Medullary Thyroid Carcinoma

Marybeth S. Hughes and Yasmine Assadipour

Introduction

Medullary thyroid cancer (MTC), which develops from parafollicular cells of the thyroid gland, is caused in most cases by an activating mutation in the rearranged during transfection (RET) proto-oncogene, and in some sporadic cases, by a mutation in the rat sarcoma (RAS) proto-oncogene. Patients with a known germ-line risk factor should be screened for serum calcitonin levels. Diagnosis is made by nodules on ultrasound which can be fine-needle aspirated and tested for calcitonin. All patients diagnosed with MTC should be offered genetic screening. Lymph node involvement is very common. Up to one third of patients have distant metastases on diagnosis. Appropriate surgical management includes a total thyroidectomy, central neck lymph node dissection, and lateral neck lymph node dissection if clinically indicated. Calcitonin and carcinoembryonic antigen are useful as tumor markers in surveillance. Local recurrences and isolated distant metastases should be addressed surgically. New modalities developed based on the specific genetic makeup of MTCs are being introduced for patients with metastatic disease, including tyrosine kinase inhibitors.

Anatomy and Physiology of Parafollicular Cells

The parafollicular cells from which MTC originates are embryologically derived from the neural crest [1]. These cells migrate from the third and fourth branchial pouches to the superolateral aspects of each thyroid lobe, and account for approximately 1 % of the cells in the gland [2].

The parafollicular cells are also referred to as C cells for the hormone they secrete, Calcitonin. Calcitonin is a 32-amino-acid protein which interacts with surface receptors on osteoclasts to decrease calcium absorption. However, calcitonin ultimately has a minimal impact on peripheral serum calcium levels, and patients with elevated calcitonin levels very rarely have drastic hypocalcemia. Calcitonin as a tumor marker is integral to the diagnosis of MTC in sporadic and hereditary syndromes, and for the detection of recurrence in the follow-up of patients with MTC. If the basal serum level is elevated but not confirmatory, diagnosis can be confirmed with a stimulated level. Calcitonin secretion can be stimulated by intravenous infusion of pentagastrin, although this is no longer available in many countries. High-dose intravenous calcium stimulation has also been reintroduced into clinical practice to stimulate calcitonin secretion [3]. C cells additionally release carcinoembryonic antigen (CEA), which can also be used as a tumor marker to detect recurrence on follow-up [4].

Risk Factors for Medullary Carcinoma

The most significant risk factor in the carcinogenesis of parafollicular cells is an activating mutation in the RET proto-oncogene. The RET proto-oncogene is located on chromosome 10q11.12, and encodes a tyrosine kinase receptor highly expressed on cells derived from the neural crest, branchial arches, and the urogenital system [5]. Upon ligand binding, the RET receptor dimerizes and several cytoplasmic tyrosine residues are phosphorylated, leading to the induction of downstream signal transduction pathways. RET mutations in MTC cause constitutive activation of the mitogen-activated protein kinase (MAPK) pathway, leading to cell division and proliferation. The (PI3)-K/AKT pathway is also activated, inhibiting apoptosis [6]. This combination of uncontrolled cell division and resistance to apoptotic stimuli leads to

M. S. Hughes (✉)
Director of the Surgical Oncology Research Fellowship, Thoracic and Gastrointestinal Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, 10 Center Drive MSC 1201 Room 4W-3742, Bethesda, MD 20892, USA
e-mail: hughesm@mail.nih.gov

Y. Assadipour
Surgical Oncology, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

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tumor formation. Fifty percent of sporadic MTC cases have a documented somatic RET mutation. Additionally, familial medullary thyroid cancer (FMTC), multiple endocrine neoplasia (MEN) 2A, and MEN2B, which account for 25% of MTC cases, are all caused by RET mutations [7–9]. Specific mutations in RET leading to the respective phenotypes of FMTC, MEN2A, and MEN2B have been identified [10, 11]. Half of FMTC incidences are related to mutations on exon 10, 13, and 14. Mutations that highly activate RET have an increased risk for developing MTC and an earlier age of presentation. The American Thyroid Association (ATA) has developed a risk stratification system correlating genotype to risk level for aggressive MTC, with level A being the lowest risk and level D being the highest risk for aggressive MTC. FMTC mutations are generally less aggressive, with no level D mutations found in families with FMTC (Table 1).

RAS mutations have also been identified in spontaneous MTC. The RAS proto-oncogenes code for three highly similar GTPases, H-RAS, on chromosome 11p15.5, K-RAS, on chromosome 12p12.1, and N-RAS on chromosome 1p13.2. These GTPases have been shown to play an important role in many human cancers through activation of the MAPK cascade. H-RAS and K-RAS mutations are found in over 50% of RET-negative MTCs [12]. The fact that RAS and RET mutations in MTC are almost mutually exclusive of one another suggests that both RET and RAS can act as driver mutations in MTC [13].

Table 1 Common RET mutations in sporadic and FMTC and ATA risk stratification

Phenotype	Exon	Codon	ATA risk
Sporadic MTC	13	768	A
–	16	918	D
–	–	–	–
FMTC	11	630	B
–	–	631	B
–	–	634	B or C[a]
–	–	649	A
–	–	666	A
–	13	768	A
–	14	804	A
–	–	819	A
–	–	833	A
–	–	844	A
–	15	866	A
–	–	891	A

MTC medullary thyroid cancer, *FMTC* familial medullary thyroid cancer, *ATA* American Thyroid Association
Category A: Lowest risk of aggressive MTC
Category B: Second lowest risk of aggressive MTC
Category C: Second highest risk of aggressive MTC
Category D: Highest risk of aggressive MTC
[a] 634-bp duplication confers a risk level B; 634-point mutations confer a risk level C

Diagnosis of Medullary Thyroid Cancer

In patients with a known hereditary risk factor, MTC usually presents as an elevated screening calcitonin level or nodule(s) on screening thyroid and neck ultrasounds. These patients tend to have a lower incidence of lymph node involvement and higher cure rates as a result of the routine screening. Patients with sporadic MTC often present with a palpable thyroid nodule or neck mass. The presence of a thyroid nodule in the setting of elevated serum calcitonin is essentially diagnostic of MTC. MTC can also be confirmed with ultrasound-guided fine needle aspiration (FNA) demonstrating C cells on cytology, and more accurately, measuring calcitonin levels in the aspiration needle washout, a test known as FNA calcitonin [14, 15].

There are important gender differences in calcitonin levels, with males having more parafollicular C cells and higher calcitonin levels at baseline than women. Therefore, gender-specific thresholds have been determined, with a basal calcitonin level of 20 pg/mL in women and 100 pg/mL in men, and stimulated calcitonin level of 250 pg/mL in women and 500 pg/mL in men having a positive predictive value of 100% in detecting an occult MTC [16].

Clinical Features of Medullary Thyroid Cancer

MTCs account for 5% of all thyroid cancers. The most common age range of presentation is 35–45 years of age. The incidence in men and women is more evenly matched than other thyroid cancer histologies, with only slightly more than half of the patients with MTC being women.

Sporadic MTCs are usually solitary lesions, while hereditary MTC presents with multicentric and bilateral disease in over 80% of cases. Involvement of both central and lateral cervical lymph nodes is common in both sporadic and hereditary MTC. Early lymph node involvement is very common, with lymph node metastases occurring even with small primary tumors less than 1 cm in size (Fig. 1). The incidence of lymph node metastases increases with the size of the primary tumor [17]. In both sporadic and hereditary MTC, microscopic lymph node involvement in the central compartment level VI nodes was observed in 50–80% of patients. High rates of micrometastases to the lateral neck level III and IV nodes were also appreciated, including the contralateral lateral neck nodes in patients with unilateral disease [17, 18]. Distant metastases are most frequently to the liver, lung, and bones. Rarely, brain and skin can also be sites of metastases.

Patients with MTC may experience anterior neck pain, which was found to be more common in MTC as compared to other differentiated thyroid cancers. In one series, the presence of neck pain translated to a more advanced stage

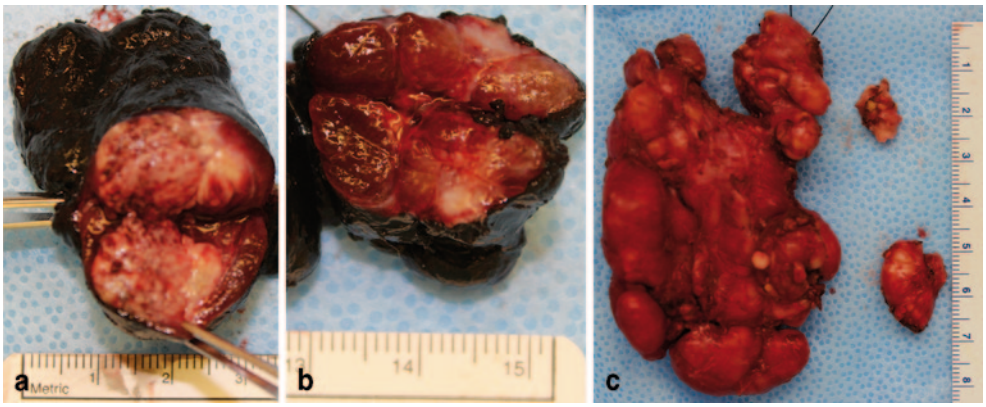

Fig. 1 Thyroid gland and right lateral lymph node compartments from a patient with bilateral synchronous lesions, lymph node metastases, and liver metastases: **a** *left* thyroid gland with primary tumor measuring 4 mm in greatest diameter, **b** *right* thyroid gland with primary tumor measuring 6 mm in greatest diameter, **c** *right* lateral neck compartments III, IV, and V had significant tumor burden involving the phrenic nerve, which was spared. Note that despite the primary tumors being small, lymph node involvement was extensive and the patient also had liver metastases. (Courtesy of Martha Quezado, M.D., Department of Pathology, National Institutes of Health)

of disease, with 82% of patients with anterior neck pain being stage III or IV, and only 36% of patients without pain being stage III or IV [19]. In addition to calcitonin and CEA, MTCs can also secrete vasoactive intestinal peptide (VIP), and infrequently, adrenocorticotropic hormone (ACTH) [20]. Therefore, in rare circumstances patients may have **Cushing's** syndrome as part of their presentation. Patients presenting with systemic symptoms related to calcitonin or VIP burden, including bone pain, diarrhea, or flushing, almost universally have distant metastases [21].

Meeting the criteria for FMTC necessitates two generations with MTC and no evidence of hyperparathyroidism or pheochromocytoma as first described by **Dr John Farndon** [22]. Other proposed definitions include MTC in four family members with no evidence of other MEN2 manifestations [23]. Overall, FMTC has a later age of presentation and is less aggressive biologically than MTCs in the sporadic or MEN2 setting [22]. Whether FMTC is a distinct entity or a specific phenotypic presentation of MEN2A is not concretely defined at this time, and some consider FMTC to be a variant of MEN2A.

Pathologic Features

MTCs are usually found in the upper third of the thyroid gland, due to the normal anatomic location of parafollicular cells. Grossly, the tumors appear well circumscribed, and nonencapsulated. Histologically, hyperchromatic spindle and polygonal tumor cells can be appreciated in sheets or nests separated by fibrovascular septa. The vast majority of MTCs have extracellular deposits of amyloid protein visible on microscopic examination. On immunohistochemistry, they stain positively for calcitonin and CEA (Fig. 2). In addition to the tumor, there are often areas of C cell hyperplasia (CCH) in patients with hereditary MTC. The diagnosis of CCH is made when three low power fields (area 1.93 mm^2) contain over 50 calcitonin-positive cells which do not demonstrate any nuclear abnormalities, defects in the follicular basal lamina, or infiltration of the thyroid interstitium, as such qualities would be indicative of microscopic MTC [24].

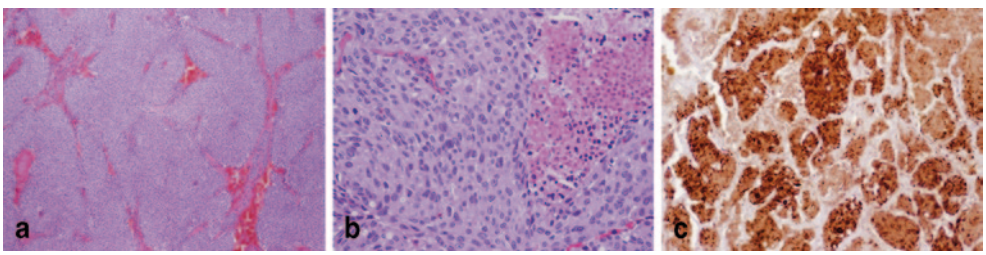

Fig. 2 Histopathology of medullary thyroid cancer: **a** hematoxylin and eosin stained MTC at 4× magnification view, demonstrating sheets and nests of tumor cells separated by fibrovascular septa, **b** at 20× magnification view, spindle and polygonal tumor cells with hyperchromatic nuclei can be appreciated, **c** MTCs are highly positive for calcitonin on immunohistochemistry, which stains brown. (Courtesy of Martha Quezado, M.D., Department of Pathology, National Institutes of Health)

Staging of Medullary Thyroid Carcinoma

Once a patient is diagnosed with MTC based on thyroid ultrasound and FNA, a basal serum calcitonin and detailed neck ultrasound should be obtained. The patient should undergo RET mutation testing, and pheochromocytoma should be ruled out using 24-h urine or plasma-free metanephrines and normetanephrines, and adrenal computed tomography (CT) or magnetic resonance imaging (MRI) if there is any uncertainty regarding biochemical screening results. Patients with no clinically appreciable lymph nodes on physical exam and neck ultrasound, and a basal calcitonin level under 400 pg/mL can proceed to surgical management for their MTC. If there are palpable nodes by physical exam, suspicious lymph nodes by ultrasound, or a basal calcitonin level over 400 pg/mL, a full metastatic workup should be initiated.

The metastatic workup for MTC should evaluate the liver using a sensitive imaging modality such as an MRI with contrast. Additionally, a neck and chest CT should be performed to further evaluate the neck compartments and determine whether lung metastases, which can frequently be bilateral, are present. (18 F)-fluorodeoxyglucose positron emission tomography can also be useful in detecting metastatic disease [25].

Staging is then categorized by the American Joint Committee on Cancer (AJCC) tumor, node, metastases (TNM) classification system which has been adapted for all thyroid carcinomas, including differentiated thyroid carcinoma histologies (see Chap. 15 on well-differentiated thyroid cancer).

Prognostic Factors in Medullary Thyroid Cancer

Age, gender, symptoms at presentation, extent of thyroidectomy, and TNM stage have been shown in univariate analysis to be significant prognostic factors in MTC. In a multivariate analysis, increasing age and advanced TNM stage were the only independent negative prognostic factors for survival [21, 26, 27]. Survival decreases dramatically with increasing stage (Table 2). Increased primary tumor size, positive lymph nodes, and distant metastases all decrease survival [28]. Early diagnosis and treatment have been shown to improve outcomes [29]. In patients with early MTC, treatment with total thyroidectomy and lymph node dissection results in a 95% cure rate [21].

Table 2 Ten-year survival in MTC by stage

TNM stage	Overall survival (%)
I	100
II	93
III	71
IV	21

TNM tumor, node, metastases, *MTC* medullary thyroid cancer

A preoperative basal calcitonin level over 500 pg/mL is an excellent predictor of failure to achieve biochemical remission after surgery [30]. Biochemically persistent disease following total thyroidectomy is prognostic of decreased survival, likely because this indicates advanced stage and metastases [29]. Likewise, calcitonin doubling time (DT) is a strong and independent predictor of survival. In one series, a DT over 2 years corresponded to a survival of 100% at 10 years, compared to a DT under 6 months, which had a survival of 8% at 10 years [31]. In the same series, CEA levels did not always parallel calcitonin levels, and did not correlate with survival. Previous studies have shown CEA is less specific in predicting recurrence and survival, but may correspond to a less-differentiated cell population and worse prognosis when elevated [32–34]. Rapidly increasing tumor marker levels are highly suggestive of distant metastases, hence their ability to predict survival. Distant metastases are the cause of death in half of the patients with MTC. 1-, 5-, and 10-year survival after determining the presence of distant metastases is 51, 26, and 10–20%, respectively [21].

Some studies of sporadic versus hereditary MTC suggested a difference in survival, while others have not [21, 27, 29]. What has been clearly demonstrated is the specific RET mutation, rather than if it is a somatic or germ-line mutation, has great prognostic significance in MTC because it predicts how aggressively a tumor will behave, which is the basis for the ATA risk stratification guidelines. Among sporadic cases of MTC, the presence of a somatic RET mutation correlates with larger tumors, nodal and distant metastases, advanced stage at diagnosis, worse outcome, and decreased survival [35].

Surgical Management of Medullary Thyroid Carcinoma

The cornerstone of management for all patients with locally contained disease is a total thyroidectomy with central lymph node dissection (complete removal of all lymph nodes from the level VI compartment), and provides the best chance for cure in patients with MTC [25]. The complete central lymph node dissection does increase the risk of hypoparathyroidism postoperatively. Care must be taken to preserve the parathyroid glands and their blood supply, or to remove the glands and perform an autotransplantation. Permanent hypoparathyroidism occurs in 3–4% of patients who undergo a central neck dissection [36]. The risk of transient or permanent injury to the recurrent laryngeal nerve is also slightly elevated with a lymph node dissection. However, the central compartment dissection is a vital component of appropriate treatment for MTC, and increases the cure rate [37]. Additionally, if any nodes in compartments II, III, IV, or V are

suspicious on ultrasound or intraoperatively, or a patient has a calcitonin level over 400 pg/mL, these nodes should be removed [17, 38, 39]. Indeed, undertreated patients with only partial thyroidectomy or incomplete lymph node dissections have worse outcomes [40].

For patients with FMTC, prophylactic thyroidectomy can be considered based on the most recent ATA guidelines. Patients with level A and B germ-line mutations may delay prophylactic thyroidectomy, provided annual surveillance is in place and the family history suggests less aggressive tumor biology. Patients with level C germ-line mutations are recommended to undergo prophylactic thyroidectomy before the age of 5, and patients with level D germ-line mutations are recommended to undergo prophylactic thyroidectomy before the age of 1, although level D germ-line mutations are not generally observed in FMTC [25].

Postoperative Surveillance

Calcitonin and CEA levels should be checked 2 months following a total thyroidectomy with lymph node dissection, and every 6 months afterward. If calcitonin levels are undetectable for 2 years, this interval may be increased to annual surveillance [25].

Patients with detectable calcitonin levels postoperatively are not considered cured. These patients likely had an incomplete surgical resection, or have metastatic disease. In any patient with biochemical recurrence, a neck ultrasound and FNA or biopsy of any suspicious masses is recommended. In the event of biochemical persistence or recurrence, when basal serum calcitonin levels reach above 150 pg/mL, a full metastatic workup is recommended.

Management of Locally Recurrent Medullary Thyroid Carcinoma

For patients found during postoperative surveillance to have a local recurrence, surgical intervention should be considered. Subcentimeter indeterminate lymph nodes can be followed with serial ultrasounds. In one large retrospective study of patients presenting with persistent MTC and serum calcitonin under 1000 pg/mL who previously had no or incomplete neck dissection, reoperation and completion of lymph node dissection lead to biochemical cure in 44% of patients with no prior lymph node dissection, and 18% biochemical cure in patients with incomplete lymph node dissection [41]. While this has not yet been validated in a randomized control trial, this suggests complete lymph node dissections can significantly increase cure rates. External beam radiation therapy (EBRT) may also be used for locoregional control, to relieve pain, and avoid compressive complications [42]. Common toxicities are acute mucositis and dysphagia, and there is no current evidence that EBRT improves survival [43, 44].

Management of Metastatic Medullary Thyroid Carcinoma

Although total thyroidectomy and lymph node dissection will not be curative in patients with distant metastases, palliation of symptoms related to mass effect in the neck, such as pain, tracheal involvement, or esophageal compression, is absolutely indicated. If an R0 resection will not be possible, lymph node dissection can be limited to avoid unnecessary injury to the recurrent laryngeal nerves. However, recently a large retrospective review of a cohort with MTC showed thyroidectomy and lymph node resection improved survival in patients with distant metastases [28]. Given this new information, although the most recent ATA guidelines recommend limited surgery in patients with distant metastatic disease, it may not be in the patient's best interest to rely on medical management alone, or perform an incomplete dissection. The potential survival benefits must be balanced against potentially grave morbidities. If there is extensive compression or invasion of the trachea, a tracheostomy may be required for palliation. Patients with residual gross disease can undergo EBRT to improve locoregional control [45]. However, it is important to appreciate that postradiation fibrosis will make any potential future interventions significantly more technically challenging, and therefore EBRT is best considered in patients who would otherwise not be appropriate surgical candidates.

Isolated brain metastases can be addressed with surgical intervention or EBRT. Patients with multiple distant metastases, such as the liver and lung, do not benefit from having metastases addressed surgically. Additionally, traditional chemotherapies are not particularly efficacious in controlling disease burden or symptoms, in addition to being highly toxic. Recently developed targeted molecular therapies can address metastatic disease in a more refined manner.

Monoclonal antibodies to tyrosine kinase receptors, including RET, can inhibit tyrosine kinase activity, decreasing cell proliferation and other downstream effects of activated tyrosine kinases. The first tyrosine kinase inhibitor (TKI) approved by the Food and Drug Administration (FDA) for use in advanced MTC was vandetanib, an oral multikinase inhibitor of RET, vascular endothelial growth factor receptor (VEGFR), and endothelial growth factor receptor (EGFR), which has been shown to prolong progression-free survival, with a mortality rate not related to progressive disease of 2.2% [46, 47]. Vandetanib has also been shown to control Cushing's syndrome caused by an ACTH-secreting MTC [48]. Since its approval, two other oral multikinase inhibitors

have been approved by the FDA for treatment of advanced MTC: sorafenib and cabozantinib.

Sorafenib targets both RET and VEGFR, and has also been shown to increase progression-free survival, cause partial responses in approximately 20% of patients, and stabilize disease in 70% of patients with MTC [49]. In a meta-analysis of all phase II trials of sorafenib for metastatic thyroid cancer of all histologies, the mortality rate not related to progressive disease was 3.7% [50]. Therefore, while sorafenib is quite efficacious in stabilizing disease progression, there are more adverse events compared to vandetanib, and appropriate patient selection is crucial.

Cabozantinib targets RET, VEGF, and hepatocyte growth factor (MET). In a phase III trial conducted on patients with MTC, cabozantinib was shown to prolong progression-free survival as well as overall survival, regardless of RET mutation status [51, 52]. Therefore, it may be particularly useful in patients without an RET mutation who have a weak or no response to vandetanib.

Sunitinib, a TKI currently FDA approved for the use in advanced pancreatic neuroendocrine tumors, has been shown to work synergistically with cisplatin against MTC in vitro, introducing a new potential role for traditional cytotoxic chemotherapy in the treatment of stage IV MTC [53, 54].

Future Directions

Another pathway found to be important in the carcinogenesis of MTC is the mammalian target of rapamycin (mTOR) pathway. Inhibition of mTOR in vitro has been shown to suppress growth in RET mutated MTC cell lines [55, 56]. Therefore, mTOR inhibitors such as everolimus, which have been approved for several other malignancies, may have therapeutic value in MTC. While no phase I, II, or III trials have been completed to evaluate the safety and efficacy of everolimus in MTC, in one study two patients with progressive metastatic MTC showed partial responses [57].

Immunotherapy may also have a role in the treatment of MTC. A phase I trial of a recombinant yeast-CEA vaccine (GI-6207) has shown good safety and tolerance, and one patient with MTC in the trial had a significant inflammatory response at their sites of metastatic disease [58].

Nelfinavir, a protease inhibitor previously used in the treatment of human immunodeficiency virus (HIV), may also have activity against MTC cells by targeting the heat shock protein 90 (HSP90), a chaperone protein required for RET stability. Nelfinavir was able to decrease RET protein levels, block downstream effects of RET, and induce apoptosis in human MTC cell lines in vitro [59].

Recently, the calcium/calmodulin-dependent kinase II (CaMKII) has been shown to be overactive in MTC cells with RET mutations. CaMKII is a serine/threonine protein kinase which among its many signaling functions can activate the MAPK pathway. An endogenous inhibitor of CAMKII, hCamKIINα has also been identified, and an inverse relationship between hCamKIINα expression and local tumor extension as well as lymph node metastases has been observed [60]. This suggests that inhibition of CaMKII can temper tumor behavior. Therefore, CaMKII has the potential to be a very useful target of molecular therapy in patients with stage IV MTC.

The more that is understood about the molecular biology of MTC, the more potential targets can be identified to create new molecular therapies specific to targeting MTC. As with all cancer treatments, the future lies in tailored approaches based on the genetic and cellular abnormalities which cause MTC.

Key Summary Points

- Medullary thyroid cancer originates from parafollicular C cells.
- Hereditary MTC and many forms of sporadic MTC are caused by mutations in the RET proto-oncogene, with a relationship between level of over activation of the RET tyrosine kinase and aggressiveness of tumor behavior.
- Diagnosis of MTC is most accurately made with FNA calcitonin.
- Staging workup includes a metastatic workup for patients with positive lymph nodes on physical exam or ultrasound, and all patients with a calcitonin level above 400 pg/mL.
- Appropriate surgical management of MTC includes a total thyroidectomy, central lymph node dissection, and in patients with clinically concerning lateral nodes or calcitonin level above 400 pg/mL, lateral lymph node dissection.
- Postoperative surveillance includes serum calcitonin and CEA levels to monitor for recurrence and neck ultrasound if there is evidence of biochemical recurrence.
- Local recurrences can be managed by observation, EBRT, or surgical intervention, which may improve cure rates.
- Patients with stage IV disease may still benefit from total thyroidectomy and lymph node dissection for local disease control as well as a potential survival benefit.
- Molecular-targeting therapies, such as TKIs, which can specifically target tumors with a constitutively activated RET mutation, are a promising modality for treating patients with stage IV MTC.
- Future therapies targeting proteins unique to parafollicular C cells and over activated pathways in MTC cells may provide a new and more refined strategy for treating stage IV MTC.

References

1. Williams ED. Histogenesis of medullary carcinoma of the thyroid. J Clin Pathol. 1966;19(2):114–8. (PubMed PMID: 5948665. Pubmed Central PMCID: PMC473198. Epub 1966/03/01. Eng).
2. Dubois PM, Alizon E, David L. [Calcitonin-cells in the thyroid of the human fetus. Immunocytochemical study (author's transl)]. Ann Endocrinol (Paris). 1979;40(1):53–4. (PubMed PMID: 443736. Epub 1979/01/01. Les cellules a calcitonine dans la thyroide du foetus humain. Etude par immunocytochimie. fre).
3. Mian C, Perrino M, Colombo C, Cavedon E, Pennelli G, Ferrero S, et al. Refining calcium test for the diagnosis of medullary thyroid cancer: cutoffs, procedures, and safety. J Clin Endocrinol Metab. 2014;99(5):1656–64. (PubMed PMID: 24552221. Epub 2014/02/21. eng).
4. Chan JK, Tse CH. Parafollicular C-cells do contain carcinoembryonic antigen. Am J Surg Pathol. 1988;12(3):247–8. (PubMed PMID: 3344889. Epub 1988/03/01. eng.)
5. Nakamura T, Ishizaka Y, Nagao M, Hara M, Ishikawa T. Expression of the ret proto-oncogene product in human normal and neoplastic tissues of neural crest origin. J Pathol. 1994;172(3):255–60. (PubMed PMID: 8195928. Epub 1994/03/01. eng).
6. Ichihara M, Murakumo Y, Takahashi M. RET and neuroendocrine tumors. Cancer Lett. 2004;204(2):197–211. (PubMed PMID: 15013219. Epub 2004/03/12. eng).
7. Donis-Keller H, Dou S, Chi D, Carlson KM, Toshima K, Lairmore TC, et al. Mutations in the RET proto-oncogene are associated with MEN 2A and FMTC. Hum Mol Genet. 1993;2(7):851–6. (PubMed PMID: 8103403. Epub 1993/07/01. eng).
8. Mulligan LM, Kwok JB, Healey CS, Elsdon MJ, Eng C, Gardner E, et al. Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. Nature 1993;363(6428):458–60. (PubMed PMID: 8099202. Epub 1993/06/03. eng).
9. Santoro M, Carlomagno F, Romano A, Bottaro DP, Dathan NA, Grieco M, et al. Activation of RET as a dominant transforming gene by germline mutations of MEN2A and MEN2B. Science 1995;267(5196):381–3. (PubMed PMID: 7824936. Epub 1995/01/20. eng).
10. Figlioli G, Landi S, Romei C, Elisei R, Gemignani F. Medullary thyroid carcinoma (MTC) and RET proto-oncogene: mutation spectrum in the familial cases and a meta-analysis of studies on the sporadic form. Mutat Res. 2013;752(1):36–44. (PubMed PMID: 23059849. Epub 2012/10/13. eng).
11. Romei C, Pardi E, Cetani F, Elisei R. Genetic and clinical features of multiple endocrine neoplasia types 1 and 2. J Oncol. 2012;2012:705036. (PubMed PMID: 23209466. Pubmed Central PMCID: PMC3503399. Epub 2012/12/05. eng).
12. Moura MM, Cavaco BM, Pinto AE, Leite V. High prevalence of RAS mutations in RET-negative sporadic medullary thyroid carcinomas. J Clin Endocrinol Metab. 2011;96(5):E863–8. (PubMed PMID: 21325462. Epub 2011/02/18. eng).
13. Agrawal N, Jiao Y, Sausen M, Leary R, Bettegowda C, Roberts NJ, et al. Exomic sequencing of medullary thyroid cancer reveals dominant and mutually exclusive oncogenic mutations in RET and RAS. J Clin Endocrinol Metab. 2013;98(2):E364–9. (PubMed PMID: 23264394. Pubmed Central PMCID: PMC3565108. Epub 2012/12/25. eng).
14. Trimboli P, Cremonini N, Ceriani L, Saggiorato E, Guidobaldi L, Romanelli F, et al. Calcitonin measurement in aspiration needle washout fluids has higher sensitivity than cytology in detecting medullary thyroid cancer: a retrospective multicentre study. Clin Endocrinol. 2014;80(1):135–40. (PubMed PMID: 23627255. Epub 2013/05/01. eng).
15. Diazzi C, Madeo B, Taliani E, Zirilli L, Romano S, Granata AR, et al. The diagnostic value of calcitonin measurement in wash-out fluid from fine-needle aspiration of thyroid nodules in the diagnosis of medullary thyroid cancer. Endocr Pract. 2013;19(5):769–79. (PubMed PMID: 23757613. Epub 2013/06/13. eng).
16. Machens A, Hoffmann F, Sekulla C, Dralle H. Importance of gender-specific calcitonin thresholds in screening for occult sporadic medullary thyroid cancer. Endocr Relat Cancer. 2009;16(4):1291–8. (PubMed PMID: 19726541. Epub 2009/09/04. eng).
17. Moley JF, DeBenedetti MK. Patterns of nodal metastases in palpable medullary thyroid carcinoma: recommendations for extent of node dissection. Ann Surg. 1999;229(6):880–7 (discussion 7–8. PubMed PMID: 10363903. Pubmed Central PMCID: PMC1420836. Epub 1999/06/11. eng).
18. Scollo C, Baudin E, Travagli JP, Caillou B, Bellon N, Leboulleux S, et al. Rationale for central and bilateral lymph node dissection in sporadic and hereditary medullary thyroid cancer. J Clin Endocrinol Metab. 2003;88(5):2070–5. (PubMed PMID: 12727956. Epub 2003/05/03. eng).
19. Guerrero MA, Lindsay S, Suh I, Vriens MR, Khanafshar E, Shen WT, et al. Medullary thyroid cancer: it is a pain in the neck? J Cancer. 2011;2:200–5. (PubMed PMID: 21509150. Pubmed Central PMCID: PMC3079917. Epub 2011/04/22. eng).
20. Hijazi YM, Nieman LK, Medeiros LJ. Medullary carcinoma of the thyroid as a cause of Cushing's syndrome: a case with ectopic adrenocorticotropin secretion characterized by double enzyme immunostaining. Hum Pathol. 1992;23(5):592–6. (PubMed PMID: 1568756. Epub 1992/05/01. eng).
21. Kebebew E, Ituarte PH, Siperstein AE, Duh QY, Clark OH. Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. Cancer 2000;88(5):1139–48. (PubMed PMID: 10699905. Epub 2000/03/04. eng).
22. Farndon JR, Leight GS, Dilley WG, Baylin SB, Smallridge RC, Harrison TS, et al. Familial medullary thyroid carcinoma without associated endocrinopathies: a distinct clinical entity. Brit J Surg. 1986;73(4):278–81. (PubMed PMID: 3697657. Epub 1986/04/01. eng).
23. Eng C, Clayton D, Schuffenecker I, Lenoir G, Cote G, Gagel RF, et al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. International RET mutation consortium analysis. JAMA 1996;276(19):1575–9. (PubMed PMID: 8918855. Epub 1996/11/20. eng).
24. Perry A, Molberg K, Albores-Saavedra J. Physiologic versus neoplastic C-cell hyperplasia of the thyroid: separation of distinct histologic and biologic entities. Cancer 1996;77(4):750–6. (PubMed PMID: 8616768. Epub 1996/02/15. eng).
25. Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19(6):565–612. (PubMed PMID: 19469690. Epub 2009/05/28. eng).
26. Wells SA, Jr., Pacini F, Robinson BG, Santoro M. Multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma: an update. J Clin Endocrinol Metab. 2013;98(8):3149–64. (PubMed PMID: 23744408. Epub 2013/06/08. eng).
27. Hyer SL, Vini L, A'Hern R, Harmer C. Medullary thyroid cancer: multivariate analysis of prognostic factors influencing survival. Eur J Surg Oncol. 2000;26(7):686–90. (PubMed PMID: 11187027. Epub 2001/02/24. eng).
28. Esfandiari NH, Hughes DT, Yin H, Banerjee M, Haymart MR. The effect of extent of surgery and number of lymph node metastases on overall survival in patients with medullary thyroid cancer. J Clin Endocrinol Metab. 2014;99(2):448–54. (PubMed PMID: 24276457. Pubmed Central PMCID: PMC3913800. Epub 2013/11/28. eng).
29. Rendl G, Manzl M, Hitzl W, Sungler P, Pirich C. Long-term prognosis of medullary thyroid carcinoma. Clin Endocrinol. 2008;69(3):497–505. PubMed PMID: 18331612. (Epub 2008/03/12. eng).

30. Machens A, Schneyer U, Holzhausen HJ, Dralle H. Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level. J Clin Endocrinol Metab. 2005;90(4):2029–34. (PubMed PMID: 15634717. Epub 2005/01/07. eng).
31. Barbet J, Campion L, Kraeber-Bodere F, Chatal JF. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. J Clin Endocrinol Metab. 2005;90(11):6077–84. (PubMed PMID: 16091497. Epub 2005/08/11. eng).
32. Busnardo B, Girelli ME, Simioni N, Nacamulli D, Busetto E. Nonparallel patterns of calcitonin and carcinoembryonic antigen levels in the follow-up of medullary thyroid carcinoma. Cancer 1984;53(2):278–85. (PubMed PMID: 6690009. Epub 1984/01/15. eng).
33. Saad MF, Fritsche HA, Jr., Samaan NA. Diagnostic and prognostic values of carcinoembryonic antigen in medullary carcinoma of the thyroid. J Clin Endocrinol Metab. 1984;58(5):889–94. (PubMed PMID: 6707192. Epub 1984/05/01. eng).
34. Gawlik T, d'Amico A, Szpak-Ulczok S, Skoczylas A, Gubala E, Chorazy A, et al. The prognostic value of tumor markers doubling times in medullary thyroid carcinoma—preliminary report. Thyroid Res. 2010;3(1):10. (PubMed PMID: 21047422. Pubmed Central PMCID: PMC2987862. Epub 2010/11/05. eng).
35. Elisei R, Cosci B, Romei C, Bottici V, Renzini G, Molinaro E, et al. Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: a 10-Year follow-up study. J Clin Endocrinol Metab. 2008;93(3):682–7. (PubMed PMID: 18073307).
36. Stamatakos M, Paraskeva P, Katsaronis P, Tasiopoulou G, Kontzoglou K. Surgical approach to the management of medullary thyroid cancer: when is lymph node dissection needed? Oncology 2013;84(6):350–5. (PubMed PMID: 23689063. Epub 2013/05/22. eng).
37. Greenblatt DY, Elson D, Mack E, Chen H. Initial lymph node dissection increases cure rates in patients with medullary thyroid cancer. Asian J Surg. 2007;30(2):108–12. (PubMed PMID: 17475579. Epub 2007/05/04. eng).
38. Dralle H, Machens A. Surgical management of the lateral neck compartment for metastatic thyroid cancer. Current Opin Oncol. 2013;25(1):20–6. (PubMed PMID: 23079930. Epub 2012/10/20. eng).
39. Tamagnini P, Iacobone M, Sebag F, Marcy M, De Micco C, Henry JF. Lymph node involvement in macroscopic medullary thyroid carcinoma. Brit J Surg. 2005;92(4):449–53. (PubMed PMID: 15672437. Epub 2005/01/27. eng).
40. Pelizzo MR, Boschin IM, Bernante P, Toniato A, Piotto A, Pagetta C, et al. Natural history, diagnosis, treatment and outcome of medullary thyroid cancer: 37 years experience on 157 patients. Eur J Surg Oncol. 2007;33(4):493–7. (PubMed PMID: 17125960. Epub 2006/11/28. eng).
41. Machens A, Dralle H. Benefit-risk balance of reoperation for persistent medullary thyroid cancer. Ann Surg. 2013;257(4):751–7. (PubMed PMID: 23023200. Epub 2012/10/02. eng).
42. Fife KM, Bower M, Harmer CL. Medullary thyroid cancer: the role of radiotherapy in local control. Eur J Surg Oncol. 1996;22(6):588–91. (PubMed PMID: 9005145. Epub 1996/12/01. eng).
43. Terezakis SA, Lee KS, Ghossein RA, Rivera M, Tuttle RM, Wolden SL, et al. Role of external beam radiotherapy in patients with advanced or recurrent nonanaplastic thyroid cancer: Memorial Sloan-kettering Cancer Center experience. Int J Radiat Oncol Biol Phys. 2009;73(3):795–801. (PubMed PMID: 18676097. Epub 2008/08/05. eng).
44. Martinez SR, Beal SH, Chen A, Chen SL, Schneider PD. Adjuvant external beam radiation for medullary thyroid carcinoma. J Surg Oncol. 2010;102(2):175–8. (PubMed PMID: 20648590. Pubmed Central PMCID: PMC2908956. Epub 2010/07/22. eng).
45. Schwartz DL, Rana V, Shaw S, Yazbeck C, Ang KK, Morrison WH, et al. Postoperative radiotherapy for advanced medullary thyroid cancer–local disease control in the modern era. Head Neck. 2008;30(7):883–8. (PubMed PMID: 18213725. Epub 2008/01/24. eng).
46. Robinson BG, Paz-Ares L, Krebs A, Vasselli J, Haddad R. Vandetanib (100 mg) in patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Endocrinol Metab. 2010;95(6):2664–71. (PubMed PMID: 20371662. Pubmed Central PMCID: PMC2902067. Epub 2010/04/08. eng).
47. Wells SA, Jr., Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012;30(2):134–41. (PubMed PMID: 22025146. Pubmed Central PMCID: PMC3675689. Epub 2011/10/26. eng).
48. Nella A, Lodish M, Fox E, Balis F, Quezado M, Whitcomb P, et al. Vandetanib successfully controls medullary thyroid cancer-related Cushing syndrome in an adolescent patient. J Clin Endocrinol Metab. 2014;99(9):3055–9. (PubMed PMID: 24617713. Epub 2014/03/13. Eng).
49. Lam ET, Ringel MD, Kloos RT, Prior TW, Knopp MV, Liang J, et al. Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer. J Clin Oncol. 2010;28(14):2323–30. (PubMed PMID: 20368568. Pubmed Central PMCID: PMC2881718. Epub 2010/04/07. eng).
50. Thomas L, Lai SY, Dong W, Feng L, Dadu R, Regone RM, et al. Sorafenib in metastatic thyroid cancer: a systematic review. Oncologist 2014;19(3):251–8. (PubMed PMID: 24563075. Pubmed Central PMCID: PMC3958462. Epub 2014/02/25. eng).
51. Elisei R, Schlumberger MJ, Muller SP, Schoffski P, Brose MS, Shah MH, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol. 2013;31(29):3639–46. (PubMed PMID: 24002501. Epub 2013/09/05. eng).
52. Viola D, Cappagli V, Elisei R. Cabozantinib (XL184) for the treatment of locally advanced or metastatic progressive medullary thyroid cancer. Future Oncol. 2013;9(8):1083–92. (PubMed PMID: 23902240. Epub 2013/08/02. eng).
53. Lopergolo A, Nicolini V, Favini E, Dal Bo L, Tortoreto M, Cominetti D, et al. Synergistic cooperation between sunitinib and cisplatin promotes apoptotic cell death in human medullary thyroid cancer. J Clin Endocrinol Metab. 2014;99(2):498–509. (PubMed PMID: 24276455. Epub 2013/11/28. eng).
54. Ravaud A, de la Fouchardiere C, Asselineau J, Delord JP, Do Cao C, Niccoli P, et al. Efficacy of sunitinib in advanced medullary thyroid carcinoma: intermediate results of phase II THYSU. Oncologist 2010;15(2):212–3; (author reply 4. PubMed PMID: 20189981. Pubmed Central PMCID: PMC3227944. Epub 2010/03/02. eng).
55. Gild ML, Landa I, Ryder M, Ghossein RA, Knauf JA, Fagin JA. Targeting mTOR in RET mutant medullary and differentiated thyroid cancer cells. Endocr Relat Cancer 2013;20(5):659–67. (PubMed PMID: 23828865. Epub 2013/07/06. eng).
56. Tamburrino A, Molinolo AA, Salerno P, Chernock RD, Raffeld M, Xi L, et al. Activation of the mTOR pathway in primary medullary thyroid carcinoma and lymph node metastases. Clin Cancer Res. 2012;18(13):3532–40. (PubMed PMID: 22753663. Epub 2012/07/04. eng).
57. Faggiano A, Ramundo V, Dicitore A, Castiglioni S, Borghi MO, Severino R, et al. Everolimus is an active agent in medullary thyroid cancer: a clinical and in vitro study. J Cell Mol Med. 2012;16(7):1563–72. (PubMed PMID: 21883896. Epub 2011/09/03. eng).
58. Bilusic M, Heery CR, Arlen PM, Rauckhorst M, Apelian D, Tsang KY, et al. Phase I trial of a recombinant yeast-CEA vaccine (GI-6207) in adults with metastatic CEA-expressing carcinoma. Cancer Immunol Immunother. 2014;63(3):225–34. (PubMed

PMID: 24327292. Pubmed Central PMCID: PMC3944709. Epub 2013/12/12. eng).

59. Kushchayeva Y, Jensen K, Recupero A, Costello J, Patel A, Klubo-Gwiezdzinska J, et al. The HIV protease inhibitor nelfinavir dowregulates RET signaling and induces apoptosis in medullary thyroid cancer cells. J Clin Endocrinol Metab. 2014;99(5):E734–45. (PubMed PMID: 24483157. Epub 2014/02/04. Eng).
60. Russo E, Salzano M, De Falco V, Mian C, Barollo S, Secondo A, et al. Calcium/calmodulin-dependent protein kinase II and its endogenous inhibitor alpha in medullary thyroid cancer. Clin Cancer Res. 2014;20(6):1513–20. (PubMed PMID: 24449826. Epub 2014/01/23. eng).