Diagnosis, treatment, and follow-up of medullary thyroid carcinoma: recommendations by the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism

Diagnóstico, tratamento e seguimento do carcinoma medular de tireoide: recomendações do Departamento de Tireoide da Sociedade Brasileira de Endocrinologia e Metabologia

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ABSTRACT

Introduction: Medullary thyroid carcinoma (MTC) originates in the thyroid parafollicular cells and represents 3-4% of the malignant neoplasms that affect this gland. Approximately 25% of these cases are hereditary due to activating mutations in the REarranged during Transfection (*RET*) proto-oncogene. The course of MTC is indolent, and survival rates depend on the tumor stage at diagnosis. The present article describes clinical evidence-based guidelines for the diagnosis, treatment, and follow-up of MTC. **Objective:** The aim of the consensus described herein, which was elaborated by Brazilian experts and sponsored by the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism, was to discuss the diagnosis, treatment, and follow-up of individuals with MTC in accordance with the latest evidence reported in the literature. **Materials and methods:** After clinical questions were elaborated, the available literature was initially surveyed for evidence in the MedLine-PubMed database, followed by the Embase and Scientific Electronic Library Online/Latin American and Caribbean Health Science Literature (SciELO/Lilacs) databases. The strength of evidence was assessed according to the Oxford classification of evidence levels, which is based on study design, and the best evidence available for each question was selected. **Results:** Eleven questions corresponded to MTC diagnosis, 8 corresponded to its surgical treatment, and 13 corresponded to follow-up, for a total of 32 recommendations. The present article discusses the clinical and molecular diagnosis, initial surgical treatment, and postoperative management of MTC, as well as the therapeutic options for metastatic disease. **Conclusions:** MTC should be suspected in individuals who present with thyroid nodules and family histories of MTC, associations with pheochromocytoma and hyperparathyroidism, and/or typical phenotypic characteristics such as ganglioneuromatosis and Marfanoid habitus. Fine-needle nodule aspiration, serum calcitonin measurements, and anatomical-pathological examinations are useful for diagnostic confirmation. Surgery represents the only curative therapeutic strategy. The therapeutic options for metastatic disease remain limited and are restricted to disease control. Judicious postoperative assessments that focus on the identification of residual or recurrent disease are of paramount importance when defining the follow-up and later therapeutic management strategies. Arq Bras Endocrinol Metab. 2014;58(7):667-700

Keywords

Medullary thyroid carcinoma; MEN 2A; MEN 2B; *RET* proto-oncogene; diagnosis; treatment; follow-up

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RESUMO

Introdução: O carcinoma medular de tireoide (CMT) origina-se das células parafoliculares da tireoide e corresponde a 3-4% das neoplasias malignas da glândula. Aproximadamente 25% dos casos de CMT são hereditários e decorrentes de mutações ativadoras no proto-oncogene *RET*

(REarranged during Transfection). O CMT é uma neoplasia de curso indolente, com taxas de sobrevida dependentes do estádio tumoral ao diagnóstico. Este artigo descreve diretrizes baseadas em evidências clínicas para o diagnóstico, tratamento e seguimento do CMT. **Objetivo:** O presente consenso, elaborado por especialistas brasileiros e patrocinado pelo Departamento de Tireoide da Sociedade Brasileira de Endocrinologia e Metabologia, visa abordar o diagnóstico, tratamento e seguimento dos pacientes com CMT, de acordo com as evidências mais recentes da literatura. **Materiais e métodos:** Após estruturação das questões clínicas, foi realizada busca das evidências disponíveis na literatura, inicialmente na base de dados do MedLine-PubMed e posteriormente nas bases Embase e SciELO – Lilacs. A força das evidências, avaliada pelo sistema de classificação de Oxford, foi estabelecida a partir do desenho de estudo utilizado, considerando-se a melhor evidência disponível para cada questão. **Resultados:** Foram definidas 11 questões sobre o diagnóstico, 8 sobre o tratamento cirúrgico e 13 questões abordando o seguimento do CMT, totalizando 32 recomendações. Como um todo, o artigo aborda o diagnóstico clínico e molecular, o tratamento cirúrgico inicial, o manejo pós-operatório e as opções terapêuticas para a doença metastática. **Conclusões:** O diagnóstico de CMT deve ser suspeitado na presença de nódulo tireoidiano e história familiar de CMT e/ou associação com feocromocitoma, hiperparatireoidismo e/ou fenótipo sindrômico característico, como ganglioneuromatose e *habitus* marfanoides. A punção aspirativa por agulha fina do nódulo, a dosagem de calcitonina sérica e o exame anatomopatológico podem contribuir na confirmação do diagnóstico. A cirurgia é o único tratamento que oferece a possibilidade de cura. As opções de tratamento da doença metastática ainda são limitadas e restritas ao controle da doença. Uma avaliação pós-cirúrgica criteriosa para a identificação de doença residual ou recorrente é fundamental para definir o seguimento e a conduta terapêutica subsequente. Arq Bras Endocrinol Metab. 2014;58(7):667-700

Descritores

Carcinoma medular de tireoide; NEM 2A; NEM 2B; proto-oncogene *RET*; diagnóstico; tratamento; seguimento

INTRODUCTION

Medullary thyroid carcinoma (MTC) originates in the thyroid parafollicular or C cells and represents 3-4% of the malignant neoplasms that affect this gland (1) (A). Overall, 10,590 new cases of thyroid cancer were estimated among Brazilian women in 2012 (National Cancer Institute/Instituto Nacional do Câncer [Inca]; www.inca.gov.br/estimativa/2012). Assuming that the percentage of MTC is similar to that reported in other countries, about 430 new cases of MTC would be diagnosed each year.

MTC can be sporadic or hereditary (20-25%). The familial form is part of a genetic syndrome known as multiple endocrine neoplasia type 2 (MEN 2). The most common form of this syndrome is MEN 2A, which is characterized by MTC (95%), pheochromocytoma (50%), and hyperparathyroidism (20%), while MEN 2B includes MTC (90%), pheochromocytoma (45%), ganglioneuromatosis (100%), Marfanoid habitus (65%), and eye abnormalities (*e.g.*, thickened corneal nerves, conjunctivitis sicca, and an inability to cry tears). Familial MTC (FMTC) is defined by the presence of MTC alone, and its diagnosis is based on the absence of pheochromocytoma or hyperparathyroidism in 2 or more family generations or the presence of mutations classically associated with FMTC (2,3) (D). Activating mutations in the REarranged during Transfection *(RET)* proto-oncogene are the cause of the hereditary disease form, and therefore molecular diagnosis is of paramount importance in MTC management (4) (A). Approximately 50% of sporadic MTC cases exhibit somatic mutations in the *RET* gene (4,5) (A/B).

Calcitonin is a specific biomarker with a high sensitivity for MTC diagnosis. Neoplastic C cells also produce the carcinoembryonic antigen (CEA), which can be used as a prognostic marker during the follow-up of individuals with MTC (6,7) (B). Sporadic MTC is an indolent and usually solitary tumor, whereas the hereditary form is usually multicentric. Diagnosis of the sporadic form is usually established late in life (approximately the fifth or sixth decade). Neck lymph node metastases are detected in approximately 50% of cases at the time of diagnosis, while distant metastases occur in 20% of cases (8-11) (B). Early surgical intervention is the only curative therapeutic approach (11) (B). The 10-year survival rate of patients with diseases that only affect the thyroid is 95%, while that in individuals with distant metastases varies from 15-40% (12) (B).

The recommendations described below resulted from the efforts of the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism to formulate evidence-based clinical guidelines for the care of individuals with MTC. Our main goal is to assist clinicians with the selection of the best strategies for patient management according to the characteristics of the Brazilian health system.

MATERIALS AND METHODS

The present consensus complies with the strategic policy of the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism for the development of national consensuses for the main diseases of the thyroid gland that are specifically formulated for the Brazilian population, while considering the actual situation of the national health system. The Program Guidelines, which were elaborated by the Brazilian Medical Association (Associação Médica Brasileira [AMB]) and the Federal Council of Medicine (Conselho Federal de Medicina [CFM]), served as a model for the present recommendations. The authors were selected according to their academic and scientific activities and clinical experiences with the management of these diseases. The clinical questions most relevant to the clinical practice were then formulated. A search for relevant articles was performed in the databases MedLine-PubMed, Embase, and Scientific Electronic Library Online/Latin American and Caribbean Health Science Literature (SciELO-Lilacs). The grade of recommendation or strength of evidence (Table 1) of the studies was established according to the Oxford classification (13) (D), which is based on the study design used, while considering the best available evidence and the Brazilian experience. This method was also used in the AMB/CFM Program Guidelines, to which the Brazilian medical community and academic milieu grew accustomed.

The search of the MedLine-PubMed, Embase, and SciELO databases allowed the identification of studies that focused on several features related to the diagnosis, treatment, and follow-up of MTC. The recommendations presented herein summarize the relevant aspects of each clinical question and are categorized as a function of the evidential strength on which they are based, as described in table 1.

Table 1. Definition of the grades of recommendation and strength of evidence according to the Oxford classification (adapted from reference 13) (D)

Recommendation	Strength of evidence
A	Experimental or observational studies with greater consistency
B	Experimental or observational studies with lesser consistency
C	Case reports (uncontrolled studies)
D	Opinions without critical evaluations and those based on consensuses, physiological studies, or animal models

PART I: MTC: DIAGNOSIS

1. When should we suspect MTC?

The most common clinical presentation of MTC is the appearance of a single thyroid nodule. Thyroid nodules might also eventually appear within the context of a multinodular goiter or might represent an incidental finding in imaging exams of the neck (14) (D). Neck lymph node enlargement is present in 50% of these cases (8,9) (B). Although the detection of fast-growing or hardened lymph nodes or their fixation to adjacent structures is suggestive of malignancy, this does not specifically indicate MTC. The presence of associated endocrine neoplasms (pheochromocytoma, hyperparathyroidism), cutaneous lichen amyloidosis on the interscapular region, ganglioneuromas, typical facies, or a history of thyroid cancer and/or of *RET* mutations in first-degree relatives might be suggestive of hereditary MTC (2-4,15) (D/D/B/C). In a small fraction of patients, MTC exhibits systemic manifestations such as diarrhea, flushing, Cushing's syndrome due to the ectopic secretion of adrenocorticotropic hormone (ACTH), or fractures secondary to bone metastases (2,3,15) (D/D/C).

There are no specific clinical findings that permit a firm diagnosis of MTC. For this reason, if CMT is suspected, the physician should order diagnostic tests, including fine-needle aspiration biopsy (FNAB) and serum calcitonin measurements.

Recommendation 1

A thyroid nodule is the most common clinical manifestation of MTC. MTC must be specifically suspected in individuals with family history of thyroid cancer, *RET* mutations, and/or associations with pheochromocytoma, hyperparathyroidism, cutaneous lichen amyloidosis and/or typical findings upon physical examination such

as Marfanoid habitus and mucosal neuromas (Recommendation B).

2. What is the role of fine-needle aspiration biopsy (FNAB) in the diagnosis of MTC?

FNAB is among the most important tools for the diagnostic assessment of thyroid nodules. The characteristic cytological findings in MTC include the presence of predominantly isolated cells or cells arranged in isolated cohesive groups, with a round-to-oval, polyhedral, or fusiform shape, and the predominance of 3-dimensional arrangements; abundant or scarce cytoplasm that usually contains acidophil granulation; 2 or more typically round nuclei of variable size (usually present in alterations associated with endocrine disorders) and eccentric position; and the presence of amyloid, which usually appears as clumps of amorphous matter detected by Congo red staining. Further cytological findings include the presence of fusiform cells and cytoplasmic (comet-like) projections (16) (B).

The sensitivity of FNAB for diagnosing MTC in a thyroid nodule varies from 46.1-63% (17-19) (B). Although non-diagnostic, the FNAB findings in MTC are indicative of surgery in 99% of cases (17-19) (B). Approximately 82% of MTC cases are correctly identified by FNAB, while 9% are false-negative results (18,19) (B).

The most frequent reasons for FNAB failure are inadequate sampling and multinodular goiters (because the malignant nodule might not be selected for assessment) (20) (B). Additionally, differential diagnosis between MTC and other malignant thyroid neoplasms (particularly follicular lesions, Bethesda category III or IV) might be difficult because the cytological findings can be similar (20,21) (B).

The measurement of calcitonin in the washout fluid has been recommended to improve the diagnostic sensitivity of FNAB for MTC (22,23) (B/C). In a recent retrospective study, the cytology detected MTC in 21/37 lesions with 56.8% sensitivity whereas the measurement of calcitonin in the washout fluid showed sensitivity and specificity rates of 100% using a cutoff of 36 pg/mL (24) (B).

The failure to diagnose MTC in a cytological examination might negatively impact the therapeutic management of patients (20) (B). Immunochemical staining for calcitonin might be useful in doubtful cases (25) (C). Other methods that might facilitate the diagnosis of MTC include scanning electron microscopy and assessments of calcitonin mRNA expression; however, these are not part of the diagnostic routine (25-28) (C).

Recommendation 2

FNAB should be included in assessments of thyroid nodules suspected of MTC (Recommendation B). Diagnosis might be facilitated by the use of additional techniques such as calcitonin measurement in the FNAB washout fluid (Recommendation B) and immunocytochemistry (Recommendation C).

3. What is the role of the serum calcitonin measurement in thyroid nodule assessments?

The indication for serum calcitonin measurements in thyroid nodule assessments remains controversial. According to the basal calcitonin levels, the positive predictive values of this test are 8.3%, 25%, and 100% for calcitonin levels of 20-50 pg/mL, 50-100 pg/mL, and > 100 pg/mL, respectively (29) (A). According to some authors, the basal calcitonin levels should be measured first, followed by a pentagastrin stimulation test if the basal calcitonin levels exceed 10 pg/mL. The risk of MTC is greater than 50% if the pentagastrin-stimulated calcitonin values > 100 pg/mL (30) (D). In comparison with the ultrasensitive calcitonin, the pentagastrin test still shows better diagnostic capability (31) (A). However, the pentagastrin stimulation test is not available in Brazil. The calcium stimulation test can be used as an alternative (32) (B). Nevertheless, recent studies have shown that with the improved sensitivity of the new assays, both basal and stimulated calcitonin have similar accuracy, which reduces the relevance of the stimulation tests in multiple conditions (33) (B).

Calcitonin is a sensitive and specific biomarker for the diagnosis of C cell hyperplasia and/or MTC. Increased calcitonin levels might also be present in other diseases such as chronic kidney failure, hyperparathyroidism, neuroendocrine neoplasms, lung and prostate tumors and autoimmune thyroiditis (34,35) (D/B), which are considered classic causes of false-positive results. Presence of heterophile antibodies (human antibodies with broad reactivity with antibodies of other species) can also interfere in dosage, causing falsely elevated values (or, less frequently, false-positive results) (36) (B). Of note, recent study conducted in Brazil found no changes in the serum

calcitonin levels of individuals with Hashimoto's thyroiditis (37) (B). False-negative results might be due to the hook effect and, less often, to non-calcitonin-secreting MTC (38,39) (C).

Compared with FNAB, the sensitivity of the calcitonin measurement for preoperative diagnosis of MTC is higher (approximately 100% sensitivity and 95% specificity) (18,40,41) (B). Individuals with MTC that was diagnosed from a calcitonin measurement during the investigation of thyroid nodules exhibit better postoperative outcomes than do those diagnosed by FNAB, with 10-year survival rates of 86.8% and 43.7%, respectively (42) (B).

In North America, studies of cost-effectiveness obtained results favorable to the inclusion of calcitonin measurements in initial thyroid nodule assessments (43,44) (D/B). Those data lend further support to the usefulness of calcitonin measurements in nodule investigations. Those results notwithstanding, the low prevalence of MTC (0.42-2.85%), the test costs, and problems with the standardization of the cutoff points cast doubts on the actual benefit provided by calcitonin measurements (42,45-47) (B). Additionally, the reproducibility of those results in our milieu is doubtful. For those reasons, the Brazilian consensus for thyroid nodules does not recommend the measurement of serum calcitonin in the initial nodule assessment (14) (B). However, measurement of calcitonin in the FNAB washout fluid may be useful in nodules with undetermined results (Bethesda category III/IV), considering the difficulties of FNAB to differentiate MTC from other thyroid malignancies (particularly follicular lesions) (24) (B).

The prevalence of MTC in individuals with multinodular goiters varies from 0-3.1% (48) (A). It is worth bearing in mind that FNAB might yield false-negative results in cases of multinodular goiters because not all nodules can be feasibly assessed (49) (D). Additionally, small MTC foci might not be identified with thyroid ultrasound (US). For all those reasons, the serum calcitonin measurement might be useful for detecting MTC in cases of multinodular goiter (50,51) (A).

Recommendation 3

MTC screening via a serum calcitonin measurement in individuals with thyroid nodules remains controversial. Because of problems with reference value standardization and its doubtful cost-effectiveness, the measurement of serum calcitonin is not indicated in the routine investigation of thyroid nodules (Recommendation B).

4. What are the meanings of the serum levels of tumor markers for the initial diagnosis of MTC?

MTC secretes a variety of products, including calcitonin, CEA, amyloid, somatostatin, ACTH, vasoactive intestinal peptide (VIP), and serotonin, among others (52,53) (B). Calcitonin is the most important biomarker and is used in the diagnosis, surgical planning, postoperative management, and prognosis of individuals with MTC (54) (D).

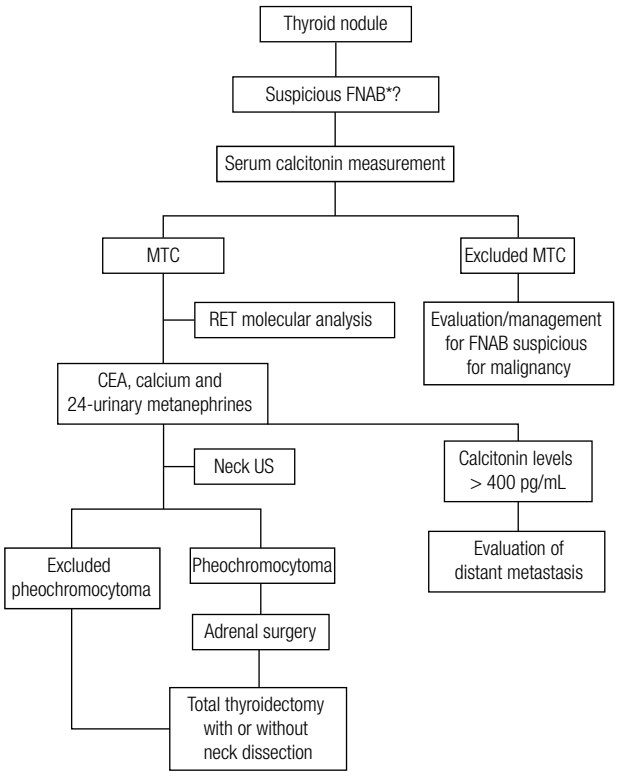
In individuals with MTC, the preoperative calcitonin levels correlate with the tumor size and the presence of metastases (6,7) (B). Calcitonin levels < 100 pg/mL are associated with an average tumor diameter of 3 mm, while levels > 1,000 pg/mL are associated with an average tumor diameter of 2.5 cm. Neck lymph node metastases might be present with basal calcitonin levels of 10-40 pg/mL, while metastatic disease should be suspected at levels of 150-400 pg/mL. The presence of lymph node metastases or calcitonin levels > 400 pg/mL indicate the need to identify distant metastases (6,7) (B).

Additionally, the serum CEA levels might be used for the risk stratification of individuals with MTC. CEA levels > 30 ng/mL are suggestive of lymph node metastases in the ipsilateral central and lateral neck compartments, while levels > 100 ng/mL correlate with contralateral lymph node metastases and distant metastases. Values > 30 ng/mL were found to correlate with low cure rates (55) (B).

The preoperative serum calcitonin levels seem to correlate more strongly with extensions of MTC, as compared to the neck US findings. Basal calcitonin levels of 20, 50, 200, and 500 pg/mL exhibited correlations with metastases in the lymph nodes of the ipsilateral, lateral, and central compartments, contralateral central compartment, contralateral lateral compartment, and superior mediastinum, respectively (56) (B).

Recommendation 4

Preoperative calcitonin levels correlate with the tumor size and stage and indicate the presence of local and/or distant metastases (Recommendation B). The individuals with suspected MTC and calcitonin levels > 150 ng/mL must be investigated for the presence of locoregional and distant metastases by imaging tests (please see Recommendation 6, Flowchart 1) (Recommendation B).



Flowchart 1. Initial diagnostic approach of medullary thyroid carcinoma.

5. What is the value of neck US for the diagnosis of MTC?

Thyroid US is a relevant part of a thyroid nodule assessment. US allows an accurate assessment of the nodule size and characteristics, as well as the identification of other nodules. Some nodule characteristics evidenced by US correlate with a higher risk of malignancy, including hypoechogenicity, microcalcifications, irregular margins, predominantly central vascularization, and the presence of enlarged neck lymph nodes (57-59) (B).

Most individuals with MTC (> 90%) exhibit hypoechoic nodules, intranodular calcifications, and an absence of the halo sign on US; further possible findings include the presence of intranodular (79%) and perinodular (50%) blood flow (60) (B). Some cases exhibit intranodular bright echogenic foci that correspond to amyloid-surrounded calcium deposits (61) (B).

Neck US is the most sensitive imaging method for neck metastasis detection (10) (B). Approximately 75% of patients with MTC that is clinically detectable by palpation exhibit lymph node metastases (8) (B). As the presence of lymph node and/or distant metastases indicates the need for changes in the therapeutic management, US might be considered indispensable for treatment planning. The sensitivity of preoperative neck US is considered as moderate, since 32% and 14% of individuals exhibit false-negative results in the central and ipsilateral areas, respectively (62) (B). However, a recent study described higher rates of sensitivity of US in predicting metastasis in the lateral and central neck (93.8% and 30.0%, respectively) (63) (B). One important limitation of US is that it is operator-dependent, and therefore the results vary as a function of the operator's experience. This most likely explains why a larger number of neck lymph node metastases are detected with surgical dissection, compared to US. Nevertheless, the sensitivity, specificity, and diagnostic accuracy of US for the preoperative detection of neck metastases are superior to those of computed tomography (CT; 77, 70, and 74% *vs.* 62, 79, and 68%, respectively) (64) (B). Preoperative neck US is a valuable tool in assessing patients with thyroid nodules; it provides useful information predicting cervical lymph node metastasis, especially in the in the lateral neck, and thus defining surgical extension (63) (B).

Recommendation 5

Neck US is indicated in all individuals with suspected MTC (Recommendation B). In addition to identifying characteristics suggestive of malignancy in the thyroid nodules and allowing the performance of US-guided FNAB, US is the most sensitive test for detecting neck metastases and thus contributes to therapeutic planning (Recommendation B).

6. Which complementary tests should be performed before thyroidectomy in patients with suspected MTC?

The aim of the preoperative assessment of individuals with suspected or confirmed MTC is to establish the extension of thyroid disease and to identify the eventual presence of associated comorbidities such as hyperparathyroidism and/or pheochromocytoma in hereditary cases.

The presence of local and/or distant metastases interferes with surgery planning in individuals with MTC. Neck metastases appear early during the course of MTC (9,65) (B). Distant metastases are detected in 7-17% of all cases at the time of diagnosis and frequently appear in multiple sites (lungs, liver, bones, and less often in the brain and skin) (10,11,66,67) (B/B/B/A).

Neck US must be performed in all affected individuals (56-58) (B). Findings suggestive of neck metastases or calcitonin levels > 400 pg/mL indicate the need

for additional tests (6,7) (B). It is worth noting that the radiological detection of distant metastases is quite improbable when the calcitonin levels are < 250 pg/mL (68) (B). The most efficacious approach to diagnosing distant metastases includes a combination of CT of the neck and chest and magnetic resonance imaging (MRI) of the liver (10) (B). The risk of distant metastases is similar in individuals with sporadic or hereditary MTC (7) (B).

Pheochromocytoma is a tumor that originates in the chromaffin cells of the adrenal medulla and occurs in approximately 30-50% of individuals with MEN 2A or 2B. Adrenomedullary disease is more frequently bilateral (up to 78% of cases) in MEN 2, thus contrasting with sporadic pheochromocytoma, which usually appears as a single unilateral lesion. Additionally, pheochromocytoma tends to appear earlier in individuals with MEN 2 and seldom metastasizes. The clinical manifestations of pheochromocytoma are caused by catecholamine hypersecretion and include the most frequent manifestations of arterial hypertension, tachycardia, headaches, and excessive sweating (69,70) B/C). Nevertheless, some individuals might merely exhibit a discrete increase in catecholamine levels that is unattended by any signs or symptoms (71) (D).

Individuals with hereditary MTC should be screened for pheochromocytoma, given their high risk of that disease (72) (B). As up to 10% of apparently sporadic MTC have a *RET* germline mutation, the presence of pheochromocytoma should be excluded in any patient with suspected MTC before the thyroidectomy, due to the high risk of anesthesia and the surgical procedure (73,74)(D/B). A pheochromocytoma diagnosis is based on the identification of excessive catecholamine production by measuring the plasma and/or urine catecholamine and/or metanephrine levels. The measurement of plasma fractionated metanephrines seems to be the most useful test in cases of hereditary pheochromocytoma, with sensitivity and specificity rates of 99% and 98%, respectively. The sensitivity and specificity rates of urine metanephrines, plasma catecholamines, and urine catecholamines are 97-100% and 93-94%, 76-84% and 81-88%, and 84-86% and 88-99%, respectively (75,76) (B). Therefore, normal fractionated plasma metanephrines levels practically rule out pheochromocytoma in high-risk patients such as those with genetic syndromes (77-79) (B/B/D). When plasma fractionated metanephrine measurements are unavailable, urine levels might be assessed.

Computed tomography or MRI of the abdomen might be performed to identify the localization of a pheochromocytoma. CT of the abdomen was able to identify the localization of hereditary adrenal tumors in 76% of the evaluated cases (80) (B). Some CT-detectable nodule features might be helpful for the differential diagnosis among various types of adrenal lesions, including adenoma, pheochromocytoma, and carcinoma. The lesion density is 1 of the parameters that helps to distinguish adrenal adenomas from non-adenomas because adenoma densities are low due to their high intracellular lipid contents. CT densities are measured in Hounsfield units (HU); with a cutoff point of 10 HU, non-contrast-enhanced CT exhibits a 75% sensitivity rate and 100% specificity rate for the differentiation between adrenal adenomas and non-adenomas. Adenoma densities are usually lower than those of other tumors (pheochromocytoma, carcinoma), and contrast washout occurs faster in adenomas, compared to other adrenal lesions. A > 50% washout at 10 minutes after administration exhibits 100% sensitivity and specificity for the identification of adrenal adenomas, compared to pheochromocytomas, carcinomas, and metastatic lesions (81-83) (B).

Hyperparathyroidism occurs in approximately 10-20% of individuals with MEN 2A and is either asymptomatic or presents with manifestations secondary to hypercalcemia (84) (D). In suspected cases of hereditary MTC associated with MEN 2A, a serum albumin-adjusted calcium measurement should be included in the preoperative investigation (73,85) (D).

Recommendation 6 (Flowchart 1)

Neck US must be performed in all affected individuals for detection of locoregional metastases. In individuals with suspected locoregional metastases or calcitonin levels > 400 pg/mL, the presence of distant metastases must be investigated before surgery (Recommendation B). The presence of pheochromocytoma must be investigated by the measurement of plasma fractionated metanephrines or urine metanephrine levels, if not available the blood measurement (Recommendation B). Once the diagnosis is confirmed, the adrenal tumor must be removed before thyroidectomy (Recommendation B). The presence of hyperparathyroidism might be investigated through a serum calcium level measurement after adjusting for the albumin concentration (Recommendation D).

7. Which individuals with confirmed or suspected MTC should be subjected to *RET* proto-oncogene molecular testing?

The *RET* proto-oncogene comprises 21 exons and encodes a tyrosine-kinase receptor that is expressed in neural crest-derived cells, including the thyroid C cells, adrenal medulla, and parathyroid glands. The RET protein comprises 3 domains: an extracellular cysteine-rich domain with cadherin-like repeats, a transmembrane domain, and an intracellular domain with 2 tyrosine-kinase domains (TK1 and TK2). Hereditary MTC affects approximately 1 in every 30,000 individuals and is caused by germline mutations in the *RET* proto-oncogene, an autosomal dominant genetic syndrome with approximately 100% penetrance and a variable phenotype. The mutations mainly affect the *RET* exons 10, 11, and 16, and less commonly the exons 5, 8, 13, 14, and 15 (84,86) (D).

Several studies have found correlations between specific *RET* mutations and the various clinical syndromes associated with MEN 2. Mutations at codon 634 (exon 11) are associated with the presence of pheochromocytoma and/or hyperparathyroidism, while mutations at codon 918 (exon 16) are specific for MEN 2B. Similarly, mutations at codons 768 and 804 are associated with FMTC (Table 2) (87,88) (B/D).

Molecular diagnosis is superior to clinical and/or biochemical diagnosis for the identification of asymptomatic individuals who are at risk of neoplasia (89-91) (B/C/B). Molecular testing allows the identification of the *RET* mutations that cause MEN 2A and MEN 2B in 95–100% of the evaluated cases (92,93) (B/D).

Genetic screening should be performed in all individuals with MTC, rather than in the cases suspected of the hereditary form only, as 4-10% of apparently sporadic MTCs exhibit germline *RET* mutations; these occur particularly among young patients and/or those with multifocal disease (42,94-96) (B).

Therefore, investigations of *RET* proto-oncogene mutations are of paramount importance in the diagnostic assessment of and therapeutic planning for individuals with MTC.

Recommendation 7

A molecular assessment is indicated for all individuals with C cell hyperplasia, (familial or apparently sporadic) MTC, and/or MEN 2 (Recommendation B). The molecular diagnosis might guide the choice of therapeutic procedures and consequently change the natural course of disease, indicate genetic counseling, and help to establish the disease prognosis (Recommendation B).

Table 2. Correlations between the clinical presentations and germline RET mutations in hereditary medullary thyroid carcinoma

Phenotype	Clinical presentation	%	*RET* germline mutation Exon (Codons)
Sporadic	MTC	75-80	None
Hereditary		20-25	
MEN 2A	MTC, pheochrocytoma, hyperparathyroidism	80-90	**8** (G533) **10** (C609, C611, C618, C620) **11** (C630, C633, C634*, 635/insertion, S649) **13** (E768, L790, Y791) **14** (V804) **15** (S891) **16** (R912)
MEN 2B	MTC, pheochrocytoma, marfanoid habitus	1-5	**14** (V804+E805, V804+Y806, V804 e S904) **15** (A883) **16** (M918T*)
FMTC	MTC	10-15	**5** (R321) **8** (531/9 duplication, G533) **10** (C609, C611, C618, C620) **11** (C630, C633, C634, 635/insertion, S649) **13** (E768, L790, Y791) **14** (V804) **15** (Y891) **16** (R912)

MEN: multiple endocrine neoplasia; MTC: medullary thyroid carcinoma. * Most frequent mutations.

8. When should the relatives of individuals with MTC be assessed? What is the relevance of a *RET* molecular assessment in such individuals?

Hereditary MTC is an autosomal dominant disease, and therefore the likelihood of transmission from 1 generation to the next is 50% (89) (B). Following the identification of a *RET* mutation in an individual (proband), all of his or her first-degree relatives should be subjected to genetic assessment. The molecular analysis of the *RET* proto-oncogene in a proband's relatives is of paramount importance because it allows for early diagnosis and treatment and consequently better prognosis (87,93) (B). For these reasons, the indication of molecular testing is considered essential and is recommended in the guidelines developed by the American Thyroid Association (ATA) and the European Thyroid Association (ETA), as well as in the Clinical Guidelines on Medullary Thyroid Carcinoma for Private Health Insurance and Plans from the Brazilian Medical Association and the National Regulatory Agency for Private Health Insurance and Plans (73, 97,98) (D).

Total thyroidectomy should be considered in asymptomatic carriers of *RET* mutations (73,89) (D/B). The appropriate age for prophylactic surgery depends on the results of *RET* molecular testing, the clinical data, and the serum calcitonin levels. The various mutation types correlate with the degree of MTC aggressiveness, and therefore molecular testing facilitates decision-making with respect to the extent of surgery and the age at which surgery should performed. Additionally, the preoperative serum calcitonin levels contribute to surgery planning and the establishment of disease prognosis, in addition to being used in postoperative follow-ups (6,99,100) (B/C/B). The presence of neck metastases should be also investigated with physical examinations and US before surgery (60,62,100) (B).

Based on genotype-phenotype correlation studies, ATA formulated a series of recommendations for prophylactic thyroidectomy in asymptomatic *RET* mutation carriers. The different types of mutations are classified in 4 risk-based categories according to the tumor aggressiveness (A < B < C < D). In individuals with ATA A and B mutations (codons 768, 790, 791, 804 and 891 and 609, 611, 618, 620, and 630, respectively), the risk of MTC is moderate, and in most cases, prophylactic surgery might be performed after the age of 5 years. Individuals with mutations in codon 634 (ATA risk level C) are at risk of developing MTC early in life, and prophylactic surgery should be performed before the age of 5 years (101) (B). Individuals with phenotype MEN 2B-associated mutations (ATA risk level D) have an even higher risk of early MTC development and therefore should be subjected to prophylactic thyroidectomy prior to 1 year of age or at the time of diagnosis (73) (D).

In children and young adults with *RET* mutations, the presence of a palpable thyroid nodule at the time of diagnosis correlates strongly with persistent or recurrent MTC (100) (B). Those data reinforce the relevance of the early investigation of *RET* mutations.

Relatives who test negative for *RET* mutations are considered to have no risk of MTC and/or associated neoplasms and might thus be released from further follow-up.

Recommendation 8

All first-degree relatives of individuals with MTC and germline *RET* mutations should be subjected to molecular screening (Recommendation B).

9. Does the mutation type interfere with the clinical presentation of MTC?

Most families with MEN 2A exhibit mutations in 1 of the 5 cysteine residues in exon 10 (codons 609, 611, 618, and 620) or 11 (codon 634) of the *RET* extracellular domain (Table 2). All mutations in codon 634 are associated with pheochromocytoma and/or hyperparathyroidism (87,92) (B). Specific amino acid changes in the same codon interfere with the genotype--phenotype correlation. In individuals with MEN 2A, mutation C634R is associated with a higher rate of metastasis at the time of diagnosis, compared to mutations C634W and C634Y (102) (B).

The risk of pheochromocytoma in individuals with MEN 2 varies as a function of the mutated codon. The adrenal tumor occurrence rates are 28%, 21%, and 3% in carriers of mutations in the highest-risk category (mutations in codon 918), in the high-risk category (mutations in codons 634, 630, 609, 611, 618, and 620), and in the lower-risk category (mutations in codons 768, 790, 791, 804, and 891) (72) (B). Mutation C634W correlates strongly with a high penetrance of pheochromocytoma (103) (B).

A specific mutation in codon 16 (M918T) has been found in approximately 95% of individuals with MEN 2B, the mutation A883F (exon 15) has been identified in 2-3% of the cases, and the double mutation V804M/Y806C (exon 14) in the same allele has been described in 1 patient with MEN 2B. Mutations in codons 883 and

918 correlate with the occurrence of MTC at a younger age, an increased risk of metastasis, and an increased disease-specific mortality (86,92,104) (D/B/B).

Approximately 90% of families with hereditary MTC exhibit mutations in *RET* exon 10 (codons 609, 611, 618, and 620) and exon 11 (codon 634) (6,10) (B). Substitutions in the tyrosine-kinase domain-coding exons 13 (codons 768, 790, and 791), 14 (codons 804 and 844), and 15 (codon 891) are less common. In such cases, MTC appears later, and the prognosis is more favorable compared to that of other forms of MTC (92) (B).

However, it is worth noting that individuals from the same family who carry the same *RET* mutation can exhibit variable phenotypic expressions and degrees of tumor aggressiveness (102) (B). In recent years, the presence of *RET* gene variants or polymorphisms has been associated with changes in the clinical presentation and natural history of MEN 2 (86,105) (D/B).

Recommendation 9

The knowledge of the type of *RET* mutation provides relevant information about the clinical presentation of MEN 2 and the biological behaviors of the associated neoplasms (Recommendation B).

10. In addition to endocrine tumors, what are the clinical manifestations associated with *RET* proto-oncogene mutations?

In addition to pheochromocytoma and hyperparathyroidism, hereditary MTC is rarely associated with cutaneous lichen amyloidosis and Hirschsprung's disease (106-108) (C/B/D).

Cutaneous lichen amyloidosis (CLA) is an itchy hyperpigmented skin lesion that appears on the upper area of the back (interscapular region). The association between mutations in *RET* codon 634 and CLA was first described in 1989 (106) (B). CLA can appear early and usually precedes thyroid disease (106,107) (C/B).

Inactivating *RET* germline mutations appear in 10-40% of cases of Hirschsprung's disease; this disease comprises the congenital absence of the intestinal intermuscular (Auerbach's), and superficial (Meissner's) and deep (Henle's) submucosal plexuses, leading to symptoms of intestinal obstruction during the neonatal period, as well as constipation, abdominal distension, and vomiting in adulthood. Mutations in exon 10 are associated with the concomitant occurrence of MEN 2 and Hirschsprung's disease (108) (B). The affected individuals carry a single mutation, thus suggesting that the effects of that mutation vary as a function of the tissues in which *RET* is expressed (109) (C).

Recommendation 10

The presence of CLA or Hirschsprung's disease indicates the suspected occurrence of hereditary MTC and therefore the need to perform a *RET* molecular assessment (Recommendation B).

11. When and how to screen for pheochromocytoma and hyperparathyroidism?

MEN 2A is the most common form of MEN and is characterized by the occurrence of MTC, pheochromocytoma, and hyperparathyroidism. MTC occurs in 95% of individuals with MEN 2A, while the risks of unilateral or bilateral pheochromocytoma and hyperparathyroidism are 57%, and 15-30%, respectively (84,110) (D/D). Adrenal disease is usually benign, multicentric, and bilateral, and, as a rule, it is detected after the onset of MTC. Hyperparathyroidism usually involves all of the parathyroid glands, and gland hyperplasia is the most commonly detected histological lesion in early-stage disease. However, when diagnosis is delayed, adenoma occurs concomitantly with hyperplasia (84) (D). MEN 2B is the less common variety of MEN 2 and exhibits a more aggressive form of MTC, as well as the occurrence of pheochromocytoma; however, hyperparathyroidism does not occur (84) (D).

A recent study assessed the mean age at onset of pheochromocytoma in individuals with MEN 2A, according to the ATA risk categories described above. The authors found that the first pheochromocytomas were diagnosed at ages 25, 34, 40, and 56 year old in individuals classified as ATA risk levels D, C, B, and A, respectively and that the occurrence frequencies were 27, 32, 17, and 3% in categories D, C, B, and A, respectively (111) (B).

The youngest ages at pheochromocytoma diagnosis were 12 and 5 years old in carriers of mutations in codons 918 and 634, respectively (72,112,113) (B/D/B). Less aggressive mutations such as those in codons 609, 611, and 618 and in codons 768, 790, and 891 are associated with a later onset of pheochromocytoma, specifically at ages 19 and 28 years old, respectively (72,114) (B/B). Therefore, the investigation of adrenal tumors in patients with MEN 2 should begin at 8 years of age

in carriers of mutations in codons 918, 634, and 630, and after 20 years of age in the remainder of the cases (72) (B). Assessments might be performed by measuring the plasma or urine metanephrine levels (77-79) (B/B/D). The ruling out of pheochromocytoma is of paramount importance in cases of hereditary MTC because the adrenal tumor should be treated before the thyroidectomy.

Hyperparathyroidism rarely occurs in children, as the mean age at diagnosis is 38 years old in individuals with MEN 2A (115,116) (B/B). Serum calcium and albumin measurements should begin at 8 years of age in carriers of mutations in codons 630 and 634, and at 20 years of age in carriers of other mutations associated with MEN 2A, and should be repeated annually. Recently, a case of hyperparathyroidism diagnosed in a 5-year-old child with MEN 2A was reported (117) (C).

Recommendation 11

In asymptomatic cases or in the absence of adrenal masses, urine and/or fractionated plasma metanephrines measurements should begin at 8 years of age in individuals with MEN 2B or 2A who carry mutations in codons 630 or 634, and after 20 years of age in the remainder of individuals with MEN 2A.

Hyperparathyroidism screening must be performed annually by measuring the total calcium and albumin levels, starting at 8 years age in carriers of mutations in *RET* codons 630 and 634 and at 20 years of age in the remainder of individuals with MEN 2A.

PART II: MTC – SURGICAL TREATMENT

1. What is the surgical treatment for individuals with MTC limited to the thyroid gland?

Upon preoperative assessment, MTC is considered to be limited to the thyroid gland if there is no evidence of involvement of adjacent structures, or lymph node or distant metastases. In such cases, the indicated surgical treatment comprises total thyroidectomy with (elective) prophylactic dissection of the central compartment (levels VI and VII; Figure 1) (66,118-120) (B). Given the risk of hidden metastatic disease, prophylactic dissection of the lateral compartments might be added, particularly when the tumor is > 1 cm, if metastases are found in the central compartment, or elevated calcitonin levels (121-123) (B/B/D).

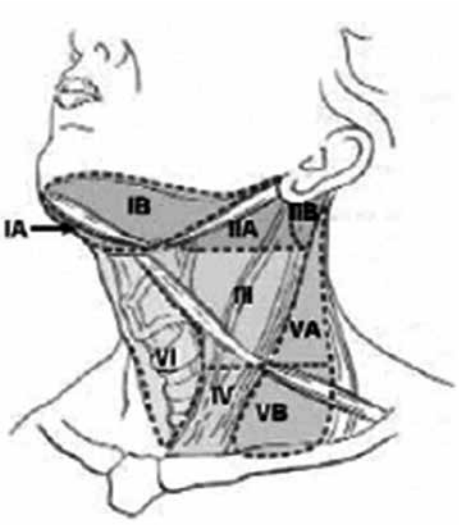


Figure 1. Cervical lymph nodes anatomy.

Recommendation 1

The surgical treatment recommended for individuals with MTC limited to the thyroid gland is total thyroidectomy and elective dissection of the central compartment (Recommendation B).

2. What is the surgical approach for individuals with MTC and locoregional disease diagnosed during the preoperative assessment?

In individuals with MTC, the presence of locoregional disease indicates the need for a total thyroidectomy associated with dissection of the lymph nodes in the central compartment (levels VI and VII; Figure 1) (104) (B). Lateral lymph node dissection (levels, II, III, IV, and V) is indicated when metastases are suspected in any of those levels (121) (B). The benefit of prophylactic lateral dissection when metastases are only located in the central compartment is controversial. Some authors support the US preoperative evaluation for the detection of metastases and argue against prophylactic dissection. However, due to the high incidence of lymph node metastases and the risk of occult metastatic disease, others indicate compartment oriented lymph node dissections in the first surgery because of the complications associated with re-interventions (73,121-123) (D/B/B/D).

The current American Joint Committee on Cancer (AJCC) 6th edition TNM (tumor, node, metastasis) classification system is used for postoperative staging of MTC (Table 3) (124). The likelihood of a cure is low in cases with extrathyroid disease. The biochemical cure

Table 3. American Joint Committee on Cancer TNM Classification

Primary tumor (T)
T0 – No evidence of primary tumor
T1 – Tumor 2 cm or less in greatest dimension limited to the thyroid (Supplementum to the 6th edition: T1a, tumor 1 cm or less; T1b, tumor more than 1 cm but not more than 2 cm)
T2 – Tumor more than 2 cm, but not more than 4 cm, in greatest dimension limited to the thyroid
T3 – Tumor more than 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extra-thyroidal extension (*e.g.* extension to sternothyroid muscle or perithyroid soft tissues)
T4a – Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b – Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
Regional lymph nodes (N) are the central compartment, lateral cervical, and upper mediastinal lymph nodes
NX – Regional lymph nodes cannot be assessed
N0 – No regional lymph node metastases
N1 – Regional lymph node metastases
N1a – Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/ Delphian lymph nodes)
N1b – Metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes
Distant metastases (M)
MX – Distant metastasis cannot be assessed
M0 – No distant metastasis
M1 – Distant metastasis
Stage
• Stage I: T1, N0, M0
• Stage II: T2, N0, M0
• Stage III: T3, N0, M0 T1, N1a, M0 T2, N1a, M0 T3, N1a, M0
• Stage IVA: T4a, N0, M0 T4a, N1a, M0 T1, N1b, M0 T2, N1b, M0 T3, N1b, M0 T4a, N1b, M0
• Stage IVB: T4b, any N, M0
• Stage IVC: any T, any N, M1

Sixth edition (115).

rates in individuals with preoperative basal calcitonin levels > 300 pg/mL, a primary tumor > 10 mm, and persistent metastatic disease after lymph node dissection are below 50% (7) (B). As a rule, only 10-40% of individuals with neck metastases achieve biochemical cures (7,119) (B), while relapses occur in 3.3% of the individuals who attain normal basal calcitonin levels after a follow-up of 0.7-7.5 years (125) (B). Similar cure rates (~38%) are reported in individuals who are subjected to extensive surgery (7) (B). Therefore, as extensive surgery is not associated with higher cure rate, less aggressive procedures should be indicated in cases with advanced local disease or distant metastases in order to maintain control of local disease while preserving the parathyroid function, vocal cords, and deglutition (73,104) (D/B).

Recommendation 2

In cases with locoregional disease, total thyroidectomy with central compartment lymph node dissection is indicated (Recommendation B). Lateral lymph node dissection is indicated when metastases are present or suspected (Recommendation B). Less aggressive surgery should be indicated in cases with advanced local disease and/or distant metastases to achieve local disease control while preserving the patient's voice, deglutition, and parathyroid function (Recommendation B).

3. What is the management of individuals with postoperative diagnoses of MTC?

In individuals with MTC that was diagnosed after a total lobectomy (thyroid lobe and isthmus), thyroidectomy can be complemented by central compartment dissection or only expectant management in selected cases (126,127) (B). According to some authors, the latter alternative might apply to individuals with undetectable calcitonin levels at 2 months after thyroidectomy, unifocal MTC limited to the gland, tumor-free surgical margins, the absence of C cell hyperplasia, the absence of neck lymph node metastases in physical examination or on US, and a diagnosis of sporadic MTC based on negative *RET* molecular testing (120,126,127) (B).

Recommendation 3

Completion thyroidectomy and prophylactic central compartment dissection are indicated in patients with postoperative diagnoses of MTC (Recommendation B). Expectant management might be considered in selected cases (Recommendation B).

4. What is the approach to the parathyroid glands in surgery for MTC?

As a rule, normal parathyroid glands should be preserved when thyroidectomy is performed. However, those glands might be accidentally removed or their vascularization might be compromised during surgery, espe-

cially for those glands located in the lower poles. The risk increases when a central compartment dissection is performed (124,125) (D/B). When devascularization occurs, the affected glands should be grafted onto the sternocleidomastoid muscle. In cases with a risk of hyperparathyroidism, such as the presence of MEN 2A-related mutations, grafting should be performed in the non-dominant forearm to facilitate the gland removal procedure in the event of recurrent hyperparathyroidism (128-130) (B).

The hyperparathyroidism occurs in approximately 10 to 20% of patients with MEN 2A. It is usually associated with mild and often asymptomatic disease, especially in young patients. When indicated treatment, it is important to establish whether the disease is restricted to one or multiple glands and then, decide the most appropriate surgical procedure. The following surgical procedures may be used, depending on the number of glands involved: total parathyroidectomy with autotransplantation, subtotal parathyroidectomy, or removal of a single gland (128,129) (B). The occurrence of permanent hypoparathyroidism is usually associated with total parathyroidectomy, although also already been reported after subtotal parathyroidectomy, or even after excision of two glands (130) (D). In cases of hyperparathyroidism that appear in individuals who previously underwent surgery for MTC, the affected gland should be identified via imaging methods such as US, CT, or sestamibi scintigraphy before surgery (129,131) (B). The successful use of calcimimetics has been reported in cases of persistent hyperparathyroidism (132) (B).

Recommendation 4

In cases without preoperative hyperparathyroidism, the "*in situ*" preservation of the parathyroid glands is always desirable. When the glands are accidentally removed or there is a risk of devascularization, the glands should be autografted into the sternocleidomastoid muscle (Recommendation B). In cases with hyperparathyroidism, MEN 2A, or prior surgery for MTC, the affected parathyroid gland should be identified with imaging methods to decide upon a subtotal or total parathyroidectomy, followed by a forearm autograft (Recommendation B).

5. What is the surgical approach in asymptomatic individuals with *RET* mutations?

Asymptomatic individuals with *RET* proto-oncogene mutations should be assessed before surgery by measuring the serum calcitonin levels and using neck US to identify the presence of thyroid nodules and lymph node metastases, as these indicate the need for a different surgical approach (6,64) (B). In such cases, the ATA guidelines recommend the application of a risk categorization system relative to the minimum age at the onset of MTC and the tumor aggressiveness, including the likelihood of metastasis, likelihood of cure, morbidity, and mortality (73,133) (D). That system clusters codons into risk levels ranging from A (least aggressive) to D (most aggressive; see **Part I: MTC – Diagnosis – Question 8 of the present consensus**). Based on the risk level that corresponds to the affected *RET* codon, therapeutic decision-making is performed according to the best age for so-called prophylactic thyroidectomy and the need for neck dissection. Preferably, the surgical approach should be performed in reference centers with experienced surgeons and a large volume of thyroid surgeries.

Additionally, the likelihood of pheochromocytoma onset and the age at which to begin investigating this onset are estimated according to those risk levels (see **Part I: MTC – Diagnosis – Question 6 of the present consensus**). When pheochromocytoma is diagnosed, it should be subjected to surgical treatment before MTC (122,134,135) (B).

Recommendation 5

The surgical approach in asymptomatic individuals with *RET* proto-oncogene mutations should consider the risk stratification according to the codon that exhibits the mutation, as follows:

- **Group D** (MEN 2B): total thyroidectomy in the first year of life; if there is evidence of lymph node metastases, the thyroid nodule is > 5 mm, or the serum calcitonin level is > 40 pg/mL, central compartment dissection is also indicated. Individuals older than 1 year of age are indicated for (elective) "prophylactic" central dissection.
- **Group C**: total thyroidectomy before 5 years of age.
- **Groups A and B**: total thyroidectomy after 5 years of age if there is a lack of evidence for MTC (normal basal serum calcitonin levels and normal neck US).

Individuals in groups A, B, and C should only be subjected to central compartment dissection if there is clinical and/or imaging evidence of metastatic disease, the nodule size is ≥ 5 mm, and the serum calcitonin level is > 40 pg/mL (Recommendation B).

6. What is the surgical approach in individuals with MTC and distant metastases?

The presence of distant metastases makes a biochemical cure of MTC unlikely. For this reason, the presence of distant metastases should be carefully assessed when the serum calcitonin level is > 400 pg/mL (125,136,137) (B/B/D). The surgical treatment of individuals with metastatic disease should focus on local disease control and mainly on the patients' quality of life (137) (D).

Recommendation 6

The surgical treatment of individuals with advanced local disease or distant metastases should be less aggressive and aimed at local disease control, while preserving the patient's voice, deglutition, and the parathyroid function and avoiding potential hemorrhagic complications due to the invasion of vascular structures (Recommendation B).

7. What are the indications for mediastinal lymph node dissection in MTC patients?

The mediastinum is divided into a superior portion, which is located above the pericardium, and 3 inferior divisions, the anterior, middle, and posterior. The middle mediastinum contains the heart and pericardium, the anterior mediastinum is bounded anteriorly by the pericardium and posteriorly by the sternum and contains mainly the thymus, and the posterior mediastinum is the area behind the pericardium and contains the esophagus and the thoracic aorta, among other structures (138) (B). The superior mediastinum contains the thymus and the brachiocephalic artery anteriorly and the trachea and esophagus posteriorly. The superior mediastinum corresponds to level VII of the neck lymph nodes and is included in the dissection of the central compartment (104,139) (B). Therefore, elective superior mediastinal dissection is usually performed during surgery for MTC via the cervical access. The presence of metastases in lymph nodes of inferior mediastinum, diagnosed by imaging methods (CT or MRI), can be considered as distance metastatic disease, which significantly decreases the chance for cure. Thus, the dissection of this area should only be offered as a palliative treatment in patients with high risk of airway obstruction or bleeding (64,121) (B).

Recommendation 7

Elective superior mediastinal dissection is usually performed during surgery for MTC (Recommendation B). The dissection of the lower mediastinum should be considered only as a palliative treatment in patients with high risk of airway obstruction or bleeding (Recommendation B).

8. What is the required preoperative care for individuals with MTC and suspected or confirmed pheochromocytoma?

In individuals with pheochromocytoma and MTC, adrenalectomy should precede thyroidectomy. An investigation of pheochromocytoma is mandatory in cases with suspected MEN 2 (72,74,140) (B/B/D) and is also indicated in individuals with apparently sporadic MTC that has not yet been subjected to *RET* molecular testing. Although the occurrence of pheochromocytoma is rather unlikely in these cases, its eventual identification before thyroid surgery is critical, as the complications that arise in undiagnosed cases are severe (72,74) (B).

A diagnosis of pheochromocytoma is established through the identification of excessive catecholamine production by measuring the plasma and/or urine levels of catecholamines and/or metanephrines. The measurement of plasma metanephrines seems to be most useful in cases of hereditary pheochromocytoma, with sensitivity and specificity rates of 99% and 98%, respectively. When a plasma metanephrine measurement is not available, urine levels might be assessed (75,76) (B). CT or MRI of the abdomen should be performed to establish the localization of the pheochromocytoma. CT can identify the localization of hereditary adrenal tumors in 76% of evaluated cases (80) (B).

Adrenalectomy is indicated for the treatment of pheochromocytoma, preferably by laparoscopy after appropriate preoperative preparation and before surgery for MTC or hyperparathyroidism. The resection of the adrenal medulla (adrenal-sparing surgery), in an attempt to preserve the cortex and avoid adrenal insufficiency, should be considered in cases of bilateral pheochromocytoma (73,140) (D). A recent multicenter study involving a large number of patients with MEN 2A-associated pheochromocytoma showed that

the recurrence rate in these cases is low (3%), when performed in specialized centers (141) (B). Preparation for surgery should be individualized according to patient symptomatology. In general, it is recommended the use of alpha-blockers for 1-2 weeks to reduce systemic vasoconstriction (140) (D). Release salt intake and / or saline infusion may also be indicated for the expansion of blood volume (140) (D).

Recommendation 8

A proper investigation is needed to confirm or rule out the presence of pheochromocytoma before thyroidectomy (Recommendation B). In individuals with pheochromocytoma and MTC, adrenal surgery should precede thyroidectomy (Recommendation B).

PART III: MTC – FOLLOW-UP

1. Which tests should be performed during the postoperative follow-up of individuals with MTC?

After surgery, patients should be assessed regarding the presence of residual disease, the localization of metastases, and the identification of progressive disease.

Measurements of the serum levels of calcitonin and CEA are of paramount importance during the postoperative follow-ups of individuals with MTC because these biomarkers might indicate the presence and volume of residual disease (142) (B). However, as their nadirs might occur after several weeks (142,143) (B/C), measurements should be performed at least 2-3 months after surgery.

The specificities of immunometric assays for calcitonin measurement that use 2 monoclonal or 1 monoclonal and 1 polyclonal antibody are 95-100% (40,41) (B/A). To avoid mistakes in the interpretation of results, it should be noted that the absolute values provided by different assays might not be fully comparable. Additionally, the possibility of a hook effect or non-calcitonin-secreting tumors should be considered (false low calcitonin levels) (38,39) (C).

The calcitonin levels might decrease from 24 hours to 4 weeks after surgery, but this could also occur several months later in some cases (142,144,145) (B). Persistently high calcitonin levels might be found in patients with kidney failure or liver cirrhosis and MTC, due to an increase in the hormone half-life caused by decline of the renal or hepatic function, thus requiring a differential diagnosis with an actual increase in secretion due to a persistent thyroid neoplasm (146,147) (C/D).

In most individuals with sporadic MTC, the calcitonin levels tend to remain high due to residual disease. The likelihood of attaining undetectable calcitonin levels is 83-95% in individuals without lymph node metastases who were subjected to thyroidectomy and neck dissection, but the frequency decreases to 21-30% when neck lymph node metastases are present (9,121,148) (B).

Although also CEA behaves as a marker of MTC, its levels are not always elevated in all patients and do not systematically correlate with the calcitonin levels. The CEA levels might return to normal values after surgery, even in the presence of elevated calcitonin levels; this might be due to the presence of small residual neoplastic foci. In contrast, in individuals with progressive disease, the CEA levels might increase without a corresponding elevation in the calcitonin levels. Increased serum CEA levels are considered to indicate a poor prognosis (149) (C).

Recommendation 1

Measurements of serum calcitonin and CEA should be performed 2-3 months after surgery (Recommendation B). If normal calcitonin values are observed, these measurements should be repeated 6-12 months later. Persistently calcitonin/CEA levels are suggestive of persistent or recurrent disease. In such cases, an investigation must be continued to establish the extent of disease.

2. Which factors determine the prognosis of individuals with MTC?

The likelihood of attaining a cure for MTC mostly depends on the tumor stage at the time of diagnosis and a full surgical resection. The main factors associated with poor prognosis include an older age at diagnosis, the primary tumor size, the presence of local and distant metastases, the presence of somatic mutations, and the calcitonin doubling time (150-152) (B).

The most recent data about the 10-year survival rates for MTC are 95.6%, 75.5% and 40% for patients with tumors confined to the thyroid, local and distant metastases, respectively (12) (B), and are similar to those previously reported (100%, 93%, 71% e 21%, for stages I, II, III e IV, respectively) (153) (B). The sur-

vival rates are higher, the regional control of disease is better, and the occurrence of distant metastases is less frequent in individuals < 45 years of age (154) (B). A tumor size < 0.5 cm correlates with the absence of postoperative clinically or laboratory detectable disease (155) (B).

Stage T4b tumors and/or the presence of lymph node and/or distant metastases are associated with lower remission and survival rates (156) (B). Additionally, the localization of metastases influences the prognosis; for example, bone metastases are associated with a poorer prognosis, compared to metastases in soft tissues (11) (B).

Prophylactic thyroidectomy is indicated in all *RET* mutation carriers, and minimally invasive surgery might be considered in asymptomatic carriers. The type of *RET* mutation correlates with the biological behavior of MTC, and therefore identifying the mutation type might facilitate decision-making with respect to the most adequate age for and the extent of surgery (73,99) (D/C). The use of prophylactic surgery improves the cure rates (100) (B). In individuals with hereditary MTC, a palpable thyroid nodule and lymph node metastases at the time of diagnosis are associated with persistent disease (100) (B).

The calcitonin and CEA levels might remain steadily high for several years or might exhibit rapid and progressive increases. Serial calcitonin and CEA measurements allow a more accurate assessment of the marker levels through calculations of their doubling times (DT); these might be performed with a tool available at the ATA website (http://www.thyroid.org/thyroid-physicians-professionals/calculators/thyroid-cancer-carcinoma/). The calcitonin DT has prognostic value in individuals with MTC, as it correlates with the survival and tumor recurrence rates (157) (B). A calcitonin DT calculation requires a minimum of 4 measurements at 6-month intervals. The 5 and 10 – year survival rates are 25% and 8%, respectively, when the DT is < 6 months, and 92% and 37%, respectively, when the DT ranges from 6 months to 2 years. The prognosis was found to be even more favorable in individuals with a DT > 2 years (158) (B).

CEA is a less specific marker of MTC, and the comparison of its DT relative to that of calcitonin revealed diverging results. In one study that compared those markers in a multivariate analysis, both markers behaved as independent predictors of survival; however, the calcitonin DT had a better performance (158) (B). In contrast, according to another study, the CEA DT had a greater impact on prognosis (159) (B). Those conflicting results notwithstanding, both markers are useful and allow the identification of high-risk individuals. Therefore, when the calcitonin and CEA DTs indicate rapidly progressing disease, a more thorough assessment that includes imaging tests should be considered whenever possible to localize the disease and indicate the proper treatment.

Recently, Tuttle and Ganly (137) (D) formulated a novel approach to the assessment of postoperative MTC progression, consisting of a dynamic risk stratification similar to that developed for well-differentiated thyroid carcinomas (Table 4). An excellent response is defined as undetectable calcitonin levels after adequate surgical treatment, and the likelihood for achieving such responses is greater when the preoperative calcitonin and CEA levels are low, the primary tumor is small, there are no neck metastases, and the disease is in an early stage. Under such conditions, the 5 and 10 – year recurrence rates vary from < 1 – 8.5%, and the survival rates after surgery are 97-99% at 5 years and 95-97% at 10 years (137,160,161) (D/B/B).

Table 4. Risk stratification system for evaluation of medullary thyroid carcinoma after initial therapy

Response to initial therapy	Definitions
Excellent	No clinical, imaging or biochemical evidence of disease
Biochemical incomplete	Increased levels of tumor makers (calcitonin, CEA), without structural evidence of the disease
Structural incomplete	Persistent anatomical disease; presence distant metastases
Indeterminate	Unspecific abnormalities on imaging tests, non-normalized tumor marker levels, or no detectable evidence of anatomical disease

Incomplete responses are exhibited by 45-70% of the cases and are characterized by evidence of persistent disease after the initial treatment (73,136,137,161) (D/B/D/B). Additionally, the presence of distant metastases after the initial treatment is considered an incomplete response to the initial treatment. The 5 and 10 – year survival rates of individuals with persistently elevated calcitonin levels are 80-86% and 70%, respectively (153,161-163) (B/A). The cases with unspecific abnormalities on imaging tests, non-normalized tumor marker levels, or no detectable evidence of anatomical and biochemical disease are classified as indeterminate responses (137,164) (D/B).

Recommendation 2

The main prognostic factors of survival in individuals with MTC are age, the tumor stage at the time of diagnosis, and the calcitonin and CEA doubling times (Recommendation B). In individuals with hereditary MTC, the main prognostic factor of cure and survival is the performance of a prophylactic thyroidectomy following the identification of *RET* gene mutations (Recommendation B).

3. Which tests should be performed in individuals with persistently detectable calcitonin levels after initial surgery?

The postoperative serum calcitonin levels determine the strategies used for further assessments. Calcitonin levels < 150 pg/mL correlate with the presence of locoregional disease, but the likelihood of distant metastases is low or they are few in number (68,165) (B).

The initial assessment test is neck US. The rate of local MTC relapse might be as high as 58% (62,68,166) (B/B/D). The sensitivity of neck US for diagnosing locoregional metastases is 97%, compared to 72% with CT and 55% with positron emission tomography (PET)-CT (10) (B). When suspected metastatic lymph nodes are found, a puncture biopsy might help to elucidate the diagnosis, and the sensitivity and specificity of this test increase when calcitonin is measured in the washout fluid (22) (B). CT can identify 100% of the cases with mediastinal lymph node involvement, versus 65% with PET-CT (10) (B).

The presence of distant metastases might be investigated with CT of the neck and/or chest, MRI, bone scintigraphy, and [^{18}F]-fluorodeoxyglucose (^{18}F-FDG) PET-CT. The sensitivities of these tests for detecting metastatic disease vary from 50-80%. The likelihood of identifying metastatic disease is lower in individuals with discrete calcitonin elevation (10,167-170) (B), but high when the calcitonin levels exceed 150 pg/mL (165) (B).

The median calcitonin levels in individuals with 1 and 2-4 metastatic sites are 1,510 pg/mL and 18,450 pg/mL, respectively (165) (B). The most frequent sites of distant metastasis are the liver (49%), bones (45%), and lungs (35%) (10) (B). The sensitivities of CT and US for diagnosing liver metastases are similar (90% and 85%, respectively), but lower than that of MRI (100%) (10) (B). Bone scintigraphy is indicated for investigating low-mechanical risk lesions (ribs, sternum, clavicles, and skull), and axial skeleton MRI is indicated for high-mechanical risk lesions (spine, pelvic bones, and long bones). CT is the most accurate method for diagnosing lung metastases. Therefore, the best test combination for detecting distant metastases includes chest CT, liver MRI, and bone scintigraphy and/or axial skeleton MRI (10) (B).

Experiences with the use of [^{18}F]-dihydroxyphenylalanine (^{18}F-DOPA) PET in metastatic MTC remain limited. This method has a sensitivity rate of 63% and might be used to investigate metastases in cases of slowly progressive MTC (168,171) (B). Metaiodobenzylguanidine (MIBG) scintigraphy might be useful in some cases, while somatostatin receptor scintigraphy is an additional option when the serum calcitonin levels are > 800 pg/mL (172) (B).

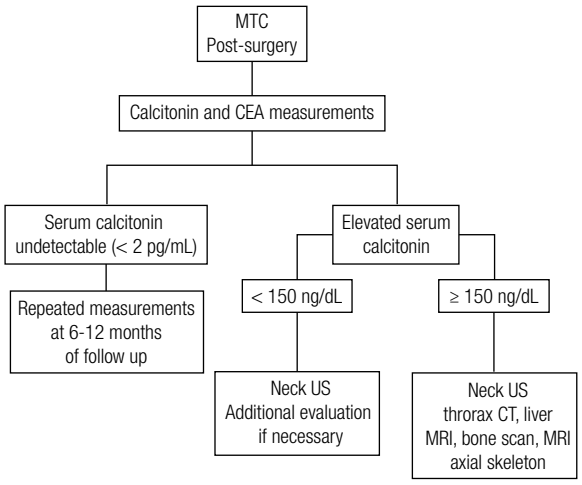
In individuals with high calcitonin levels and negative imaging tests, ^{18}F-FDG PET-CT had sensitivity, specificity, and diagnostic accuracy rates of 88%, 84.6%, and 87%, respectively, for the detection of occult recurrences of MTC (173) (B). In a comparison of ^{18}F-FDG, ^{18}F-DOPA, and ^{68}Ga-somatostatin analogue PET-CT in individuals with recurrent MTC, the metastatic lesion detection rates were 28%, 85%, and 20%, respectively. According to those data, ^{18}F-DOPA PET-CT seems to be the most useful method for detecting MTC recurrences in individuals with elevated serum calcitonin levels (174) (B). However, other studies showed no significant differences between PET ^{18}F-DOPA and ^{18}F-FDG in the same population (175) (B).

Recommendation 3 (Flowchart 2)

Basal calcitonin levels < 150 pg/mL are associated with the presence of locoregional disease, and neck US should be the first test used in the assessment (Recommendation B). The likelihood of detecting distant metastases is higher among patients with calcitonin levels > 150 pg/mL. In such cases, chest CT, abdominal MRI, and bone scintigraphy should be performed to establish the presence of mediastinal and lung, liver, and bone metastases, respectively (Recommendation B).

4. Which tests should be performed during the follow-up of individuals with undetectable calcitonin levels after surgery?

Serum calcitonin is the most sensitive marker of residual MTC after surgery. According to some studies, the calcitonin levels are below the threshold of detection in 100% of the individuals subjected to total



Flowchart 2. Evaluation of patients with medullary thyroid carcinoma post-surgery.

thyroidectomy (176) (B). The likelihood of residual/recurrent disease in individuals with undetectable basal and post-pentagastrin stimulation calcitonin levels after surgery was reported to be approximately 3% (125) (B).

The likelihood that calcitonin levels will become undetectable after total thyroidectomy is 95% in individuals with thyroid gland-restricted disease. The presence of neck metastases reduces the likelihood that calcitonin will return to normal values to 30% (9). Although the average time for the recurrence of MTC is 3.2 ± 2.2 years, the calcitonin levels should be measured every 6-12 months for a still-undefined period of time, including after they have become undetectable after surgery, due to the risk of disease relapse (125) (B).

It is worth observing that a few cases of individuals with advanced MTC and normal serum calcitonin levels were reported (39,177) (C). Those patients' follow-ups should include imaging modalities. Measurements of the calcitonin levels in the FNAB washout fluid might facilitate the proper diagnoses of suspected MTC metastatic lesions (22,23) (B/C).

Recommendation 4

Measurements of serum calcitonin levels should be performed every 6-12 months for a still-undefined period of time in individuals with undetectable levels after surgery due to the risk of disease relapse (Recommendation B). Measurements of the calcitonin level in the FNAB washout fluid might facilitate the diagnoses of suspected lesions (Recommendation B).

5. When is the pentagastrin or calcium stimulation test for calcitonin indicated in patients already subjected to surgery?

In some individuals with undetectable basal calcitonin levels, pentagastrin and/or calcium stimulation might increase these levels, thus indicating the presence of residual disease. However, the localization of residual disease is very difficult to establish with imaging methods in the vast majority of such cases (134,176,178) (B/B/C). Further disadvantages associated with these stimulation tests are their costs, side effects, and the unavailability of pentagastrin in Brazil.

Recommendation 5

The pentagastrin/calcium stimulation test is not indicated for the follow-up of individuals with undetectable basal serum calcitonin, as positive results denote residual diseases that are difficult to locate with imaging methods (Recommendation B).

6. What should comprise the management of patients with persistently detectable calcitonin levels after primary surgery?

Curative reoperation (to achieve undetectable serum calcitonin levels) is indicated in individuals who exhibit evidence of persistent disease due to an incomplete primary surgery or a disease recurrence in the neck. The presence of inoperable distant metastases should be ruled out before a cervical reoperation is considered. Surgery might also have palliative indications in cases with the risk of compression or invasion of the trachea or the great vessels (179) (D). Expectant management, including periodical clinical and laboratory assessments, is indicated in cases of indolent disease that have already been subjected to appropriate surgical treatments (179) (D). Follow-up measurements of serum calcitonin in individuals with MTC might determine the later management.

Discrete increases in the calcitonin levels (< 150 pg/mL) at 2-3 months after surgery are associated with locoregional disease or small distant metastases in most cases (68,165) (B). When residual or recurrent disease is detected in the neck, surgical reintervention should be considered. The rates of calcitonin normalization after cervical reoperation vary from 16-38% (180-184) (B). A retrospective study found that reoperation allowed the identification of residual disease in the lateral lymph nodes in 64% of cases, in the central compartment in 22%, and in the anterior medi-

astinum in 14% of cases. The serum calcitonin levels returned to normal in only 6% of the investigated individuals; however, the remainder of the sample exhibited 50% reductions or stabilization of the calcitonin levels (181) (B). Another study followed up individuals who were subjected to reoperation for MTC over a period of 8-10 years and found calcitonin levels < 10 pg/mL in 26% of the participants and < 100 pg/mL in an additional 20.4% of patients. Disease could not be detected with imaging methods in any of those individuals (184) (B).

Although reoperation might reduce the disease progression in selected individuals, a biological cure of MTC is seldom achieved in such cases. For that reason, the surgical approach to recurrent or persistent MTC in individuals with no or minimal distant metastases should include dissection of the affected central (level VI) or lateral (levels IIA, III, IV, and V) compartments. Expectant management is recommended for cases in which the anatomical localization of the metastases cannot be established (179).

Significantly elevated calcitonin levels (> 150 pg/mL) at 2-3 months after surgery are usually associated with the presence of distant metastases, and the higher the calcitonin level, the higher the likelihood of identifying the lesion localization (185) (B). As a rule, the management of individuals with calcitonin levels > 150 pg/mL is similar to that of patients with lower levels (186) (D).

The therapeutic strategy for individuals with locoregional and distant metastases should be decided on an individual basis, while considering the indolent course of MTC and the morbidity associated with the available treatments. The presence of neck lymph nodes < 1 cm and asymptomatic distant metastases does not suggest a need for intervention, as treatment has not proven beneficial in such cases. Possible therapeutic options include surgery, percutaneous interventions, liver metastasis embolization, radiotherapy, and tyrosine-kinase inhibitors (187) (D). It is worth observing that the likelihood of a cure in individuals with distant metastases is minimal. The relative risks and benefits of any procedure should be carefully assessed when deciding whether palliative therapy or watchful waiting is indicated.

Recommendation 6

Serum calcitonin is the most relevant biomarker for the follow up individuals with MTC (Recommendation B). Discrete increases in the calcitonin levels (< 150 pg/mL) usually denote the presence of locoregional disease (Recommendation B). More substantial elevations (> 150 pg/mL) are suggestive of distant metastases (Recommendation B). The best methods for investigating metastases are US for the neck, CT for the chest, MRI for the liver, and bone scintigraphy and/or axial skeleton MRI for the bones (Recommendation B).

A new surgical procedure should be considered in presence of residual or recurrent local disease (Recommendation B). In patients with distant metastases, the treatment strategy should be individualized, taking into consideration the indolent course of CMT and the morbidity associated with available therapies (Recommendation D).

7. What is the appropriate management for individuals with increased calcitonin levels and negative imaging tests?

Individuals with detectable calcitonin levels after surgery should be assessed with imaging methods to locate the disease site. When imaging tests fail to identify the disease foci, the patients should be subjected to periodical assessments at intervals determined by the calcitonin and CEA DT, as these are markers of disease progression (158,165) (B). To calculate the DTs, the serum calcitonin and CEA levels should be measured every 6 months, and the ideal interval for assessments of individuals with MTC corresponds to one-fourth of the DT or each year, whichever is shorter.

Recommendation 7

Individuals with elevated serum calcitonin levels and negative imaging tests should be assessed at least every 6 months, and these assessments should include measurements of the calcitonin and CEA levels to calculate their DTs (Recommendation B).

8. What should comprise the treatment of individuals with MTC and distant metastases?

The following questions should be considered during decision-making, with respect to the best management of individuals with metastatic MTC:

- Is the patient symptomatic or asymptomatic?
- Where are the metastases located?
- Are there lesions that require intervention due to imminent risk or associated symptoms (*e.g.*, brain lesions, painful bone lesions or those with a risk of fracture, or chest pain and the risk of bronchial obstruction)?

- Is the locoregional disease controlled?
- What is the speed of metastatic disease progression?

The treatment of distant metastases is indicated in cases associated with an imminent risk of serious complications such as brain metastases, lesions that cause spinal cord compression or airway affection, hormone-secreting metastases, or bone metastases that exhibit an active or imminent risk of fracture. Expectant management might be indicated in asymptomatic individuals who exhibit small indolent metastases. Patients with rapidly progressive disease, as evidenced by imaging or laboratory testing, are candidates for systemic novel drug treatment.

The disease progression speed might be assessed from the calcitonin and CEA DTs or imaging results that have been interpreted according to the Response Evaluation Criteria In Solid Tumors (RECIST), in which increases > 20% in the sum of the lesions' diameters are classified as progressive disease (158,165,188) (B).

Recommendation 8

Systemic treatment should be considered for symptomatic individuals and/or those with documented significant disease progression (according to radiological methods and/or a calcitonin or CEA DT < 6 months) (Recommendation B).

9. What should comprise the treatment of individuals with hormone-secreting metastases?

The ectopic production of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) and the secretion of VIP, insulin, and glucagon were described in individuals with MTC (52,53,189,190) (B/B/D/C).

Diarrhea might appear due to increased intestinal motility (191) (C) or the hypersecretion of calcitonin and/or VIP (52,192) (B/C). According to recommendations, treatment should initially include antimotility agents (loperamide or codeine). Further options for unsuccessful cases include the use of somatostatin analogues (193-195) (B) and the selective resection or arterial chemoembolization of liver metastases to reduce the hypercalcitonemia caused by those lesions (196,197) (B/C).

MTC comprises 2-6% of ectopic Cushing's syndrome cases (198,199) (B/C), and treatment might include surgery or chemoembolization for liver metastases. Additionally, adrenolytic drugs (ketoconazole, milotane, or metyrapone) might be used, while bilateral adrenalectomy is indicated in uncontrolled cases (198-200) (B/C/C). Recently, it has been reported a sorafenib-induced reduction of cortisol and ACTH levels, associated with dramatic clinical improvement, in a patient with advanced MTC and ectopic ACTH syndrome (201) (C).

Recommendation 9

Advanced MTC metastatic disease might be attended by systemic hormonal changes secondary to the increased calcitonin levels and/or the ectopic production of some specific hormones. Treatment should be planned on an individual basis according to the clinical manifestations of the existing dysfunction (Recommendation B).

10. What are the indications for chemotherapy and/or radiotherapy in the management of individuals with metastatic MTC?

Radiotherapy

The role of radiotherapy in the treatment of MTC is rather limited (202-204) (B/B/D). In individuals at a high risk of local recurrence (locally invasive tumors, microscopic residual disease, and neck lymph node involvement), radiotherapy was shown to reduce the local recurrence rate in 86% of patients at a 10 – year follow-up (205) (B).

The indication for radiotherapy in systemic metastatic disease is restricted to the palliative treatment of painful bone metastases or those at risk of fracture, as described for bone metastases secondary to other types of tumors (206) (B), and to the treatment of hemoptysis or airway obstruction in individuals with extensive mediastinal and/or lung involvement (204,207) (D/C).

Systemic chemotherapy

The results of studies of single or combined chemotherapy agents have not been satisfactory. No phase III studies with large numbers of patients have been conducted. A combination of doxorubicin, dacarbazine, and streptozocin induced partial responses in 15% of a sample of individuals with MTC (208,209) (B). Additionally, the results were limited in studies that used cyclophosphamide, vincristine, cisplatin, and bleomycin (208,210-212) (B). Therefore, as conventional

chemotherapy has not been effective, it is exclusively recommended for selected individuals with rapidly progressive metastatic disease.

Recommendation 10

Radiotherapy should be considered for local disease control (Recommendation B), the palliative treatment of painful bone metastases or those at risk of fracture (Recommendation B), and for the treatment of hemoptysis or airway obstruction in individuals with extensive mediastinal and/or lung involvement (Recommendation D). The effects of conventional chemotherapy are limited, and thus it should only be considered in selected cases (significant progression of the tumor mass) (Recommendation B).

11. What new drugs are available for the management of individuals with metastatic MTC?

In recent years, cumulative knowledge about the molecular mechanisms and intracellular signaling pathways involved in the pathogenesis of neoplasms such as MTC has allowed the development of novel targeted therapies.

Uncontrolled tyrosine-kinase receptor activation is one of the main mechanisms involved in cancer development and progression (213,214) (D). Vascular endothelial growth factor (VEGF) performs critical functions in physiological and pathological angiogenesis, as well as in lymphangiogenesis (215) (D). Inhibition of VEGF action by blocking its receptors represents a novel approach to anticancer therapy (213,216,217) (B/D/D). Recent studies conducted with novel drugs that inhibit VEGF and its receptors in thyroid tumors yielded satisfactory results (218). In addition to VEGF, MTC pathogenesis also involves the presence of somatic or germline mutations in the *RET* proto-oncogene. *RET* comprises 21 exons and encodes a tyrosine-kinase receptor that is expressed in neural crest-derived cells (2,4) (D). Therefore, the use of drugs with anti-tyrosine kinase activities represents a novel therapeutic option for MTC management.

The initial results of clinical studies that used novel drugs such as tyrosine-kinase inhibitors to treat MTC were published in 2008 (www.clinicaltrials.gov). Clinical trials that employ such agents use RECIST to assess the responses to treatment as follows: complete response (disappearance of all target lesions), partial response (at least a 30% reduction in the sum of the longest target lesion diameters), progressive disease (at least a 20% increase in the sum of the longest target lesion diameters), and stable disease (neither sufficient shrinkage to qualify as a partial response nor sufficient increase to qualify as progressive disease) (219) (D).

Overall, the partial response rate is approximately 30%, whereas stable disease is the most commonly achieved outcome. Two tyrosine-kinase inhibitors have been approved by the FDA (U. S. Food and Drug Administration) to treat rapidly progressive metastatic MTC, specifically vandetanib and cabozantinib (http://www.fda.gov/); however, only the former has been approved in Brazil.

Vandetanib is an oral agent that selectively targets the RET receptor, VEGF receptors (VEGFR), and the epidermal growth factor receptor (EGFR) (220,221) (D/D). A phase III clinical trial assessed the efficacy of vandetanib in 331 individuals with metastatic MTC who were randomized to receive vandetanib (300 mg) or a placebo. The results showed a significant increase in progression-free survival in the vandetanib-treated group, compared to the placebo group (30.2 *vs.* 19.2 months, respectively; hazard risk (HR) = 0.46, 95% confidence interval (CI) = 0.31-0.69). The rate of mortality at 2 – year follow-up was 15% (222,223) (B). Another Phase II clinical study evaluated 19 patients using a reduced dose of vandetanib (100 mg/d). In this small group of patients, vandetanib used was associated with decreased progression-free survival with fewer adverse effects (224) (B). This same dose (100 mg/d) was also successfully used in children with MEN 2B (225) (B). A recent systematic review on the use of vandetanib in MTC indicates the medication in patients with loco regional disease unresectable, symptomatic distant metastatic disease and disseminated metastatic disease (226) (B). Preclinical studies have indicated that *RET* codon 804 mutations (V804L, V804M) induce resistance to vandetanib (227) (B).

Cabozantinib (XL184) is a powerful inhibitor of the hepatocyte growth factor receptor (MET), VEGFR2, and RET. A multicenter randomized study of 300 individuals with documented MTC progression during the previous 14 months found a significant increase in progression-free survival in the cabozantinib-treated group (140 mg/d), compared to the placebo group (11.2 *vs.* 4.0 months, respectively; RR = 0.28, 95% CI = 0.19-0.40, $p < 0.0001$) (228,229) (B).

The effect of vandetanib or cabozantinib on the survival rate of MTC patients remains unknown, but interim analyses of the overall survival did not show a difference between the study drug-treated and placebo groups (222,228) (B/B).

Table 5 summarizes the main available drugs, as well as their corresponding targets and outcomes (222,228-242) (B/B/B/C/B/C/B/C/C/B/C/B/C/C/B/C).

The most common side effects of the tyrosine-kinase inhibitors include diarrhea, nausea, skin rash, hypertension, and fatigue (243) (D). Additionally adverse events include neutropenia, leukopenia, hand-foot syndrome, stomatitis, proteinuria, abdominal pain, face swelling, thrombocytopenia and QTc prolongation – it is suggested that patients be monitored by conducting periodic electrocardiograms. The levothyroxine dose for replacement therapy usually needs to be increased. As a rule, the side effects of these inhibitors are well tolerated, and toxicity is controllable in most individuals. Nevertheless, severe adverse events have also been reported, including aspiration pneumonia, respiratory failure, septicemia, acute heart failure, and arrhythmia (222,231,236,244-248) (B/B/B/B/C/C/B/C).

Other therapeutic approaches for metastatic MTC are currently being investigated, including anti-CEA antibody-targeted radiotherapy, gene therapy, and other radiopharmaceuticals. Currently, such medications are only used in research protocols (249,250) (D/D).

Recommendation 11

The results reported to date indicate that tyrosine-kinase inhibitors represent a relevant therapeutic option for the treatment of locally advanced or metastatic MTC (Recommendation A). Nevertheless, the corresponding data regarding long-term survival are not yet available. As a function of their side effect profiles, caution is required when identifying patients who might benefit from these drugs (Recommendation D). Currently, two tyrosine-kinase inhibitors, vandetanib and cabozantinib, have been approved by the FDA for the treatment of rapidly progressive metastatic MTC, while only the former has been approved in Brazil.

12. What should comprise the management of distant metastases?

Bone metastases

The incidence of bone metastases in thyroid carcinoma is approximately 5.0%, with median survival time after metastasis of 5.3 ± 1.3 years; patients with hypercalcemia have lower survival (251) (B). The term skeletal-related event (SRE) is used to quantify the morbidity associated with bone metastases. The clinical determinants that compose the SRE include spinal cord compression, pathologic fractures, and the need for external radiotherapy or surgery to afford pain relief or control tumor-related hypercalcemia. Imaging exams are essential to determine the location and extent of the bone lesions; skeletal CT or MRI and FDG-PET/CT are the best currently available methods (10,252) (B/D)

The management of bone metastases depends on their number, localization and associated symptoms. If the disease is localized, surgical resection significantly improves patient prognosis and survival, and may be curative (253) (D). Spinal cord compression indicates emergency surgery and the use of systemic corticosteroids. Active or imminent fractures in body-supporting bones require surgical treatment. Radiotherapy is useful

Table 5. Tyrosine kinase inhibitors for treatment of medullary thyroid carcinoma

Drugs approved	Targets	Patients (n)	Dose[a]	PFS drug *vs.* Placebo (months)	Hazard Ratio[b]	References
Vandetanib (ZD6474)	VEGFR-1, VEGFR-2, VEGFR-3, RET, EGFR	331	300 mg	30.5 *vs.* 19.3	0.46	222
Carbozantinib (XL 184)	VEGFR-2, RET, MET	330	140 mg	11.2 *vs.* 4.0	0.28	228,229
Investigational drugs	**Targets**	**Patients (n)**	**Dose[a]**	**Partial response (%)**	**Stable Disease[c] (%)**	**References**
Montesanib (AMG 706)	VEGFR-1, VEGFR-2, VEGFR-3, C-KIT, RET, PDGFR	91	125 mg	2	48	230,231
Sorafenib (BAY 43-9006)	VEGFR-2, VEGFR-3, c-Kit, RET	21	400 mg	6	50	232,233
Sunitinib (SU 11248)	VEGFR-1, VEGFR-2, VEGFR-3, RET, c-Kit	7	37,5 mg	28	46	234,235,236
Axitinib (AG-013736)	VEGFR-1, VEGFR-2, VEGFR-3, c-Kit	11	5 mg	18	27	237,238
Imanitib (STI571)	RET, c-Kit, PDGFR	9	600 mg	0	55	239,240
		15	600 mg	0	27	241

a. The drugs were used once daily, except for the treatment with sorafenib; axitinib were administered twice daily.
b / c. Results are expressed as hazard ratio of objective response (b; drug *vs.* placebo) and rate of disease control (c).

for painful bone metastases, when surgery is contraindicated, or if resection was incomplete (252,253) (B/D).

The indication of bisphosphonates given per the intravenous route for the control of bone metastasis-related pain has been well established in other solid and hematological malignancies (254-256) (B). One recent study showed that zoledronic acid could effectively reduce skeletal-related events, including bone fractures, spinal cord compression, and hypercalcemia in individuals with differentiated thyroid carcinoma and bone metastases (257) (B).

Liver metastases

The liver is the most frequent site of MTC metastases. The overall survival of patients with liver metastases who underwent radiofrequency ablation was 6 years (258) (B). The lesions are usually multiple and disseminated (259) (B). Treatment should be considered for large or progressive lesions, as well as for those associated with the occurrence of diarrhea and/or pain. The available options for treatment include chemoembolization (40-60% achieve partial response/disease stabilization) and tyrosine kinase inhibitor therapy for progressive disease (197,243) (C/D).

Lung and mediastinal metastases

Mediastinal lymph node involvement is frequent in advanced MTC, and its presence usually indicates an incurable disease. Therefore, when the lymph node affection is stable and not associated with clinical manifestations, expectant management is indicated, and the patients should be monitored with imaging methods and measurements of the calcitonin/CEA levels (188) (B).

When airway compression or bleeding occur, surgery, radiotherapy, or radiofrequency ablation should be considered for the management of lung and/or mediastinal metastases (260) (D).

Brain metastases

Individuals with isolated brain metastases are candidates for surgical resection. Radiotherapy might be considered if surgery is not possible (261-263) (B).

Recommendation 12

The currently available treatments for individuals with distant metastases of MTC, which include surgery, chemotherapy, radiotherapy, and tyrosine-kinase inhibitors, are palliative and might be indicated in selected cases to control the disease progression or to improve the patient's quality of life.

13. When are radioactive iodine treatment and/or levothyroxine suppressive therapy indicated in individuals with MTC?

Unlike differentiated thyroid cancer, which originates in the follicular cells, MTC originates in the C or parafollicular cells; therefore, radioactive iodine treatment and/or levothyroxine suppressive therapy are not indicated for MTC management (73) (D). In recent studies, the use of radioactive iodine did not show any effects relevant to the postoperative management of individuals with MTC (264) (B).

Recommendation 13

Neither radioactive iodine treatment (Recommendation B) nor levothyroxine suppressive therapy is indicated in MTC (Recommendation B).

SUMMARY OF RECOMMENDATIONS

To summarize, the main recommendations for the diagnostic assessment, treatment, and follow-up of MTC are as follows:

PART I: MTC – DIAGNOSIS

1. A thyroid nodule is the most common clinical manifestation of MTC. MTC should be specifically suspected in individuals with family history of MTC, *RET* mutations or associations with pheochromocytoma, hyperparathyroidism, cutaneous lichen amyloidosis, Marfanoid habitus, or mucosal neuromas.
2. FNAB should be included in assessments of thyroid nodules suspected of MTC. The differential diagnosis might be facilitated by the use of additional techniques such as the measurement of calcitonin in the FNAB washout fluid and immunocytochemistry.
3. MTC screening via a serum calcitonin measurement in individuals with thyroid nodules remains controversial. Because of problems with reference value standardization and its doubtful cost-effectiveness, the measurement of serum calcitonin is not indicated in the routine investigation of thyroid nodules.

4. The preoperative calcitonin levels correlate with the tumor size and the presence of local or distant metastases. The individuals with suspected MTC and calcitonin levels > 150 ng/mL must be investigated for the presence of locoregional and distant metastases by imaging tests (**Flowchart** 1).
5. Neck US is indicated in all individuals with suspected MTC (Recommendation B). In addition to identifying characteristics suggestive of malignancy in the thyroid nodules and allowing the performance of US-guided FNAB, US is the most sensitive test for detecting neck metastases and thus contributes to therapeutic planning.
6. In individuals with neck metastases and/or calcitonin levels > 400 mg/mL, the presence of distant metastases should be investigated before surgery. The presence of pheochromocytoma must be investigated by the measurement of plasma fractionated metanephrines or urine metanephrine levels, if not available the blood measurement. The presence of hyperparathyroidism might be investigated through a serum calcium level measurement after adjusting for the albumin concentration.
7. A molecular assessment is indicated for all individuals with C cell hyperplasia, (familial or apparently sporadic) MTC, and/or MEN 2. The molecular diagnosis might guide the choice of therapeutic procedures might guide the choice of therapeutic procedures and could consequently change the natural course of disease, indicate genetic counseling, and help to establish the disease prognosis.
8. All first-degree relatives of individuals with MTC and germline RET mutations should be subjected to molecular screening.
9. The knowledge of the type of RET mutation provides relevant information about the clinical presentation of MEN 2 and the biological behaviors of the associated neoplasms
10. The presence of CLA or Hirschsprung's disease indicates the suspected occurrence of hereditary MTC and therefore the need to perform a RET molecular assessment.
11. In asymptomatic cases or in the absence of adrenal masses, urine and/or fractionated plasma metanephrines measurements should begin at 8 years of age in individuals with MEN 2B or 2A who carry mutations in codons 630 or 634, and after 20 years of age in the remainder of individuals with MEN 2A. Hyperparathyroidism screening must be performed annually by measuring the total calcium and albumin levels, starting at 8 years age in carriers of mutations in RET codons 630 and 634 and at 20 years of age in the remainder of individuals with MEN 2A.

PART II. MTC – SURGICAL TREATMENT

1. The surgical treatment recommended for individuals with MTC limited to the thyroid gland is total thyroidectomy and elective dissection of the central compartment.
2. In cases with locoregional disease, total thyroidectomy with central compartment lymph node dissection is indicated (B). Lateral lymph node dissection is indicated when metastases are present or suspected (B). Less aggressive surgery is indicated in cases with advanced local disease and/or distant metastases to achieve local disease control while preserving the patient's voice, deglutition, and parathyroid function.
3. In cases with a postoperative MTC diagnosis, completion thyroidectomy and prophylactic central dissection are indicated. Watchful waiting might apply to selected individuals.
4. In cases without preoperative hyperparathyroidism, the "*in situ*" preservation of the parathyroid glands is always desirable. When the glands are accidentally removed or there is a risk of devascularization, the glands should be autografted into the sternocleidomastoid muscle. In cases with hyperparathyroidism, MEN 2A, or prior surgery for MTC, the affected parathyroid gland should be identified with imaging methods to decide upon a subtotal or total parathyroidectomy, followed by a forearm autograft.
5. The surgical approach in asymptomatic carriers *RET* proto-oncogene mutations should consider the risk stratification according to the affected codon, as follows:

   – Group D (MEN 2B): total thyroidectomy within the first year of life. In cases with evidence of lymph node metastases, nodule sizes >

5 mm, or serum calcitonin levels > 40 pg/mL, central compartment dissection is also indicated. Individuals older than 1 year of age are indicated for (elective) "prophylactic" central dissection.

– **Group C**: total thyroidectomy before 5 years of age.

– **Groups A and B**: total thyroidectomy after 5 years of age in the absence of evidence of MTC (normal serum calcitonin levels and neck US). Contrariwise, surgery should be performed before 5 years of age.

Individuals in groups A, B, and C should be subjected to central compartment dissection when there is clinical and/or imaging evidence of metastatic disease, the nodule size is ≥ 5 mm, and the serum calcitonin level is > 40 pg/mL (D).

6. Individuals with advanced local disease or distant metastases should be subjected to less aggressive surgeries aimed at achieving local disease control while preserving the patient's voice, deglutition, and parathyroid functions, as well as avoiding hemorrhagic complications due to the invasion of vascular structures (D).
7. Elective superior mediastinal dissection is usually performed during surgery for MTC. The dissection of the lower mediastinum should be considered only as a palliative treatment in patients with high risk of airway obstruction or bleeding.
8. In individuals with pheochromocytoma and MTC, adrenalectomy should precede thyroidectomy. Therefore, the presence of pheochromocytoma should be established or ruled out before thyroid surgery is performed.

PART III. MTC – FOLLOW-UP

1. Serum calcitonin and CEA levels should be measured 2-3 months after surgery. Once the calcitonin levels normalize, this measurement should be repeated after 6-12 months. Persistently elevated calcitonin/CEA levels are suggestive of disease persistence or recurrence and indicate the need for further investigation to establish the disease extension.
2. The main prognostic factors of survival in individuals with MTC are age, the tumor stage at the time of diagnosis, and the calcitonin and CEA doubling times. In individuals with hereditary MTC, the main prognostic factor of cure and survival is the performance of a prophylactic thyroidectomy following the identification of RET gene mutations.
3. Basal calcitonin levels < 150 pg/mL are associated with the presence of locoregional disease, and neck US should be the first test used in the assessment. The likelihood of detecting distant metastases is higher among patients with calcitonin levels > 150 pg/mL. In such cases, chest CT, abdominal MRI, and bone scintigraphy should be performed to establish the presence of mediastinal and lung, liver, and bone metastases, respectively.
4. Measurements of serum calcitonin levels should be performed every 6-12 months for a still-undefined period of time in individuals with undetectable levels after surgery due to the risk of disease relapse. Measurements of the calcitonin level in the FNAB washout fluid might facilitate the diagnoses of suspected lesions.
5. The pentagastrin/calcium stimulation test is not indicated for the follow-up of individuals with undetectable basal serum calcitonin, as positive results denote residual diseases that are difficult to locate with imaging methods.
6. Serum calcitonin is the most relevant biomarker for the follow up individuals with MTC. Discrete increases in the calcitonin levels (< 150 pg/mL) usually denote the presence of locoregional disease. More substantial elevations (> 150 pg/mL) are suggestive of distant metastases. The best methods for investigating metastases are US for the neck, CT for the chest, MRI for the liver, and bone scintigraphy and/or axial skeleton MRI for the bones.
7. Individuals with elevated serum calcitonin levels and negative imaging tests should be assessed at least every 6 months, and these assessments should include measurements of the calcitonin and CEA levels to calculate their DTs.
8. Systemic treatment should be considered for symptomatic individuals and/or those with documented significant disease progression (according to radiological methods and/or a calcitonin or CEA DT < 6 months).

9. Advanced MTC metastatic disease might be attended by systemic hormonal changes secondary to the increased calcitonin levels and/or the ectopic production of some specific hormones. Treatment should be planned on an individual basis according to the clinical manifestations of the existing dysfunction.
10. Radiotherapy should be considered for local disease control, the palliative treatment of painful bone metastases or those at risk of fracture, and for the treatment of hemoptysis or airway obstruction in individuals with extensive mediastinal and/or lung involvement. The effects of conventional chemotherapy are limited, and thus it should only be considered in selected cases (significant progression of the tumor mass).
11. The results reported to date indicate that tyrosine-kinase inhibitors represent a relevant therapeutic option for the treatment of locally advanced or metastatic MTC (Recommendation A). Nevertheless, the corresponding data regarding long-term survival are not yet available. As a function of their side effect profiles, caution is required when identifying patients who might benefit from these drugs (Recommendation D). Currently, two tyrosine-kinase inhibitors, vandetanib and cabozantinib, have been approved by the FDA for the treatment of rapidly progressive metastatic MTC, while only the former has been approved in Brazil. Advanced metastatic MTC might be associated with systemic hormonal changes consequent to increased calcitonin levels and/or the ectopic production of specific hormones. Treatment should be established on an individual basis according to the clinical manifestations of the existing dysfunction.
12. The currently available treatments for individuals with distant metastases of MTC, which include surgery, chemotherapy, radiotherapy, and tyrosine-kinase inhibitors, are palliative and might be indicated in selected cases to control the disease progression or to improve the patient's quality of life.
13. Neither radioactive iodine treatment nor levothyroxine suppressive therapy is indicated in MTC.

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