

## Advances in Diagnostics and Therapy of Medullary Thyroid Carcinoma (MTC)– A Mini-Review

### Abstract

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine neoplasm that arises from parafollicular C cells of the thyroid gland. Unlike the typical papillary carcinoma, medullary carcinoma develops more rapidly and causes distant metastases resistant to chemotherapy. The treatment options for MTC are surgery or pharmacotherapy. In recent years, major advances have been made especially in the pharmacological treatment of MTC. This paper aims to review the methods of diagnosis and treatment of MTC, taking into consideration the most recent findings. PubMed, PubMed Central, and Google Scholar databases were searched using keywords related to medullary thyroid carcinoma, its molecular and imaging diagnosis, thyroidectomy, and systemic pharmacotherapy. English-language articles were searched and selected after analyzing abstracts. Types of articles included mainly original articles and meta-analyses. From the initial search, 39 articles were retrieved for final analysis. This mini-review describes diagnostic methods for MTC focusing on testing biomarker levels. The most important, calcitonin, correlates linearly with tumor growth. First-line therapy for MTC is based on total thyroidectomy along with cervical lymphadenectomy. In some cases, systemic therapy based mainly on tyrosine kinase (TK) inhibitors is necessary. Research is also being conducted into gene therapy and blockage of tumor mitochondrial metabolism. MTC is a rapidly growing neuroendocrine tumor requiring radical surgical treatment. In cases where it is not possible, treatments that block the process of tumor carcinogenesis at various stages are used. New substances are being developed constantly to allow more effective treatment.

**Keywords:** *Medullary thyroid carcinoma, Cancer management, Diagnostics, Thyroidectomy, Biomarkers, Neuroendocrine neoplasm*

### Introduction

Medullary thyroid cancer (MTC) is a neuroendocrine neoplasm originating from parafollicular C cells of the thyroid gland. It represents less than 5% of all malignancies diagnosed within the thyroid gland making it an extremely rare lesion.<sup>[1]</sup> The neoplasm is capable of secreting calcitonin and carcinoembryonic antigen (CEA), making it possible to suspect in biochemical test results.<sup>[2]</sup> The lesions are most often localized in the posterior upper regions of the thyroid lobes where there are larger clusters of neuroendocrine C cells. This cancer can occur sporadically but 25% of cases are associated with an inherited syndrome of other endocrinopathies (MEN2A or MEN2B) or familial without comorbidities. It is characteristically associated with the presence of mutations in the RET proto-oncogene. MTC manifests as a palpable nodule within the thyroid gland, at such a stage metastasis to the cervical lymph nodes (in 70% of patients) and

distant metastasis to the liver, lungs, bones, and brain (in 10-15% of patients) are already found. Another fairly common symptom is diarrhea caused by high levels of calcitonin.<sup>[1, 3]</sup>

### Materials and Methods

The mini-review was performed based on PubMed, PubMed Central, and Google Scholar online databases. Papers concerning mostly the last 10 years of MTC management were taken into consideration. Various forms of the following terms: “medullary thyroid cancer”, “MTC diagnosis”, “thyroidectomy”, “calcitonin” and “MTC systematic treatment” were used for research. Original articles and meta-analyses were selected after analyzing abstracts. Of publications from the fields of surgical oncology, clinical oncology, and endocrinology, those that comprehensively described the topic were accepted. Finally, 39 articles have been studied for this mini-review.

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## Diagnostics

Diagnosis of MTC is based on biochemical tests, imaging studies, and analysis of biopsy material. Imaging procedures such as ultrasound and computed tomography help localize a lesion noted on clinical examination. When distant metastases are suspected, multidetector tomography or magnetic resonance imaging of the liver with contrast and bone scintigraphy are additionally recommended. PET scanning with 18F-fluorodeoxyglucose is less sensitive in detecting metastases.<sup>[4]</sup> Performing fine-needle aspiration (FNA) biopsy is a useful method, but may result in misdiagnosis of MTC as non-neuroendocrine thyroid (papillary) neoplasm or other types of cancer (sarcoma, plasmacytoma). Therefore, such a result should be confirmed by biochemical tests which play the greatest role in the diagnosis of medullary thyroid cancer.<sup>[5]</sup> A sensitive marker in the diagnosis of MTC is calcitonin. An increase in its serum level correlates with an increase in tumor mass. A level that raises suspicion of MTC oscillates between 60-100 pg/ml, and a level of 500 pg/ml may indicate the existence of distant metastases. However, it should be remembered that calcitonin levels can be falsely elevated by the use of proton pump inhibitors, renal failure, or hypercalcemia.<sup>[1, 4]</sup> By the fact that MTC is an extremely rare tumor, not all guidelines recommend routine measurement of calcitonin levels in patients diagnosed with thyroid tumors. Therefore, there are other markers in the study to aid in diagnosis.<sup>[6]</sup> One of these is CEA, which has correlated with the stage of medullary carcinoma in the studies. Compared to calcitonin which has a linear relationship with MTC progression, CEA levels are significantly elevated (approximately >270 ng/ml) in advanced disease. Meanwhile, levels >500 ng/ml are associated with significant patient mortality.<sup>[7]</sup> Recently the use of Ca19.9 antigen has been proposed as a biomarker of poor prognosis of MTC, which had elevated levels in 16% of patients participating in a clinical trial.<sup>[8]</sup> It also seems reasonable to study the correlation of procalcitonin levels in medullary carcinoma. There have been found a sensitivity and specificity of 96% and the usefulness of this marker in calcitonin-negative patients with MTC is under consideration.<sup>[9]</sup> Despite the emergence of more recent studies and attempts to find further markers (e.g., circulating miR-375 micro-RNA), calcitonin and CEA remain the standard diagnostic markers.<sup>[1, 10]</sup> (Table 1) summarizes the information about MTC markers. Diagnosis requires a broader clinical view due to the possibility of false positives associated with other cancers like pancreatic or colorectal cancer where the relevant markers may also be elevated.

**Table 1. Biomarkers used in MTC diagnostics.**

Markers	Notices
Calcitonin	increases along with MTC mass, increasing level (from 60-100 pg/ml) arouses MTC suspicion
CEA	elevated level (>270 ng/ml) rather in advanced MTC
Ca19.9	appears to be related to poor prognosis in the course of MTC
Procalcitonin	helpful in patients with MTC in suspect but with negative calcitonin
miR-375 micro-RNA	currently in clinical trials

## Therapy

MTC management is currently initiated with total thyroidectomy with lymphadenectomy. Distant metastases demonstrate a poor response to chemotherapy and radiotherapy, for this reason, new therapeutic options like TK inhibitors, gene therapy, or immunotherapy are being introduced. In recurrent MTC, calcitonin level is an important parameter. Implementation of systemic treatment is considered when the level of this marker increases after thyroidectomy.<sup>[11]</sup>

## Surgical treatment

According to contemporary guidelines, surgical intervention is the first-line treatment for MTC. The vast majority of MTC cases are still operated on using traditional surgery, although transoral endoscopic thyroidectomy with vestibular access is also being increasingly used.<sup>[5, 12-14]</sup> It is essential to pay attention to the risk of accidental resection of the parathyroid glands during the procedure, which will be associated with hypoparathyroidism in the future.<sup>[15]</sup> Nowadays, thanks to autofluorescence, we can accurately visualize these anatomical structures and avoid their accidental damage.<sup>[16]</sup> Due to the low (about 6%) risk of recurrence of the neoplastic process in the opposite lobe, total thyroid resection combined with resection of the lymph nodes of the middle compartment is recommended instead of hemithyroidectomy.<sup>[17]</sup> A more personalized approach should be discounted for patients with metastatic lesions. Less radical removal of the medial and lateral compartment lymph nodes than described above is being considered to minimize the side effects and long-term complications of this procedure.<sup>[18, 19]</sup>

## Systemic treatment

One of the breakthroughs in systemic therapy for MTC was the development of tyrosine kinase (TK) inhibitors. Simultaneous laboratory and clinical studies yielded several new substances from this group of drugs. They can be classified in terms of chemical structure into pyridine or purine inhibitors. However, some substances can inhibit other factors and protooncogenes (multi-inhibitors). Kapiteijn E. *et al.* presented that the use of targeted TK inhibitors like gefitinib contributed to disease stabilization lasting 24 weeks in some patients.<sup>[20]</sup> During this period the effects of axitinib as a multiple kinase inhibitor, as well as vandetanib and sorafenib were also studied. The use of sunitinib showed the highest percentage of tumor stabilization, reaching up to 87%.<sup>[21, 22]</sup> Alectinib showed promise due to its lack of inhibition of the vascular endothelial growth factor 2 (VEGFR2), resulting in a marked reduction in its undesirable anti-angiogenic effect. Carboxamide and quinazoline inhibitors showed similar prospects.<sup>[23, 24]</sup> The result of a clinical trial on the efficacy of cabozatinib published by Krajewska J. *et al.* stated that the compound is an effective therapeutic option with acceptable toxicity in MTC patients. The substance is a multi-inhibitor blocking VEGF, EGF factor tyrosine kinase, MET, and RET protooncogenes. Depending on the presence of the disease-conditioning RET M918T mutation, survival ranged from 11 to 44 months.<sup>[25]</sup> The substance has also been in clinical trials for the treatment of other solid tumors and blood cancers,

however, there have been reports of side effects (diarrhea, hypertension, hand-foot syndrome) Nevertheless, cabozantinib is registered as a drug in MTC and a second-line treatment, e.g. in renal cell carcinoma, and has also been shown to be active against tumor metastases (blocking AXL kinase).<sup>[26, 27]</sup> Another TK inhibitor, lenvatinib had broad effects, on factors VEGFR-1, 2, and 3, FGFR-1-4, PDGFRa, and the aforementioned RET proto-oncogene. The 59 patients with inoperable MTC showed a disease control rate of 80%, which was the highest recorded rate for this group of drugs in the study conducted by Maia A.L. *et al.*<sup>[28]</sup> Del Rivero J. *et al.* conducted a trial to determine a safe co-administration of the aforementioned vandetanib with bortezomib (an inhibitor of 26S proteasome activity). Bortezomib inhibited RET expression and reduced tumor mRNA but its activity in therapy was deemed insufficient to continue the study.<sup>[29]</sup> Recent reports list further kinase inhibitors being investigated for MTC therapy. Selpercatinib as a highly selective inhibitor acts on multiple RET mutations, while pralsetinib shows 8-28 times greater potency against wild-type RET mutations. Average response rates of 73 and 71%, respectively, have been demonstrated; with the increasing number of mutations in MTC, such data are a great hope for the future of therapy.<sup>[30-32]</sup> Dicitore A. *et al.* examined the RET protooncogene pathway and the activity of the cAMP-dependent protein kinase A involved in it. The in vitro anticancer activity of 8-chloroadenosine-3',5'-cyclic monophosphate (8-ClcAMP), and cAMP-selective analogs of type I protein kinase A on cancer cell lines was evaluated. It was shown that 8-ClcAMP was particularly effective in inhibiting the proliferation of tumor cells which allowed the potential use of cAMP analogs in therapy.<sup>[33]</sup> Also, salinomycin, a polyether ionophore antibiotic, was investigated by searching for RET protooncogene-blocking activity. Its anti-cancer effect results from blocking the PI3K/Akt/mTOR pathway. Certain salinomycin derivatives reduced RET expression by blocking the LRP6-Frizzled-Wnt complex. The results allowed salinomycin to be considered a promising substance for further clinical trials in the treatment of MTC.<sup>[34]</sup> Kinase and RET inhibitors appear to have greater efficacy in the treatment

of MTC than standard chemotherapy. A review by Hadoux J. *et al.* included multiple studies describing patients receiving various cycles of chemotherapy. The response rate seemed not to exceed 20%, and the combination of 5-fluorouracil + dacarbazine or capecitabine alone was considered the most effective.<sup>[35]</sup> This fact distinguishes MTC from other neuroendocrine neoplasms like pheochromocytoma or gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NENs). Another group of drugs used in therapy were retinoids in combination with a radioactive iodine isotope, but due to their low response rate, they have not found wider acceptance.<sup>[36]</sup> Also due to numerous side effects, depsipeptide, a histone deacetylase inhibitor, has not been implemented for wider treatment.<sup>[37]</sup> In contrast, thalidomide and its non-teratogenic derivative, lenalidomide, have shown promising results. Stabilization of the pathological lesion was observed in half of the patients.<sup>[38]</sup> Several different substances also contribute to MTC therapy. Combrestatine A4 phosphate causes reorganization of the microtubules of dividing tumor cells and the result of its administration was the arrest of disease progression for at least a year in half of the patients using it. Sodium iodide symporter would be a suitable target for MTC gene therapy under development. Somatostatin analogs lanreotide and octreotide, widely used in all other types of neuroendocrine lesions, also have gained in importance in the MTC therapy.<sup>[39, 40]</sup> Recently, the focus has been on mitochondrial metabolism during MTC development. The compound triphenyl-phosphonium-carboxy-proxyl mitoquinone (MitoQ) is capable of suppressing MTC cells by disrupting mitochondrial metabolism in cancer cells including those resistant to the main drugs, vandetanib or cabozantinib. Another success was the identification of mortalin (a mitochondrial chaperone of the Hsp70 family), which is overexpressed in MTCs - its destruction can induce the death of pathological cancer cells. The rhodocyanine dye MKT-077 is capable of this but has not undergone clinical trials due to renal toxicity. Other benzothiazole derivatives of MKT-077 are under investigation, with the hope of being them in MTC therapy.<sup>[41]</sup> The management of patients with MTC is reviewed in (Figure 1).

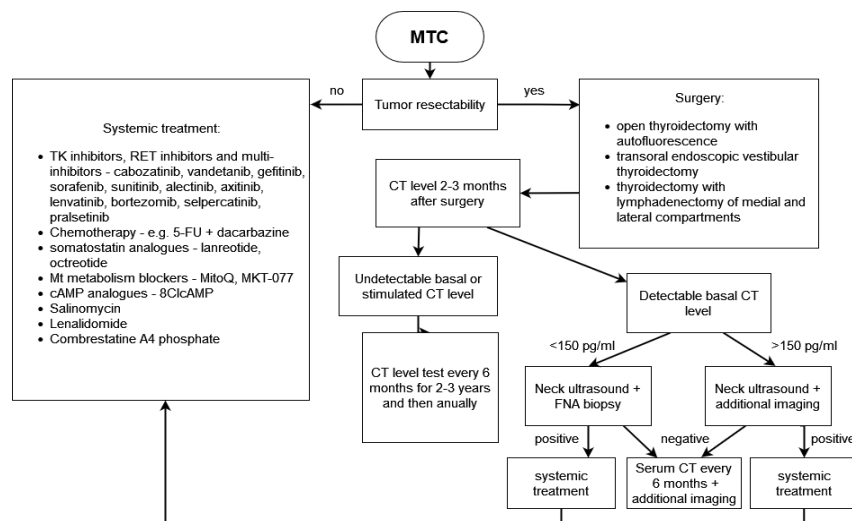


Figure 1. Management algorithm for patients with MTC.

## Conclusion

MTC is a rare neuroendocrine neoplasm most often associated with genetic mutations, it is more malignant than papillary thyroid carcinoma and its suspicion may be raised by symptoms associated with excessive calcitonin secretion. Measurement of biomarkers (especially calcitonin) plays the greatest role in MTC diagnosis as it should be remembered that FNA is not sensitive in detecting MTC. The therapy of choice for MTC is radical thyroidectomy with cervical lymphadenectomy. MTC distant metastases do not respond to chemotherapy and radiotherapy therefore specialized systemic treatment is required for inoperable lesions or the presence of metastases. Over the past 10 years, significant progress has been made in the discovery of new drug groups based on gene therapy and blocking the MTC carcinogenesis pathway, which provides a hopeful glimpse into the future of MTC therapy.

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## Conflict of interest

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## Ethics statement

None.

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