bjs/znaa047.
21. Andreas, Machens Peter, Kaatzsch Kerstin, Lorenz Lars-Christian, Horn Claudia, Wickenhauser Kurt Werner, Schmid Henning, Dralle Udo, Siebolts. Abandoning node dissection for desmoplasia-negative encapsulated unifocal sporadic medullary thyroid cancer. Surgery. 2021 https://doi.org/10.1016/j.surg.2021.07.035.
22. Aubert S, Berdelou A, Gnemmi V, Behal H, Caiazzo R, D'Herbomez M, et al. Large sporadic thyroid medullary carcinomas: predictive factors for lymph node involvement. Virchows Arch. 2018;472(3):461–8. https://doi.org/10.1007/s00428-018-2303-7.
23. Boi F, Maurelli I, Pinna G, Atzeni F, Piga M, Lai ML, et al. Calcitonin measurement in wash-out fluid from fine needle aspiration of neck masses in patients with primary and metastatic medullary thyroid carcinoma. J Clin Endocrinol Metab. 2007;92(6):2115–8. https://doi.org/10.1210/jc.2007-0326.
24. Trimboli P, Guidobaldi L, Bongiovanni M, Crescenzi A, Alevizaki M, Giovanella L. Use of fine-needle aspirate calcitonin to detect medullary thyroid carcinoma: a systematic review. Diagn Cytopathol. 2016;44(1):45–51. https://doi.org/10.1002/dc.23375.
25. Diazzi C, Madeo B, Taliani E, Zirilli L, Romano S, Granata AR, et al. The diagnostic value of calcitonin measurement in wash-out fluid from fine-needle aspiration of thyroid nodules in the diagnosis of medullary thyroid cancer. Endocr Pract. 2013;19(5):769–79. https://doi.org/10.4158/EP12420.OR.
26. Karagiannis AK, Girio-Fragkoulakis C, Nakouti T. Procalcitonin: a new biomarker for medullary thyroid cancer? A systematic review. Anticancer Res. 2016;36(8):3803–10.
27. Giovanella L, Imperiali M, Piccardo A, Taborelli M, Verburg FA, Daurizio F, et al. Procalcitonin measurement to screen medullary thyroid carcinoma: a prospective evaluation in a series of 2705 patients with thyroid nodules. Eur J Clin Investig. 2018;48(6):e12934. https://doi.org/10.1111/eci.12934.
28. Niederle MB, Scheuba C, Gessl A, Li S, Koperek O, Bieglmayer C, et al. Calcium-stimulated calcitonin - The "new standard" in the diagnosis of thyroid C-cell disease - clinically relevant gender-specific cut-off levels for an "old test". Biochem Med (Zagreb). 2018;28(3):030710. https://doi.org/10.11613/BM.2018.030710.
29. Cote GJ, Grubbs EG, Hofmann MC. Thyroid C-cell biology and oncogenic transformation. Recent Results Cancer Res. 2015;204:1–39. https://doi.org/10.1007/978-3-319-22542-5_1.

30. Costante G, Meringolo D. Calcitonin as a biomarker of C cell disease: recent achievements and current challenges. Endocrine. 2020;67(2):273–80. https://doi.org/10.1007/s12020-019-02183-6.
31. Bieglmayer C, Vierhapper H, Dudczak R, Niederle B. Measurement of calcitonin by immunoassay analyzers. Clin Chem Lab Med. 2007;45(5):662–6. https://doi.org/10.1515/CCLM.2007.124.
32. Bieglmayer C, Scheuba C, Niederle B, Flores J, Vierhapper H. Screening for medullary thyroid carcinoma: experience with different immunoassays for human calcitonin. Wien Klin Wochenschr. 2002;114(7):267–73.
33. Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567–610. https://doi.org/10.1089/thy.2014.0335.
34. Kebebew E, Greenspan FS, Clark OH, Woeber KA, Grunwell J. Extent of disease and practice patterns for medullary thyroid cancer. J Am Coll Surg. 2005;200(6):890–6. https://doi.org/10.1016/j.jamcollsurg.2004.12.011.
35. Panigrahi B, Roman SA, Sosa JA. Medullary thyroid cancer: are practice patterns in the United States discordant from American Thyroid Association guidelines? Ann Surg Oncol. 2010;17(6):1490–8. https://doi.org/10.1245/s10434-010-1017-0.
36. Chang EHE, Lutfi W, Feinglass J, Reiher AE, Moo-Young T, Bhayani MK. National trends in the surgical treatment of non-advanced medullary thyroid cancer (MTC): an evaluation of adherence with the 2009 American Thyroid Association guidelines. World J Surg. 2016;40(12):2930–40. https://doi.org/10.1007/s00268-016-3643-6.
37. Cox C, Chen Y, Cress R, Semrad AM, Semrad T, Gosnell JE, et al. Are there disparities in the presentation, treatment and outcomes of patients diagnosed with medullary thyroid cancer?-An analysis of 634 patients from the California Cancer Registry. Gland Surg. 2016;5(4):398–404. https://doi.org/10.21037/gs.2016.04.02.
38. Karga H, Giagourta I, Papaioannou G, Doumouchtsis K, Polymeris A, Thanou S, et al. Changes in risk factors and tumor node metastasis stage of sporadic medullary thyroid carcinoma over 41 years, before and after the routine measurements of serum calcitonin. Metabolism. 2011;60(5):604–8. https://doi.org/10.1016/j.metabol.2010.06.004.
39. Machens A, Dralle H. Surgical cure rates of sporadic medullary thyroid cancer in the era of calcitonin screening. Eur J Endocrinol. 2016;175(3):219–28. https://doi.org/10.1530/EJE-16-0325.
40. Cheung K, Roman SA, Wang TS, Walker HD, Sosa JA. Calcitonin measurement in the evaluation of thyroid nodules in the United States: a cost-effectiveness and decision analysis. J Clin Endocrinol Metab. 2008;93(6):2173–80. https://doi.org/10.1210/jc.2007-2496.
41. Verbeek HH, de Groot JWB, Sluiter WJ, Muller Kobold AC, van den Heuvel ER, Plukker JT, et al. Calcitonin testing for detection of medullary thyroid cancer in people with thyroid nodules. Cochrane Database Syst Rev. 2020;3:CD010159. https://doi.org/10.1002/14651858.CD010159.pub2.
42. Pacini F, Castagna MG, Brilli L, Pentheroudakis G, Group EGW. Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23(Suppl 7):110–9. https://doi.org/10.1093/annonc/mds230.
43. Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, et al. Guidelines for the management of thyroid cancer. Clin Endocrinol. 2014;81(Suppl 1):1–122. https://doi.org/10.1111/cen.12515.
44. Cohen R, Campos JM, Salaun C, Heshmati HM, Kraimps JL, Proye C, et al. Preoperative calcitonin levels are predictive of tumor size and postoperative calcitonin normalization in medullary thyroid carcinoma. Groupe d'Etudes des Tumeurs a Calcitonine (GETC). J Clin

Endocrinol Metab. 2000;85(2):919–22. https://doi.org/10.1210/jcem.85.2.6556.
45. Pomares FJ, Rodriguez JM, Nicolas F, Sola J, Canteras M, Balsalobre M, et al. Presurgical assessment of the tumor burden of familial medullary thyroid carcinoma by calcitonin testing. J Am Coll Surg. 2002;195(5):630–4. https://doi.org/10.1016/s1072-7515(02)01499-0.
46. Yip DT, Hassan M, Pazaitou-Panayiotou K, Ruan DT, Gawande AA, Gaz RD, et al. Preoperative basal calcitonin and tumor stage correlate with postoperative calcitonin normalization in patients undergoing initial surgical management of medullary thyroid carcinoma. Surgery. 2011;150(6):1168–77. https://doi.org/10.1016/j.surg.2011.09.043.
47. Machens A, Dralle H. Biomarker-based risk stratification for previously untreated medullary thyroid cancer. J Clin Endocrinol Metab. 2010;95(6):2655–63. https://doi.org/10.1210/jc.2009-2368.
48. Niederle MB, Scheuba C, Riss P, Selberherr A, Koperek O, Niederle B. Early diagnosis of medullary thyroid cancer: are calcitonin stimulation tests still indicated in the era of highly sensitive calcitonin immunoassays? Thyroid. 2020;30(7):974–84. https://doi.org/10.1089/thy.2019.0785.
49. Toledo SP, Lourenco DM Jr, Santos MA, Tavares MR, Toledo RA, Correia-Deur JE. Hypercalcitoninemia is not pathognomonic of medullary thyroid carcinoma. Clinics. 2009;64(7):699–706. https://doi.org/10.1590/S1807-59322009000700015.
50. Machens A, Haedecke J, Holzhausen HJ, Thomusch O, Schneyer U, Dralle H. Differential diagnosis of calcitonin-secreting neuroendocrine carcinoma of the foregut by pentagastrin stimulation. Langenbeck's Arch Surg. 2000;385(6):398–401. https://doi.org/10.1007/s004230000169.
51. Schneider R, Waldmann J, Swaid Z, Ramaswamy A, Fendrich V, Bartsch DK, et al. Calcitonin-secreting pancreatic endocrine tumors: systematic analysis of a rare tumor entity. Pancreas. 2011;40(2):213–21. https://doi.org/10.1097/MPA.0b013e3182015f5d.
52. Vahidi S, Stewart J, Amin K, Racila E, Li F. Metastatic medullary thyroid carcinoma or calcitonin-secreting carcinoid tumor of lung? A diagnostic dilemma in a patient with lung mass and thyroid nodule. Diagn Cytopathol. 2018;46(4):345–8. https://doi.org/10.1002/dc.23852.
53. Allelein S, Ehlers M, Morneau C, Schwartz K, Goretzki PE, Seppel T, et al. Measurement of basal serum calcitonin for the diagnosis of medullary thyroid cancer. Horm Metab Res. 2018;50(1):23–8. https://doi.org/10.1055/s-0043-122237.
54. Kahaly GJ, Algeciras-Schimnich A, Davis TE, Diana T, Feldkamp J, Karger S, et al. United States and European multicenter prospective study for the analytical performance and clinical validation of a novel sensitive fully automated immunoassay for calcitonin. Clin Chem. 2017;63(9):1489–96. https://doi.org/10.1373/clinchem.2016.270009.
55. Niederle B, Sebag F, Brauckhoff M. Timing and extent of thyroid surgery for gene carriers of hereditary C cell disease – a consensus statement of the European Society of Endocrine Surgeons (ESES). Langenbeck's Arch Surg. 2014;399(2):185–97. https://doi.org/10.1007/s00423-013-1139-5.
56. Scheuba C, Kaserer K, Moritz A, Drosten R, Vierhapper H, Bieglmayer C, et al. Sporadic hypercalcitoninemia: clinical and therapeutic consequences. Endocr Relat Cancer. 2009;16(1):243–53. https://doi.org/10.1677/ERC-08-0059.
57. Scheuba C, Kaserer K, Bieglmayer C, Asari R, Riss P, Drosten R, et al. Medullary thyroid microcarcinoma recommendations for treatment - a single-center experience. Surgery. 2007;142(6):1003–10. https://doi.org/10.1016/j.surg.2007.09.016.
58. Daumerie C, Maiter D, Gruson D. Serum calcitonin estimation in medullary thyroid cancer: basal or stimulated levels? Thyroid Res. 2013;6(Suppl 1):S4. https://doi.org/10.1186/1756-6614-6-S1-S4.

59. Fugazzola L, Di Stefano M, Censi S, Repaci A, Colombo C, Grimaldi F, et al. Basal and stimulated calcitonin for the diagnosis of medullary thyroid cancer: updated thresholds and safety assessment. J Endocrinol Investig. 2021;44(3):587–97. https://doi.org/10.1007/s40618-020-01356-9.
60. Barbot N, Calmettes C, Schuffenecker I, Saint-Andre JP, Franc B, Rohmer V, et al. Pentagastrin stimulation test and early diagnosis of medullary thyroid carcinoma using an immunoradiometric assay of calcitonin: comparison with genetic screening in hereditary medullary thyroid carcinoma. J Clin Endocrinol Metab. 1994;78(1):114–20. https://doi.org/10.1210/jcem.78.1.7904611.
61. Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S, et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab. 2007;92(2):450–5. https://doi.org/10.1210/jc.2006-1590.
62. Frank-Raue K, Schott M, Raue F. Im Namen der Sektion Schilddruse der DGE. [recommendation for calcitonin screening in nodular goiter]. Dtsch Med Wochenschr. 2018;143(15):1065–9. https://doi.org/10.1055/a-0585-8097.
63. Selberherr A, Riss P, Scheuba C, Niederle B. Prophylactic "first-step" central neck dissection (level 6) does not increase morbidity after (total) thyroidectomy. Ann Surg Oncol. 2016;23(12):4016–22. https://doi.org/10.1245/s10434-016-5338-5.
64. Moley JF. Medullary thyroid carcinoma: management of lymph node metastases. J Natl Compr Cancer Netw. 2010;8(5):549–56. https://doi.org/10.6004/jnccn.2010.0042.
65. Essig GF Jr, Porter K, Schneider D, Arpaia D, Lindsey SC, Busonero G, et al. Multifocality in sporadic medullary thyroid carcinoma: an international multicenter study. Thyroid. 2016;26(11):1563–72. https://doi.org/10.1089/thy.2016.0255.
66. Scollo C, Baudin E, Travagli JP, Caillou B, Bellon N, Leboulleux S, et al. Rationale for central and bilateral lymph node dissection in sporadic and hereditary medullary thyroid cancer. J Clin Endocrinol Metab. 2003;88(5):2070–5. https://doi.org/10.1210/jc.2002-021713.
67. Kim JH, Pyo JS, Cho WJ. Clinicopathological significance and prognosis of medullary thyroid microcarcinoma: a meta-analysis. World J Surg. 2017;41(10):2551–8. https://doi.org/10.1007/s00268-017-4031-6.
68. Machens A, Holzhausen HJ, Dralle H. Skip metastases in thyroid cancer leaping the central lymph node compartment. Arch Surg. 2004;139(1):43–5. https://doi.org/10.1001/archsurg.139.1.43.
69. Mathiesen JS, Kroustrup JP, Vestergaard P, Stochholm K, Poulsen PL, Rasmussen AK, et al. Survival and long-term biochemical cure in medullary thyroid carcinoma in Denmark 1997-2014: a Nationwide study. Thyroid. 2019;29(3):368–77. https://doi.org/10.1089/thy.2018.0564.
70. Momin S, Chute D, Burkey B, Scharpf J. Prognostic variables affecting primary treatment outcome for medullary thyroid cancer. Endocr Pract. 2017;23(9):1053–8. https://doi.org/10.4158/EP161684.OR.
71. Gimm O, Ukkat J, Dralle H. Determinative factors of biochemical cure after primary and reoperative surgery for sporadic medullary thyroid carcinoma. World J Surg. 1998;22(6):562–7; discussion 7-8. https://doi.org/10.1007/s002689900435.
72. Ito Y, Miyauchi A, Kihara M, Higashiiyama T, Fukushima M, Miya A. Static prognostic factors and appropriate surgical designs for patients with medullary thyroid carcinoma: the second report from a single-institution study in Japan. World J Surg. 2018;42(12):3954–66. https://doi.org/10.1007/s00268-018-4738-z.
73. Machens A, Hauptmann S, Dralle H. Prediction of lateral lymph node metastases in medullary thyroid cancer. Br J Surg. 2008;95(5):586–91. https://doi.org/10.1002/bjs.6075.

74. McMullen C, Rocke D, Freeman J. Complications of bilateral neck dissection in thyroid cancer from a single high-volume center. JAMA Otolaryngol Head Neck Surg. 2017;143(4):376–81. https://doi.org/10.1001/jamaoto.2016.3670.
75. Machens A, Gimm O, Ukkat J, Hinze R, Schneyer U, Dralle H. Improved prediction of calcitonin normalization in medullary thyroid carcinoma patients by quantitative lymph node analysis. Cancer. 2000;88(8):1909–15.
76. Polistena A, Sanguinetti A, Lucchini R, Galasse S, Monacelli M, Avenia S, et al. Timing and extension of lymphadenectomy in medullary thyroid carcinoma: a case series from a single institution. Int J Surg. 2017;41(Suppl 1):S70–S4. https://doi.org/10.1016/j.ijsu.2017.04.026.
77. Scheuba C, Kaserer K, Weinhausl A, Pandev R, Kaider A, Passler C, et al. Is medullary thyroid cancer predictable? A prospective study of 86 patients with abnormal pentagastrin tests. Surgery. 1999;126(6):1089–95; discussion 96.
78. Machens A, Holzhausen HJ, Dralle H. Prediction of mediastinal lymph node metastasis in medullary thyroid carcinoma. Br J Surg. 2004;91(6):709–12. https://doi.org/10.1002/bjs.4525.
79. Brierley J, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours. 8th ed. Chichester, West Sussex/Hoboken: John Wiley & Sons, Inc.; 2017.
80. Bugalho MJ, Domingues R, Santos JR, Catarino AL, Sobrinho L. Mutation analysis of the RET proto-oncogene and early thyroidectomy: results of a Portuguese cancer centre. Surgery. 2007;141(1):90–5. https://doi.org/10.1016/j.surg.2006.03.025.
81. Elisei R, Romei C, Cosci B, Agate L, Bottici V, Molinaro E, et al. RET genetic screening in patients with medullary thyroid cancer and their relatives: experience with 807 individuals at one center. J Clin Endocrinol Metab. 2007;92(12):4725–9. https://doi.org/10.1210/jc.2007-1005.
82. Eng C, Smith DP, Mulligan LM, Healey CS, Zvelebil MJ, Stonehouse TJ, et al. A novel point mutation in the tyrosine kinase domain of the RET proto-oncogene in sporadic medullary thyroid carcinoma and in a family with FMTC. Oncogene. 1995;10(3):509–13.
83. Romei C, Cosci B, Renzini G, Bottici V, Molinaro E, Agate L, et al. RET genetic screening of sporadic medullary thyroid cancer (MTC) allows the preclinical diagnosis of unsuspected gene carriers and the identification of a relevant percentage of hidden familial MTC (FMTC). Clin Endocrinol. 2011;74(2):241–7. https://doi.org/10.1111/j.1365-2265.2010.03900.x.
84. Schuffenecker I, Ginet N, Goldgar D, Eng C, Chambe B, Boneu A, et al. Prevalence and parental origin of de novo RET mutations in multiple endocrine neoplasia type 2A and familial medullary thyroid carcinoma. Le Groupe d'Etude des Tumeurs a Calcitonine. Am J Hum Genet. 1997;60(1):233–7.
85. Wiench M, Wygoda Z, Gubala E, Wloch J, Lisowska K, Krassowski J, et al. Estimation of risk of inherited medullary thyroid carcinoma in apparent sporadic patients. J Clin Oncol. 2001;19(5):1374–80. https://doi.org/10.1200/JCO.2001.19.5.1374.
86. Elisei R, Alevizaki M, Conte-Devolx B, Frank-Raue K, Leite V, Williams GR. 2012 European thyroid association guidelines for genetic testing and its clinical consequences in medullary thyroid cancer. Eur Thyroid J. 2013;1(4):216–31. https://doi.org/10.1159/000346174.
87. Hubert J, Wolfe Kenneth EW., Melvin Sergio J, Cervi-Skinner Abdul A, AL Saadi Joseph F, Juliar Charles E, Jackson Armen H, Tashjian. C-Cell Hyperplasia Preceding Medullary Thyroid Carcinoma. New England Journal of Medicine 1973;289(9):437–41 https://doi.org/10.1056/NEJM197308302890901.
88. Samuel A., Wells Furio, Pacini Bruce G., Robinson Massimo, Santoro. Multiple Endocrine Neoplasia Type 2 and Familial Medullary Thyroid

Carcinoma: An Update. The Journal of Clinical Endocrinology & Metabolism 2013;98(8):3149–64. https://doi.org/10.1210/jc.2013-1204.
89. Morris LF, Waguespack SG, Edeiken-Monroe BS, Lee JE, Rich TA, Ying AK, et al. Ultrasonography should not guide the timing of thyroidectomy in pediatric patients diagnosed with multiple endocrine neoplasia syndrome 2A through genetic screening. Ann Surg Oncol. 2013;20(1):53–9. https://doi.org/10.1245/s10434-012-2589-7.
90. Machens A, Lorenz K, Dralle H. Individualization of lymph node dissection in RET (rearranged during transfection) carriers at risk for medullary thyroid cancer: value of pretherapeutic calcitonin levels. Ann Surg. 2009;250(2):305–10. https://doi.org/10.1097/SLA.0b013e3181ae333f.
91. Machens A, Elwerr M, Thanh PN, Lorenz K, Schneider R, Dralle H. Impact of central node dissection on postoperative morbidity in pediatric patients with suspected or proven thyroid cancer. Surgery. 2016;160(2):484–92. https://doi.org/10.1016/j.surg.2016.03.007.
92. Kluijfhout WP, van Beek DJ, Verrijn Stuart AA, Lodewijk L, Valk GD, van der Zee DC, et al. Postoperative complications after prophylactic thyroidectomy for very young patients with multiple endocrine Neoplasia type 2: retrospective cohort analysis. Medicine (Baltimore). 2015;94(29):e1108. https://doi.org/10.1097/MD.0000000000001108.
93. R., Elisei M., Alevizaki B., Conte-Devolx K., Frank-Raue V., Leite G.R., Williams. 2012 European Thyroid Association Guidelines for Genetic Testing and Its Clinical Consequences in Medullary Thyroid Cancer. European Thyroid Journal 2012;1(4)216–31 https://doi.org/10.1159/000346174.
94. Brauckhoff M, Machens A, Lorenz K, Bjoro T, Varhaug JE, Dralle H. Surgical curability of medullary thyroid cancer in multiple endocrine neoplasia 2B: a changing perspective. Ann Surg. 2014;259(4):800–6. https://doi.org/10.1097/SLA.0b013e3182a6f43a.
95. Cupisti K, Wolf A, Raffel A, Schott M, Miersch D, Yang Q, et al. Long-term clinical and biochemical follow-up in medullary thyroid carcinoma: a single institution's experience over 20 years. Ann Surg. 2007;246(5):815–21. https://doi.org/10.1097/SLA.0b013e31813e66b9.
96. Kebebew E, Kikuchi S, Duh QY, Clark OH. Long-term results of reoperation and localizing studies in patients with persistent or recurrent medullary thyroid cancer. Arch Surg. 2000;135(8):895–901. https://doi.org/10.1001/archsurg.135.8.895.
97. Roman S, Lin R, Sosa JA. Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1252 cases. Cancer. 2006;107(9):2134–42. https://doi.org/10.1002/cncr.22244.
98. Engelbach M, Görges R, Forst T, Pfützner A, Dawood R, Heerdt S, et al. Improved diagnostic methods in the follow-up of medullary thyroid carcinoma by highly specific calcitonin measurements. J Clin Endocrinol Metab. 2000;85(5):1890–4. https://doi.org/10.1210/jcem.85.5.6601.
99. Machens A, Lorenz K, Dralle H. Time to calcitonin normalization after surgery for node-negative and node-positive medullary thyroid cancer. Br J Surg. 2019;106(4):412–8. https://doi.org/10.1002/bjs.11071.
100. Ismailov SI, Piulatova NR. Postoperative calcitonin study in medullary thyroid carcinoma. Endocr Relat Cancer. 2004;11(2):357–63. https://doi.org/10.1677/erc.0.0110357.
101. Elisei R, Pinchera A. Advances in the follow-up of differentiated or medullary thyroid cancer. Nat Rev Endocrinol. 2012;8(8):466–75. https://doi.org/10.1038/nrendo.2012.38.
102. Franc S, Niccoli-Sire P, Cohen R, Bardet S, Maes B, Murat A, et al. Complete surgical lymph node resection does not prevent authentic recurrences of medullary thyroid carcinoma. Clin Endocrinol. 2001;55(3):403–9. https://doi.org/10.1046/j.1365-2265.2001.01339.x.

103. Machens A, Dralle H. Prognostic impact of N staging in 715 medullary thyroid cancer patients: proposal for a revised staging system. Ann Surg. 2013;257(2):323–9. https://doi.org/10.1097/SLA.0b013e318268301d.
104. Rowland KJ, Jin LX, Moley JF. Biochemical cure after reoperations for medullary thyroid carcinoma: a meta-analysis. Ann Surg Oncol. 2015;22(1):96–102. https://doi.org/10.1245/s10434-014-4102-y.
105. Gawlik T, d'Amico A, Szpak-Ulczok S, Skoczylas A, Gubala E, Chorazy A, et al. The prognostic value of tumor markers doubling times in medullary thyroid carcinoma - preliminary report. Thyroid Res. 2010;3(1):10. https://doi.org/10.1186/1756-6614-3-10.
106. Barbet J, Campion L, Kraeber-Bodere F, Chatal JF, Group GTES. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. J Clin Endocrinol Metab. 2005;90(11):6077–84. https://doi.org/10.1210/jc.2005-0044.
107. Tappenden P, Carroll C, Hamilton J, Kaltenthaler E, Wong R, Wadsley J, et al. Cabozantinib and vandetanib for unresectable locally advanced or metastatic medullary thyroid cancer: a systematic review and economic model. Health Technol Assess. 2019;23(8):1–144. https://doi.org/10.3310/hta23080.
108. Schlumberger M, Elisei R, Muller S, Schoffski P, Brose M, Shah M, et al. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. Ann Oncol. 2017;28(11):2813–9. https://doi.org/10.1093/annonc/mdx479.
109. Wells SA Jr, Gosnell JE, Gagel RF, Moley J, Pfister D, Sosa JA, et al. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Oncol. 2010;28(5):767–72. https://doi.org/10.1200/JCO.2009.23.6604.
110. Wells SA Jr, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012;30(2):134–41. https://doi.org/10.1200/JCO.2011.35.5040.