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Recent Advances in the Diagnostics and Management of Medullary Thyroid Carcinoma: Emphasis on Biomarkers and Thyroidectomy in Neuroendocrine Neoplasms

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Abstract

Medullary thyroid carcinoma (MTC) is an uncommon neuroendocrine tumor that originates from the parafollicular C cells in the thyroid. Unlike the more common papillary carcinoma, MTC tends to progress more aggressively and is prone to metastasis that is often unresponsive to chemotherapy. The main therapeutic approaches for MTC include surgical intervention and pharmacological treatments. Recent years have seen significant progress, particularly in the pharmacological management of MTC. This review aims to examine the diagnostic and treatment strategies for MTC, incorporating the latest findings. A thorough search was conducted in databases such as PubMed, PubMed Central, and Google Scholar, using keywords related to MTC, its molecular and imaging diagnostics, thyroidectomy, and systemic pharmacotherapy. Only articles published in English were considered, and abstracts were reviewed for relevance. The selected articles primarily included original research studies and meta-analyses. A total of 39 articles were included for detailed analysis. This mini-review highlights the diagnostic techniques for MTC and emphasizes the importance of biomarker-level testing. In particular, calcitonin shows a strong correlation with tumor progression. The standard treatment for MTC includes total thyroidectomy accompanied by cervical lymph node dissection. In certain cases, systemic therapy, particularly with tyrosine kinase (TK) inhibitors, is also indicated. Ongoing research is investigating innovative treatments such as gene therapy and the inhibition of tumor mitochondrial metabolism. MTC is a fast-growing neuroendocrine tumor that requires comprehensive surgical treatment. When surgery is not feasible, therapies that target different stages of tumor carcinogenesis are employed. The development of new pharmacological agents continues to improve treatment outcomes.

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

Introduction

Medullary thyroid carcinoma (MTC) is an uncommon neuroendocrine tumor that develops from the parafollicular C cells in the thyroid gland. Representing less than 5% of all thyroid cancers, it remains a relatively rare condition [1]. The tumor is known to produce calcitonin and carcinoembryonic antigen (CEA), which serve as biomarkers detectable through biochemical assays [2]. MTC often arises in the upper posterior regions of the thyroid lobes, where C cells are more concentrated. While most MTC cases occur sporadically, about 25% are linked to inherited endocrine syndromes like MEN2B or MEN2A, or present within families without additional endocrine disorders. A hallmark of MTC is the presence of mutations in the RET proto-oncogene. Clinically, patients may notice a palpable thyroid nodule. At diagnosis, metastasis is common, with 70% of cases involving cervical lymph node spread and 10-15% exhibiting distant metastases to organs such as the liver, bones, lungs, and brain. Additionally, high calcitonin levels often cause gastrointestinal symptoms, including diarrhea [1, 3].

This review aims to examine the diagnostic and treatment strategies for MTC, incorporating the latest findings.

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Materials and Methods

For this mini-review, a comprehensive search was conducted on PubMed, PubMed Central, and Google Scholar. Research articles published over the last decade focusing on the management of MTC were prioritized. Key search terms included "MTC diagnosis," "medullary thyroid cancer," "thyroidectomy," "calcitonin," and "MTC systemic treatment." Abstracts were reviewed, and only original research papers and meta-analyses were chosen. The articles selected were from the fields of surgical oncology, clinical oncology, and endocrinology provided they offered an in-depth analysis of the topic. In total, 39 studies were included in this review.

Results and Discussion

Diagnostics

The diagnosis of medullary thyroid carcinoma (MTC) involves biochemical assessments, imaging techniques, and biopsy analysis. Imaging modalities like ultrasound and computed tomography are essential for pinpointing lesions detected during clinical examination. If distant metastasis is suspected, additional imaging, such as multidetector tomography, contrast-enhanced magnetic resonance imaging (MRI) of the liver, and bone scintigraphy is recommended. However, 18F-fluorodeoxyglucose positron emission tomography (PET) scans have a lower sensitivity for identifying metastases [4]. Fine-needle aspiration (FNA) biopsy is commonly performed but can sometimes lead to misdiagnosis, identifying MTC as a non-neuroendocrine thyroid tumor (e.g., papillary carcinoma) or other malignancies (such as sarcomas or plasmacytomas). Therefore, such findings should be corroborated with biochemical tests, which are crucial in MTC diagnosis [5]. One of the most reliable biomarkers for diagnosing MTC is calcitonin, whose serum levels increase proportionally with tumor size. Suspicion of MTC is raised when calcitonin levels range between 60-100 pg/ml, while levels reaching 500 pg/ml may signal distant metastases. However, elevated calcitonin levels can also occur due to factors such as proton pump inhibitors, renal impairment, or hypercalcemia [1, 4]. Due to the rarity of MTC, not all guidelines advocate for routine calcitonin measurement in patients with thyroid tumors. Consequently, alternative biomarkers are being investigated to assist with diagnosis [6]. Carcinoembryonic antigen (CEA) has been identified as a potential marker, with its levels correlating with the MTC stage. Unlike calcitonin, which exhibits a direct relationship with tumor progression, elevated CEA levels (typically > 270 ng/ml) are associated with advanced stages, and levels exceeding 500 ng/ml are linked to higher mortality rates [7]. Recent studies have also proposed the Ca19.9 antigen as a prognostic biomarker for MTC, with elevated levels observed in 16% of clinical trial participants [8]. Additionally, the potential role of procalcitonin as a diagnostic marker in MTC is under evaluation, with findings suggesting a sensitivity and specificity of 96%, especially in calcitonin-negative patients [9]. Despite ongoing research into other markers, such as circulating miR-375 micro-RNA, calcitonin, and CEA continue to serve as the primary diagnostic indicators for MTC [1, 10]. **Table 1** provides a summary of these markers. It is essential to adopt a comprehensive clinical approach, as other cancers, such as pancreatic or colorectal cancer, may also lead to false-positive results by elevating similar biomarkers.

Table 1. Biomarkers used in MTC diagnostics

Marker	Notes
Calcitonin	Levels rise with MTC tumor size, and a range of 60-100 pg/ml raises suspicion for MTC.
CEA	Elevated levels (> 270 ng/ml) are typically observed in advanced MTC stages.
Ca19.9	Linked to poor prognosis in MTC cases.
Procalcitonin	Useful in cases of MTC suspicion where calcitonin levels are negative.
miR-375 micro-RNA	Currently under investigation in clinical trials for potential diagnostic value in MTC.

Therapeutic approaches

The standard approach to managing MTC begins with total thyroidectomy along with lymph node dissection. However, distant metastases often show limited response to conventional chemotherapy and radiotherapy, prompting the exploration of newer treatment strategies, including tyrosine kinase (TK) inhibitors, gene therapy, and immunotherapy. For recurrent MTC, monitoring calcitonin levels is crucial. An increase in this biomarker post-thyroidectomy signals the potential need for systemic treatment [11].

Surgical interventions

Current treatment guidelines place surgery as the primary approach for MTC. Most patients undergo traditional surgical procedures, although transoral endoscopic

thyroidectomy via vestibular access is gaining popularity [5, 12-14]. A significant concern during surgery is the inadvertent removal of the parathyroid glands, which can result in hypoparathyroidism. To prevent this, modern techniques using autofluorescence allow for precise visualization of these structures, minimizing the risk of unintentional damage [15, 16]. Due to the relatively low recurrence rate (around 6%) of the tumor in the contralateral thyroid lobe, total thyroidectomy coupled with resection of central compartment lymph nodes is preferred over hemithyroidectomy [17]. For patients with metastatic disease, a tailored approach is advised. This might involve less extensive removal of lymph nodes in the medial and lateral compartments to reduce potential side effects and long-term complications of more aggressive surgeries [18, 19].

Systemic treatment of MTC

Tyrosine kinase (TK) inhibitors represent a significant advancement in the treatment of MTC. Both laboratory and clinical investigations have introduced several promising compounds within this class, which can be divided into pyridine and purine inhibitors, with some functioning as multi-target inhibitors that act on various factors and proto-oncogenes. A study by Kapiteijn *et al.* [20] showed that the use of gefitinib, a targeted TK inhibitor, stabilized the disease for up to 24 weeks in certain patients. Other inhibitors, such as axitinib (a multi-kinase inhibitor), vandetanib, and sorafenib, were also examined during this period. Among them, sunitinib showed the most significant tumor stabilization, achieving a response rate of up to 87% [21, 22]. Alectinib has demonstrated potential due to its lack of VEGFR2 inhibition, preventing the unwanted anti-angiogenic effects typically associated with this target. Other compounds, including carboxamide and quinazoline inhibitors, have shown promising results [23, 24]. A clinical trial by Krajewska *et al.* [25] highlighted the efficacy of cabozantinib, a multi-inhibitor drug targeting VEGF, EGF, MET, and RET proto-oncogenes, showing survival rates ranging from 11 to 44 months based on the presence of the RET M918T mutation. Cabozantinib has also been studied for use in treating other solid tumors and blood cancers, although side effects such as diarrhea, hypertension, and hand-foot syndrome were reported. Nonetheless, it is approved for use in MTC and as a second-line treatment for renal cell carcinoma, also showing activity against tumor metastases by inhibiting AXL kinase [26, 27].

Lenvatinib, another TK inhibitor, targets multiple factors including VEGFR-1, 2, and 3, FGFR-1-4, PDGFRα, and RET, and demonstrated an 80% disease control rate in a study of 59 patients with inoperable MTC, marking it as one of the most effective drugs in its category [28]. Del Rivero *et al.* [29] investigated the combination of vandetanib and bortezomib (an inhibitor of 26S proteasome activity), but while bortezomib reduced RET expression, its therapeutic potential was insufficient to continue further studies.

Emerging kinase inhibitors are also showing promise in MTC treatment. Selpercatinib, a highly selective RET inhibitor, and pralsetinib, which is up to 28 times more potent against wild-type RET mutations, have demonstrated response rates of 73% and 71%, respectively. With the growing number of RET mutations in MTC, these findings provide hope for future treatment advances [30-32]. A study by Dicitore *et al.* [33] focused on the cAMP-dependent protein kinase A pathway, which plays a role in RET proto-oncogene activity. The compound 8-chloroadenosine-3',5'-cyclic monophosphate (8-ClcAMP) demonstrated significant anti-cancer activity by inhibiting tumor cell proliferation [33]. Additionally, salinomycin, a polyether ionophore antibiotic, was investigated for its ability to block RET proto-oncogene activity, showing promise by inhibiting the PI3K/Akt/mTOR pathway. Certain derivatives of salinomycin also reduced RET expression by targeting the LRP6-Frizzled-Wnt complex, suggesting its potential as a candidate for future clinical trials [34].

Compared to conventional chemotherapy, kinase and RET inhibitors have shown greater efficacy in treating MTC. A review by Hadoux and Schlumberger [35] noted that chemotherapy response rates typically did not exceed 20%, with the combination of 5-fluorouracil and dacarbazine or capecitabine being considered the most effective treatment regimen. This distinguishes MTC from other neuroendocrine tumors like pheochromocytoma or gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs). Retinoids, when combined with radioactive iodine, have also been explored but have not gained widespread acceptance due to their low response rates [36]. Depsipeptide, a histone deacetylase inhibitor, has not been widely adopted for MTC treatment due to significant side effects [37]. In contrast, thalidomide and its non-teratogenic derivative, lenalidomide, have shown encouraging results, with stabilization observed in half of the patients [38]. Other agents, such as combrestatine A4 phosphate, which

disrupts microtubules during cell division, have led to disease stabilization in half of the patients for at least a year. Sodium iodide symporter (NIS) is also being explored for its potential in MTC gene therapy. Somatostatin analogs, like lanreotide and octreotide, are also gaining interest as part of MTC therapy due to their established effectiveness in other neuroendocrine tumors [39, 40]. Recently, mitochondrial metabolism has become a focus of MTC research. MitoQ, a compound that suppresses MTC cells by disrupting mitochondrial function, has shown effectiveness against drug-resistant cancer cells. Additionally, the mitochondrial chaperone mortalin, overexpressed in MTC, is being targeted by the dye MKT-077, although it has not undergone clinical trials due to renal toxicity. Other derivatives of MKT-077 are currently under investigation for their potential role in MTC treatment [41]. **Figure 1** provides an overview of the management approach for MTC patients.

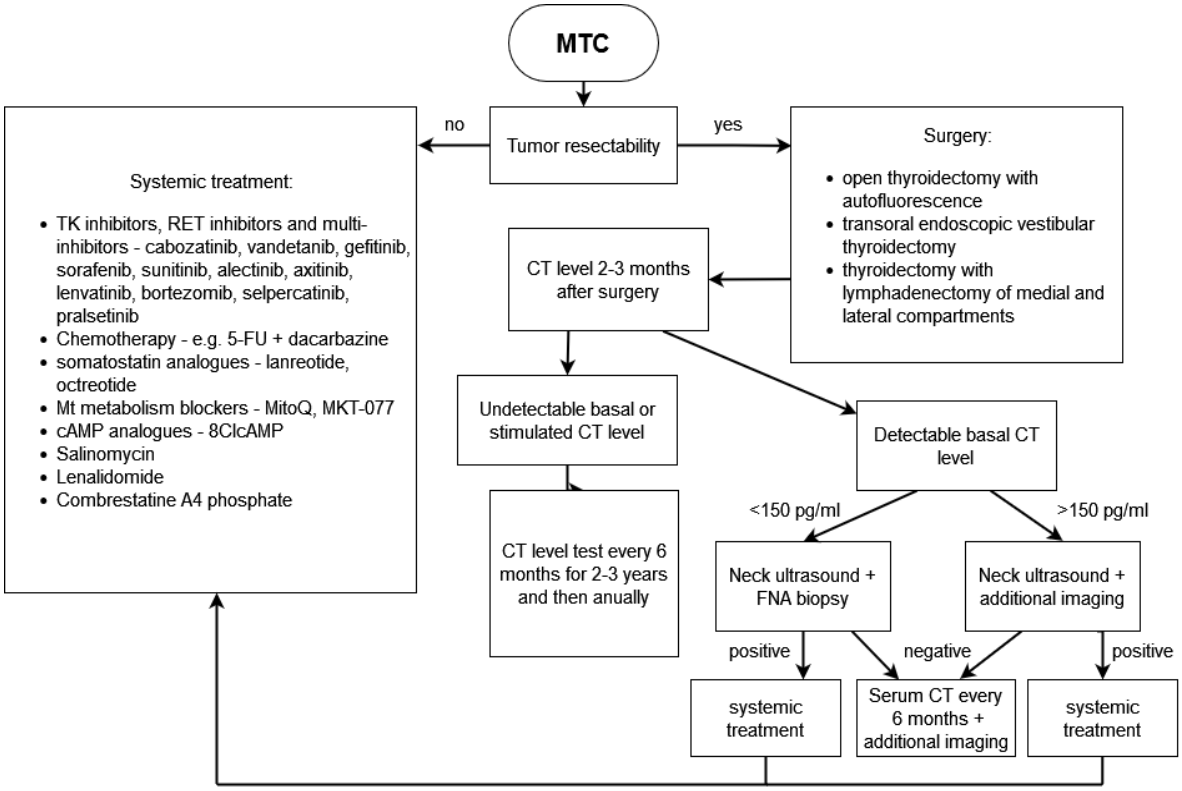

Figure 1. Management algorithm for patients with MTC.

Conclusion

Medullary thyroid carcinoma (MTC) is an uncommon neuroendocrine tumor primarily linked to genetic mutations. It is generally more aggressive than papillary thyroid carcinoma, and its diagnosis is often prompted by clinical signs indicative of excessive calcitonin secretion. The most critical diagnostic tool for MTC is the measurement of biomarkers, particularly calcitonin, as fine-needle aspiration (FNA) has limited sensitivity in detecting this type of cancer. The standard treatment for MTC involves total thyroidectomy followed by cervical lymph node dissection. For patients with distant metastases, chemotherapy and radiotherapy have minimal effect, necessitating alternative systemic therapies for inoperable tumors or metastatic cases. Significant advancements have been made over the last decade in developing novel therapeutic agents targeting gene pathways and the mechanisms driving MTC carcinogenesis, offering promising prospects for future treatments.

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