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REVIEW

Management of hereditary medullary thyroid carcinoma

Theodora Pappa[1,2] · **Maria Alevizaki**[2]

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Abstract Hereditary medullary thyroid carcinoma (MTC) represents up to one-third of MTC cases and includes multiple endocrine neoplasia syndrome type 2A (and its variant familial MTC) and 2B. The aim of this paper is to provide an overview of the disease focusing on the management of hereditary MTC patients, who have already developed tumor, as well as discuss the recommended approach for asymptomatic family members carrying the same mutation. A PubMed search was performed to review recent literature on diagnosis, genetic testing, and surgical and medical management of hereditary MTC. The wide use of genetic testing for *RET* mutations has markedly influenced the course of hereditary MTC. Prophylactic thyroidectomy of *RET* carriers at an early age eliminates the risk of developing MTC later in life. Pre-operative staging is a strong prognostic factor in patients, who have developed MTC. The use of recently approved tyrosine kinase inhibitors (vandetanib, cabozantinib) holds promising results for the treatment of unresectable, locally advanced, and progressive metastatic MTC. Genetic testing of the *RET* gene is a powerful tool in the diagnosis and prognosis of MTC. Ongoing research is expected to add novel treatment options for patients with advanced, progressive disease.

Keywords Medullary thyroid carcinoma · *RET* gene mutation · Familial medullary thyroid carcinoma

✉ Maria Alevizaki
mani@otenet.gr

[1] Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, The University of Chicago, Chicago, IL, USA

[2] Endocrine Unit, Department of Medical Therapeutics, Alexandra Hospital, Athens University School of Medicine, 80 Vassilissis Sofias Avenue, 11528 Athens, Greece

Introduction

Medullary thyroid carcinoma (MTC) is a form of thyroid cancer originating from the neural crest-derived parafollicular cells (C-cells) of the thyroid gland, which secrete calcitonin (CT). It represents 1–2 % of all thyroid malignancies. MTC was first described by Hazard et al., who reported a series of patients harboring a thyroid solid tumor with non-follicular histology, amyloid deposits in the stroma, fibrosis, multicentricity, and a high rate of lymph node metastases [1]. MTC occurs sporadically in approximately 70–75 % of cases, and in a hereditary form as part of multiple neoplasia syndromes (MEN) type 2, including MEN2A [and its variant familial MTC (FMTC)] and MEN2B, in the remaining cases. Compared to sporadic disease, hereditary MTC is frequently bilateral, multifocal, and associated with C-cell hyperplasia.

The aim of this review is to provide an update on the standard practice for hereditary MTC focusing mainly on the management of the disease that involves not only the patient, but also the entire family, and to highlight the value of genetics in the long-term care of hereditary MTC patients. The recently released guidelines of the American Thyroid Association (ATA) for the management of MTC will also be discussed [2].

Genetics and pathophysiology of hereditary MTC

The locus of *RET* proto-oncogene is on the long arm of chromosome 10 (10q11.2) [3]; it spans 21 exons and encodes a tyrosine kinase transmembrane receptor (Fig. 1). The receptor has three domains: an extracellular domain, which binds to the ligand (ECD) and includes a cadherin-like region, a calcium-binding site and a cysteine-rich

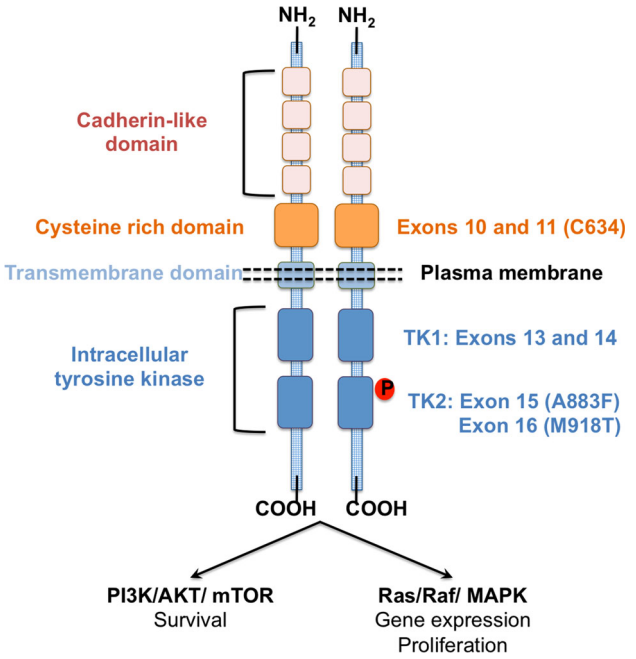

Fig. 1 Structure of the RET tyrosine kinase receptor and location of commonly mutated *RET* exons. *TK* tyrosine kinase domain, *P* phosphorylation site, *PI3K* phosphatidylinositol 3-kinase, *AKT* protein Kinase B, *mTOR* mechanistic target of rapamycin, *MAPK* mitogen-activated protein kinase

region important for dimerization, a hydrophobic transmembrane domain (TD) and an intracellular component with two tyrosine kinase domains, that mediate the downstream signaling pathway (Fig. 1).

RET dimerization is a prerequisite for the auto-phosphorylation of the tyrosine residues and, subsequently, the activation of the receptor. Germline *RET* gain-of-function mutations are responsible for hereditary MTC; mutations in the cysteine-rich region result in ligand-independent dimerization of the mutant receptor and constitutive activation of the tyrosine kinase. Mutations occurring in the transmembrane domain induce non-covalent interactions bringing RET monomers in closer proximity. Lastly, mutations in the tyrosine kinase domain lead to conformational change of its catalytic core activating the RET cascade without dimerization.

A significant body of literature has demonstrated the superiority of genetic testing compared to screening based only on phenotype and CT levels as the first step in the diagnosis of hereditary MTC [4]. The widespread use of genetic testing has facilitated early diagnosis and intervention in hereditary MTC, which are important determinants of a favorable outcome. Furthermore, it allows the correct classification of an MTC case as sporadic or hereditary. In a recent study, Romei et al. demonstrated that 7 % of apparently sporadic cases (with negative family history and no other endocrinopathies) were re-classified as having hereditary MTC following genetic screening for germline *RET* mutations [5]. Family members of the hereditary MTC patients were also tested and 30 % of them were found to be carriers of the same *RET* mutation. Depending on the result of the genetic testing, they received counseling regarding their risk to develop MEN2 and need for further clinical investigation and follow-up. These findings are in accordance with the ATA guidelines recommending genetic testing for *RET* mutations to all patients with MTC and first-degree relatives of those with confirmed hereditary MTC [2]. Similar findings were reported by Sarika et al. [6].

Over 150 germline activating *RET* mutations have been so far identified and reported in web databases and recent literature reviews [7–9].

Overview of MEN2 syndromes: genotype-phenotype correlation

The MEN2A syndrome is characterized by the presence of MTC, pheochromocytoma (PHEO), primary hyperparathyroidism (PHPT), and occasionally cutaneous lichen amyloidosis (CLA). Most mutations occur in exons 10 (codon 609, 611, 618, or 620) or 11 (codon 634). Practically all patients develop MTC following a stage of C-cell hyperplasia. PHEO is present in 40–50 % of MEN2A patients and it is commonly multicentric and bilateral; it is characterized by consistently elevated plasma and urine metanephrine levels, that reflect the metabolism of epinephrine within the tumor. 10–20 % of patients have PHPT, which frequently involves multiple glands [10]; CLA, a pruritic papular skin lesion mainly in the interscapular region corresponding to dermotomes T2–T6, is less common and almost exclusively associated with *RET* mutations in codon 634, which is also the most commonly mutated codon in MEN2A [5, 11]. Of note, *RET* mutations in codon 634 are associated with a higher incidence of PHEO and PHPT than mutations in exon 10 [2, 12]. There is also co-segregation of MEN2A with Hirschsprung's disease (HD) commonly involving the Janus mutation at the cysteine-rich area on codon 620. Although it is paradoxical that *RET* mutations associated with MEN2A are gain-of-function and those associated with HD loss-of-function, it has been suggested that this dual phenotypic mutation at C620 may impair RET-induced cell migration and differentiation, but simultaneously promote cell proliferation [13]. Other adaptor proteins interacting with RET may modulate its function and phenotypic expression [14].

Familial MTC is considered a variant of MEN2A; affected individuals harbor germline *RET* mutations but present only with MTC and without PHEO or PHPT. Establishing the diagnosis of FMTC is difficult and often a long-term follow-up is required to confirm that no adrenal or

parathyroid tumors develop [15, 16]. In the study of Romei et al., approximately one-third of *RET* mutations occurred in codon 804 with V804 M being the most prevalent; although there was significant variability of *RET* mutations, the majority involved non-cysteine codons. MEN2A is the most frequent MEN2 syndrome, with FMTC being the most prevalent form covering 50–65 % of MEN2 cases [5].

The clinical picture of MEN2B includes the presence of MTC (100 %), PHEO (30–50 %), multiple mucosal neuromas (occurring in almost all patients), and intestinal ganglioneuromas frequently accompanied by a marfanoid habitus. The aggressiveness of MTC in MEN2B is a characteristic feature of the syndrome and the onset of MTC can be at a very young age. The *RET* M918T mutation is found in most MEN2B patients and is classified as the highest risk category (HST) according to the recent ATA guidelines [2]. Less than 5 % of MEN2B patients have the A883F mutation, which may have a less aggressive course [17, 18].

RET variants of unknown significance

In the last years, a few rare *RET* variants have been identified (such as A883T, Y791F, M918V), termed variants of unknown significance (VUS), the functional activity of which has not been fully characterized. Although all of them have been associated with the presence of MTC, it is recommended that their transforming activity and aggressiveness be validated before they are considered causative of MTC. Useful tools include in vitro assays, such as the estimation of focus formation units by transfecting cell lines with mutant vectors, and in silico analyses, which are based on sequence homology and physical properties of amino acids and predict the degree of the biological effect caused by the variant at the protein level [19].

Double tandem or multiple *RET* mutations have been identified in MEN2A and MEN2B patients following sequencing of the entire coding region of the *RET* gene, which are usually associated with an atypical clinical course [20, 21]. Management of these cases and making recommendations regarding the timing of prophylactic thyroidectomy are very challenging; it requires close follow-up of the families and consideration of their biochemical profile (baseline and stimulated calcitonin levels), combined with in vitro and in silico findings.

The standard practice on genetic testing nowadays is a single- or two-tiered analysis; in the first approach, the most frequently mutated codons are tested (in exons 10 and 11), as well as exons 13–16 and exon 8 in some laboratories (factoring in the ethnic background [22–24]). In the second analysis, the most commonly mutated exons are initially sequenced and, if the results are negative or inconsistent with the patient's phenotype, the remaining *RET* exons are tested. The existence of multiple *RET* mutations associated with unusual clinical phenotypes is an additional argument why sequencing the entire *RET* coding region should probably not be reserved only for cases with negative initial findings or discrepancy between genotype and phenotype—which is the current recommendation [2]—but expand to include all new MTC cases (hereditary and sporadic). With the cost of sequencing markedly decreasing over the years, it would be interesting to perform a cost-effectiveness analysis comparing the codon-oriented analysis with sequencing of the entire *RET* coding region [25].

Counseling of carriers and timing of prophylactic thyroidectomy

Genetic testing for *RET* mutations allows the early identification of carriers. This has revolutionized the course of hereditary MTC, because prophylactic thyroidectomy can be offered to all asymptomatic carriers in order to remove the thyroid gland prior to the development of MTC (eliminating the risk of disease), or at a stage in which the tumor has smaller dimensions and is confined to the gland without lymph node involvement, thus significantly improving outcome and reducing the rate of persistent and/or recurrent disease. The beneficial role of prophylactic thyroidectomy in *RET* mutation carriers has been illustrated in various studies; additional prognostic factors affecting the long-term survival rate include the patient's age, mutation site, and basal calcitonin levels [26]. It cannot be stressed enough that thyroidectomy should be performed by surgeons in tertiary care centers with expertise in the management of children with MEN2 syndromes, especially since complication rates, such as hypoparathyroidism and laryngeal nerve damage, are higher in pediatric than adult patients.

Based on the recent ATA guidelines, prophylactic thyroidectomy is recommended for children with MEN2B syndrome harboring the M918T mutation very early in life, within the first year or even the first 6 months [2]. The value of CT levels is limited in these cases, because CT values are normally high in infancy. The decision to perform central (level VI) neck dissection depends on the presence of suspicious lymph nodes and whether the parathyroid glands can be identified and preserved in situ or auto-transplanted [2]. The appropriate timing of prophylactic thyroidectomy for children with MEN2B lacking the M918T mutation, such as those with the A883F variant, cannot be easily established because of their rarity and should be planned collaboratively by the pediatrician, the surgeon. and the child's parents.

Children with MEN2A and C634 mutations constitute the "high-risk" category and thyroidectomy should be performed at age 5 years or earlier if calcitonin levels are elevated [2]. Furthermore, it is recommended that they undergo annual

physical examination, including cervical ultrasound and estimation of basal CT levels, starting from age 3, because they may develop MTC very early in life. Factors affecting the extent of surgery and the need for central neck dissection include basal CT levels over 40 pg/ml and positive imaging or direct evidence of lymph node involvement.

Asymptomatic carriers of other *RET* mutations belong to the "moderate risk" category, in which there is significant variability in the age of onset and the aggressiveness of MTC. Annual testing in these cases should start at age 5, whereas the timing of prophylactic thyroidectomy is less stringent and depends on serum CT levels; in a single-center Italian study, Elisei et al. showed that it is safe to plan thyroidectomy in *RET* mutation carriers at the time-point that stimulated CT levels become detectable [27]. Serum pre-operative CT levels are useful in determining the extent of surgery; in a cohort of 308 *RET* carriers, normal CT values were associated with the absence of lymph node metastasis and it was suggested that CT levels could aid the decision to perform or forego central neck dissection [28]. It appears that the combination of genetic classification and biochemical profile is an efficient approach of planning prophylactic thyroidectomy in moderate risk *RET* mutation carriers. A summary of current ATA recommendations on prophylactic thyroidectomy is presented in Table 1.

Screening for other endocrinopathies (PHEO and PHPT) in asymptomatic carriers is not the focus of this review and the reader is referred to the recent ATA guidelines [2].

Initial diagnostic evaluation: cytology, pathology, and biomarkers

Patients with sporadic or undiagnosed hereditary MTC almost always present initially with a thyroid nodule, typically located in the upper- to mid-third of the lateral thyroid lobes. Micro-calcifications, hypo-echogenicity, and irregular margins are common ultrasound findings. The standard practice in nodules over 1 cm is to perform fine needle aspiration (FNA); although the appearance of MTC on cytology is variable, characteristic features include a dispersed cell pattern of polygonal or triangular cells, azurophilic perinuclear cytoplasmic granules, eccentric nuclei with chromatin granularity resembling "salt and pepper," and amyloid deposits [29]. The cytological diagnosis of MTC can be supported by immunohistochemical (IHC) analysis of the FNA sample with positive staining for CT, chromogranin, or carcinoembryonic antigen (CEA) and absent staining for thyroglobulin (Tg) and, additionally, with measurement of CT levels in the FNA washout fluid [30, 31].

Pathological examination of the entire thyroid gland and IHC analysis showing positive staining for CT, CEA, and chromogranin and negative for Tg will confirm the diagnosis of MTC; in hereditary MTC, it is critical that the pathological evaluation includes the entire thyroid to determine the presence or absence of C-cell hyperplasia, preceding the development of MTC [32], and of multifocal disease. The pathology report will also provide information on possible co-existence of MTC with papillary or follicular thyroid carcinoma, which may be co-incidental or due to shared tumorigenic stimuli [33].

Serum calcitonin, a 32 amino acid peptide secreted by the C-cells of the thyroid gland, is the most important diagnostic and prognostic biomarker of MTC. Measurement of CT in the initial presentation of a patient with a thyroid nodule has been an issue of controversy between European and the US endocrinologists. Although baseline CT levels are routinely measured in most European centers and few US studies have found routine CT screening to be cost effective [34], the ATA guidelines do not make a definite recommendation for or against it [2].

Table 1 Summary of recommendations on timing of prophylactic thyroidectomy for *RET* mutation carriers based on the ATA classification of *RET* mutations

Mutation	ATA risk category	Timing of thyroidectomy	Factors for central neck dissection	Start annual examination
M918T	Highest	Within first year	Suspicious lymph nodes Preservation of parathyroid glands	Not applicable
C634	High	5 years OR earlier if ↑ CT	CT > 40 pg/ml Positive imaging Suspicious lymph nodes during surgery	3 years
All remaining	Moderate	Upon elevated CT levels OR Around 5 years if long-term evaluation is concerning	Elevated CT levels	5 years

ATA American thyroid association, *CT* calcitonin

It includes cervical ultrasound and measurement of serum basal calcitonin levels

Reference ranges for CT are higher in males compared to females; there are scant data on the reference range in children, especially under the age of 3 years, whereas CT levels are very high in infancy [35]. It is important that reference ranges are established in clinics performing CT stimulation testing with calcium or pentagastrin. Generally, a threshold of stimulated CT levels over 100 pg/ml may be considered abnormal [36]. Moreover, other conditions associated with elevated CT levels should be considered when evaluating baseline CT levels, such as chronic renal failure, PHPT, use of protein pump inhibitors, autoimmune thyroiditis, mastocytosis, neuroendocrine tumors, lung and prostate cancer, and heterophilic antibodies.

CEA is a glycoprotein also secreted by C-cells, but it is not a specific biomarker of MTC. CEA can be elevated in inflammatory diseases of the gastrointestinal tract, benign lung conditions, non-thyroidal cancers, and in the presence of heterophile antibodies. CEA is mainly used in combination with CT to assess the post-operative course and disease progression of MTC patients. Simultaneous increases of both CT and CEA levels indicate disease progression, whereas increased CEA values accompanied by stable or decreasing CT levels demonstrate poor differentiation; when both CT and CEA levels are low or normal in a patient with clinically evident MTC, the de-differentiation is even more pronounced [37]. Pro-calcitonin measurements may be of use in such cases [38].

Medullary micro-carcinoma

The term micro-MTC has been coined to describe sporadic or hereditary MTC smaller than 1 cm. The majority of micro-MTCs are incidental findings in thyroidectomies performed for unrelated reasons, such as other thyroid carcinomas, or following measurement of CT levels for nodular thyroid disease; they generally have a favorable prognosis and only few cases show metastatic potential [39, 40]. It has been suggested that the term micro-MTC be used for tumors smaller than 0.5 cm; Pillarisetti et al. demonstrated that no patient with MTC less than 0.5 cm in diameter had nodal metastases or post-operative hypercalcitoninemia [41]. Post-operative CT levels may be a good prognostic marker in these cases [42].

Therapeutic surgery

The surgical management of clinically evident MTC in hereditary cases is similar to that of sporadic ones. Once the initial diagnosis of MTC is established, pre-operative imaging with neck ultrasound will provide important information regarding the localization of the tumor and any lymph nodal metastases and determine the extent of thyroidectomy. When there is evident metastatic disease or basal CT levels exceed 500 pg/ml, systemic staging should be performed including computerized tomography of neck and chest (to assess lung and mediastinal lymph nodes), computerized tomography or magnetic resonance imaging (MRI) of the liver and axial MRI and bone scintigraphy. In hereditary MTC, the presence of PHEO and PHPT should also be excluded; if they co-exist, surgery for PHEO should precede that for MTC to avoid the risk of precipitating a PHEO crisis [2].

The cornerstone of therapy in MTC patients is surgical and an efficient first operation removing the entire tumor burden is a predictor of favorable outcome and highest survival rate. Early diagnosis of MTC, when the tumor is small, confined to the thyroid without lymph node involvement, and optimized surgery result in the highest rates of biochemical and clinical cure [43]. Disease stage at diagnosis is a strong prognostic factor, along with pre- and post-operative CT levels and patient's age at diagnosis [44–47]; in hereditary MTC diagnosis and initial treatment at an earlier age are associated with improved outcome [48].

The standard surgery for patients with no evidence of lymph node or distant disease includes total thyroidectomy and dissection of level VI compartment (central neck). In older studies, approximately 3 out of 4 MTC patients already had lymph node involvement. Similar to papillary thyroid carcinoma, MTCs located in the middle and lower regions of the gland metastasize to the central lymph node compartment, whereas tumors in the upper pole spread initially to the ipsilateral lateral compartment.

Pre-operative basal CT levels correlate strongly with the extent of lymph node metastases [49] and pre-operative CEA levels are also higher with increasing number of affected lymph nodes [50]; these biomarkers may, therefore, be used to determine the extent of initial surgery.

In patients with cervical nodal disease, thyroidectomy with central neck dissection and resection of the involved lateral necks compartments should be performed, whereas when basal CT levels exceed 200 pg/ml, contralateral neck dissection should be considered [2]. In cases of locally advanced or metastatic disease, surgery should be palliative to preserve speech, swallowing, and function of the parathyroid glands.

When the diagnosis of MTC follows a unilateral hemithyroidectomy and genetic testing reveals hereditary MTC, completion thyroidectomy with central neck dissection should be performed, because MTC development in the contralateral lobe is very likely to occur.

A schematic overview of the management of hereditary MTC patients presenting after the tumor develops is shown in Fig. 2.

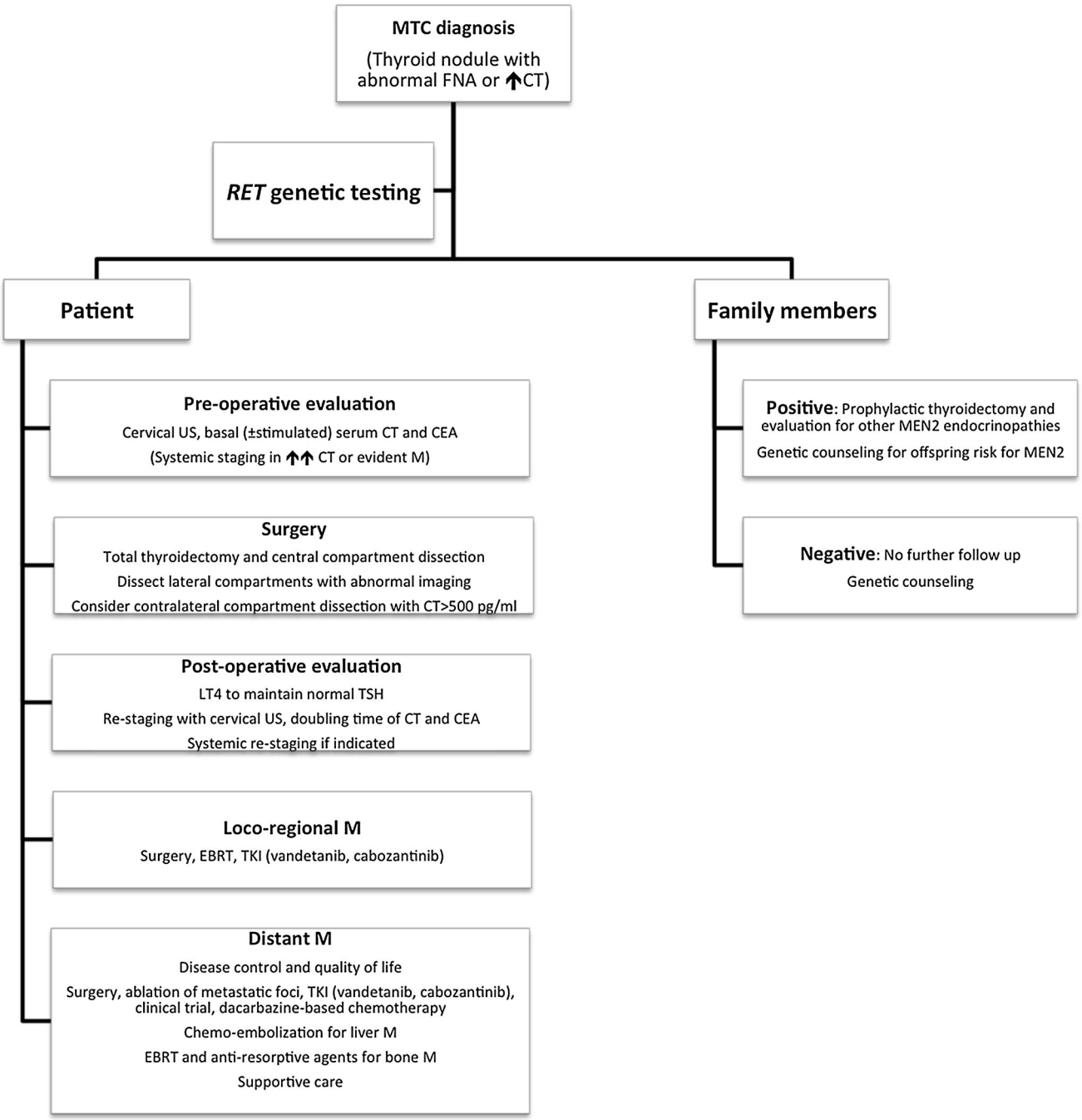

Fig. 2 Diagram illustrating the main steps in the management of hereditary MTC. *MTC* medullary thyroid carcinoma, *FNA* fine needle aspiration, *CT* calcitonin, *RET* re-arranged during transfection, *MEN* multiple endocrine neoplasia, *US* ultrasound, *CEA* carcinoembryonic antigen, *M* metastasis, *LT4* levothyroxine, *EBRT* external beam radiation therapy, *TKI* tyrosine kinase inhibitor

Post-operative evaluation and management

Following total thyroidectomy, levothyroxine therapy should not be suppressive, but aim at TSH levels within the normal range, whereas replacement with calcium and vitamin D should be given in symptomatic hypocalcemic patients.

The post-operative staging of MTC patients aims at evaluating the risk of recurrence and includes physical exam, cervical ultrasound, and measurement of serum CT and CEA levels repeated every 6 months. Normal or undetectable basal and stimulated CT levels are associated with better prognosis [51, 52]. Imaging modalities are similar to the ones used in the pre-operative staging (see above). Another useful index of MTC progression is the doubling time of serum CT or CEA. In a study of 55 MTC patients, Giraudet et al. demonstrated that 94 % of patients

with doubling times less than 25 months showed MTC progression, whereas 86 % of those with doubling times over 24 months had stable disease [53].

Management of regional metastatic MTC

The preferred management of persistent or recurrent disease with only regional and no distant metastases is dissection of compartments (central or lateral), in which there is abnormal imaging or biopsy [2]. Therapy with radioactive iodine is ineffective in MTC patients, unless there is admixture with papillary or follicular thyroid carcinoma [54]. External beam radiation therapy (EBRT) has a role in unresectable disease or as adjuvant treatment to reduce the risk for regional recurrence in high-risk patients [55]. Conventional cytotoxic chemotherapy does not elicit a satisfactory response in MTC and is not recommended. Other alternatives that should be considered include tyrosine kinase inhibitors (TKIs), such as vandetanib or cabozantinib, in symptomatic or structurally progressive disease (see below section on tyrosine kinase inhibitors) [56].

Management of distant metastases

The goal of managing patients with metastatic disease is to provide local disease control and maintain acceptable quality of life. In asymptomatic disease, observation, surgical resection, and ablation of metastatic foci (with radiofrequency ablation or embolization) are valid alternatives. When MTC progresses and the disease becomes symptomatic, therapy may include TKIs (vandetanib or cabozantinib), or enrollment in a clinical trial with another TKI, dacarbazine-based chemotherapy [57] or radiolabeled molecules [(^{90}Yttrium-DOTA)-TOC] [58].

Palliative care includes alleviation of diarrhea with loperamide or somatostatin analogs, analgesics for pain relief, adrenal enzyme inhibitors for ectopic Cushing's syndrome (ketoconazole, metyrapone, mitotane, mifepristone), EBRT to spine and pelvis bone metastases to avoid fractures and preserve mobility, EBRT to mediastinum to avoid airway obstruction, chemo-embolism for liver metastases, and antiresorptive agents (bisphosphonates, denosumab) for osseous metastases [58].

Targeted therapy with tyrosine kinase inhibitors and novel drug targets

In the last 5 years, two multi-targeted TKIs, namely vandetanib and cabozantinib, have been approved for the treatment of symptomatic, advanced, or progressive MTC, which is not eligible for surgery. Two phase-III clinical trials showed increased progression-free survival (PFS) compared to placebo [59, 60]. Both agents were shown to lead to stable disease in 30 % and partial regression in 35 % of cases. Currently, there are no data showing survival benefit using these TKIs suggesting that they have a cytostatic rather than cytotoxic effect.

Besides RET, vandetanib also targets vascular endothelial growth receptor -2 (VEGFR-2), VEGFR-3, and endothelial growth factor receptor (EGFR) [61]. In the randomized controlled phase III trial mentioned above, the median PFS in patients treated with vandetanib was 30.5 months compared to 19.3 months in the placebo group; objective radiologic response was superior in treated patients (45 %) compared to the control group (13 %) [59]. The most important side effect often requiring dose reduction is QT interval prolongation, whereas other common side effects include fatigue, rash, photosensitization, and hypertension [59].

Cabozantinib targets RET, as well as c-MET and VEGFR2. In a randomized controlled trial, treatment with 140 mg cabozantinib significantly improved PFS (11.2 vs. 4 months in placebo group) and objective radiologic response (28 vs. 0 % of control group). Its major side effects are gastrointestinal perforation and hemorrhage, fistula formation, diarrhea, abdominal discomfort, fatigue, hypertension, and hand-foot syndrome [60].

It appears that *RET* mutation status may to some extent predict response to TKI treatment; In the study of Fox et al., tumors with the M918T mutation showed increased sensitivity to vandetanib [62]. There are also in vitro data suggesting that the V804 M and B804L mutations confer resistance to vandetanib [63].

Sorafenib and sunitinib are not FDA-approved for MTC, but may be considered in progressive disease not responsive to other TKIs, because they may alleviate symptoms caused by metastases and by substances secreted by the tumor and have clinical response [64–66]. Other multi-targeted therapies (e.g., pazopanib) are under investigation [67]. The main characteristics of TKIs currently used for the treatment of MTC are presented in Table 2.

Clinical research is ongoing to identify new mechanisms underlying MTC progression and metastasis. Recently, Santarpia et al. applied bioinformatics miRNA profiling in paired primary and metastatic MTC tumors and identified ten potential miRNA targets involved in metastatic MTC pathways, such as TGF-beta, PI3 K-Akt-mTOR, Wnt/beta-catenin, and NOTCH pathways [68]. In the same line, Puppin et al. demonstrated that gene expression associated with miRNA biogenesis is deregulated in RET-driven tumors [69]. Advances in our knowledge of mechanisms of metastatic disease will accelerate the development of novel drug molecules and more sophisticated therapies for progressive MTC.

Table 2 Profile of tyrosine kinase inhibitors used for the management of advanced, progressive MTC

Drug	Targets	PFS (vs. placebo) in months	ORR (vs. placebo) %	Major AE
Vandetanib (ZD6474)	RET, VEGFR-2, VEGFR-3, EGFR, PDGFR	30.5 (19.3)	45 (13)	QT prolongation, diarrhea, fatigue, rash, photosensitization, hypertension
Cabozantinib (XL184)	RET, c-MET, VEGFR2, KIT, AXL, FLT3	11.2 (4)	28 (0)	GI perforation, hemorrhage, fistula formation, diarrhea, abdominal discomfort, fatigue, hypertension, hand-foot syndrome
Sorafenib (BAY 43-9006)	RET, VEGFR, PDGFR, RAF, KIT, FLT3			Hand-foot syndrome, hypertension, diarrhea, infection, leukopenia, musculoskeletal pain
Sunitinib (SU11248)	RET, VEGFR-1, VEGFR-2, PDGFR, KIT, FLT3, CSF1R			Fatigue, diarrhea, hand-foot syndrome, leukopenia, musculoskeletal pain
Pazopanib	c-KIT, FGFR, PDGFR, VEGFR	9.4		Hypertension, fatigue, anorexia, diarrhea, abnormal liver tests

PFS progression-free survival, *ORR* objective radiologic response, *AE* adverse events, *GI* gastrointestinal

Summary: Conclusions

Hereditary MTC is a rare disease with significant morbidity and mortality. Genetic testing for *RET* mutations has drastically changed the course of the disease allowing early identification of carriers and prophylactic thyroidectomy, which eliminates the risk for MTC development. Moreover, it is a useful tool in the long-term management of these patients, who are at risk for other endocrinopathies (PHEO, PHPT). Surgical and medical therapy of hereditary MTC patients who are diagnosed after the tumor develops is similar to sporadic cases. It seems that *RET*-mutated tumors may have a favorable response to treatment with recently approved TKIs, such as vandetanib. Ongoing research is expected to lead to the discovery of novel molecules for patients with advanced metastatic MTC.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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