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MEDULLARY THYROID CARCINOMA (MTC): A CURRENT REVIEW OF EPIDEMIOLOGY, DIAGNOSIS, AND THERAPY

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ABSTRACT

Background: Medullary Thyroid Carcinoma (MTC) is a rare neuroendocrine tumor (1–5% of all thyroid cancers) characterized by disproportionately high mortality (13%), often complicated by advanced-stage diagnosis and early metastasis. This malignancy is uniquely driven by RET proto-oncogene mutations.
Aim: This review aims to comprehensively analyze contemporary MTC management strategies, focusing on advancements in precision diagnostics, targeted therapies, and identifying critical challenges related to therapeutic resistance and clinical guideline standardization.
Materials and Methods: An extensive synthesis of the current literature, prioritizing comprehensive review articles and meta-analyses published within the last five years, was conducted using multiple electronic databases (PubMed, Scopus).
Results: Recent breakthroughs include the highly effective and well-tolerated selective RET inhibitors (selpercatinib, pralsetinib), which offer improved outcomes compared to older multikinase inhibitors (MKIs). Diagnostic modalities are enhanced by advanced functional imaging (e.g. [18F]F-DOPA-PET/CT). Despite improved overall survival, the major clinical hurdle remains acquired drug resistance, mediated by RET kinase domain mutations and activation of bypass signaling pathways (MET, EGFR). Furthermore, substantial variability persists across international guidelines regarding optimal prophylactic surgery timing and criteria for initiating systemic treatment.
Conclusion: Future efforts must concentrate on establishing unified, dynamic risk stratification protocols, standardizing advanced imaging utilization, and implementing liquid biopsy (ctDNA) guided sequential therapy to effectively overcome acquired resistance and ensure durable long-term disease control.

KEYWORDS

Medullary Thyroid Carcinoma, Thyroid Carcinoma, RET Gene, RET Inhibitors, MEN Syndrome, Tyrosine Kinase Inhibitors

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1.Introduction

Medullary Thyroid Carcinoma (MTC) is a relatively rare neuroendocrine histological subtype of thyroid cancer, originating from the parafollicular C cells responsible for calcitonin production (Kaliszewski et al., 2022; Pelizzo et al., 2023). Although uncommon, it is characterized by high aggression and a disproportionately high percentage of thyroid cancer-related deaths (13%) (Gild et al., 2023). MTC occurs spontaneously or as a component of various inherited syndromes, such as Multiple Endocrine Neoplasia (MEN) types 2 and 3 (previously termed MEN2B) and Familial Medullary Thyroid Cancer (FMTC), which is currently classified as a subtype of MEN2 (Forma et al., 2025). The molecular basis for the development of this neoplasm is a mutation in the RET proto-oncogene. In hereditary cases, this is a germline mutation, while a somatic mutation is found in 40–60% of sporadic cases (Román-González et al., 2025). The diagnostic and treatment approaches for MTC distinctively diverge from those employed for well-differentiated thyroid cancer (Kim & Kim, 2021).

2.Methodology

This is a review based on an exhaustive analysis of scientific publications retrieved from multiple electronic databases: PubMed, PubMed Central, Google Scholar, and Scopus.

To ensure the provision of the most current and evidence-based knowledge on the topic, the analysis primarily focused on comprehensive review articles and meta-analyses published within the last five years.

2.1. Inclusion criteria:

The following types of scientific literature were considered for inclusion in this review:

- Articles focusing on the epidemiology, diagnosis, molecular pathogenesis (RET alterations), clinical staging, surgical management, and systemic therapy of Medullary Thyroid Carcinoma (MTC).
- Publications retrieved from the following primary databases: PubMed, PubMed Central, Google Scholar, and Scopus.
- Preference was given to high-level evidence, including comprehensive review articles, meta-analyses, and clinical practice guidelines from major international scientific societies.
- Studies published within the last five years (2020–2025) were primarily selected to ensure the currency of the evidence.

2.2. Exclusion criteria:

The following types of literature were generally excluded from the primary synthesis of this review:

- Primary research papers (e.g., small cohort studies, case reports) were excluded unless they provided unique, highly relevant, and recent data on novel diagnostic or therapeutic modalities not yet covered in review articles or guidelines.
- Publications not peer-reviewed or not retrieved from the predetermined academic databases.
- Non-English language articles, unless highly critical to the topic.
- Literature published before 2020, unless considered foundational knowledge (e.g., seminal studies on MTC staging or early molecular findings) or essential for historical context.

2.3. AI

Artificial intelligence tools were employed in this study solely as assistive instruments under human supervision. They were used for translation of selected sections of the manuscript, refinement of academic English (grammar,style,and clarity), and to improve efficiency in data processing. At no stage did AI replace human judgment - all data interpretation, classification, and formulation of conclusions were performed exclusively by the authors.

3.Results

3.1 Epidemiology

Thyroid Cancers (TC) are the most common endocrine malignancies and are ranked as the 7th most prevalent cancer worldwide, with a mortality rate positioned as the 24th highest among all cancers. Among them, we distinguish the most frequent differentiated histological subtypes (DTC) - papillary carcinoma (PTC) and follicular carcinoma (FTC) and the undifferentiated types - medullary thyroid carcinoma (MTC) and anaplastic carcinoma (ATC) (Forma et al., 2025). MTC accounts for roughly 1–5% of all TC cases, with the majority being sporadic (75%) and hereditary cases making up 25% (Matrone et al., 2022). Sporadic cases are more common in women, whereas hereditary cases occur with equal frequency in both sexes. The highest incidence of spontaneous MTC is observed between 40 and 60 years of age, with a mean age of 50 years (Forma et al., 2025). This pattern does not apply to hereditary cases, which can manifest as early as infancy (MEN2A, MEN3) or between 20 and 40 years of age for FMTC (Jacob et al., 2022; Yasir et al., 2023). Prognosis is contingent upon numerous factors, including age, resection status, and the histologic grade of the carcinoma. Generally, older patients with higher-grade lesions and incomplete resection demonstrate a poorer prognosis (Zhang et al., 2024a). A higher grade worsens the prognosis, which is linked to a higher frequency of distant metastases and an increased risk of local recurrence (Forma et al., 2025). MTC is associated with a worse prognosis compared to well-differentiated thyroid cancers, primarily due to the higher incidence of distant metastases and delayed diagnosis (Ramos Santillan et al., 2024). Distant metastases are observed in 7%–23% of patients at diagnosis and represent a well-established strong predictor of disease-specific mortality (Jung et al., 2016; Oh et al., 2024). Historical data indicate that the 5- and 10-year overall survival (OS) rates for MTC patients have typically ranged from 70–94% and 57%–90%, respectively (Cupisti et al., 2007; Jung et al., 2016), while recurrence-free survival (RFS) rates at 5 and 10 years varied between 83%–86% and 65%–66% (Lee et al., 2016). The most recent studies incorporating advancements in the diagnosis and treatment of this cancer suggest 5- and 10-year overall survival rates of 92.7% and 89.4%, and RFS rates of 71.1% and 56.1%, respectively (Oh et al., 2024). Survival outcomes reported for patients with MEN3 have demonstrated a disease progression and stage-dependent survival comparable to that observed in patients with MEN2A or sporadic MTC (Raue & Frank-Raue, 2018). Nevertheless, there is a clear need for more comprehensive, updated information regarding the long-term outcomes of MTC.

3.2 Pathogenesis

C-cell hyperplasia within the context of hereditary syndromes is classified as a premalignant condition, occasionally termed “in situ MTC”. These cases typically present with histological atypia. The RET proto-oncogene is responsible for encoding a receptor tyrosine kinase that acts upstream of several established oncogenic pathways. Pathogenic RET variants in MTC often result in the constitutive activation of RET via phosphorylation. This deregulation consequently drives uncontrolled activation of downstream pathways, leading to the amplification of cellular proliferation and altered migration and differentiation (Gild et al., 2023).

MEN2 is an autosomal dominant hereditary cancer syndrome resulting from missense gain-of-function mutations in the RET proto-oncogene on chromosome 10. More than 100 RET gene mutations have been identified in association with the occurrence of MEN2A syndrome (Raue & Frank-Raue, 2018).

The primary cause of MEN3 is the Met918Thr germline RET mutation (Castinetti et al., 2019).

A clear genotype-phenotype correlation exists concerning the clinical behavior of MTC, notably with the RET M918T variant being specifically linked to aggressive disease (Román-González et al., 2025).

3.3. Clinical Features

The most common clinical presentation of sporadic MTC is an asymptomatic solitary thyroid nodule, typically found in the upper pole. Consequently, it is often diagnosed at an advanced stage (Kim & Kim, 2021). Lymph node metastases are primarily found in the cervical nodes, present in 50% of patients at initial presentation (Haddad et al., 2025). The mediastinal nodes are usually affected next in sequence (Moley, 2010). Distant metastases are typically localized in the liver, lungs, bones, and brain (Kazakou et al., 2021). These metastases cause symptoms in 10% of patients upon admission. Furthermore, 15% of patients with the sporadic form report symptoms of compression or infiltration of the upper aerodigestive tract. Symptoms may also be associated with the calcitonin and hormonally active peptides (adrenocorticotropic hormone, calcitonin gene-related peptide) secreted by the tumor. These symptoms include diarrhea and flushing, which occur particularly often with advanced MTC. Cushing's syndrome may also appear rarely (Haddad et al., 2025).

MEN2 demonstrates high penetrance for MTC and can be concurrently associated with bilateral pheochromocytoma and primary hyperparathyroidism (Raue & Frank-Raue, 2018). MEN2A, which is the more common subtype, is characterized by the presence of two or more specific endocrine tumors (MTC, pheochromocytoma, or parathyroid adenoma/hyperplasia). Certain patients also exhibit cutaneous lichen amyloidosis in the scapular region of the upper back or Hirschsprung disease (Balinisteanu et al., 2023). The rarer MEN3 is characterized by medullary thyroid carcinoma, pheochromocytoma, and at least one extra-endocrine feature in about half of patients, including marfanoid body habitus, mucosal neuromas, and gastrointestinal signs. This subtype is marked by significantly greater aggressiveness and the occurrence of MTC at a younger age (Raue & Frank-Raue, 2018). To improve the prognosis in MEN syndromes, it is necessary to raise healthcare workers' awareness regarding the extra-secretory manifestations of these syndromes (Castinetti et al., 2019). FMTC is regarded as a clinical variation of MEN2A, distinguished by lower penetrance for pheochromocytoma and hyperparathyroidism, alongside a later presentation of MTC (Balinisteanu et al., 2023).

3.4. Diagnosis

MTC patients can be identified either through pathological diagnosis or via proactive genetic screening (Haddad et al., 2025). The diagnosis of sporadic MTC primarily relies on fine-needle aspiration (FNA) biopsy followed by immunohistochemical staining for calcitonin. It is also occasionally diagnosed after thyroidectomy based on biopsy results that were initially classified as indeterminate or suspicious for malignancy (Kim & Kim, 2021). Prior to surgery, every patient, including those with sporadic disease, must undergo assessment for hyperparathyroidism and pheochromocytoma (Haddad et al., 2025). In patients with confirmed pheochromocytoma, laparoscopic adrenalectomy must always be performed before thyroid surgery to prevent hypertensive crisis, which can be provoked by both anesthesia and the surgical procedure itself (Kurzawinski et al., 2025). Preoperative imaging should also include thyroid and neck ultrasound, encompassing the central and lateral neck compartments (Haddad et al., 2025).

Magnetic Resonance Imaging (MRI) is frequently used in the structural evaluation of recurrent or metastatic MTC for initial staging and subsequent assessment of treatment response. Computed tomography (CT) is generally preferred for visualizing lymph nodes and lung metastases. Importantly, distant metastasis does not constitute a contraindication to surgical intervention (Haddad et al., 2025).

Calcitonin, secreted by C cells, serves as a reasonably sensitive biomarker for MTC, though its specificity is limited, as it can be elevated in other malignant conditions (e.g., carcinoid and small cell lung cancers) and nonmalignant states (e.g., hypercalcemia, pregnancy, renal failure, sepsis, pheochromocytoma, autoimmune thyroiditis). Preoperative calcitonin concentrations align with the extent of metastatic disease. Levels below <53 pg/mL suggest a low probability of lymph node metastases, whereas levels exceeding 500 pg/mL imply a high likelihood. When levels surpass >1000 pg/mL, distant metastatic disease is strongly suspected, necessitating comprehensive preoperative staging with extended structural imaging or PET (Costante & Meringolo, 2020; Danila et al., 2019). A rising calcitonin level in a patient with recurrent MTC should prompt clinical evaluation and, depending on availability, the performance of PET or other advanced imaging studies (Danila et al., 2019; Gild et al., 2023). Despite its sensitivity, the routine measurement of basal serum calcitonin concentration as a screening tool is generally not recommended (Haddad et al., 2025). Carcinoembryonic antigen (CEA) is another significant diagnostic, prognostic, and predictive biomarker (Kim & Kim, 2021). Rapid doubling times for calcitonin and CEA reliably predict a more aggressive disease course. Basal serum measurements of calcitonin and CEA, taken 2 or 3 months postoperatively, form the primary basis of follow-up for residual disease. Postoperative imaging is justified even in the absence of extremely high serum markers. A low or normal calcitonin level three months after surgery strongly indicates a complete surgical response (Costante & Meringolo, 2020). Conversely, a detectable basal calcitonin or elevated CEA level should prompt a neck ultrasonography examination. Patients with persistently undetectable calcitonin and normal CEA can be monitored with annual serum marker measurements. It should be noted that calcitonin levels may prove unreliable for monitoring tumor response in patients undergoing RET inhibitor therapy (Haddad et al., 2025).

Germline RET mutation analysis is mandatory for all MTC patients. Genetic counseling should also be provided to first-degree relatives if a pathogenic germline RET variant is identified in the patient. Risk stratification relies on the specific RET alteration, leading to established guidelines for timing risk-reducing thyroidectomy to minimize MTC-related mortality in asymptomatic RET carriers (Wells et al., 2015). Somatic RET testing in sporadic MTC can significantly broaden the therapeutic options available to the patient and should be performed universally (Gild et al., 2023).

Positron emission tomography (PET) utilizing novel radioligands, particularly [18F]F-DOPA which offers higher lesion detection sensitivity, is effective for the enhanced detection of both recurrent and metastatic MTC (Gild et al., 2023). The substantial utility of this imaging modality for both diagnosis and prognostic assessment in MTC patients has been substantiated by numerous studies (Asa et al., 2021; Califano et al., 2022; Zhang et al., 2024b). This may allow for replacement of multiple imaging studies previously utilized in metastatic MTC, thereby reducing the need for repeated patient visits and hospitalizations in healthcare facilities, improving patient quality of life, and lowering infection risk.

3.5. Staging and grading

The staging of medullary thyroid carcinoma was separated from other thyroid cancers in the eighth edition of the AJCC Cancer Staging Manual in 2017. Staging criteria are based on tumor size, the presence or absence of extrathyroidal invasion, locoregional nodal metastases, and distant metastases (Amin et al., 2017). The staging of this neoplasm is complex because some professional societies do not use the TNM classification to guide therapy, as it often lacks other important prognostic factors. Instead, they incorporate numerous tumor and patient characteristics, including age and gender (Haddad et al., 2025). Predicting overall survival (OS) in MTC is notably challenging due to its inherent heterogeneous nature. From a histological standpoint, a grading system has been proposed for this neoplasm. This system rated three histological features (Ki-67 proliferative index, mitotic count, and the presence of coagulative necrosis) and categorized the tumor into low, intermediate, and high grades, which subsequently correlated with patient prognosis (Fuchs et al., 2020).

3.6. Treatment

The only curative approach for this neoplasm remains the complete surgical resection of the thyroid tumor and any locoregional metastases. Consequently, this is considered a primary prognostic factor (Kim & Kim, 2021). The procedure should involve total thyroidectomy, with neck dissection considered for patients with tumors <1 cm and unilateral disease, and total thyroidectomy with bilateral central neck dissection (Level VI) recommended for patients with tumors ≥1 cm or bilateral disease. Postoperatively, all patients must receive levothyroxine at a dosage designed to keep TSH within the normal range. TSH suppression is not advised in these patients because C cells do not express TSH receptors. MTC cells are unable to concentrate iodine.

Therefore, unlike differentiated carcinomas, there is no therapeutic utility for iodine-131 in MTC. External beam radiation therapy (EBRT) remains insufficiently evaluated as an adjuvant treatment for MTC. While rarely recommended, it can be administered for the palliation of painful or progressing bone metastases (Haddad et al., 2025). Traditional chemotherapy protocols, such as those using dacarbazine and doxorubicin, are no longer advised for MTC treatment (Wells et al., 2015).

Prophylactic surgery should be considered in patients with a family history of MTC and/or MEN2 who carry a RET gene mutation, in order to prevent MTC development (Forma et al., 2025). Determining the appropriate age for thyroidectomy in children diagnosed with MEN2A is an evolving area of practice (Haddad et al., 2025). In MEN3, thyroidectomy performed no later than 1 year of age is associated with a high probability of cure, but most children with this syndrome are not diagnosed at that age. A retrospective, international, multicenter study involving 345 patients reported the presence of MTC in 97% of patients undergoing thyroidectomy at a median age of 14 years. Adrenal-sparing surgery is possible in MEN3 syndrome, offering a high chance of preserving normal adrenal function (Castinetti et al., 2019).

The modern systemic treatment landscape for progressive metastatic MTC comprises antiangiogenic multikinase inhibitors (MKIs), including cabozantinib and vandetanib, which inhibit tumor growth pathways, as well as highly specific RET inhibitor therapies, such as selpercatinib and pralsetinib (Román-González et al., 2025). MKIs may be suitable for certain patients with unresectable recurrent or persistent MTC, but they are often unsuitable for those with stable or slow-progressing, indolent disease. MKIs have been shown to extend progression-free survival and are considered Category 1 preferred options, though they are associated with adverse effects (Kim & Kim, 2021). Vandetanib carries a risk of cardiac toxicity, specifically QTc interval prolongation. Cabozantinib is contraindicated in cases of severe hemorrhage. Selpercatinib (Category 1) or pralsetinib (Category 2B) are the preferred therapeutic choices for patients diagnosed with RET-mutation positive disease (Haddad et al., 2025).

Several promising novel therapeutic agents are currently in development for MTC. Pretargeted anti-CEA radioimmunotherapy using iodine-131 demonstrates the potential to enhance OS in a subgroup of patients exhibiting increased calcitonin doubling times (Haddad et al., 2025). Peptide receptor radionuclide therapy (PRRT) also presents a viable perspective, owing to the common neuroendocrine origin shared with tumors responsive to PRRT. Specifically, 177Lu-DOTATATE has shown clinical utility, with 62% of somatostatin receptor-positive metastatic MTC patients demonstrating a radiological response, and 51% achieving both a symptomatic and a biochemical response (Parghane et al., 2020). Preclinical research has indicated the potential use of genetically engineered T cells specifically targeting CEA, calcitonin, and the RET p.Met918Thr mutation as a novel treatment strategy for metastatic MTC (Erickson et al., 2022). Given that MTCs can exhibit substantial PD-L1 expression, pembrolizumab may represent another promising avenue for future treatment options (Fonseca et al., 2021).

The development of acquired resistance to multikinase inhibitors, resulting in clinical progression, represents a significant ongoing challenge in MTC therapy. Resistance mechanisms typically fall into two categories: "on-target" alterations occurring within the kinase domain, or "off-target" or bypass pathway alterations (Gild et al., 2023). Liquid biopsies examining circulating tumor DNA (ctDNA) offer a promising tool for the early identification of resistant clones, allowing clinicians to recognize resistance before radiological or clinical progression and enabling the timely implementation of subsequent lines of therapy (Wijewardene et al., 2021). New-generation RET-specific inhibitors designed to overcome acquired on-target resistance mechanisms are already being evaluated in first-in-human Phase I studies.

In patients experiencing symptoms related to tumor-secreted peptides, somatostatin analogs (octreotide, lanreotide) may prove effective (Haddad et al., 2025).

4. Discussion

The management of MTC has been profoundly transformed by the molecular understanding of the disease, pivoting the field towards precision oncology. The high dependency on the RET proto-oncogene, either somatically or in the germline, establishes a clear molecular target that differentiates MTC from the management strategies applied to well-differentiated thyroid cancers (Kim & Kim, 2021; Gild et al., 2023).

The advent of highly selective RET inhibitors (Selpercatinib and Pralsetinib) represents the most substantial therapeutic advancement in metastatic MTC. Their improved potency and reduced off-target toxicity compared to earlier multikinase inhibitors (MKIs) translate into significantly better progression-free survival (Román-González et al., 2025; Haddad et al., 2025). This confirms the molecular hypothesis that highly specific targeting of the oncogenic driver is superior to broad kinase inhibition.

Despite these successes, the discussion must center on the major limitation of targeted therapy: acquired resistance. Mechanisms of resistance, identified in preclinical models and now observed clinically, are predictable and involve both on-target mutations within the RET kinase domain and bypass mechanisms, such as the activation of MET or EGFR signaling. The realization that resistance is often subclonal and stochastic dictates a proactive management approach. This underscores the necessity of liquid biopsy (ctDNA) not only for detecting minimal residual disease (MRD) but, more critically, for real-time identification of acquired resistance mutations that necessitate switching to next-generation RET inhibitors or employing rational combination therapy. The ongoing development of new selective inhibitors targeting common resistance mutations is an area of urgent clinical need.

Diagnostic and prognostic tools also require standardized integration. While clinical and radiological progression remain the primary factors for initiating systemic therapy, the prognostic value of functional imaging, particularly [18F]F-DOPA-PET/CT, is becoming clearer, correlating positively with tumor burden and providing superior prognostic information over anatomical imaging. The continuing controversy among international guidelines (ATA, ESMO, NCCN) regarding the use of [18F]F-DOPA-PET/CT and the optimal timing for prophylactic thyroidectomy in moderate-risk MEN2 patients limits universal best practice implementation. Dynamic risk stratification, incorporating serum calcitonin doubling time and novel biomarkers, offers a path toward a unified, biologically informed algorithm for intervention.

Finally, novel therapeutic strategies, including Peptide Receptor Radionuclide Therapy (PRRT) and immunotherapy, offer hope for patients refractory to RET inhibition. The demonstrated efficacy of PRRT in SSTR-positive metastatic MTC patients provides a tolerable alternative. Intriguingly, the durable long-term overall survival observed in a small cohort of MTC patients treated with dual immune checkpoint blockade, despite a lack of objective radiological response, suggests that immunotherapy's benefit may be sustained through mechanisms not captured by standard oncological endpoints, advocating for a shift in how these therapies are assessed in future trials.

5. Conclusions

The evolution of Medullary Thyroid Carcinoma management necessitates urgent international efforts to generate current, large-scale epidemiological data that accurately reflect improvements stemming from advanced diagnostics and novel systemic therapies. A critical priority is the establishment of unified clinical guidelines by synthesizing the heterogeneous recommendations across various global professional societies. Such consensus should standardize the integration of dynamic risk stratification (utilizing calcitonin/CEA doubling times and novel biomarkers for prognosis) and clarify the precise role of [18F]F-DOPA-PET/CT in the staging and risk assessment of patients with high biochemic disease burden (500pg/mL).

The foremost contemporary challenge in systemic MTC therapy is the circumvention of acquired resistance to kinase inhibitors, which arises from both on-target RET domain mutations and bypass pathway activation (e.g., MET, EGFR). Future research must focus on validating next-generation RET inhibitors and developing rational combination strategies informed by liquid biopsy results to anticipate and overcome these resistance mechanisms. Despite the complexities, the considerable progress made in molecular diagnostics and targeted therapy promises substantially improved control and clinical outcomes for this aggressive disease in the near future.

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Declaration of the use of generative AI and AI-assisted technologies in the writing process

In preparing this work, the author used ChatGPT (OpenAI) for the purpose of translating some sections from Polish to English and refining the language/style. After using this tool, the author reviewed and edited the content as needed and accepts full responsibility for the substantive content of the publication.

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