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REVIEW ARTICLE

Consensus on management of advanced medullary thyroid carcinoma on behalf of the Working Group of Thyroid Cancer of the Spanish Society of Endocrinology (SEEN) and the Spanish Task Force Group for Orphan and Infrequent Tumors (GETHI)

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Abstract
Background Of all thyroid cancers, <5 % are medullary (MTC). It is a well-characterized neuroendocrine tumor arising from calcitonin-secreting C cells, and *RET* gene plays a central role on its pathogeny.
Methods The electronic search was conducted using MEDLINE (PubMed), EMBASE and Cochrane Central Register of Controlled Trials. Quality assessments of selected current articles, guidelines and reviews of MTC were performed.
Results This consensus updates and summarizes biology, treatment and prognostic considerations of MTC.
Conclusions Multidisciplinary teams and specialized centers are recommended for the management of MTC patients. In the metastatic setting, those patients with large volume of disease are candidates to start systemic treatment mainly if they are symptomatic and the tumor has progressed in the last 12–14 months. Wait and see strategy should be offered to patients with: disseminated disease with only high levels of calcitonin and no macroscopic structural disease, low burden and absence of progression.

Keywords Cabozantinib · Calcitonin · Carcinoembryonic antigen · Medullary thyroid carcinoma · Thyroid cancer · Review · Vandetanib

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Introduction

Of all thyroid cancers, <5 % are medullary thyroid carcinoma (MTC) and yet, it is a well-characterized neuroendocrine tumor arising from the neural crest-derived parafollicular C cells of the thyroid, mostly located in the posterior upper third of the lateral lobes of the thyroid gland, and produce calcitonin and carcinoembryonic antigen [1].

There are two types of MTC: sporadic (75 %), which occur in individuals with no MTC family history, and inherited (25 %), which are part of several familial syndromes (MEN2), with autosomal dominant heritance pattern. MEN2A associates MTC in virtually all patients, pheochromocytoma in half and hyperparathyroidism in 15–20 % of the cases. In MEN2B, MTC occurs in all patients early and is more aggressive in comparison with MEN2A, pheochromocytoma is generally bilateral and

multicentric, and mucosal neuromas and Marfan-like phenotype are the trademarks of this subtype and are apparent from childhood.

In Europe, the incidence of MTC is approximately 1500–2000 new cases per year, of which only one-fourth will be diagnosed at advanced stages of the disease [2]. Occult disease is found in the form of small, indolent tumors in up to 7 % of autopsies [3].

Despite its scant prevalence, its genetics are surprisingly well understood and comprise the basis for treatment and prognosis.

This revision is based on the most salient, updated characteristics of this disease. It is the result of collaboration between the *Grupo Español de Tumores Huérfanos e Infrecuentes* (GETHI) and the Grupo de Cáncer de Tiroides de la *Sociedad Española de Endocrinología y Nutrición* (SEEN).

Biology

The rearranged during transfection (*RET*) gene plays a central role in MTC and is located on chromosome 10q11.2. It encodes a tyrosine kinase transmembrane receptor that is activated by GDNF (glial cell line-derived neurotrophic factor) [1, 4, 5]. The *RET* gene participates in controlling cell growth, differentiation, aggressiveness and survival [6], and its germ line mutations are found practically in all patients with familial MTC syndrome. On the other hand, somatic *RET* mutations are present in around half of sporadic MTC cases [7, 8].

Germ line mutations in different codons have been identified. The mutations occurring in familial syndromes are the best known. For instance, mutations in codons 609, 611, 618 and 620 of exon 10 and codon 634 of exon 11 are present in more than 80 % of familial MTC patients. *RET* mutations in codon 634, often associated with pheochromocytoma and hyperparathyroidism, are present in close to 80 % of MEN2A. The vast majority of MEN2B display point mutations in codon 918 of exon 16 [2].

Some mutations are associated with major aggressiveness, high probability of lymph node metastases, recurrent and persistent disease and poor survival [9]. The 2015 ATA guidelines establish three categories: "high," "higher" or "highest," to designate progressive increases in aggressiveness of the MTC [10].

Besides *RET*, other molecular changes affect some of the growth factors involved in angiogenesis, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), hepatocyte growth factor receptor (HG-FR) and mesenchymal-epithelial transition factor receptor (c-MET). This accounts for the high vascularization of these tumors, which facilitates distant metastases [11]. Somatic mutations in either *RET* or *RAS* are also present in most sporadic tumors [12, 13].

Diagnosis

The typical scenario for initial diagnosis is an asymptomatic thyroid nodule with suspicious ultrasound features in which cytological evaluation is compatible with MTC. The presence of high serum calcitonin levels supports the diagnosis.

The advanced disease is frequently presented with some cervical lymph node enlargement. Pain arising from tumor growth or bone metastases and respiratory symptoms (dyspnea, chest pain or recurrent respiratory infections) resulting from lung metastases are relatively common in patients with advanced disease. Despite their frequency, hepatic metastases do not usually cause symptoms. MTC is a neuroendocrine tumor but is seldom associated with symptoms derived from peptide hormone secretion [1].

Biopsy of suspicious lesions is the basis for definitive diagnosis. It is advisable to have enough tissue sample for further molecular assessments, if needed.

It is well established that calcitonin and CEA are the current tumor markers for MTC and must be evaluated in the disease assessment during the follow-up. Calcitonin is the most reliable marker of MTC, especially to monitor patients who exhibited increased levels at diagnosis [14]. While valuable during follow-up, CEA is both less sensitive and less specific for the diagnosis. It has a low positive predictive value, as it also presents high values in other non-tumor conditions such as cirrhosis, renal insufficiency, gastritis, colitis, Crohn's disease, pancreatitis and smoking, as well as many other different tumors.

Preoperative serum calcitonin levels will aid in individualizing the extent of surgery, whereas postoperatively, calcitonin determinations every 3 months will guide follow-up. Basal calcitonin values exceeding 150 pg/mL are typically seen in patients who develop distant metastases. Postoperative calcitonin levels correlate with MTC size, C cell hyperplasia, tumor or metastases size and loco-regional recurrence or persistent disease [15]. In selected cases, a pentagastrin stimulation can help to exclude residual disease in patients with undetectable circulating calcitonin. A patient is deemed to be in total biochemical remission when both basal calcitonin and stimulated serum calcitonin are undetectable; this predicts a 10-year survival rate >97 % [15].

Doubling times of calcitonin and CEA provide valid data regarding postoperative MTC burden, progression and

survival [10, 16, 17], in that the overall survival for patients with a doubling time of calcitonin <6 months is approximately 2 years and around 8 years for those with a doubling time of 6–24 months [14].

When calcitonin and/or CEA levels rise, imaging techniques are fundamental to determine tumor extension. Ultrasound (US) of the cervical region is a technique of choice to evaluate the primary tumor, residual or local recurrent disease, and regional lymph node involvement. Furthermore, it offers the possibility of making biopsy possible although it is not useful for detecting mediastinal disease.

CT or magnetic resonance imaging (MRI) of the neck, thorax and abdomen is useful at diagnosis to appraise the presence of distant metastases in the most common locations (liver, lungs, mediastinum and bone). The indication for these techniques relies on the calcitonin levels and is normally ordered when calcitonin levels are higher than 150 pg/ml) [10]. Hepatic metastases are hyperechoic on US and may be confused with hemangiomas. Head CT or MRI is not indicated unless the presence of brain metastases is suspected. Since most bone metastases are lytic in nature, they may go undetected by bone scintigraphy and other nuclear medicine techniques. However, some of them have been used to detect recurrent MTC lesions, when there are elevated levels of calcitonin, and conventional imaging techniques yield negative results [18, 19].

^{18}F-Fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) offers no advantage in this context, given MTC's low uptake (standardized uptake value <5), except for tumors with more aggressive clinical behavior or growth [18]. Preliminary data suggest that the use of other PET tracers, such as ^{18}F-DOPA and ^{68}Ga-DOTATOC or ^{68}Ga-DOTATATE may detect MTC better than ^{18}F-FDG. In this setting, ^{18}F-DOPA has greater sensitivity to detect the presence of lesions and the number of these with an overall sensitivity of 70 % compared with 44 % of ^{18}F-FDG PET/TC [20].

The most widely used radiopharmaceuticals in neuroendocrine tumors display low sensitivity in MTC. Metaiodobenzylguanidine (MIBG) is a radiopharmaceutical specific for tumors originating from the neural crest, and MIBG-I^{131} or MIBG-I^{123} scintigraphy, used mainly in pheochromocytoma, shows high specificity (up to 95 %) but low sensitivity (35 %) for the detection of MTC, which limits their use in MTC. Meanwhile, [^{111}In] diethylenetriaminepentaacetic acid (DTPA)-octreotide (Octreoscan) has higher sensitivity to detect involved lymph nodes in patients with occult MTC, typically associated with less aggressive behavior (70 %), and to select patients with inoperable tumors for peptide receptor radionuclide therapy [18].

Treatment

MTC treatment depends primarily on surgery, and the prognosis is good when localized disease can be fully excised. The use of surgery is more limited and controversial in disseminated disease. Generally speaking, adjuvant surgery is contemplated in advanced disease to debulk the tumor burden, relieve symptoms and prevent complications. Usually, surgery is not recommended for systemic metastases, given that miliary hepatic or disseminated lung disease is common. The consensus of a multidisciplinary team of specialists in thyroid cancer is advised when considering surgery in the setting of advanced MTC disease [22].

By itself, the presence of metastatic disease does not justify automatic systemic treatment. It should be postponed in silent, disseminated MTC with low tumor burden or high calcitonin values without macroscopic structural disease if there is no evidence of progression on imaging studies. In contrast, in cases of clear imaging evidence of tumor progression over the last 12–14 months, large volume of disease, and/or symptoms disease, systemic treatment should be initiated [21]. Active treatment is also indicated to control distant metastases that can cause collateral harm, such as brain and lung metastases, in patients with symptoms of excessive hormonal secretion or in those who have an active pathological fracture [10].

Most new treatments and drugs are currently being developed and target tyrosine kinase receptors. To date, most international regulatory bodies have approved the multikinase inhibitors vandetanib and cabozantinib to treat aggressive, advanced MTC.

Vandetanib acts by inhibiting several membrane receptors including VEGFR-2, VEGFR-3, *RET*, epidermal growth factor receptor (EGFR) and, to a lesser extent, VEGFR-1 and was the first drug approved by the American Food and Drug Administration (FDA) and European Medicine Agency (EMA) for the treatment of advanced MTC [23–25].

In the phase III, double-blind, randomized clinical ZETA (Zactima Efficacy in Thyroid Cancer Assessment) trial comparing vandetanib against placebo in sporadic or hereditary MTC, median progression-free survival in the vandetanib-treated group was higher [median not reached in the vandetanib arm vs. 19.3 months in the placebo arm, hazard ratio (HR) 0.46; 95 % confidence interval (CI) 0.31–0.69, $p < 0.001$] after 24 months of follow-up. Vandetanib was also advantageous regarding response (45 vs. 13 %, $p < 0.001$) and disease control (87 vs. 71 %, $p < 0.001$) rates. All subgroups benefitted more from vandetanib regardless of gender, performance status, initial disease stage, sporadic or hereditary tumor, number of prior treatments and treatment response. The high

percentage (41 %) of patients whose *RET* mutation status was unknown precluded definitive conclusions as to the benefit of vandetanib based on this variable [26].

Vandetanib has been associated with several adverse effects that tend to be mild and easily managed. A phase IV randomized trial (NCT01496313) is underway to appraise differences in response and toxicity in patients with MTC treated with 300 versus 150 (half dose) mg once daily. Common side effects of vandetanib include dermatological and cardiologic complaints, diarrhea, fatigue, headache, hypocalcemia, hypoglycemia, increased transaminase levels and thyroid dysfunction. Dermatological toxicity, with as other EGFR inhibitors, is associated principally with a papulopustular rash and photosensitivity observed in all patients. An important cardiologic toxicity detected in treatment with vandetanib and with other tyrosine kinase inhibitors is the QTc prolongation. Electrocardiogram and echocardiograms are therefore indicated prior to initiating vandetanib, as it is contraindicated in patients with QTc >480 ms. The use of 5-HT3 antagonists (except palonosetron) and metoclopramide is discouraged for the treatment of nausea, as they can increase the risk of prolonging the QTc interval.

The effect of combining vandetanib and other antineoplastic agents such as irinotecan, bortezomib (NCT00923247), and mammalian target of rapamycin (mTOR) inhibitor are currently being investigated to boost treatment effectiveness [27].

Cabozantinib is a tyrosine kinase potent ATP-competitive inhibitor that acts on VEGFR-2, MET and *RET* receptor, and against KIT, AXL and FMS-like tyrosine kinase 3 (FLT3) [28]. The EXAM (Efficacy of XL184 in Advanced Medullary) study was a phase III, double-blind randomized efficacy trial of cabozantinib versus placebo. The study's primary aim was achieved, i.e., cabozantinib did indeed prolong progression-free survival (11.2 vs. 4 months, HR 0.28, 95 % CI 0.19–0.40, $p < 0.001$) [29]. Response rate results were unquestionable—cabozantinib exhibited a 28 % response rate, while placebo was 0 % ($p < 0.001$). Moreover, individual changes in calcitonin levels at 3 months correlated significantly with radiological response at the same time point ($p < 0.0001$).

Common side effects of cabozantinib included diarrhea, palmar-plantar erythrodysesthesia, weight loss, anorexia, fatigue, hypertension and hypocalcemia. Given the high rate of toxicity-motivated interruptions and dose reductions,

Table 1 EXAM and ZETA studies in medullary thyroid carcinoma: indirect comparison

Variable	EXAM study Cabozantinib	EXAM study Placebo	ZETA study Vandetanib	ZETA study Placebo
Dosage	140 mg daily		300 mg daily	
Common signaling	VEGFR-2, RET		VEGFR-2, RET	
Specific signaling	MET, KIT, AXL, FLT3		EGFR, VEGFR-3	
Phase III clinical trial	NCT00704730		NCT00410761	
Number of patients	219	111	231	100
Progression-free survival	11.2 months	4	30 months (estimated)[a]	19.3
Statistical significance: *p*	<0.001		<0.001	
Response rate	28 %	0 %	45 %	13 %
Statistical significance: *p*	<0.001		<0.001	
Disease control rate	94 %	27 %	87 %	71 %
Dose reduction	79 %	9 %	35 %	3 %
Discontinuation due to toxicity	16 %	8 %	8 %	0 %
Grade ≥3 adverse events	69 %		47 %	
Grade ≥3 diarrhea	34 (15.9 %)	2 (1.8 %)	25 (11 %)	2 (2 %)
Grade ≥3 palmar-plantar syndrome	27 (12.6 %)	0	NA	NA
Grade ≥3 fatigue	20 (9.3 %)	3 (2.8 %)	13 (6 %)	1 (1 %)
Grade ≥3 hypertension	18 (7.9 %)	1 (1 %)	20 (9 %)	0
Grade ≥3 QTc prolongation	NA	NA	18 (8 %)[a]	1 (1 %)
Grade ≥3 loss of appetite	10 (5 %)	1 (1 %)	9 (4 %)	0
Grade ≥3 rash	2 (1 %)	0	8 (4 %)	1 (1 %)
Grade 5 adverse events (death)	5 %		2 %	

EXAM Efficacy of XL184 in Advanced Medullary Thyroid Cancer, *ZETA* Zactima Efficacy in Thyroid Cancer Assessment, *VEGFR-3* vascular endothelial growth factor receptor 3, *RET* rearranged during transfection, *MET* mesenchymal-epithelial transition, *KIT* tyrosine protein kinase kit or CD117, *FLT3* FMS-like tyrosine kinase 3, *EGFR* epidermal growth factor receptor, *NA* not applicable

[a] Median progression-free survival: vandetanib estimated at 30 months (not reached)

plans are in place to evaluate a lower starting dose versus 140 mg.

It is worth noting that one of the inclusion criteria for patients in the cabozantinib study was documented progression at study entry; additionally, they presented high comorbidities and poor prognosis. In contrast, the vandetanib trial did not include the tumor progression criterion and hence, most of the sample had fairly indolent disease.

Table 1 presents a comparison of clinical outcomes with vandetanib and cabozantinib as regards activity and tolerability.

External beam radiotherapy (EBR) has a limited role in the treatment of these patients. It might be administered locally to the neck in inoperable patients, as well as in those who maintain high calcitonin levels postoperatively [30]. Likewise, MTC is not iodine avid, so treatment with radioactive iodine is not indicated.

MTC is relatively resistant to traditional chemotherapy, and it should, therefore, not be contemplated as first-line therapy for advanced disease [10]. The earliest studies that evaluated the role of chemotherapy in MTC were performed more than 30 years ago. The outcomes lacked rigor and accuracy because different methodologies were used to evaluate response. Doxorubicin was the most widely studied agent with a response rate of 0–22 % assessed by Response Evaluation Criteria in Solid Tumors (RECIST). This limited response is very short-lived and is associated with high toxicity. Other chemotherapeutic agents such as platin, taxanes and gemcitabine similarly have poor activity [31].

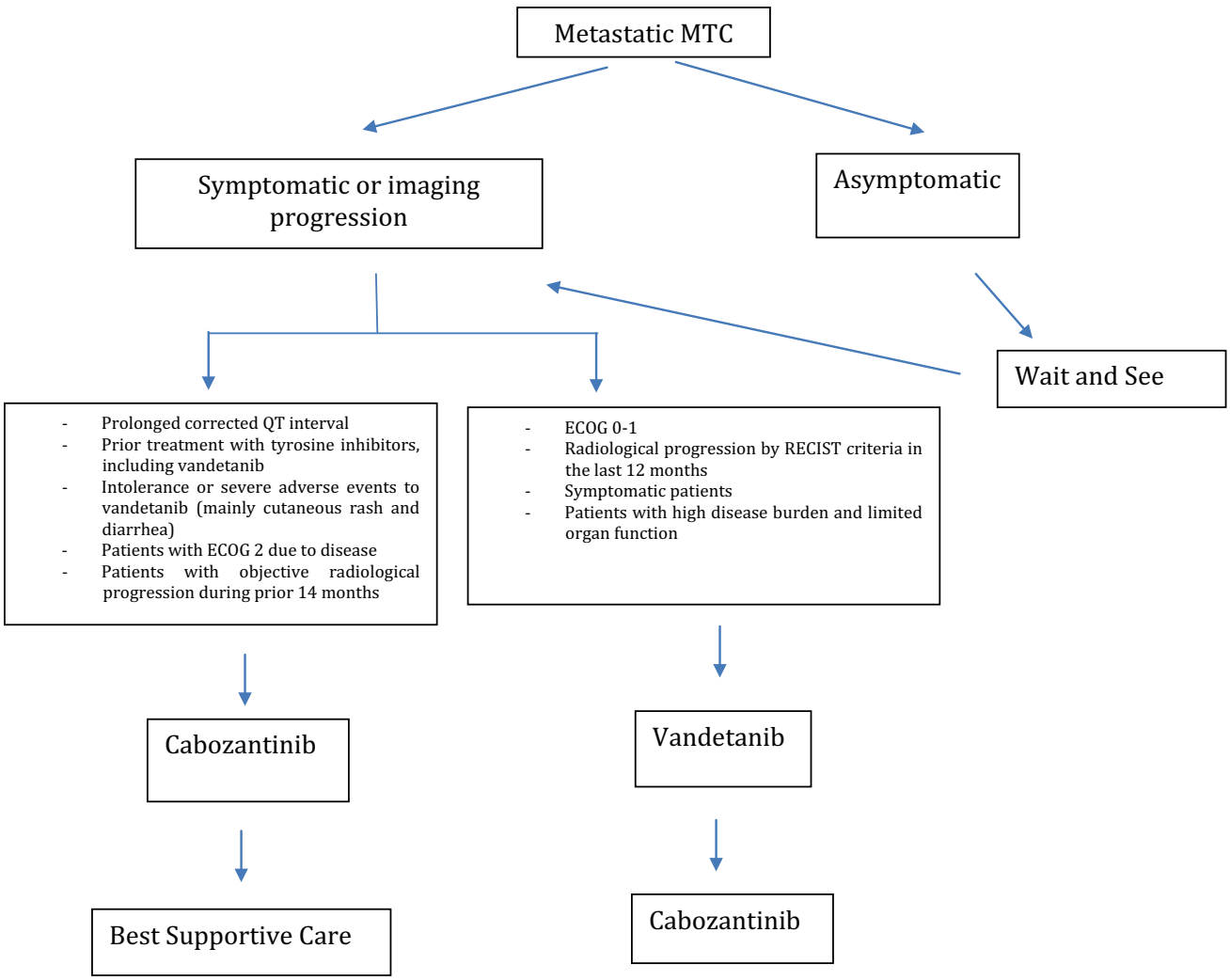

Fig. 1 Multidisciplinary approach algorithm for the management of advanced medullary thyroid carcinoma. *MTC* medullary thyroid carcinoma, *RECIST* Response Evaluation Criteria in Solid Tumors, *ECOG* Eastern Cooperative Oncology Group

Diarrhea and Cushing's syndrome, both associated with hormonal secretion, generally require intensive treatment. Selected patients may be candidates for aggressive local therapies like surgical debulking or hepatic transarterial chemoembolization [10]. Loperamide or somatostatin analogues can be effective to treat diarrhea. MCT-induced Cushing's syndrome tends to have a poor prognosis and debilitates patients; therefore, a prompt therapy with multimodal medical treatment targeting hypersecretion of cortisol is needed; bilateral adrenalectomy might also be contemplated and may be often the best option [10].

In properly selected cases, loco-regional neck or mediastinal recurrence is best treated by reoperation. EBR should be delivered postoperatively, when neck involvement is extensive [14]. Surgical resection should be considered in patients with isolated or limited brain or bone metastases, while EBR can be indicated for inoperable brain or osseous lesions [10]. Cement injection and bisphosphonates may be used in treating bone metastases [14].

When considering hepatic transarterial chemoembolization for cases displaying only liver metastases, it should be performed earlier rather than later. Partial responses have been observed in approximately 40 % of patients [32].

Figure 1 summarizes the multidisciplinary management of advanced MTC.

Prognosis

The most reliable marker to follow up the evolution of the disease is serum calcitonin levels. There is a clear relationship between calcitonin doubling times and outcome [10]. The presence of elevated CEA levels is an indication of cell undifferentiating and worsens the overall prognosis.

MTC comprises 3 % of all thyroid cancers and 13.4 % of all thyroid-related deaths. MTC's pathological aggressiveness is intermediate between differentiated (papillary and follicular) and undifferentiated (anaplastic) thyroid carcinoma.

At the time of diagnosis, about half of the cases will present metastasis beyond the thyroid, primarily to the neck and mediastinal node basins, and some (15–20 %) will have distant metastases. The vast majority (90 %) of individuals with metastatic disease will die as a result of progression being the disease stage a decisive prognostic factor [33].

The most decisive survival factor is tumor stage. Thus, overall 10-year survival rates are roughly 93–100 % in early disease (stages I–II), around 70 % in locally advanced disease (stage III) and just about 20–10 % in stage IV or relapse.

Table 2 Prognostic factors in medullary thyroid carcinoma

Prognostic factors	Good prognosis	Bad prognosis
RET mutations	609, 611, 618, 620, 634, 768, 790, 791, 804, 891 codons	883, 918 codon
Gender	Female	Male
Age at surgery	Young	Old
Plasma calcitonin	Low	High
Procalcitonin/calcitonin-related peptide	High	Low
Calcitonin immunoreactivity	High	Low
CEA (carcinoembryonic antigen)	Low	High
Amyloid substance	Positive	Negative
MTC types	MEN2A and familial MTC	MEN2B and sporadic
Vascular invasion	Absent	Present
DNA ploidy	Diploid	No diploid
Tumor size	Small	Large
Surgical resection	Complete	Incomplete
Extra-thyroid disease	Negative	Positive
Lymph node metastasis	Negative	Positive
Distant metastasis	Negative	Positive

Survival is higher when complete resection is possible. In patients with unresectable disease or distant metastases, median overall survival is 2–3 years [34].

Age is also an important prognostic factor. Between 95 and 75 % of patients under the age of 40 are still alive 5 and 10 years after diagnosis, respectively, while survival decreases from 65 to 50 % in patients older than 40.

Somatic *RET* mutation correlates with poor outcomes in sporadic MTC not only because of the greater likelihood of disease persistence, but also because of exhibiting lower survival rates long term. Of greater note, the presence of a somatic *RET* mutation is associated with lymph node involvement at diagnosis, which is known to indicate scant possibilities for a definitive cure [5]. Lymph node metastases at diagnosis, larger tumors and vascular invasion were all independent predictors of recurrence, persistent disease and metastases [35].

Table 2 summarizes the most significant prognostic factors in MTC.

Conclusions

Given its biopathological, serological, imaging and clinical distinctiveness, advanced MTC should be managed by a multidisciplinary team at specialized centers where endocrinologists, pathologists, clinical biochemists,

radiologists, radiation and medical oncologists, head and neck surgeons can all collaborate to achieve optimal patient outcomes [36]. Advanced MTC has gone from being a disease with no systemic treatment to currently being treated with tyrosine kinase inhibitors such as vandetanib or cabozantinib. However, it is cured only rarely and by means of surgery. Better understanding of the molecular biology underlying this tumor is needed, as well as the mechanisms of resistance to the drugs used to treat it.

Further research is crucial if we are to respond to certain questions such as: when treatment should be started; how to find accurate, sensitive techniques to detect the presence of micrometastases in patients with only elevated circulating tumor markers; and what the best systemic sequential or combined treatment is, as well as which are the most accurate predictive or prognostic biomarkers.

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