

Medullary Thyroid Cancer

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MEDULLARY THYROID CANCER

Medullary thyroid cancer (MTC) is an uncommon malignant tumor derived from the parafollicular cells (C cells) of the thyroid. It was initially described by Hazard et al in 1959. Sipple conceptualized the association of MTC and pheochromocytoma, which is now known as multiple endocrine neoplasia (MEN)-2A, along with which primary hyperparathyroidism is also associated. MTC may occur in some situations in association with pheochromocytoma, ganglioneuromas, and marfanoid habitus in MEN-2B (Table 1).¹ Mutations in the rearranged during transfection (RET)

proto-oncogene have been identified in patients with MEN-2 and a subset of sporadic MTCs.^{2,3}

C cells are of neuroendocrine origin and evolve from the neural crest, subsequently migrating to the ultimobranchial body, which fuses with the developing thyroid gland. The C cells constitute 1% of the cells of the thyroid gland and produce a 32-amino acid peptide named calcitonin. Calcitonin inhibits bone resorption and protects against hypercalcemia. Calcitonin is also produced by neuroendocrine cells in the adrenals, pancreas, lungs, prostate, and other tissues and in any cell type during sepsis. Under normal physiological conditions, C cells are the predominant source of

Table 1 Hereditary Medullary Thyroid Carcinoma	
Syndrome	Components
MEN-2A or Sipple's syndrome	<ul style="list-style-type: none">• MTC• Pheochromocytoma• Parathyroid adenomas
Variants of MEN-2A	<ul style="list-style-type: none">• Familial medullary thyroid carcinoma• MEN-2A with cutaneous lichen amyloidosis• MEN-2A with Hirschsprung's disease
MEN-2B	<ul style="list-style-type: none">• MTC• Pheochromocytoma• Intestinal ganglioneuromatosis• Marfanoid habitus
MTC: medullary thyroid carcinoma; MEN: multiple endocrine neoplasia.	

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Table 2
Mode of Clinical Presentation in Patients with Medullary Thyroid Carcinoma⁵

Clinical presentation	Number of patients (n = 40)	Percentage
Goiter with lymphadenopathy	12	30
Solitary thyroid nodule	7	17.5
Isolated goiter	7	17.5
Isolated cervical lymph node enlargement	6	15
Pheochromocytoma	5	12.5
Familial screening	1	2.5
Mode of presentation unclear from medical records	2	5

calcitonin and hence are a useful tumor marker for MTC.¹

Clinical Presentation

Sporadic MTC accounts for 75–80% of all cases of the disease.^{4,5} The mean age at presentation is 45–55 years, with a female predominance in Western literature.^{6,7} In the Indian setting, the mean age at presentation was around 41–46 years, with a male predominance.^{5,8} Women presented a decade earlier than men at 1 center.⁸

The most common presentation is that of a painless thyroid swelling (65%), of whom, 50% have associated lymphadenopathy. It can also present with isolated cervical lymph node enlargement (15%) or be detected during evaluation for MEN-2 in a patient with pheochromocytoma or during screening of family members of those affected by MEN-2. Details of the clinical presentation of patients with MTC in a tertiary care centre are summarized in Table 2.⁵ Sporadic MTCs are more commonly unicentric; hereditary MTCs associated with MEN-2A and 2B are most often bilateral and multicentric.¹ It is more aggressive and metastasizes earlier in MEN-2B than in MEN-2A.⁹ The secretion of calcitonin, calcitonin gene-related peptide, prostaglandins, and vasoactive intestinal polypeptide may precipitate symptoms of diarrhea and flushing.¹⁰ About 50% have clinically evident lymph node metastases at diagnosis.⁵ The central compartment lymph nodes (level VI) are most commonly involved, followed by ipsilateral level II–V nodes and subsequently the contralateral nodes. The other common sites

of metastases include mediastinal lymph nodes, liver, lungs, and bone.^{11,12} Around 5% have distant metastasis at diagnosis.⁴

In MEN-2, the earliest abnormality is focal C-cell hyperplasia. These foci become nodular, evolving into microscopic MTC and subsequently visible MTC. MTC develops later in the course of the disease and is less aggressive in familial MTC (FMTC) when compared to MEN-2A.¹

Molecular Pathogenesis

Germline mutations in the RET proto-oncogene have been identified in patients with hereditary MTC and somatic RET mutations in a proportion of sporadic MTC.¹² The RET gene encodes a receptor tyrosine kinase that is expressed in the neural crest-derived cell lineages. The RET receptor plays a crucial role in regulating cell proliferation, migration, differentiation, and survival through embryogenesis. Under normal conditions, RET can be activated by a complex of co-receptors and ligands, which include the glial-derived neurotrophic factor (GDNF) family of ligands (GFLs) and glycosylphosphatidylinositol-anchored GDNF family α receptors (GFR α). Interaction of GFR α /GFL complex with RET leads to autophosphorylation of tyrosine residues. The C cells are more susceptible to oncogenic RET activation than the adrenal medulla or parathyroid in MEN-2A, leading to an earlier presentation and a higher penetrance of MTC. Mutations in the extracellular cysteine-rich domain are generally found in MEN-2A and convert a cysteine residue to a non-cysteine residue. The mutation leaves

an unpaired cysteine residue in an RET monomer to form an aberrant intermolecular disulfide bond with another mutated monomer. The two mutated RET molecules are constitutively dimerized and activated. Mutations in the intracellular tyrosine kinase residues are generally found in MEN-2B and FMTC; these activate tyrosines, leading to aberrant phosphorylation of substrates preferred by cytoplasmic tyrosine kinases such as C-Src and C-Abl rather than the substrates preferred by normal receptor tyrosine kinase. The mutated RET no longer needs dimerization to become active and signals independent of the ligand. This further leads to an activation of downstream signaling pathways.¹³

Diagnosis

A high index of clinical suspicion is warranted in a patient presenting with a thyroid nodule, with a family history suggestive of MEN-2A (associated young onset hypertension due to pheochromocytoma and primary hyperparathyroidism with fractures or renal stones), MEN-2B (association of pheochromocytoma, marfanoid habitus, mucosal neuromas, or chronic constipation due to intestinal ganglioneuromas), or a family history of MTC.

Tumor Markers

The diagnosis of MTC is established by demonstrating elevated serum calcitonin levels. Calcitonin is a highly sensitive biomarker of MTC, and a majority of patients with MTC exhibit significantly elevated levels. Pre-operative calcitonin levels correlate with the tumor size and the stage of the disease. Calcitonin levels <100 pg/mL were associated with a median tumor size of 3 mm (98% <1 cm), while levels >1000 pg/mL correlated with a median tumor diameter of 2.5 cm.¹⁴ The positive predictive value of basal calcitonin in the pre-operative diagnosis of MTC with values >20 and <50, >50 and <100, and >100 pg/mL were 8.3%, 25%, and 100%, respectively.¹⁵ Nodal metastases could be first observed at basal calcitonin levels of 10–40 pg/mL. Distant metastasis and extrathyroidal extension were evident in patients with calcitonin levels of 150–400 pg/mL.¹⁶ Elevation of serum calcitonin can occur in C-cell hyperplasia, autoimmune thyroiditis, chronic renal failure, pregnancy, and mastocytosis.¹⁷ Calcitonin elevation is also observed in non-thyroidal neuroendocrine tumors arising from the foregut, pancreas, insulinoma, glucagonoma, VIPoma, carcinoid, prostate cancer, small-cell lung cancer, and large-cell lung cancer with neuroendocrine differentiation.¹⁸ The glucagon-like peptide (GLP)-1 receptor agonist liraglutide has been demonstrated

to increase calcitonin release and cause C-cell hyperplasia in rats and, to a lesser extent, in mice. In contrast, humans and cynomolgus monkeys have low GLP-1 receptor expression in thyroid C cells, and liraglutide does not increase calcitonin release in primates.¹⁹ In a study of 10,864 patients with thyroid nodules, 0.4% had high serum calcitonin concentrations and were proven to have MTC.²⁰ There is no consensus regarding the usefulness of a routine measurement of serum calcitonin levels in individuals with thyroid nodules.

Carcinoembryonic antigen (CEA) is also secreted by the C cells of the thyroid. Pre-operative CEA levels >30 ng/mL have been shown to be less likely associated with a surgical remission. The rate of central and lateral lymph node involvement was 70% and increased to 90% if CEA levels were >100 ng/mL. CEA levels in excess of 100 ng/mL were also associated with contralateral nodal disease and distant metastasis.²¹

Ultrasound Scan

The features suggestive of MTC include solid hypoechoic nodules, echogenic foci in 80–90% of the tumors due to amyloid deposition, and associated calcification. Similar deposits have also been observed in 50–60% of nodal metastasis. Chaotic intranodular vessels within the tumor on color-flow imaging also indicate MTC.²² On the other hand, sonological findings are highly operator dependent. They are less sensitive and specific in detecting central lymph node metastases than when compared to the lateral neck.²³

Fine-needle Aspiration Cytology

The typical cytological features include a dispersed cell pattern, polygonal appearance of the cells, binucleated cells, and the presence of amyloid.²⁴ The sensitivity of fine-needle aspiration cytology (FNAC) in detecting MTC is 63% in comparison with 98% for serum calcitonin measurement.¹⁸

Histopathology of Medullary Thyroid Cancer

On gross examination, they are firm, white or yellow, and infiltrative. Some of them are well defined and encapsulated. On light-microscopic examination, the C cells are rounded, polygonal, or spindle shaped, arranged in islands separated by fibrous tissue, trabeculae, or ribbons of cells, or uncommonly as glandular structures. The nuclei are rounded or elongated. Amyloid deposits are the hallmark, both in the primary tumor and within the metastatic deposits (Figure 1). Immunostaining for calcitonin

is a useful method to establish the diagnosis with certainty (Figure 2).²⁵

Evaluation of Metastatic Disease

The neck, chest, and abdominal computed tomographic (CT) scan are most commonly performed in the pre-operative staging of patients who have a significant elevation of calcitonin (>400 pg/mL). Arterial phase-contrast abdominal CT and contrast-enhanced magnetic resonance imaging (MRI) are useful in the detection of macroscopic liver metastases. Hepatic arteriography is more sensitive than CT abdomen in the detection of small lesions.^{18,26} Direct examination and biopsy of the liver by laparoscopy may show small deposits of metastatic MTC in patients with normal CT scanning and MRI. The metastases appear as small (<5 mm), bright, white nodules on the surface of the liver.²⁷

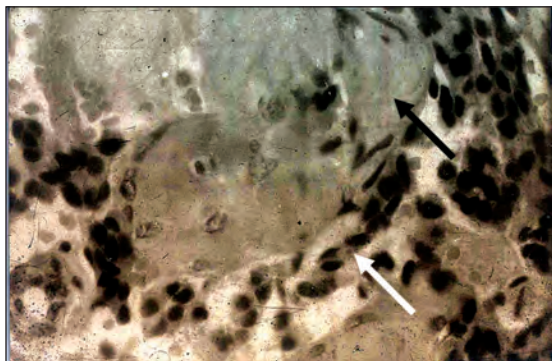


Figure 1. Histopathology of medullary thyroid carcinoma showing spindle-shaped tumor cells (white arrow) with amorphous amyloid within the tumor (black arrow).

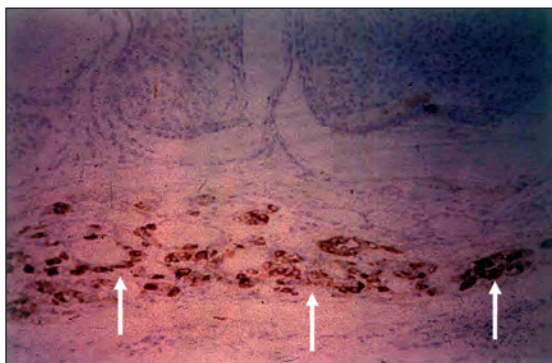


Figure 2. Calcitonin immunostaining showing tumor cells staining positive for calcitonin (white arrows).

Evaluation for MEN-2A and MEN-2B

Individuals with a family history suggestive of MEN-2A should be screened for primary hyperparathyroidism by the measurement of serum calcium, phosphorus, and albumin. Parathyroid hormone (PTH) should be estimated when serum calcium is elevated or when there is a high index of suspicion of primary hyperparathyroidism. Patients with a family history of onset of hypertension in youth (MEN-2A or MEN-2B) should have an estimation of 24-hour urine metanephrines and normetanephrines to rule out pheochromocytoma before taking up for thyroidectomy.

Genetic Testing

Patients who present with MTC should undergo DNA analysis for detection of mutations in the RET proto-oncogene because the likelihood of a germline RET mutation is relatively high (9%) in apparently sporadic MTC in an assessment of Indian patients.²⁸ MTC has nearly a 100% penetrance in MEN-2 syndromes and FMTC. Clinically relevant mutations are located on exons that are 10, 11, 13, 14, 15, and 16, and these are to be analyzed. Families at risk of MEN-2 without identifiable mutations in the exons that are mentioned should be screened for mutations in exons 5 and 8.¹³ The clinical course and aggressiveness of MTC are based on the mutations in different exons. RET mutations have been stratified into 3 groups based on their clinical behavior. Patients with MEN-2B have the most aggressive MTCs and have mutations in codon 883 or 918. These are classified as level 3. Patients with MEN-2A and FMTC with level 2 mutations (codons 609, 611, 618, 620, 630, and 634) are classified as having high risk, and patients with mutations in codons 768, 790, 791, 804, and 891 (level 1) are classified as having the least risk for the development of aggressive MTC.^{3,29}

Multiple endocrine neoplasia-2 is inherited as an autosomal dominant disorder. Hence, 50% of the offsprings of the index case are at risk. However, a physician cannot disclose reports of genetic tests to a patient's first-degree relatives without the patient's consent. Hence, the physician should inform the patient about the risk of development of the disease in first-degree relatives. It would be the moral obligation of the patient to inform his first-degree relatives to undergo genetic testing to ascertain their risk.¹⁸

All RET mutation carriers of reproductive age should be counseled about the option of pre-implantation or prenatal genetic testing. Pre-implantation genetic diagnosis is an *in vitro*

fertilization technique that isolates and tests a single embryonic cell for RET mutation. Unaffected embryos may then be transferred to the uterus. This has a potential to remove the disease from the family. Prenatal genetic testing may also be performed on samples obtained by chorionic villus biopsies or amniocentesis in the first and second trimesters of pregnancy, respectively.¹⁸

Screening for Other Components of MEN-2 among Those with Germline RET Mutations

In the absence of symptoms or an adrenal mass to suggest the possibility of pheochromocytoma, surveillance should include an annual measurement of plasma free metanephrines and normetanephrines or 24-hour urine metanephrines and normetanephrines, beginning by the age of 8 years in those with RET mutations in codons 630, 634, 804, 883, and 918, and by the age of 20 years in those with other mutations. Periodic surveillance starting at the age of 20 years is also indicated in patients with RET mutations associated with only FMTC. Surveillance for primary hyperparathyroidism should include annual measurement of albumin corrected serum calcium with or without intact PTH, beginning by the age of 8 years in carriers of RET mutations in codons 630 and 634, and by the age of 20 years in carriers of other MEN-2A RET mutations; those with FMTC mutations should also have a periodic surveillance.¹⁸

Treatment

Surgery

Patients with level 3 RET mutations should undergo a prophylactic total thyroidectomy in the first year of life. Individuals with level 2 mutations should undergo surgery before the age of 5 years and those harboring level 1 mutations between the age of 5 years and 10 years. In those with thyroid nodules >5 mm in size at any age, a basal serum calcitonin >40 pg/mL when >6 months old, or with a clinical or radiological evidence of lymph node metastasis, further evaluation is required with neck ultrasound, which should evaluate the central and lateral compartments and also the superior mediastinum. In these situations, more extensive surgery inclusive of central and lateral compartment lymph node dissection may be necessary. About 6% of all children undergoing central neck dissection suffer from hypoparathyroidism. Normal parathyroid tissue should be identified and left in situ with an adequate vascular pedicle, or, if it is not possible, transplanted into the sternomastoid or non-dominant

forearm. In those with a strong family history of primary hyperparathyroidism, it would be prudent to transplant parathyroid into the forearm and consider removal of the transplanted remnant in case of hypercalcemia.¹⁸

The MTC patients with limited local disease (with a tumor size <4 cm and metastasis to level VI cervical lymph nodes) without or with limited distant metastasis should undergo total thyroidectomy and level VI compartment lymph node dissection. Those with local metastases to the central and lateral neck compartments should undergo total thyroidectomy and central (level VI) and lateral neck (levels IIA, III, IV, and V) dissection. In the presence of extensive metastatic disease or advanced local disease, a more palliative approach should be adopted to minimize the risk of hypoparathyroidism and maintain normal speech and swallowing. Surgery is indicated when there is pain or tracheal compression.¹⁸ Somatic RET mutations are positive in 40–50% of sporadic MTC, and these individuals have a more aggressive course than those without RET mutations.³⁰

In case MTC is incidentally detected on histopathology in a patient who underwent hemithyroidectomy, patients at risk of contralateral MTC or residual metastatic disease are likely to benefit from completion thyroidectomy, including bilateral central compartment lymph node dissection. The high-risk individuals include those with germline or somatic RET mutation, histologic evidence of C-cell hyperplasia, tumor multifocality or extrathyroidal extension, positive surgical margin or metastasis, family history of MEN-2, ultrasound suspicious of contralateral tumor or lymph node metastasis, or serum calcitonin levels above the normal range. If these features are not present, the patient can be observed and followed up. When the postoperative serum calcitonin is undetectable, the risk of persistent or residual disease is low and these patients need only follow up.¹⁸

Postoperative Thyroxine Replacement

Medullary thyroid cancer is not thyroid-stimulating hormone (TSH) dependent, and hence, only replacement levothyroxine therapy should be instituted postoperatively to maintain TSH levels between 0.5 and 2.5 mIU/L.¹⁸

Postoperative Radioactive-iodine Ablation

Radioactive-iodine uptake into the follicular cells may have a bystander effect in ablating adjacent MTC and has been used in some centers in the postoperative treatment of disease confined to the thyroid.^{5,31}

Postoperative External Beam Radiotherapy

External beam radiotherapy (EBRT) does not alter the local or regional relapse rate, but in high-risk patients with extraglandular invasion, microscopic residual disease, or lymph node involvement, the locoregional relapse free rate at 10 years was better in individuals who received postoperative EBRT in comparison with those who did not receive external beam radiotherapy (86% vs 52%; $P = 0.049$).³²

Postoperative Follow-up

In view of variable time duration to normalization of serum calcitonin,³³ it is recommended to check serum calcitonin 2–3 months following surgery. Biochemical remission is dependent on the pre-operative basal calcitonin level and tumor size. In a large series, postoperative serum calcitonin was normalized in 62% of patients with node-negative disease and in 10% with node-positive disease. Remission rate was 50% in those with primary tumor >10 mm, node-negative disease, and pre-operative calcitonin >300 pg/mL. No remission was noted in those with a tumor >40 mm in diameter or basal pre-operative calcitonin >3000 pg/mL. Undetectable postoperative calcitonin was obtained in 57% with <10 lymph node metastases and, in 4% with metastasis in >10 lymph nodes.¹⁸

Calcitonin doubling time is a predictor of survival in MTC. In a retrospective series, when the calcitonin doubling time was <6 months, the 5- and 10-year survival rates were in the range of 25% and 8%, respectively; when the calcitonin doubling time was 6–24 months, the 5- and 10-year survival rates were 92% and 37%, and in those with calcitonin doubling time >2 years, survival was 100% at 10 years.³⁴ Biochemical cure predicts a survival rate of 97.7% at 10 years. In a study by Modigliani et al, survival in non-cured patients was 80.2% at 5 years and 70.3% at 10 years.³⁵ Persistent hypercalcitoninemia indicates a poorer prognosis (Figure 3).⁵ Age and stage were independent predictive factors for survival.³⁵

Modest calcitonin elevation <150 pg/mL indicates locoregional disease. An ultrasound neck should be performed to look for residual disease in the thyroid bed or lymph nodes. In those with postoperative calcitonin >150 pg/mL, suspicion of distant metastasis is high and one should consider other imaging modalities like CT scan of neck and chest, 3-phase contrast-enhanced multidetector CT of the liver or contrast-enhanced MRI, MRI of spine and pelvis, and bone scan to detect residual/recurrent disease.¹⁸ ¹³¹I-meta-iodobenzylguanidine (MIBG) has a sensitivity of 65% in localizing metastatic MTC (Figure 4).⁵

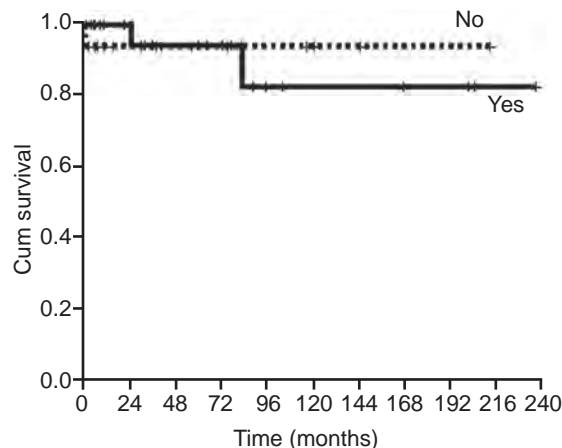


Figure 3. Survival curves for patients with persistent postoperative hypercalcitoninemia compared with those with normal postoperative calcitonin levels (time in months). $P = 0.901$ (not significant).⁵ Yes—persistent postoperative hypercalcitoninemia; No—no postoperative hypercalcitoninemia.

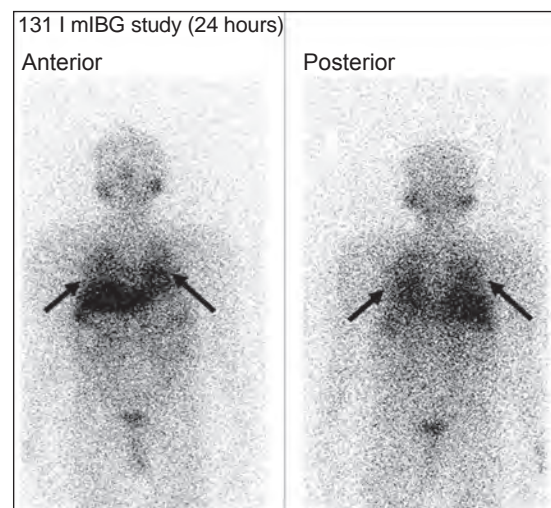


Figure 4. Meta-iodobenzylguanidine scan in patient with medullary thyroid carcinoma post-thyroidectomy and lymph node dissection showing metastasis in both lungs (black arrows).

Fluorodeoxyglucose (FDG)-positron emission tomography (PET) and ¹⁸F-dihydroxyphenylalanine (DOPA) PET are useful in localizing the disease, with a sensitivity of 44% and 63%, respectively.^{36,37} The

sensitivity and specificity of ^{18}F -DOPA PET/CT was 100% when serum calcitonin was >150 pg/mL.³⁸

Treatment of Metastatic Disease

In those with local recurrence in the thyroid bed or cervical lymph nodes (>1 cm), repeat surgical resection is indicated, including compartmental dissection of image or biopsy-positive disease in the central (level VI) or lateral (level II-A, III, IV, and V) neck compartments. Asymptomatic lymph nodes (<1 cm) can be observed. When there is no anatomic evidence of disease on imaging despite a detectable serum calcitonin, it would be most appropriate to keep the patient on follow-up. Percutaneous ethanol injection may also be considered for locoregional MTC.¹⁸

Active treatment is often indicated in patients with lesions in critical locations such as brain metastasis, impending or active spinal cord compression, airway compromise, symptomatic lesions, hormonal hypersecretion (corticotrophin-releasing hormone [CRH] or adrenocorticotrophic hormone [ACTH] secretion leading to Cushing's syndrome), and impending or active fracture of weight-bearing bones. EBRT may be considered to treat painful bone metastases and for clinically significant lesions that are not candidates for surgery. Vertebroplasty, radiofrequency ablation with or without cementation, cryosurgery, and arterial embolization are all effective in reducing pain in the given patient.¹⁸ Bisphosphonates also reduce bone pain in those subjects with skeletal metastasis.³⁹

Lung or mediastinal lesions causing local compression of an airway or bleeding may be considered for surgery, EBRT, or radiofrequency ablation. Lesions with central airway invasion may be amenable to the addition of photodynamic therapy or airway stenting.¹⁸

Liver metastases are usually multiple and disseminated throughout the liver, with diarrhea and pain. They are usually not amenable to surgery, percutaneous ethanol ablation, or radiofrequency ablation.^{18,40} They are best treated with chemo-embolization. In a series of 12 patients with MTC with hepatic metastasis, 42% had partial response, 42% had stabilization, and diarrhea improved in 40%.⁴¹

Chemotherapy: Clinical trials of chemotherapeutic regimens in persistent or recurrent MTC have shown limited efficacy, with the best response of partial remission in 10–20%. The agents used include dacarbazine, doxorubicin, and 5-fluorouracil.¹⁸

Radionuclide-targeted therapies: ^{90}Y tridium DOTA–TOC has been used in the treatment of metastatic MTC with rising calcitonin levels and

tumor uptake on ^{111}In octreoscan. Twenty-nine percent of the patients demonstrated decreasing calcitonin levels with therapy.⁴² ^{131}I -MIBG is taken by MTCs and hence may be useful for the treatment of metastatic MTC.⁵ In a small series, partial remission was achieved in 25% and meaningful palliation in 75% of patients with metastatic MTC.⁴³

New Modalities of Therapy

Tyrosine kinase inhibitors sunitinib, sorafenib, vandetanib, and motesanib have been used in the treatment of MTC.⁴⁴ With motesanib, only 2% had a partial response, while 47% experienced stable disease at 24 weeks.⁴⁵ Among patients with metastatic FMTC, vandetanib produced partial response in 17% and stable disease in 33% at 24 weeks. Calcitonin levels dropped by $>50\%$ in 66% of these patients. Sunitinib achieved a greater disease stabilization rate of 83% in MTC patients. With sorafenib, partial response was seen in 8% and minor response (defined as 23–29% reduction in tumor diameters) was achieved in another 19%. The common adverse effects of these drugs include fatigue, diarrhea, and nausea. Sunitinib causes erythrodysesthesias, neutropenia, and hypertension. Sorafenib is known to inhibit the growth plate in children. Vandetanib causes asymptomatic QT prolongation and skin rash. Motesanib increases the requirement of levothyroxine to maintain TSH suppression or a euthyroid state.⁴⁴

Treatment of Associated Problems

Diarrhea in MTC most often occurs in the setting of advanced disease in patients with hepatic metastases. Diarrhea may be hypersecretory or due to enhanced gastrointestinal (GI) motility or both. It is debilitating both in terms of nutrition and the quality of life. Therapy with loperamide or codeine is the first-line therapy. If diarrhea does not subside, treatment with somatostatin analogs or debulking of large tumor deposits could also be considered.¹⁸

The ACTH or CRH overproduction from MTC leads to Cushing's syndrome. MTC accounts for 2–6% of ectopic ACTH-dependent Cushing's syndrome. Options of treatment in this situation include debulking of large hepatic metastases (surgery or chemo-embolization), medical therapy with ketoconazole or mitotane, or bilateral adrenalectomy. Treatment with somatostatin analogs is ineffective.¹⁸

Long term Follow-up

Long term biochemical monitoring for MTC patients who achieve a complete biochemical cure should

include annual measurement of serum calcitonin. Those with detectable serum calcitonin levels postoperatively should have basal calcitonin and CEA levels measured every 6 months to determine their doubling time. Ongoing follow-up should include physical examination and measurement of calcitonin and CEA at one-fourth the shortest doubling time or annually, whichever is more frequent. CEA is also secreted by cancers of the GI tract, lung, prostate, breast, and ovary and should be interpreted with caution in individuals with co-existent cancers.¹⁸

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