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MEDULLARY THYROID CANCER: GENERAL REVIEW

Ayman A. Amin[1], Hamdy M. Hussein[2], Ahmed K. Fekry[2], Mohamed Mubark[2]

1 Surgical oncology department, National Cancer Institute, Cairo university, Cairo, Egypt.

2 General Surgery Department, Faculty of Medicine, South Valley University, Qena, Egypt

Abstract

The thyroid gland in the neck plays a crucial role in metabolism, growth, and calcium regulation. It has two lobes connected by an isthmus and is highly vascularized, receiving blood from the superior and inferior thyroid arteries. Venous drainage occurs through the superior, middle, and inferior thyroid veins, while lymphatic drainage involves nodes around the trachea and neck. Medullary thyroid cancer (MTC), originating from parafollicular C cells, accounts for 4-10% of thyroid cancers and can be sporadic or hereditary. Diagnosis includes fine-needle aspiration, calcitonin, and CEA levels, with imaging for metastasis. Treatment often involves thyroidectomy and lymph node dissection. Targeted therapies, such as RET-kinase inhibitors, are available for advanced cases. Post-surgery, monitoring serum calcitonin and CEA helps assess recurrence.

Keywords: thyroid gland, medullary thyroid cancer, RET mutation, calcitonin.

Thyroid Gland Anatomy

The thyroid gland is a midline structure in the anterior neck, functioning as an endocrine organ. It produces thyroid hormone and calcitonin, regulating metabolism, growth, and calcium levels in the blood [1]. Diseases affecting the thyroid include inflammatory conditions like thyroiditis, autoimmune disorders such as Graves' disease, and cancers including papillary, medullary, and follicular thyroid carcinomas [2].

Surgical Anatomy

The thyroid consists of two lobes connected by the isthmus, located at the second and third tracheal rings. It lies behind the strap muscles and wraps around the cricoid cartilage and tracheal rings, positioned from C5 to T1 vertebrae. The thyroid is attached to the trachea via Berry's ligament [3]. The gland, along with the esophagus, pharynx, and trachea, is housed within the visceral compartment, bounded by pretracheal fascia. The normal thyroid has symmetrical lobes with a central isthmus and often a pyramidal extension called the tubercle of Zuckerkandl [4].

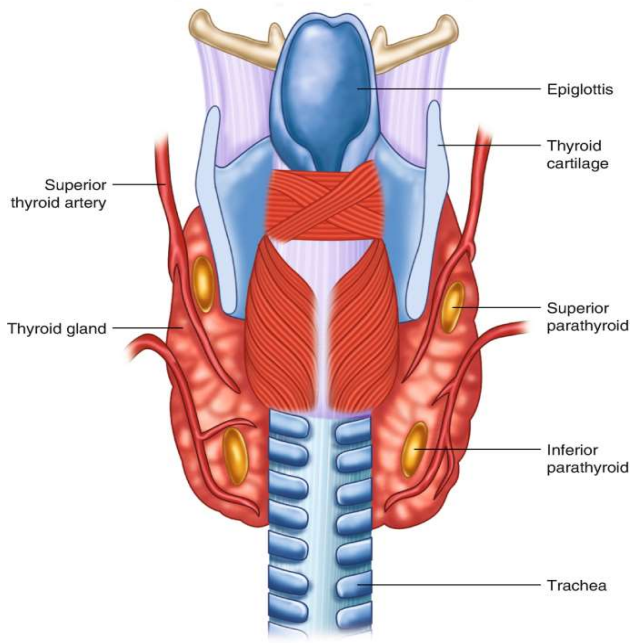

Fig (1): Diagram showing typical locations of the thyroid and parathyroid glands in the neck [5].

Blood Supply

The thyroid gland has a highly vascular supply, being six times more vascular than the kidney and three to four times more vascular than the brain. Blood supply comes from the paired superior and inferior thyroid arteries. The superior thyroid artery, branching from the external carotid artery near the superior horn of the thyroid cartilage, moves towards the gland's superior pole and divides into branches. One branch supplies the dorsal thyroid, while the superficial branch supplies muscles like the sternothyroid and sternohyoid, as well as the cricothyroid branch, isthmus, and lateral lobes [6]. The inferior thyroid artery originates from the thyrocervical trunk and reaches the posterior lateral lobe. Its largest branch, the ascending cervical artery, should not be mistaken for the inferior thyroid artery itself [7]. In 10% of people, the thyroid artery arises, often from the brachiocephalic trunk, to supply the isthmus and anterior gland [8].

Venous and Lymphatic Drainage

The thyroid is drained by the superior, middle, and inferior thyroid veins. The middle and superior veins drain into the internal jugular vein, while the inferior vein drains into either the subclavian or brachiocephalic veins. Lymphatic drainage involves the prelaryngeal, pretracheal, paratracheal, and lower deep cervical nodes, with the isthmus and inferior lateral lobes draining into the paratracheal and lower deep cervical nodes, and the superior portions of the gland draining into superior pretracheal and cervical nodes [9].

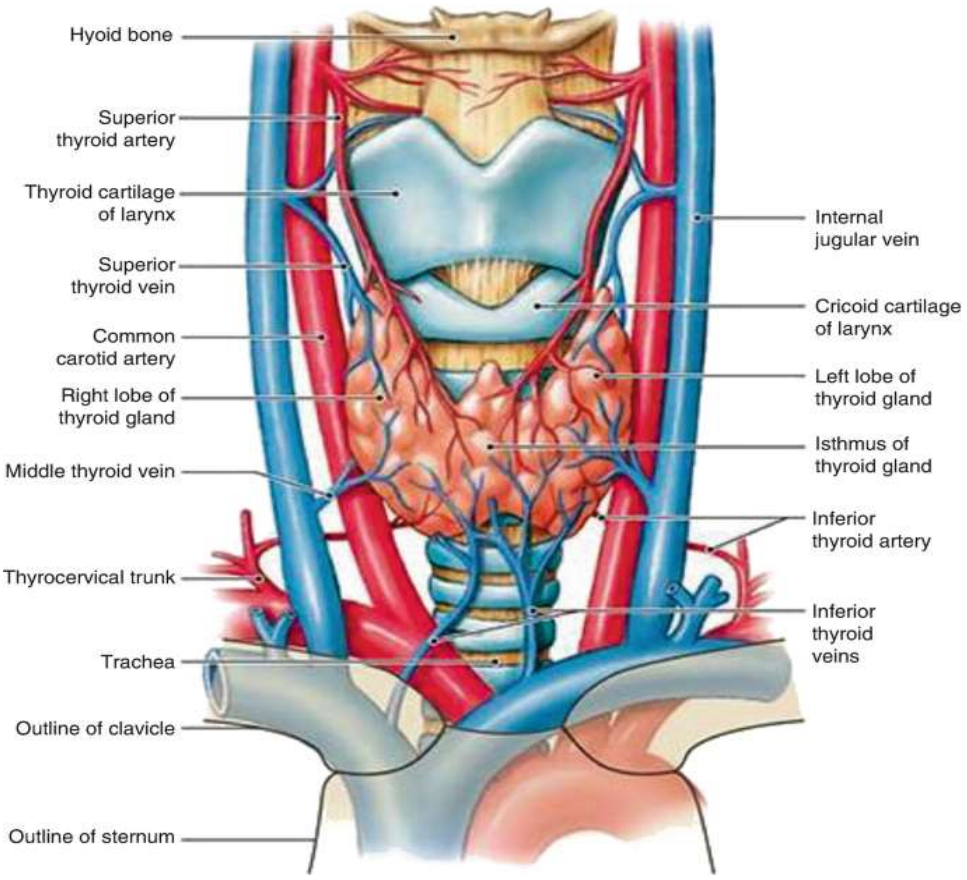

Fig (2): Blood Supply of the thyroid gland [10].

Nerve Supply: The thyroid gland is primarily innervated by the autonomic nervous system. Parasympathetic innervation comes from the vagus nerve, while sympathetic fibers originate from the inferior, middle, and superior ganglia of the sympathetic trunk [11].

Medullary Thyroid Cancer

Medullary thyroid cancer (MTC) arises from parafollicular C cells in the thyroid, producing calcitonin, which is key for diagnosis [12]. Recent advancements in molecular pathogenesis and genetic testing have led to better patient risk stratification and the identification of molecular targets for therapy [13]. Prophylactic thyroidectomy is recommended for high-risk patients, and tyrosine kinase inhibitors are approved for progressive, metastatic MTC [14].

Etiology

Seventy-five to eighty percent of MTC cases are sporadic, while the rest are familial, associated with multiple endocrine neoplasia (MEN) types 2A, 2B, and familial MTC (FMTC). Germline mutations in the RET gene are linked to MEN2 and FMTC, while 40-50% of sporadic MTCs have acquired RET mutations [15].

Epidemiology

MTC accounts for 4-10% of thyroid cancers in the U.S. Sporadic MTC peaks in the fifth to sixth decades, while MEN-associated MTC appears earlier, around the second to third decades [16].

Clinical Presentation

Sporadic MTC: Sporadic MTC represents 75% of cases, with a peak age of onset in the fourth to sixth decades [17]. A solitary thyroid nodule occurs in 75-95% of cases, with 70% having cervical lymph node metastasis at diagnosis. Up to 15% have symptoms of upper aerodigestive tract compression, and 5-10% are present with distant metastases, often in the liver, lungs, bones, and less commonly, the brain [18-20]. Calcitonin screening for MTC is controversial, but metastatic spread appears to be decreasing with early detection [21]. Systemic symptoms include diarrhea or flushing, with rare cases of ectopic Cushing's syndrome from ACTH secretion [13].

Biochemical Tests: Serum calcitonin levels correlate with tumor size and differentiation, and they are typically high in patients with palpable tumors. CEA is also used as a tumor marker, with anti-CEA antibodies employed in immunotherapy [22-23].

Imaging: MTC nodules are often solid and hypoechoic, with 16% showing microcalcifications. In comparison, 69.2% of papillary thyroid cancers are present with similar features [24-25].

Inherited MTC

MEN2A and MEN2B: These autosomal dominant syndromes are linked to distinct RET proto-oncogene mutations. MEN2A is associated with MTC, pheochromocytoma, and parathyroid hyperplasia. MTC in MEN2B appears earlier and more aggressively, often with marfanoid features [26-29].

Diagnosis

Diagnostic guidelines from the ATA (2015) and ESMO (2019) recommend fine-needle aspiration, neck ultrasound, serum calcitonin, CEA, and RET mutation analysis. CT and MRI are used to detect metastases [30].

Table (1): Comparison of the sensitivity of MTC detection [31].

Diagnostics	Sensitivity		Annotations
US	Primary tumor	75–90%	Standard procedure
	Lateral neck LN	56%	
	Central neck LN	6%	
US + serum Ctn and CEA	Primary tumor	95%	
CT	Overall	77–85%	Standard procedure

	LN	82%	
	Liver	87%	
	Bones	-	
	Lungs	100%	
MRI	Bones	89–92%	Standard procedure
	Liver	76–89%	
18F-FDOPA-PET/CT	Overall	45–93%	ATA 2015: not recommended ESMO 2019: recommended
	LN	72%	
	Liver	65%	
	Bones	68%	
	Lungs	14%	
	Lateral neck LN	75%	
	Central neck LN	28%	
68Ga-DOTA-TATE-PET/CT	Overall	84%	New
	Neck LN	56–63%	
	Mediastinal LN	100%	
	Liver	9%	
	Bones	100%	
	Lungs	57–63%	
68Ga-IMP288-PET/CT	Overall	89–92%	New
	LN	98–100%	
	Liver	98–100%	
	Bones	87–92%	
	Lungs	29–42%	

MTC: medullary thyroid cancer; CEA: carcinoembryonic antigen; Ctn: calcitonin; CT: computed tomography; LN: lymph nodes; MRI: magnetic resonance imaging; PET: positron emission tomography.

Diagnosis of MTC

MTC is sometimes diagnosed after thyroid lobectomy following a suspicious or indeterminate FNA biopsy. Histological specimens show spindle-shaped, pleomorphic cells originating from the calcitonin-producing parafollicular C cells, with no follicle formation [32].

Serum Calcitonin Screening

Serum calcitonin screening for thyroid nodules remains controversial in the U.S. due to the high rate of false positives, lack of pentagastrin stimulation testing, and the reliability of FNA biopsy. In some cases, patients with locoregional metastases may have normal unstimulated calcitonin levels [33]. However, in European countries where pentagastrin is available, basal and stimulated calcitonin tests are routinely used to aid in the preoperative diagnosis of MTC [33].

Evaluation of MTC

For patients diagnosed with MTC through cytology, evaluation should include serum calcitonin, carcinoembryonic antigen (CEA), and neck ultrasound if not already done. Genetic testing for germline RET mutations and biochemical screening for coexisting tumors, especially pheochromocytoma, are also recommended. This approach aligns with NCCN and ATA guidelines for managing MTC [30].

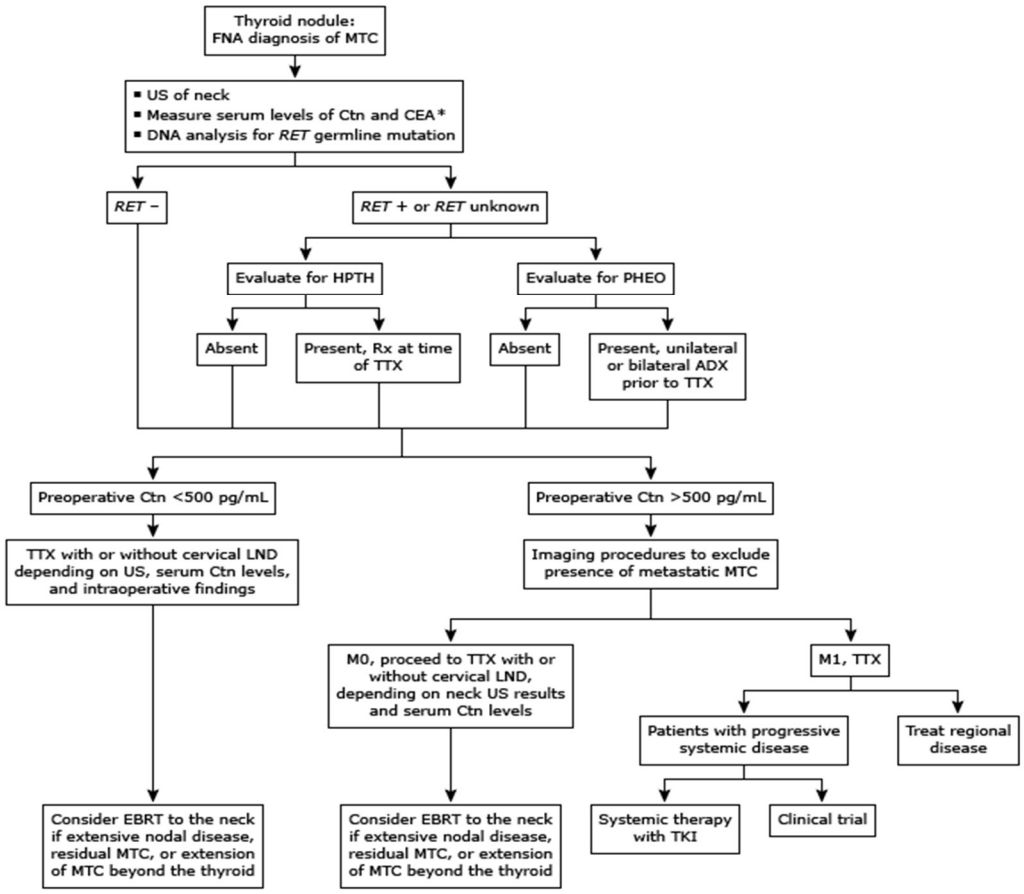

Fig (3): Evaluation and management of patients with medullary thyroid cancer diagnosed on the basis of fine needle aspiration biopsy of a thyroid nodule [34].

ADX: adrenalectomy; Ctn: calcitonin; CEA: carcinoembryonic antigen; EBRT: external beam radiotherapy; FNA: fine needle aspiration; HPTH: hyperparathyroidism; LND: lymph node dissection; MTC: medullary thyroid cancer; M: metastatic MTC; PHEO: pheochromocytoma; TKI: tyrosine kinase inhibitor; TTX: total thyroidectomy; US: ultrasound. * Ctn and CEA are measured to determine whether they are produced by the tumor, and if so, as a baseline for comparison with the results obtained after surgery. In addition, patients with preoperative Ctn >500 pg/mL require additional preoperative imaging.

Serum Calcitonin and CEA

Patients with MTC should have serum calcitonin and CEA measured. These tests identify tumors capable of hypersecreting hormones and can be compared postoperatively. Post-surgery, calcitonin and CEA doubling times are crucial markers for tumor progression and aggressiveness. For example, a study of 65 patients found 10-year survival rates of 8%, 37%, and 100% for calcitonin doubling times of less than 6 months, between 6 months and 2 years, and over 2 years, respectively [22].

Radiological Evaluation

MTC may spread locally or distantly. Neck ultrasonography is used to detect lymph node metastasis after FNA biopsy. If preoperative calcitonin exceeds 500 pg/mL, additional imaging such as chest and neck CT, liver MRI, and bone scintigraphy is required to assess metastasis [36, 37]. FDG-PET is not recommended for routine metastatic screening but is more sensitive to calcitonin levels above 1000 pg/mL [38]. Somatostatin receptor scintigraphy may help detect recurrent disease when CT is negative [39].

Genetic Screening

Germline RET testing is required for all patients with newly diagnosed sporadic MTC or C-cell hyperplasia. Sequencing of RET gene exons 10, 11, 13-16 is recommended, and further exons should be analyzed if there is a strong suspicion of hereditary syndromes. Studies suggest 6-7% of patients with sporadic MTC have RET germline mutations, while approximately 60% have somatic mutations in tumor cells, correlating with poorer prognosis [41- 43].

Testing for Coexisting Tumors

Patients with MTC, especially those with a RET mutation, should be screened for coexisting tumors like pheochromocytoma and hyperparathyroidism. This includes measuring serum calcium and plasma fractionated metanephrines before thyroidectomy [44, 45].

Staging

TNM Staging

The pTNM staging system (eighth edition) by UICC and AJCC categorizes MTC based on tumor size, extrathyroidal invasion, and metastasis [46, 47]:

- **Stage I:** Tumors <2 cm, confined to the thyroid.
- **Stage II:** Tumors >2 cm within the thyroid or any size with extrathyroidal extension into strap muscles without lymph node metastasis.
- **Stage III:** Tumors of any size with central neck lymph node metastasis (levels VI or VII), with or without strap muscle invasion.
- **Stage IV:** Distant metastases, lymph node involvement outside central neck, or gross invasion into neck structures beyond strap muscles.

Differential Diagnosis

A neck mass often represents benign thyroid nodules or cysts, with other causes including congenital anomalies, inflammatory lymph node enlargement, or neoplastic disorders [48]. Elevated calcitonin can also be due to hypercalcemia, hypergastrinemia, neuroendocrine tumors, renal insufficiency, or other thyroid conditions. Omeprazole, beta blockers, and glucocorticoids may cause hypercalcitoninemia, and heterophilic antibodies can falsely raise calcitonin levels. Elevated CEA may occur due to heterophilic antibodies, gastrointestinal inflammation, benign lung disease, nonthyroid malignancies, or smoking [35, 49].

Surgical Management of MTC

MTC Diagnosed Following Lobectomy

For MTC discovered after lobectomy, further investigation is essential to detect inherited MTC and consider total thyroidectomy to prevent contralateral MTC. Key investigations include basal serum calcitonin levels, neck ultrasonography, RET mutation screening, and a detailed family history. Observation may be considered if margins are negative, the disease is unifocal, and there is no C cell hyperplasia. Reoperation with lymph node dissection is required for positive ultrasonographic findings and elevated calcitonin levels. The ATA advises total thyroidectomy if elevated calcitonin persists after 3 months or if residual disease is evident. The BTA recommends total thyroidectomy for tumors >5 mm and serum calcitonin measurement for tumors <5 mm to determine further surgery [50].

Pre-Surgically Diagnosed MTC

Diagnosis and Treatment

MTC can be suspected through thyroid nodule cytology, elevated serum calcitonin levels, or detection of RET proto-oncogene mutations. Total thyroidectomy is preferred due to the high rates of multifocal (15%) and bilateral (5%) MTC (51,52). Radiological evidence and clinical suspicion guide this decision.

MTC Confined to the Neck

Total thyroidectomy is recommended for MTC confined to the neck, including complete tumor excision and regional lymph node removal, ensuring optimal disease-free survival. Preoperative ultrasonography and intraoperative findings aid in guiding cervical lymph node dissection [53]. Node-negative MTC patients generally have survival rates similar to the general population. For small intrathyroidal MTCs with calcitonin <20 ng/L, prophylactic central lymph node dissection (CND) may be omitted as lymph node involvement is rare [52]. Prophylactic lateral neck dissection (LND) is controversial and should be guided by serum calcitonin levels. The ATA recommends CND and ipsilateral LND for baseline calcitonin >20 ng/L, with additional contralateral LND for levels >200 ng/L. The BTA suggests ipsilateral LND based on tumor size and calcitonin levels or frozen section results, avoiding prophylactic contralateral LND without evidence of nodal involvement [52].

MTC with Nodal Involvement

For MTC with preoperative nodal involvement, total thyroidectomy with CND and dissection of involved lateral neck compartments is preferred. If basal calcitonin >200 ng/L and no distant metastasis, prophylactic dissection of uninvolved contralateral neck compartments is recommended [54].

Locally-Advanced or Metastatic MTC

Total thyroidectomy with lymph node dissection is advised for locally-advanced or metastatic MTC, often with palliative intent. A function-preserving approach is preferred to maintain speech,

swallowing, and parathyroid function. The surgical approach should be individualized based on patient preferences, comorbidities, and life expectancy [55].

Prophylactic Thyroidectomy in Inherited MTC

Indications and Guidelines

Prophylactic thyroidectomy is recommended for individuals with inherited RET proto-oncogene mutations but no clinical disease. The ATA classifies risk based on mutations: highest risk (MEN 2B syndrome, M918T mutation), high-risk (C634F/G/R/S/W/Y, A883F mutations), and moderate-risk [56]. High-risk patients should undergo total thyroidectomy with CND in infancy. MEN 2A syndrome patients with high-risk mutations are monitored closely and should have total thyroidectomy by age 5. Adults with MEN 2B syndrome and RET mutations should have prophylactic total thyroidectomy with CND [57].

Medullary Thyroid Microcarcinoma (microMTC)

Characteristics and Management

MicroMTCs, defined as MTCs <1 cm, present a 23% risk of lymph node metastasis even at 5 mm. Guidelines generally recommend thyroidectomy with central lymph node dissection (CND) for these patients [58].

Emerging Therapies

Targeted and Immunotherapy

Surgical resection is the primary treatment for MTC. For patients with extensive metastatic disease not amenable to surgery or radiotherapy, targeted therapy is an option. RET-kinase inhibitors, like selpercatinib or pralsetinib, are used for tumors with RET mutations. Multi-targeted kinase inhibitors, such as sunitinib, cabozantinib, vandetanib, lenvatinib, or sorafenib, are used for tumors without RET mutations [59]. Immunotherapy, including tumor-derived vaccines and monoclonal antibodies with radioisotopes, is investigational and not yet standard for MTC [60].

Postoperative Management

Monitoring and Thyroxin Therapy

Post-surgery, patients must be monitored for hypoparathyroidism and nerve injuries [61]. Thyroxin (levothyroxine, T4) therapy should start at 1.6 mcg/kg body weight (0.075-0.15 mg daily), with TSH levels assessed in six weeks. T4 therapy aims to maintain a euthyroid state; suppression of TSH is not necessary as MTC cells are not TSH-responsive. Radioiodine therapy is contraindicated because MTC cells do not concentrate iodine [62].

Subsequent Management

Follow-Up and Assessments

After thyroidectomy, serum calcitonin and carcinoembryonic antigen (CEA) levels are measured 2-3 months post-surgery to evaluate for residual disease. Patients with normal CEA and undetectable calcitonin are considered biochemically cured, with a five-year recurrence rate of 5%

[63]. Calcitonin levels may take months to reach their nadir, but significant declines often occur within days for those achieving biochemical remission [64, 65].

Follow-Up for Biochemically Cured Patients

For patients with undetectable calcitonin and normal CEA post-surgery, follow-up includes [65, 66]:

- Physical examination biannually for 2 years, then annually.
- Serum calcitonin and CEA measurements biannually for 2 years, then annually.
- Neck ultrasound 3-12 months post-surgery based on prior lymph node involvement.
- Additional imaging only if calcitonin or CEA levels rise during follow-up.

Persistent Hypercalcitoninemia

Risk and Prognosis

High basal serum calcitonin values three or more months post-surgery suggest residual disease. About 30-55% of patients with palpable or macroscopic MTC have persistently high calcitonin levels [67]. The prognosis varies by age and disease extent at initial surgery. In a study of 899 MTC patients, those with postoperative hypercalcitoninemia had a 70% 10-year survival rate, compared to 98% for those biochemically cured. Younger age and no lymph node involvement were associated with better outcomes [68].

Evaluation and Management

Calcitonin <150 pg/mL:

When calcitonin is detectable but <150 pg/mL two to six months after surgery, persistent locoregional disease is likely. Neck ultrasound and possibly CT or MRI should assess for macroscopic metastatic disease. If imaging is positive, detailed dissection of local and regional nodal tissue is recommended, focusing on areas with confirmed disease. If imaging is negative and calcitonin levels are stable, neck ultrasound should be conducted every 6 to 12 months for 2 to 3 years, then less frequently. Additional imaging is needed if calcitonin or CEA levels rise [69].

Calcitonin ≥150 pg/mL:

Calcitonin ≥150 pg/mL two to six months after surgery suggests possible distant metastases. Patients should undergo neck ultrasound and comprehensive imaging (CT or MRI of neck, chest, abdomen; bone scan or MRI for skeletal metastases). Liver metastases, occurring in ~45% of advanced cases, are best identified with contrast-enhanced liver CT or MRI. If imaging is negative, continued monitoring with physical exams and serum calcitonin and CEA measurements is advised. Stable calcitonin levels in the 150 to 300 pg/mL range typically require yearly neck ultrasounds, with additional imaging based on rising calcitonin or CEA values. FDG-PET scans are considered when calcitonin exceeds 500-1000 pg/mL, with a sensitivity of 78% when calcitonin >1000 pg/mL [70]. Radionuclide bone imaging and invasive localization techniques are rarely used and only if they would affect treatment decisions.

Treatment

If imaging reveals disease, treatment options include surgical resection and/or external beam radiation therapy (EBRT) [71].

Management of Persistent/Recurrent Disease

Treatment Options

For persistent or recurrent MTC, treatment includes observation, surgical resection, external beam radiation therapy (EBRT), and other therapies like radiofrequency ablation, cryo-ablation, embolization, or systemic treatments. Previously, routine surgical interventions were common, but often did not normalize serum calcitonin levels. This has led to a more selective approach to intervention and consideration of observation in some patients [70]. Management depends on factors such as disease localization, volume, location, symptoms, and progression risk [71].

Palliation of Symptoms

Diarrhea

Diarrhea, often linked to large liver metastases, significantly impacts quality of life. First-line treatments include dietary adjustments and anti-motility agents (loperamide, diphenoxylate-atropine, codeine). Somatostatin analogs may offer some relief. Surgical debulking or chemoembolization may also help [72, 73].

Ectopic Cushing's Syndrome

Vandetanib is recommended as a first-line treatment for ectopic Cushing's syndrome, due to its rapid effect on cortisol levels. Medical therapies (ketoconazole, metyrapone, mitotane, mifepristone) are less effective and less tolerated. Bilateral adrenalectomy, though effective, is challenging due to comorbidities [74].

Prognosis

Sporadic MTC usually starts between ages 50-60, while hereditary cases present earlier. Prognosis is influenced by tumor genotype, baseline biomarkers, tumor extent, metastases, sex, and age [27]. Basal serum calcitonin (bCtn) and carcinoembryonic antigen (CEA) doubling times help assess prognosis. High serum Ca9.9 positivity and CEA levels are associated with poorer outcomes. Early changes in CEA levels can predict progression-free survival ($p = 0.02$) [75]. Poorly differentiated histology and high Ki-67 expression are linked to rapid progression [76].

Hereditary MTCs generally appear earlier but show similar aggressiveness to sporadic cases. Younger age in sporadic MTCs is associated with longer survival but not with reduced cancer-related deaths [77]. Lymph node metastases are present at diagnosis in 30-60% of cases. MTC has a higher mortality rate compared to well-differentiated thyroid cancers. The 5-year survival rate is 80-97%, and the 10-year survival rate is 75-88%. Recurrence occurs in up to 50% of patients [78].**References**

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