REVIEW

Medullary thyroid cancer: molecular factors, management and treatment

EFSTATHIOS PAVLIDIS[1], KONSTANTINOS SAPALIDIS[1], FOTIOS CHATZINIKOLAOU[2], ISAAK KESISOGLOU[1]

[1]*3rd Department of Surgery, AHEPA University Hospital, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece*
[2]*Department of Forensic Medicine and Toxicology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece*

Abstract

Medullary thyroid cancer (MTC) is an infrequent neuroendocrine tumor, which amounts to 3–5% of all thyroid malignancies. Approximately 75–80% of MTCs are sporadic neoplasms. The rest of 20–25% are familial cases that belong to multiple endocrine neoplasia (MEN) syndromes, specifically MEN2 and MEN3. These cases of familial MTC are attributed to an activating germline mutation of a tyrosine kinase receptor gene, the rearranged during transfection (*RET*) proto-oncogene, located on chromosome 10q11.21. These mutations are also found in some cases of sporadic MTC. This review sets forth in summary the accepted guidelines and approaches regarding diagnosis, management, and treatment of MTC. Surgical resection is the standard care, and an early, prophylactic intervention is performed in genetic cases. Further investigation and understanding of the molecular pathways involved in the growth and advancement of MTC is required in order to provide efficient therapy in cases of progressive disease.

Keywords: medullary thyroid cancer, *RET* mutation diagnosis, management, treatment, guidelines.

⬚ Introduction

Medullary thyroid cancer (MTC) is an infrequent neuroendocrine tumor that originates from C cells (formerly known as parafollicular cells), which stem from the neural crest cells that migrate into the thyroid gland from the third and fourth branchial pouches [1, 2]. It was first reported as a specific entity in 1959, when Hazard *et al.* reviewed 600 cases of an atypical thyroid cancer with non-follicular histology and amyloid-containing stroma [3]. Although these cells are placed throughout the thyroid gland, they are predominant at the junction of the upper and middle third of each lobe, where most of the MTCs are located [1]. Parafollicular cells produce mainly calcitonin (Ct), which serves not only in diagnosis but as a prognostic marker as well [4]. MTC accounts for 3% to 5% of all thyroid gland malignancies worldwide [5]. Albeit its scarceness, MTC could be described as a solid tumor with excellent characteristics in terms of pathological, biochemical and genetic attributes [6].

MTC can be either sporadic or part of specific familial syndromes. Sporadic entities involve individual patients without a family history of MTC and are confirmed in 75–80% of all cases [7, 8]. These tumors are usually unilateral and present typically between the fourth and sixth decades of life, more frequently encountered in female patients with a 3:2 ratio [9]. The rest of 20–25% of MTCs are familial cases inherited in an autosomal-dominant way, which can be part of multiple endocrine neoplasia (MEN) syndromes, specifically MEN2 (Sipple's syndrome) and MEN3, or present as pure familial MTC (FMTC) syndrome [10, 11]. MEN2 syndrome accounts for 75% of hereditary MTC, with a peak incidence in the 30s, while patients with MEN3 develop MTC in infancy or early childhood. FMTC is the least aggressive type of hereditary MTC and usually presents in the fifth decade of life [12].

⬚ Diagnosis

Clinical features

Most commonly MTC presents as a solitary thyroid nodule. Multifocality can be found in 20% of the cases. Typically, the nodule or the mass is an incidental finding in clinical examination of the neck or in an imaging examination [13]. Apart from a palpable mass in the neck, symptoms include dysphagia, dyspnea, dysphasia, chest pain and recurrent respiratory infections, which indicate an advanced disease [14]. Lymph node metastases are present in 30–60% at the time of the initial diagnosis and are most commonly found in the ipsilateral nodes of the II–VI compartments of the neck. However, up to 40% of the patients have contralateral lymph node metastases. Metastatic lymph nodes can also be found in the mediastinum. Distant metastases to the liver, lung and bones usually exist later in the process of the malignancy [15].

Laboratory evaluation

Fine-needle aspiration (FNA) of a thyroid nodule is used in the diagnosis of MTC, while Ct and carcino-embryonic antigen (CEA) serve as the primary tumor markers. FNA has an accuracy of 50–80% but cannot always distinguish MTC based on the cytology alone [16]. In 2006, the *European Thyroid Association* (ETA) proposed routine Ct measurement in the primary workup

of thyroid nodules. Meanwhile, *American Thyroid Association* (ATA) refused to take a stand for or against this approach. The *ATA* has still taken no position regarding screening; they propose that should the screening is done, and Ct levels are greater than 100 pg/mL suspicion for MTC must be considered and surgical intervention is required. Currently, the *ETA* places emphasis on Ct screening only in the presence of clinical risk factors [17]. Pentagastrin stimulation may underpin its use in evaluating patients who have thyroid nodules, but only in cases with modest serum Ct elevations. Pentagastrin administration stimulates Ct secretion from tumors thus, guides the applicable selection of patient for operation. Calcium infusion is another method to stimulate Ct release, and a small trial proposes that this could serve as an alternative to pentagastrin; to this effect, calcium infusion warrants supplementary analysis [18, 19]. Immunohisto-chemical staining for Ct, chromogranin A and CEA offer greater veracity [20]. In case of high cytological or clinical suspicion for MTC preoperative measuring of Ct can be useful in diagnosis and staging. A Ct level higher than 150 pg/mL is usually associated with metastatic disease. Another useful tumor marker is CEA, which is elevated in more than half of the patients. These markers are also useful for prognostic purposes and for the postoperative follow-up of the patients [21].

Radiological evaluation

Scrutinize image examinations is extremely important in the diagnosis and management of MTC. The first imaging technique used in MTC is usually cervical ultrasound (US) for the evaluation of a palpable thyroid nodule or a lymph node. US scan provides vital information regarding the structure and the extension of nodular and invasive thyroid disease. It can also be used to guide the FNA to confirm the diagnosis of MTC [22]. Although ultrasonography cannot rule out malignancy, certain ultrasonographic findings such as irregular margins and microcalcifications can raise a nodule's possibility of malignancy up to 80% [23]. US scan is also superior to computed tomography (CT) in detecting cervical lymph node metastases. If metastatic disease is suspected, extended imaging workup is recommended. Metastatic disease usually involves the chest, the liver, and the bones. As a result, the current guidelines recommend contrast-enhanced chest and upper abdominal CT or magnetic resonance imaging (MRI) scan and a bone scintigraphy [24]. Lower cervical and mediastinal lymph nodes are better detected with a CT scan. CT scan is also superior in detecting lung metastases, while both CT's and MRI's sensitivity in detecting liver metastases is less than 70%. MRI may also be superior to other imaging techniques in detecting skeletal metastases, but bone scintigraphy may be a valid alternative in patients with high suspicion of bone involvement. High-resolution positron emission tomography (PET)/CT with 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG PET/CT) or somatostatin receptor imaging are not recommended in the initial workup, but they can be very useful in cases of tumors with aggressive behavior and metastases in multiple organs, which are characterized by Ct levels of over 1000 pg/mL and have a worse prognosis. Gallium-68 (^{68}Ga) PET/CT is another technique with high sensitivity in detecting bone metastases that could potentially replace bone scintigraphy and MRI [24].

Familial disease

MTC can either be sporadic, which represents 75% of the cases or familial, which represents the rest 25% [25]. Familial cases of MTC are divided into three categories, which were formerly known as subtypes of the MEN type 2 syndrome [26]. The first category is the MEN2 syndrome (previously MEN2A), that defined presence of MTC, parathyroid tumors and pheochromocytoma. The second category is the MEN3 syndrome (previously MEN2B), which is defined by the presence of MTC, pheochromocytoma, mucosal neuromas and marfanoid habitus, medullated corneal fibers and intestinal autonomic ganglion dysfunction, resulting to megacolon. The last category consists of familial cases of isolated MTC.

Hereditary MTC is transmitted as an autosomal dominant trait. In up to 80% of the cases, it is part of the MEN2 syndrome, which commonly manifests after the third decade of life, affecting equally males and females and it is characterized by bilateral, multifocal MTC. In cases of MEN3, which accounts for 8% to 15% of patients with hereditary MEN, MTC typically occurs in early childhood and local lymph node metastases are present in the first decade of life, while distant metastases are seen in the second decade. This subtype has the most aggressive course with death occurring from metastatic disease in the third or fourth decade of life. Isolated FMTC is the last category of hereditary MTC and is characterized as MTC occurring with no other accompanying familial endocrine tumors. Its summit incidence is between the fourth and the fifth decade of life and can be defined as the least aggressive form of the disease [27].

Genetic testing

The molecular and genetic pathways involved in the oncogenesis of MTC have been widely investigated in the literature. The primary oncogenic event seems to be an activating germline mutation in the rearranged during transfection (*RET*) proto-oncogene [27]. *RET* mutations can be found in more than 95% of cases of hereditary MTC and up to 65% of cases of sporadic MTC. The main difference between these two types of MTC is that in familial cases *RET* mutation is genetically transmitted and, thus, all body cells harbor the mutation, while in cases of sporadic MTC the mutation is somatic and, thus, limited to the thyroid cells only [28]. The *RET* gene is located on chromosome 10q11.21. It consists of 21 exons with roughly 55 000 base pairs and encodes a single-pass transmembrane protein that is part of the tyrosine kinase receptor (TKR) family. This receptor consists of an extracellular part that contains cadherin-like domains and an intracellular part that contains two active tyrosine kinase domains. Responsible for its activation is a glial cell line-derived neurotrophic factor (GDNF) ligand, which is a part of the transforming growth factor-*β* (TGF-*β*) superfamily. The molecular pathway of the *RET* receptor is essential in regulating cell proliferation, differentiation, motility, survival, and apoptosis and is extremely important for the development of neural crest-derived lineages, such as the thyroid C cells [29].

Genetic testing, specifically *RET* sequencing, can be used for the early detection of the germline mutation in order to identify individuals at risk and enable prophylactic treatment. *RET* genetic testing is advised in all patients with MTC [30]. Current recommendations promulgated by the *ATA* and the *National Comprehensive Cancer Network* recommend genetic testing in the context of genetic counseling. However, genetic testing has its limitations, since a positive *RET* testing does not always correlate with significant family history or onset of MTC at an early age [31].

RET mutations in the extracellular domain

Both germline and somatic *RET* mutations can cause an abnormal activation of the TKR pathway related to familial and sporadic cases of MTC, respectively. Activating mutations of the *RET* proto-oncogene can be divided into the following major categories; extracellular and intra-cellular. The most frequent mutation in the extracellular domain of *RET* pertains to a cysteine-rich domain and in most of the cases (85%) involves cysteine 634 [32]. This mutation is usually associated with MEN2 syndrome, while mutations in codons 620 and 630, located in the exons 10 and 11, respectively, are associated with isolated cases of FMTC. These mutations target highly conserved cysteine residues, which normally play a part in intra-molecular disulfide bond formation. The mutant receptors create these bonds despite the absence of a ligand leading to continuous autophosphorylation and activation of the intracellular pathway of the receptor [33].

RET mutations in the intracellular domain

Intracellular *RET* mutations are found in the *RET* kinase domain and have multiple effects on *RET* activity. These mutations are usually found in cases of MEN3 syndrome and in isolated cases of hereditary MTC. In cases of MEN3 syndrome, the most common mutation is observed in the codon 918 of exon 16, while in cases of FMTC mutations can be found in codons 768, 790, 791, 804 and 891, which, however, account for a small percentage of the cases [34]. These mutations target areas of the receptor that are associated with the adenosine triphosphate (ATP)-binding pocket and result in structural modifications. Consequently, alternative intracellular proteins are phosphorylized and activated, while the receptor no longer needs dimerization to become functional [33, 34].

Genotype–phenotype correlation in MTC

The association of specific mutations in the *RET* proto-oncogene and certain clinical characteristics has been well established in the literature. These characteristics include the age of outset, the aggressiveness of the disease and the existence or not of any endocrine tumors. The *M918T* mutation (exon 16) is considered the most typical mutation in MEN3 syndrome and is associated with the worst prognosis. These patients have the highest risk of developing aggressive MTC at an early age. Metastatic disease usually develops in the first year of life. Mutations of codon 634 (exon 11) are associated with MEN2 syndrome [35]. The most common mutation is *p.C634R*, which is also associated with the most aggressive form of the disease. These patients usually develop MTC before 10 years of age, but lymph nodes metastases commonly appear in patients older than 14 years. In cases of isolated FMTC, the most common mutation is *p.C634Y* in codon 634. In general, mutations that are located in codons other than 918 and 634 lead to a wide variety of clinical manifestations and are associated with better prognosis. In patients with exon 10 mutations, MTC usually manifests between the age of 20 and 40, while metastatic disease occurs after 30 years of age. Other *RET* mutations, such as *Y791F* and *S649L*, have been associated with mild disease [36].

⊟ Surgical treatment

Treatment of clinically evident disease

Patients with diagnosed MTC should be subjected to total thyroidectomy since all cases with hereditary MTC, as well as 30% of those with sporadic MTC have multifocal disease at the time of the diagnosis [37]. In cases of localized MTC, where there is no evidence of cervical lymph node or distant metastases, total thyroid-ectomy and central (levels VI and VII) dissection is the procedure of choice. Central lymph node dissection might be omitted safely only in patients with T1a disease [37]. The role of lateral lymph node dissection still remains controversial. Some authors advocate that lateral lymph node dissection should only be reserved for cases of positive for lateral lymph node metastatic disease imaging or histological findings. Others propose the evaluation of preoperative Ct levels and tumor size as criteria for deciding whether it is necessary or not [37, 38]. In cases of a tumor over 3 mm and Ct levels ranging between 20 pg/mL and 200 pg/mL, ipsilateral lateral lymph node dissection is advised as it increases the percentage of biochemical cure. Bilateral lateral neck dissection is reserved for tumors over 1 cm or for cases of Ct levels over 200 pg/mL, achieving a biochemical cure rate of 33.3% [39].

Prophylactic surgery

Prophylactic surgery aims to protect high-risk patients from developing a potentially fatal disease. The risk of developing MTC and metastatic disease in patients with germline *RET* mutations has been stratified depending on the earliest age of onset of MTC and metastases. As a result, *RET* mutations have been divided into four levels (A to D) by the *ATA Guidelines Task Force* based on the aggressiveness monitored in the respectively associated MTCs.

Patients with mutations in codons 883 and 918 are in danger of developing highly aggressive MTC during the first year of life. Hence, such individuals are candidates for total thyroidectomy within the first year of life. People with mutations in codon 634, the only level C mutations, should undergo total thyroidectomy by the age of five years. Patients with level B mutations (codons 609, 611, 618, 620, 630 and 631) could undergo thyroidectomy before the age of five years, nevertheless, the procedure can be delayed in cases of normal US, normal Ct levels and a less aggressive family history. In patients with the least aggressive level A mutations total thyroidectomy can be delayed to a later age if a death due to MTC has never been reported in a family member.

Postoperative surveillance

The role of postoperative surveillance is determining the presence or absence of residual disease, locating possible metastases, and identifying progressive disease. It is based on obtaining new baseline CEA and Ct levels in the early postoperative period (2–3 months) [40]. Patients with undetectable postoperative Ct levels should have their Ct and CEA levels checked twice yearly for two years and then annually thereafter. Regarding imaging techniques, the most useful tool in postoperative surveillance is the cervical US scan. An annual scan is recommended during the first three years after thyroid surgery, while biennial scan is suggested during 4–10 years following thyroidectomy. However, patients with postoperative CT levels over 150 pg/mL should be evaluated for persistent or recurrent disease with cervical and thoracic CT scans, US and MRI scans of the liver, bone scintigraphy or MRI scan and PET/CT scan [41].

Prognosis

The prognostic factors of MTC include clinical characteristics, biochemical markers, and somatic mutations [42]. The most sensitive prognostic factor is Ct's doubling time (DT). Patients with a Ct DT less than a year have a 5- and 10-year survival rate of 36% and 18%, respectively, compared to 95% of patients with Ct DT over a 12-month period. The DT of CEA can also serve as a sensitive prognostic factor. Other major and independent prognostic factors include the stage of the disease and the age of the patients. In general, the overall 5- and 10-year survival rate in patients with MTC varies from 80–97% to 75–88%, respectively [43].

Recurrence

Recurrent disease forms in almost 50% of patients with MTC. Patients with postoperative values of Ct greater than 150 pg/mL have a high likelihood of persistent or recurrent disease in the neck. These patients are candidates for reoperation [44]. However, depending on other patients' factors, such as age, comorbidities, tumor burden and symptoms, the best management option could be active surveillance. Other treatment options for patients with recurrent disease include external beam radiotherapy, radiofrequency ablation, cryoablation, embolization and systemic therapies, such as immunotherapy, chemotherapy, and molecular targeted therapy. In cases of elevated Ct and CEA levels without structurally identifiable disease the best option seems to be close observation [45].

Identifying the cellular pathways in MTC could play a pivotal role in the development of novel pharmacological targets for treatment. Pathways derive from the *RET* tyrosine kinase encompass the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and the Raf-1/mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway. Moreover, the Notch-1/hairy enhancer of split 1/achaete-scute complex-like 1 (ASCL-1) pathway has also been targeted for investigation of future systemic therapies for MTC. There is a likelihood, that in case that the agents which attack the *RET* tyrosine kinase and multiple downstream targets are combined, the effectiveness will improve [46–48].

⌗ Conclusions

MTC is a challenging disease in terms of diagnosis and management. Clinicians must be vigilant in order to identify cases of FMTC and provide patients with the right guidance and genetic testing, which could potentially lead to a life-saving prophylactic thyroidectomy. In cases of progressive, residual, recurrent and metastatic disease, decisions must be individualized, and a proper treatment plan must be implemented, electing from the wide plethora of therapeutic options available, the ones that will provide the patients with the optimal survival and disease-free rate.

Conflict of interests

The authors declare that they have no conflict of interests.

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Corresponding author
Efstathios Pavlidis, Assistant Professor of Surgery, MD, PhD, MSc, Medical School, Aristotle University of Thessaloniki, 8 Iereos Kazika Street, 55132 Thessaloniki, Greece; Phone +302310440757, e-mail: pavlidis.md@gmail.com