Review

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
50(7) 1–20

DOI: 10.1177/03000605221110698
journals.sagepub.com/home/imr
SAGE

Management of medullary carcinoma of the thyroid: a review

Ravindri Jayasinghe, Oshan Basnayake, Umesh Jayarajah and Sanjeewa Seneviratne

Abstract

Medullary thyroid carcinoma (MTC) is an uncommon malignancy of neuroendocrine origin derived from the parafollicular C cells. Although infrequent, the interest in this cancer exceeds its incidence owing to its distinctive features and its characteristic association with other endocrine tumors. Although the majority of MTCs are sporadic, hereditary varieties occur in isolation or as a part of multiple endocrine neoplasia type 2 syndrome (MEN 2). Currently, complete surgical resection of the tumor and nodal metastases with a curative intent remains the mainstay of therapy. The role of adjuvant therapy is limited, although radiotherapy and newer targeted therapies are routinely used for metastatic disease. The lack of consensus in the available guidance regarding the most appropriate diagnostic, therapeutic and follow-up strategies has caused substantial variability in clinical practice. Therefore, this review summarizes the latest available evidence and guidelines on the management of MTC with an emphasis on diagnosis, surgical treatment and follow-up.

Keywords

Medullary thyroid cancer, thyroid cancer, management, review, metastasis, guidelines

Date received: 27 February 2022; accepted: 13 June 2022

Introduction

Thyroid cancer is one of the most common cancers worldwide, affecting people in both developing and developed countries, with an incidence of 600,000 new cases diagnosed annually.[1–3] Medullary thyroid cancer (MTC) is relatively rare and

Department of Surgery, Faculty of Medicine, University of Colombo, Sri Lanka

Corresponding author:
Umesh Jayarajah, Department of Surgery, Faculty of Medicine, University of Colombo, Sri Lanka, Department of Surgery, Faculty of Medicine, P.O. Box 271, Kynsey Road, Colombo 8, Western Province, 00800 Sri Lanka.
Email: umeshe.jaya@gmail.com

accounts for approximately 1% to 2% of all thyroid cancers.[1,2,4] However, MTC is associated with high mortality, with a disproportionate rate of 8.6% of thyroid cancer-related deaths.[1] Unlike in differentiated thyroid cancers, the low incidence and limited number of large-scale studies of MTC have resulted in a paucity of high-quality evidence to reach a consensus on diagnosis and treatment.[5]

Most MTCs are sporadic (75%) although some (25%) are hereditary, either familial or occurring in association with multiple endocrine neoplasia type 2 (MEN 2) syndrome secondary to a germline mutation in the RET proto-oncogene.[6] Total thyroidectomy is the mainstay of treatment, which may be combined with central only or central and lateral neck dissection owing to frequent cervical lymph node metastases.[7] Radioactive iodine treatment, which is the primary adjuvant treatment modality in differentiated thyroid cancers, is ineffective in MTC because MTC cells do not take up iodine-131.[7] Newer modalities of targeted treatments, including tyrosine kinase inhibitors, have shown promise in advanced and recurrent disease.[8]

The goals of surgical therapy are prevention of locoregional recurrence and enhancing disease-free long-term survival. Parafollicular C cells of the thyroid produce calcitonin and carcinoembryonic antigen (CEA) which are used as markers of the extent of disease at diagnosis, biochemical cure after surgery and to detect recurrences during follow-up because these markers have a greater sensitivity than that of serial imaging.

MTC may take an aggressive course in some patients, causing early metastasis and leading to marked morbidity and mortality.[6] In other patients, sporadic MTC can take an indolent course with higher rates of survival even with established metastatic disease, which raises controversy regarding the extent of the initial surgery in sporadic variants.[9] Numerous guidelines regarding MTC have been formulated by professional bodies, namely the American Thyroid Association (ATA), European Society of Medical Oncology (ESMO) and the British Thyroid Association (BTA). However, there is high variation in the guidelines and a lack of consensus regarding clinical practice.[10–12] The purpose of this review was to summarize the available evidence and guidelines and provide an updated consensus regarding the management of MTC with an emphasis on diagnosis, surgical treatment and follow-up.

Ethics approval was not required in our institution for this study type.

Etiology

Sporadic

The sporadic variant accounts for almost 75% of all cases of MTC, which usually presents during the fourth to sixth decades of life.[1] The sporadic form shows a strong oncogene predominance, with complete activation of the RAS signaling pathway via somatic mutations in the RET or RAS genes.[13] The main oncogenic drivers in MTC are RET, which is a receptor tyrosine kinase, and RAS. The presence of these oncogenic drivers is associated with poor survival independent of the tumor stage.[14] A dose-effect relationship is evident in somatic RET mutations where the presence of more than one somatic mutation of the RET proto-oncogene within the same tumor predicts worse clinical outcomes. Furthermore, the RET mutation profiles may differ greatly, ranging from 8% to 20% within the same primary tumor and its metastases.[15]

Certain environmental risk factors, especially environmental pollutants, have been attributed to the causation of MTC; however, the evidence is inconclusive. It is

suggested that chemical pollutants, such as pesticides, industrial chemicals, phthalates, polychlorinated biphenyls (PCB) and perfluorinated compounds (PFC), brominated flame retardants, perchlorates, heavy metals and air pollutants can pose a significant risk in developing thyroid carcinoma in general.[16] However, associations with environmental risk factors have not been conclusively proven for MTC.

Hereditary

The inherited form of MTC, which is associated with MEN 2 syndrome, is subclassified into two distinct forms as MEN 2A and MEN 2B; type 2A is the most common clinical subtype.[10] The inherited form of MTC is transmitted in an autosomal dominant fashion with almost complete penetrance as a result of a variety of mutations in the RET proto-oncogene.[6] MEN 2A is characterized by the presence of MTC-associated pheochromocytoma (PHEO) or primary hyperparathyroidism (PHPT) or both in the context of a germline RET mutation.[10] MEN 2B is a relatively rare and clinically aggressive form of MEN 2 in which MTC occurs in almost all patients, who present at a younger age.[10] Familial MTC, which is characterized by the presence of only MTC without PHPT or PHEO, is now considered a variant of MEN 2A.[6,10]

Diagnosis

MTC has a higher tendency toward lymphatic spread compared with differentiated thyroid carcinoma.[10] Large node-negative tumors and small node-positive tumors generate comparable amounts of serum calcitonin.[17] The sensitivity of most advanced imaging modalities is inadequate to detect early nodal calcium deposits. [17] Therefore, early diagnosis and determining the extent of surgery remains challenging.[17] Additionally, a thorough initial diagnostic evaluation is vital with a detailed clinical and family history to identify symptoms associated with PHEO and PHPT (Table 1).

Clinical presentation

Preclinical MTC is defined as a positive RET gene mutation with a normal thyroid examination in a patient diagnosed with MTC during screening.[18] Detecting preclinical disease helps in the early identification of disease, and intervention at this stage leads to lower morbidity and mortality than those with late detection.[17]

Most patients with sporadic MTC present with a solitary thyroid nodule most often located in the upper part of the lobe because C cells predominate in this region.[6] At presentation, most (70%) patients have cervical node involvement and some (15%) may even exhibit compressive symptoms of the upper aerodigestive tract.[6] Approximately 5% to 10% of patients with sporadic MTC present with distant metastasis to the liver, lung, bones, brain and skin.[1,11] The presentation of inherited MTC patients is similar to those with sporadic MTC. [6] Patients with inherited MTC may present with systemic manifestations as a result of excess hormone secretion by the tumor, which comprises calcitonin and its related peptides and which causes facial flushing and diarrhea.[6] The rare variant known as adrenocorticotrophic hormone (ACTH)-secreting medullary thyroid cancer may present with signs of Cushing's syndrome.[6] Patients may also present with manifestations of MEN 2 syndrome.[19]

Imaging

Preoperative imaging helps determine the need, extent and nature of lymph node dissection. The first-line imaging choice is high-resolution neck ultrasonography.[19] Although this imaging method accurately detects structural neck disease, there is the

Table 1. Summary of the recommendations for the basic evaluation and diagnosis of MTC.

	BTA		ATA		ESMO		NCCN		Japan Association of Endocrine Surgeons	
Indicator	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation
Presentation										
History	4, D	Comprehensive family history in all cases	–	ND	–	ND	–	ND		
Screening	4, D	Insufficient evidence to recommend routine calcitonin screening in nodular thyroid disease	–	ND	–	ND	–	ND		
Investigation										
Initial	2+, C	US of thyroid, FNAC and baseline calcitonin levels	I B	Calcitonin: expert opinion varies Advanced MTC: Basal levels of calcitonin and CEA should be measured. Marked elevation in the serum CEA level out of proportion to a lower serum calcitonin level, or normal or low levels of both serum calcitonin and CEA, indicate poorly differentiated MTC Nodules measuring $\geq$1 cm should be evaluated by FNA. If findings are inconclusive, measure calcitonin levels in the FNA washout	–	Calcitonin measurement is mandatory for diagnosis CEA can be useful if calcitonin is not elevated; rare variation Serum calcitonin >500 ng/L is suggestive of metastatic disease and should be further investigated with whole-body imaging US to assess neck lymph node involvement, with CT and MRI recommended when additional detail is needed	2A	FNA to diagnose MTC		
Additional	4, D	Pheochromocytoma: 24-h urine sample for catecholamine and/or metanephrine measurement, or plasma norepinephrine/metanephrine Hyperparathyroidism: serum calcium; neck CT/MRI if suspect	C	Metastatic disease: Brain imaging if neurological symptoms are present	–	All patients with MTC should be offered genetic counselling Screening for somatic RET mutations is not recommended but should be done if RET inhibitor therapy is planned Contrast-enhanced whole-body CT to identify target	2A	Basal serum calcitonin levels CEA Pheochromocytoma screening, serum calcium Genetic counselling and screening for RET mutation Thyroid and neck US (central and lateral compartments)	SR	All patients with MTC should be offered genetic counselling RET gene mutation analysis is recommended in all patients with MTC

(continued)

Table 1. Continued.

	BTA		ATA		ESMO		NCCN		Japan Association of Endocrine Surgeons	
Indicator	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation
		locally-advanced disease Pentagastrin stimulation test: diagnose MTC in relatives in gene-negative inherited MTC; excludes false-positive basal calcitonin levels				lesions and the burden of systemic disease Contrast-enhanced MRI to identify brain metastasis, liver lesions and osteo-blastic lesions		Evaluation of vocal cord mobility		
'Preoperative staging	4, D	Systematic staging: (in node-positive patients with calcitonin >400 ng/L) Chest CT, liver dual-phase CT or MRI, bone scintigraphy or spinal MRI FDG-PET-CT is not recommended prior to the first time surgery	C E	Neck US in all patients with MTC. Chest and neck CECT, liver triphasic contrast-enhanced multi-detector CT, or contrast-enhanced MRI of the liver and axial MRI and bone scintigraphy in patients with extensive neck disease with regional or distant metastases or calcitonin >500 ng/L Neither FDG-PET/CT nor F-DOPA-PET/CT is recommended to detect the presence of distant metastases	–	Screening for pheochromocytoma and hyperparathyroidism is recommended in all patients Neck US in all patients, and if findings are suspicious, neck and chest CECT should be performed F-DOPA-PET is not recommended for routine staging. F-DOPA-PET, chest CT and liver and axial bone MRI are recommended if calcitonin levels are >500 ng/L or if clinical findings are suspicious Endoscopy of the upper aerodigestive tract when there is a high suspicion of infiltration	2A	Cross-sectional imaging: neck and chest contrast-enhanced CT and liver MRI or triphasic CT Ga-68 DOTATATE PET/CT or bone scan/ skeletal MRI		

MTC, medullary thyroid carcinoma; BTA, British Thyroid Association; ATA, American Thyroid Association; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; CECT, contrast-enhanced computed tomography; CEA, carcinoembryonic antigen; ND, not defined; US, ultrasonography; FNAC, fine-needle aspiration cytology; MRI, magnetic resonance imaging; 18-FDG, 18F-fluorodeoxyglucose; PET, positron-emission tomography; F-DOPA, fluorodopa; SR, strongly recommended; Ga-68 DOTATATE, gallium-68 oxodotreotide.

potential to miss lymph nodes behind the thyroid and in the upper mediastinum, which are seen in more than one-third of patients.[19] Therefore, false negative results in preoperative ultrasonography are not uncommon.[19]

Modern imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), nuclear medicine techniques, such as positron emission tomography (PET)/CT, cholecystokinin receptor subtype 2 (CCK2R)/gastrin receptor and gastrin receptor scintigraphy, immunoimaging using labeled antibodies with radionuclide targeting and bone scan/scintigraphy for patients with extensive neck disease and metastasis have revolutionized the technology in imaging and diagnostics.[20] Newer functional imaging modalities, although limited in MTC, may be of clinical use. These modalities comprise diffusion-weighted imaging (DWI) MRI, dynamic contrast-enhanced (DCE) MRI and PET/CT using fluorine-18-dihydroxyphenylalanine (18F-FDOPA), 18F-fluorodeoxyglucose (FDG) and 68Ga-labeled somatostatin (SST) analogues.[20]

Fine-needle aspiration (FNA) of a thyroid nodule can confirm the suspicion of sporadic MTC.[21] However, owing to morphological heterogeneity on FNA in some cases, the diagnosis can still be challenging.[21] MTCs classically show a dispersed cell pattern with plasmacytoid, epithelioid, polygonal or spindle cells with background stromal amyloid and absent follicles on cytology.[21] However, these findings should be further confirmed by immunohistochemical stains showing positivity for calcitonin, chromogranin and CEA with minimal thyroglobulin staining.[1,21]

Tumor markers

Complimenting ultrasonography and FNA with serum calcitonin is controversial owing to the frequently false high calcitonin values.[6] However, this issue can be minimized by confirming high calcitonin levels with a pentagastrin stimulation test.[6] Although conditions other than MTC can increase serum calcitonin levels, namely chronic renal failure, primary hyperparathyroidism and autoimmune thyroiditis, a majority of patients with calcitonin levels >100 ng/L have MTC.[22] The degree of elevation of calcitonin in MTC patients correlates well with the volume of the primary tumor and the extent of nodal and distant metastasis.[23] The degree of elevation is also a predictor of the potential of achieving biochemical cure following surgery.[23] The risk of nodal metastasis correlates with increasing calcitonin levels where a level of 500 ng/L predicts a 5% likelihood of distant metastasis with a 50% likelihood of cervical lymph node metastasis.[23]

CEA is a useful tumor marker although its sensitivity and specificity are inferior to those of calcitonin.[23] However, in the context of MTC, CEA levels correlate well with disease progression, where levels >30,000 ng/L predict lymph node metastasis in more than 70% of patients with MTC, and levels >100,000 ng/L are associated with a 75% increased risk of distant metastasis.[23]

Genetic testing and excluding coexisting disorders

Patients with newly-diagnosed sporadic MTCs should undergo genetic testing by sequencing exons 10 and 11, and 13 through 16 of the RET proto-oncogene.[24] Approximately 6% to 7% of patients with apparently sporadic MTC have unsuspected germline RET mutations, and approximately 60% of the patients with definitive sporadic MTC have somatic RET gene mutations.[24,25] Comprehensive sequencing of the remaining exons may be undertaken in patients with a strong clinical suspicion or a family history suggestive of

inherited MTC.[26] These patients should be referred for genetic counselling, and when a patient is found to be positive for a germline mutation, their family members also should undergo genetic counselling and screening.[26]

It is essential to perform a thorough evaluation for coexisting tumors in patients with MTC by measuring serum calcium to rule out hyperparathyroidism, which might require simultaneous surgical intervention.[6] Measuring plasma fractionated metanephrines to screen for PHEO is also required.[6] Patients without a family history of MEN 2 or those with negative RET gene testing results do not require such screening.[6]

Staging

Tumor-node-metastasis (TNM) staging of MTC depends on the tumor size, extrathyroidal extension, local and regional nodal involvement and distant metastasis.[27] Approximately 81% of patients with palpable MTCs were shown to have involved lymph nodes in the central compartment.[28] This finding highlights the importance of a thorough evaluation by lymph node mapping in patients with MTC. Extensive evaluation should be pursued if bulky nodal metastasis is documented, especially with a high calcitonin level (>500 ng/L).[6] Ultrasonography should be complemented by contrast-enhanced computed tomography (CECT) of the neck and chest, which helps identify neck and mediastinal disease.[10] Tri-phasic contrast CT, contrast-enhanced MRI and axial MRI or bone scintigraphy can be performed to further evaluate distant metastasis, which occurs frequently in the liver and bone.[10] 18-FDG-PET is not routinely recommended for the initial screening of patients with MTC.[1,10]

Surgical management

MTC diagnosed following lobectomy

In patients in whom MTC is discovered following thyroid lobectomy, further investigation should be undertaken to identify inherited MTC and to perform total thyroidectomy to prevent contralateral MTC.[18] Investigation should comprise basal serum calcitonin levels, neck ultrasonography, identifying RET mutations and a detailed family history.[18] Patients can be observed if all investigations are unremarkable and resection margins are negative with unifocal disease and no C cell hyperplasia.[10] Reoperation with lymph node dissection is indicated if the patient has positive ultrasonographic findings with an elevated calcitonin level.[10] The ATA recommends total thyroidectomy in sporadic cases only if serum calcitonin remains elevated 3 months after surgery or if radiological evidence demonstrates residual disease.[1] In contrast, the BTA recommends total thyroidectomy with or without central neck dissection in sporadic MTC with tumors measuring >5 mm in diameter.[29] The BTA recommends the measurement of serum calcitonin levels to guide further surgery in those with tumors measuring <5 mm in diameter[29] (Table 2).

Presurgically diagnosed MTC

MTC can be suspected in patients presenting with a thyroid nodule based on cytology, serum calcitonin levels or the detection of a germline mutation in the RET proto-oncogene.[30] Correlating radiological evidence with clinical suspicion can help regarding the decision to proceed with total thyroidectomy. Total thyroidectomy is preferred owing to the high incidence of multifocal and bilateral disease, which is observed in 15% and 5%, respectively, of patients with sporadic MTC.[30]

Table 2. Summary of recommendations for the initial treatment of MTC.

	BTA		ATA		ESMO		NCCN		Japan Association of Endocrine Surgeons	
Indicator	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation
Treatment	Key recommendation	Established MTC: Total thyroidectomy with CND (inferior limit: innominate artery, level VI & VII) Lateral compartment lymph nodes comprises: Total thyroidectomy+ CND + LND of levels IIa–Vb	B	Total thyroidectomy and CND (level VI): Patients with MTC with no neck lymph node metastasis on US and no evidence of distant metastasis	–	ND	2A	<1 cm tumor, unilateral thyroid disease: Total thyroidectomy and consider neck dissection (level VI) ≥1 cm tumor or bilateral thyroid disease: Total thyroidectomy with bilateral neck dissection (level VI)	SR, EC-G	Hereditary MTC: Total thyroidectomy even if the lesion is limited to one lobe Prophylactic CND recommended for MTC
	2+, C	Incidental, sporadic (RET-negative), unifocal microMTC: postoperative basal calcitonin to determine the need for further surgery	I	LND (levels II–V): Patients with MTC without neck metastasis on US and no distant metastasis: evidence is insufficient to recommend for or against				≥1 cm tumor or bilateral clinically or radiologically identified thyroid disease: Ipsilateral or bilateral modified neck dissection (levels II–V) High-volume disease: Prophylactic ipsilateral modified neck dissection	WR, EC-G	Sporadic MTC in one lobe: Less than total thyroidectomy (lobectomy)
	3, D	Central compartment node metastasis: Ipsilateral prophylactic lateral neck dissection Sternotomy: Evidence of mediastinal node involvement with no distant metastasis Disseminated disease: Total thyroidectomy and CND	C	Total thyroidectomy, CND and LND: patients with MTC confined to the neck and cervical lymph nodes Contralateral neck dissection: Imaging-positive in the ipsilateral neck compartment but negative in the contralateral neck compartment Extensive regional/metastatic disease: Less aggressive					WR, EC-G	Prophylactic LND on the ipsilateral or contralateral side: determined based on calcitonin level and individual prognostic factors

(continued)

Table 2. Continued.

Indicator	BTA		ATA		ESMO		NCCN		Japan Association of Endocrine Surgeons	
	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation
	4, D	Personalized decision-making depending on central compartment metastasis: CND and ipsilateral compartment node dissection at initial surgery; CND with intraoperative frozen section, two-stage procedure If no direct invasion: Sternocleidomastoid, internal jugular vein and accessory nerve should be conserved Routine dissection of level I, IIb and Va not required in the absence of suspicious nodes		surgery in the central and lateral neck (palliative)						

MTC, medullary thyroid carcinoma; CND, central lymph node compartment dissection; LND, lateral neck dissection; ND- Not defined; BTA, British Thyroid Association; ATA, American Thyroid Association; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; US, ultrasonography; microMTC, medullary thyroid microcarcinoma; SR, strongly recommended; EC-G, good expert consensus; WR, weakly recommended.

MTC confined to the neck. Total thyroidectomy is the treatment of choice for MTC confined to the neck, with complete excision of the tumor and any involved regional lymph nodes.[30] This approach offers the best chance of disease-free survival.[6] Preoperative ultrasonographic findings and intraoperative identification of positive lymph nodes may help guide the extent of cervical lymph node dissection.[6]

Node-negative MTC. Patients with node-negative MTC have an overall survival rate similar to that of the general population.[31] When there is no evidence of cervical node involvement on preoperative ultrasonography, prophylactic central lymph node compartment dissection (CND) is preferred without prophylactic lateral neck dissection (LND).[23] However, in patients with small intrathyroidal MTCs with a calcitonin level of <20 ng/L, prophylactic CND may be avoided because lymph node involvement is rare in these patients.[23]

Performing LND in patients with no ultrasonographic evidence of lymph node metastasis is controversial because doing so contributes to morbidity.[10] The ATA recommends that the extent of prophylactic LND be guided by serum calcitonin levels.[10] The ATA recommends CND and ipsilateral LND for those with a baseline calcitonin level of >20 ng/L and additional prophylactic contralateral LND for patients with serum calcitonin levels >200 ng/L.[10] The rationale behind this recommendation is that at least half of the patients with MTC having a preoperative calcitonin level of ≤1000 ng/L and will achieve biochemical cure.[1,10] The BTA recommends ipsilateral LND guided by the tumor size and calcitonin levels or by frozen section of CND nodes.[12] The BTA does not recommend prophylactic contralateral LND without evidence of central or ipsilateral nodal involvement.[12]

MTC with nodal involvement. Total thyroidectomy with CND and dissection of the involved lateral neck compartments is preferred in patients with preoperatively known nodal involvement.[1] In those with a basal calcitonin levels >200 ng/L with no evidence of distant metastasis, it is recommended to also perform prophylactic dissection of uninvolved contralateral neck compartments.[1]

Locally-advanced or metastatic MTC. Total thyroidectomy with resection of the involved lymph node compartments is recommended in most patients with a palliative intent.[32] A less aggressive function-preserving approach is preferred during surgery for the primary tumor and lymph node dissection in central and lateral neck compartments to preserve speech, swallowing, parathyroid function and mobility of the shoulder.[1] The approach should be individualized, considering the patient's wishes, other comorbidities and life expectancy.[1,32]

Prophylactic thyroidectomy in inherited MTC

Prophylactic thyroidectomy is indicated in those with inherited germline mutations in the RET proto-oncogene without clinically evident disease.[1] Prophylactic thyroidectomy is performed with the intention of minimizing long-term morbidity and mortality associated with MTC.[1] The ATA guidelines suggest a classification system with stepwise increasing risk.[1] The highest risk category comprises patients with MEN 2B syndrome and the M918T RET mutation; patients with C634F/G/R/S/W/Y and A883F RET mutations are categorized as high-risk (ATA-H), and patients with mutations other than those listed are classified as moderate-risk.[1] Those in the highest-risk category are considered for total thyroidectomy with CND within the first year of their life.[1] Those with MEN 2A syndrome

with ATA-H mutations are kept under close surveillance with annual physical examination, cervical ultrasonography and calcitonin level measurement from 3 years of age.[1] These patients should undergo total thyroidectomy and CND by 5 years of age.[1] All adult family members with suspected MEN 2B syndrome identified with a RET germline mutation following genetic screening should undergo prophylactic total thyroidectomy with CND[1] (Table 3).

Medullary thyroid microcarcinoma (microMTC)

MTCs measuring <1 cm in size are referred to as microMTCs.[33] The need for aggressive therapy in these patients remains controversial. However, evidence demonstrates a 23% risk of lymph node metastasis even in 5 mm microMTCs.[33] Therefore, most guidelines recommend that thyroidectomy with CND be considered in patients with microMTC.[33]

Emerging therapies

The primary treatment modality for MTC is surgical resection.[34] However, patients with extensive metastatic disease that cannot be treated by surgery or radiotherapy alone are candidates for targeted therapy.[34] Targeted therapy and immune therapy are both emerging therapies for patients with MTC. Patients who do not respond to targeted therapy are candidates for cytotoxic chemotherapy or biologics.[34] Selective RET-kinase inhibitors, such as selpercatinib or pralsetinib, may be used in patients who have tumors with RET mutations.[34] Multi-targeted kinases, such as sunitinib, cabozantinib, vandetanib, lenvatinib or sorafenib can be used in patients without RET mutations.[6] Immunotherapy is yet another promising treatment modality in patients with thyroid cancer, which involves increasing the patient's immunity to cancer using tumor-derived vaccines or inoculation of tumor transfectants to induce a cytokine response.[34] Monoclonal antibodies coupled with radioisotopes can be used as a form of radiotherapy; however, these novel treatments are still at the investigational stage and have not been established for routine management of MTC.[34]

Dynamic risk stratification in MTC

Dynamic risk stratification (DRS) is a relatively new concept in real-time risk evaluation that is used to provide personalized disease management during follow-up of patients with MTC. [35] Adequate risk evaluation contributes to optimum individualized therapeutic decisions. DRS is aided by histopathological, imaging and biochemical assessments. DRS has been shown to predict the individualized risk of recurrence in numerous studies, although further validation of this approach is essential to promote its widespread use.[35]

Postoperative follow-up

During the immediate postoperative period, patients should be observed for common complications, such as hypoparathyroidism and injury to the recurrent or superior laryngeal nerves.[32] Thyroxine should be started immediately following surgery with the goal of restoring a euthyroid state at an initial physiologic dose of 1.6 μg/kg body weight.[32] The adequacy of therapy is monitored by measuring serum thyroid stimulating hormone (TSH) 6 weeks later.[32] Serum TSH suppression is not beneficial in patients with MTC because C cells are not TSH responsive.[32] Adjuvant radioiodine therapy is also not indicated because MTC cells do not concentrate iodine.[32] Serum calcitonin and CEA levels are measured beginning 3 months after surgery to assess the adequacy of surgical resection,

Table 3. Summary of the guidelines for screening for MEN syndrome and prophylactic surgery.

	BTA		ATA		ESMO		NCCN		Japan Association of Endocrine Surgeons	
Indicator	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation
Screening for MEN syndrome	Key recommendation	All confirmed MTC cases should undergo RET mutation analysis (even in the absence of a positive family history)	B	Initial testing for MEN 2A is by single- or multi-tiered analysis to detect RET mutations MEN 2B: test for the RET codon M918T mutation; if negative, test for the A883F mutation Sporadic MTC patients: genetic counselling and genetic testing should be done for RET germline mutations Pheochromocytoma should be excised prior to surgery for MTC or hyperparathyroidism	–	ND	2A	MEN 2B: Investigate with basal serum calcitonin, CEA, pheochromocytoma screening, central and lateral neck compartment US, neck contrast-enhanced CT MEN 2A: Investigate with basal serum calcitonin, pheochromocytoma screening, serum calcium & PTH, central and lateral neck compartment US, neck contrast-enhanced CT		
	4, D	Prenatal testing for MEN 2B								
Prophylactic surgery for MEN syndrome	2+, C	MEN 2B: surgery within the first year of life MEN 2A+ 634 codon mutation: surgery before 5 years of age Lymph node dissection in gene carriers: based on baseline calcitonin level	C	ATA-HST with the RET M918T mutation: Thyroidectomy in the first year of life. CND depends on whether the parathyroid glands can be autotransplanted	–	M918T mutation: total thyroidectomy during the first year of life C634F or A883F mutation: total thyroidectomy at 5 years of age or earlier if calcitonin level increases Other mutations: Monitor from 5 years of age using calcitonin assays and neck US with surgery if calcitonin levels	2A	MEN 2B: Total thyroidectomy during the first year of life or at diagnosis Therapeutic neck dissection if indicated combined with prophylactic CND MEN 2A: total thyroidectomy at 5 years of age. Therapeutic ipsilateral or bilateral neck dissection. Prophylactic ipsilateral modified neck	DNR-W, EC-P	Prophylactic thyroidectomy is not uniformly recommended for asymptomatic carriers of RET mutations
			B	ATA-H: Thyroidectomy at 5 years of age; CND if calcitonin >40 ng/L with imaging evidence of metastasis ATA-MOD: physical examination, neck US						

(continued)

Table 3. Continued.

Indicator	BTA		ATA		ESMO		NCCN		Japan Association of Endocrine Surgeons	
	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation
				and measurement of serum calcitonin levels from 5 years of age. The timing of thyroidectomy should be based on the detection of an elevated serum calcitonin level		increase or following parental request		dissection for high-volume disease		

ATA, American thyroid association; BTA, British Thyroid Association; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; MEN, multiple endocrine neoplasia; MTC, medullary thyroid carcinoma; MEN 2B, multiple endocrine neoplasia type 2B; MEN 2A, multiple endocrine neoplasia type 2A; CND, central lymph node compartment dissection; CEA, carcinoembryonic antigen; ND- Not defined; ATA-H, ATA high-risk; ATA-HST, ATA highest-risk; ATA-MOD, ATA moderate-risk; US, ultrasonography; CT, computed tomography; PTH, parathormone; DNR-W, do not recommend weakly; EC-P, poor expert consensus.

Table 4. Summary of the MTC guidelines for postoperative management and the management of recurrent or persistent disease Indicator.

	BTA		ATA		ESMO		NCCN	
	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation
Postoperative management	4, D	Following total thyroidectomy: Thyroxine replacement to maintain TSH within the euthyroid range	B	Following total thyroidectomy: Serum TSH measured 4–6 weeks postoperatively and levothyroxine replacement to maintain TSH in the euthyroid range	–	ND	2A	Levothyroxine to normalize TSH postoperatively
Adjuvant Therapy	4, D	EBRT: following surgery if there is a significant risk of local recurrence Palliative radiotherapy: unresectable masses and painful bony metastases Somatostatin analogues: control severe diarrhea from metastatic disease Targeted therapies (TKIs): only within clinical trials	C	EBRT: for local tumor control in extensive regional or metastatic disease Somatostatin analogues: advanced MTC and diarrhea	ND	Progressive metastatic MTC: Cabozantinib and vandetanib used as first-line therapies Treatment with MKIs should be considered in lesions close to vital structures and with high tumor burdens or disease progression Little evidence to support radionuclide therapy but can be considered when MKIs are contraindicated	2A	EBRT: grossly incomplete tumor resection
			E	Postoperative RAI is not indicated following surgery for MTC but should be considered in patients whose primary tumor comprises mixed MTC				
			D	Single-agent or combination cytotoxic chemotherapeutic regimens should not be administered as first-line therapy in patients with persistent or recurrent MTC				
			A	Targeted therapies (TKIs): In patients with significant tumor burden and symptomatic or progressive metastatic disease, these can be used as single-agent, first-line systemic therapy in patients with advanced progressive MTC				

(continued)

Table 4. Continued.

	BTA		ATA		ESMO		NCCN	
	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation
Follow-up	4, D	Lifelong follow-up Calcitonin and CEA levels: measured 6 months after surgery to assess response Elevated, stable calcitonin levels: Conservative management Progressively increasing calcitonin levels: Imaging and further staging	C	TNM classification, determining the number of lymph node metastases and measuring postoperative serum calcitonin levels should be considered during follow-up Calcitonin and CEA should be measured 3 months postoperatively and if undetectable or within the normal range, levels should be measured every 6 months for 1 year and then yearly thereafter Calcitonin <150 ng/L: physical examination and neck US Calcitonin >150 ng/L: Imaging (neck US, chest CT, contrast-enhanced MRI, bone scintigraphy and MRI of the pelvis and axial skeleton	ND	Serum calcitonin level measured 60–90 days after surgery; levels <10 ng/L indicate a biochemical cure CEA to monitor progression of clinically-evident MTC, but this is not useful in the diagnosis Doubling times of CEA and calcitonin levels are tumor markers and predictors of tumor behavior, recurrence and cancer-related death (two consecutive measurements over a 2-year period) Calcitonin and CEA monitoring in early and long-term follow-up	2A	Follow-up using basal calcitonin and CEA levels 2–3 months after surgery Elevated calcitonin/CEA: Neck US; neck, liver and chest CECT; bone scan of the axial skeleton Follow-up with calcitonin and CEA measurements every 6–12 months Normal calcitonin/CEA: Annual calcitonin/CEA
Treatment of recurrent disease	2++, B	Reoperation (curative intent): incomplete initial surgery, basal calcitonin <1,000 ng/L + <5 disease-positive lymph nodes, absence of extrathyroidal spread	B	Repeat surgery/total thyroidectomy: presumed sporadic MEN patients with RET mutations, elevated postoperative serum calcitonin or imaging indicating residual MTC	–	ND	2A	Locoregional: surgical resection, EBRT/systemic therapy if unresectable Asymptomatic: Monitoring, consider resection/ablation

(continued)

Table 4. Continued.

	BTA		ATA		ESMO		NCCN	
	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation	Evidence	Recommendation
	4, D	Reoperation (with distant metastasis): to minimize airway compromise and compression of the esophageal or laryngeal nerves by large-volume disease	C	Repeat compartment-oriented lymph node dissection: If serum calcitonin levels are <1,000 ng/L and <5 metastatic lymph nodes removed at the initial surgery				with systemic therapy if not resectable Symptomatic disease or progression: Systematic therapy, EBRT for local symptoms, bisphosphonate or denosumab therapy for bone metastasis, supportive care

MKI, multikinase inhibitors; MTC, medullary thyroid carcinoma; CECT, contrast enhanced CT; EBRT, external beam radiotherapy; CEA, carcinoembryonic antigen; RAI, radioactive iodine; ND, not defined; BTA, British Thyroid Association; ATA, American Thyroid Association; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; TSH, thyroid-stimulating hormone; TNM, tumor-node-metastasis; US, ultrasonography; MEN, multiple endocrine neoplasia.

which also guides subsequent management.[36] Patients with undetectable calcitonin and CEA levels are considered biochemically cured and thus, have the best prognosis, with a 5-year recurrence rate of approximately 5%[36] (Table 4).

Managing persistent or recurrence disease

Residual disease is identified when a high basal serum calcitonin value is demonstrated 3 months after surgery.[32] Further management depends on the magnitude of the elevation of calcitonin and CEA levels and the doubling time, which is a sensitive marker for the aggressiveness of the tumor.[32] Residual disease can be managed with active surveillance, surgical resection, external beam radiotherapy, and with systemic and local therapies, such as radiofrequency ablation, embolization and cryoablation.[32] The treatment approach depends on the ability to localize the disease, tumor volume and location, and whether the patient is symptomatic and the likelihood of disease progression.[32] Therefore, individualized treatment plans for persistent disease should be determined with multi-disciplinary team involvement. Surgical resection and lymph node dissection is preferred in patients with biopsy-proven persistent locoregional MTC without distant metastasis.[33] However, surgery in such situations is associated with high morbidity owing to complications, such as nerve injury (recurrent laryngeal, phrenic, spinal accessory, brachial plexus), thoracic duct leaks and hypoparathyroidism.[33] Therefore, the benefits of reoperation must be weighed against the potential risks[1, 33] (Table 4).

Conclusion

MTC, a rare malignancy of neuroendocrine origin, remains a surgical disease in which total thyroidectomy with at least CND is the mainstay of treatment in the majority of patients. The low incidence of these tumors has led to minimal high-quality evidence. Additionally, the wide spectrum of tumor biology with substantial variability in clinical practice has led to a lack of consensus regarding the diagnosis and surgical management of these tumors. Further research is essential regarding determining the extent of neck dissection, risk stratification and the optimum use of tumor markers in therapy.

Availability of data and materials

The data used in this article are available on reasonable request from the corresponding author.

Author contributions

RJ, OB and UJ contributed to the concept and design of the study; acquisition of the data; analysis and interpretation of the data; drafting the article and final approval of the version to be published. SS contributed to the concept and design of the study, revising the manuscript critically for important intellectual content and final approval of the version to be published.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iDs

Ravindri Jayasinghe https://orcid.org/0000-0002-7258-2789
Umesh Jayarajah https://orcid.org/0000-0002-0398-5197

References

1. Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid

carcinoma: the American Thyroid Association Guidelines Task Force on medullary thyroid carcinoma. *Thyroid* 2015; 25: 567–610.
2. World Health Organization. Cancer Today – GLOBOCAN 2020 [cited 2022 25 March]. Available from: https://gco.iarc.fr/today/home. (Accessed 25 March 2022.)
3. Udayanga V, Jayarajah U, Colonne SD, et al. Quality of the patient-oriented information on thyroid cancer in the internet. *Health Policy and Technology* 2020; 9: 302–307. Available from: https://www.sciencedirect.com/science/article/abs/pii/S2211883720300344
4. Jayarajah U, Fernando A, Prabashani S, et al. Incidence and histological patterns of thyroid cancer in Sri Lanka 2001-2010: an analysis of national cancer registry data. *BMC cancer* 2018; 18: 163.
5. Jayarajah U, Nagodavithane K, Basnayake O, et al. Surgical management of papillary thyroid cancer: review of current evidence and consensus. *Sri Lanka J Surg* 2019; 37: 18–23.
6. Tuttle RM. Medullary thyroid cancer: Clinical manifestations, diagnosis, and staging: UpToDate; 2020 [Accessed 1 October 2020). Available from: https://www.uptodate.com/contents/medullary-thyroid-cancer-clinical-manifestations-diagnosis-and-staging?search = Medullary%20thyroid%20carcinoma&source = search_result&selectedTitle = 1∼86&usage_type = default&display_rank = 1.
7. Jayarajah U, Wijekoon M and Seneviratne SA. Prophylactic prednisolone for the prevention of early and intermediate adverse effects of radioactive iodine therapy in patients with thyroid cancer: study protocol for a single-centre, phase II/III, randomized, double-blinded, placebo-controlled clinical trial. *Trials* 2020; 21: 812.
8. Trimboli P, Castellana M, Virili C, et al. Efficacy of vandetanib in treating locally advanced or metastatic medullary thyroid carcinoma according to RECIST criteria: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)* 2018; 9: 224.
9. Fussey JM, Bradley PJ and Smith JA. Controversies in the surgical management of sporadic medullary thyroid carcinoma. *Curr Opin Otolaryngol Head Neck Surg* 2020; 28: 68–73.
10. Kloos RT, Eng C, Evans DB, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid* 2009; 19: 565–612.
11. Pacini F, Castagna MG, Brilli L, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21: v214–219.
12. British Thyroid Association. British Thyroid Association Guidelines for the management of thyroid cancer (Accessed 1 October 2020). Available from: http://www.ukeps.com/docs/BTA.pdf.
13. Agrawal N, Jiao Y, Sausen M, 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: E364–E369.
14. Elisei R, Cosci B, Romei C, 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: 682–687.
15. Romei C, Ciampi R, Casella F, et al. RET mutation heterogeneity in primary advanced medullary thyroid cancers and their metastases. *Oncotarget* 2018; 9: 9875–9884.
16. Fiore M, Oliveri Conti G, Caltabiano R, et al. Role of emerging environmental risk factors in thyroid cancer: a brief review. *Int J Environ Res Public Health* 2019; 16: 1185.
17. Machens A, Schmid KW and Dralle H. Advances in the diagnosis and surgical management of medullary thyroid carcinomas. In: Shifrin AL *Advances in Treatment and Management in Surgical Endocrinology*. 1st ed. Elsevier, 2020, pp. 11–25.
18. Koutelidakis I, Kapoulas S, Papaziogas V, et al. Surgical management of medullary thyroid cancer. *Hellenic J Surg* 2015; 87: 58–62.
19. Kouvaraki MA, Shapiro SE, Fornage BD, et al. Role of preoperative ultrasonography

in the surgical management of patients with thyroid cancer. *Surgery* 2003; 134: 946–954.
20. Kushchayev SV, Kushchayeva YS, Tella SH, et al. Medullary thyroid carcinoma: an update on imaging. *J Thyroid Res* 2019; 2019: 1893047.
21. Pusztaszeri MP, Bongiovanni M and Faquin WC. Update on the cytologic and molecular features of medullary thyroid carcinoma. *Adv Anat Pathol* 2014; 21: 26–35.
22. Niccoli P, Wion-Barbot N, Caron P, et al. Interest of routine measurement of serum calcitonin: study in a large series of thyroidectomized patients. *J Clin Endocrinol Metab* 1997; 82: 338–341.
23. Machens A and Dralle H. Biomarker-based risk stratification for previously untreated medullary thyroid cancer. *J Clin Endocrinol Metab* 2010; 95: 2655–2663.
24. Eng C, Mulligan LM, Smith DP, et al. Low frequency of germline mutations in the RET proto-oncogene in patients with apparently sporadic medullary thyroid carcinoma. *Clin Endocrinol (Oxf)* 1995; 43: 123–127.
25. Romei C, Elisei R, Pinchera A, et al. Somatic mutations of the ret protooncogene in sporadic medullary thyroid carcinoma are not restricted to exon 16 and are associated with tumor recurrence. *J Clin Endocrinol Metab* 1996; 81: 1619–1622.
26. Moline J and Eng C. Multiple endocrine neoplasia type 2: an overview. *Genet Med* 2011; 13: 755–764.
27. Amin MB and Edge SB. *AJCC Cancer Staging Manual*. Springer, 2017.
28. Moley JF and DeBenedetti MK. Patterns of nodal metastases in palpable medullary thyroid carcinoma: recommendations for extent of node dissection. *Ann Surg* 1999; 229: 880–887.
29. Perros P, Boelaert K, Colley S, et al. Guidelines for the management of thyroid cancer. *Clin Endocrinol (Oxf)* 2014; 81: 1–122.
30. Essig GF Jr, Porter K, Schneider D, et al. Multifocality in sporadic medullary thyroid carcinoma: an international multicenter study. *Thyroid* 2016; 26: 1563–1572.
31. Kuo EJ, Sho S, Li N, et al. Risk factors associated with reoperation and disease-specific mortality in patients with medullary thyroid carcinoma. *JAMA Surg* 2018; 153: 52–59.
32. Tuttle RM. Medullary thyroid cancer: Surgical treatment and prognosis: UpToDate; 2020 [cited 2020 October]. Available from: https://www.uptodate.com/contents/medullary-thyroid-cancer-surgical-treatment-and-prognosis?search = Medullary%20thyroid%20carcinoma&source = search_result&selectedTitle = 2∼86&usage_type = default&display_rank = 2.
33. Konstantinidis A, Stang M, Roman SA, et al. Surgical management of medullary thyroid carcinoma. *Updates Surg* 2017; 69: 151–160.
34. Sherman SI and Gianoukakis AG. Medullary thyroid cancer: Systemic therapy and immunotherapy. Available from: https://www.uptodate.com/contents/medullary-thyroid-cancer-chemotherapy-and-immunotherapy.
35. Krajewska J, Chmielik E and Jarząb B. Dynamic risk stratification in the follow-up of thyroid cancer: what is still to be discovered in 2017? *Endocr Relat Cancer* 2017; 24: R387–R402.
36. Modigliani E, Cohen R, Campos JM, et al. Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: results in 899 patients. *Clin Endocrinol (Oxf)* 1998; 48: 265–273.

ATA guideline evidence definitions

A: Strongly recommended
B: Recommended based on fair evidence
C: Recommended based on expert opinion
D: Recommended against based on expert opinion
E: Recommended against based on fair evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits

F: Strongly recommended against based on good evidence
I: Recommendation is neither for nor against

BTA guideline evidence definitions

Levels of evidence

1: High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs) or RCTs with a very low risk of bias
1: Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1: Meta-analyses, systematic reviews or RCTs with a high risk of bias
2: High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2: Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2: Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3: Non-analytical studies; e.g., case reports, case series
4: Expert opinion

Grades of recommendation

A: At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B: A body of evidence comprising studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C: A body of evidence comprising studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D: Evidence level 3 or 4, or extrapolated evidence from studies rated as 2+

NCCN guideline categories of evidence

- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
- Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Japan Association of Endocrine Surgeons guidelines recommendation definitions

SR: Strongly recommended
EC-G: Good expert consensus
WR: Weakly recommended
DNR-W: Do not recommend weakly
EC-P: Poor expert consensus