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REVIEW ARTICLE

Surgical management of medullary thyroid carcinoma

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Abstract Medullary thyroid cancer (MTC) is a malignant tumor of the parafollicular C cells of the thyroid and comprises only 1–2% of all thyroid cancer cases. Unlike most differentiated thyroid cancer, MTC is associated with a mean survival of 8.6 years and accounts for a disproportionate 8.6% of thyroid cancer deaths. Surgery is the mainstay of treatment for loco-regional disease and the only current means of cure for MTC. The relatively low incidence of MTC has made the comprehensive study of this disease difficult and most research to date has been based largely on single institution, retrospective, and/or non-randomized studies. Despite various professional organizations such as the American Thyroid Association establishing guidelines for the diagnosis and treatment of patients with MTC, there is still significant variation in actual practice patterns with regard to the extent of surgery, as well as the management of persistent or recurrent disease. The purpose of this review is to discuss the latest updates in the surgical treatment of MTC, as well as the management of locally advanced, recurrent, and metastatic disease based on the most recent data and expert consensus guidelines.

Keywords Medullary thyroid cancer · Endocrine tumor · Surgery · Thyroidectomy · Lymphadenectomy

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Introduction

Medullary thyroid cancer (MTC) is a malignant tumor of the parafollicular C cells of the thyroid first described histologically by Hazard and colleagues in 1959 [1]. Overall, MTC comprises only 1–2% of all thyroid cancer cases; it is associated with a mean survival of 8.6 years, accounting for 8.6% of thyroid cancer deaths in the United States [2–4]. Surgery is the mainstay of treatment for loco-regional disease, and the only current means of cure for MTC. The extent of regional lymph-node disease at presentation impacts prognosis, as does the presence of distant metastasis at the time of diagnosis, which can range from 13 to 20% [3, 5–9].

The relatively low incidence of MTC has made the comprehensive study of this disease difficult; research to date has been based largely on single institution, retrospective, and/or non-randomized studies. Various professional organizations, including the American Thyroid Association (ATA), the National Comprehensive Cancer Network (NCCN), the British Thyroid Association, the Spanish Society of Endocrinology, and the European Thyroid Association, have established guidelines for the diagnosis and treatment of patients with MTC [2, 10–14]. There is still significant variation in actual practice patterns with regard to the extent of surgery, as well as the management of persistent or recurrent disease [15]. Panigrahi et al. used the Surveillance, Epidemiology, and End Results Program (SEER) database to demonstrate that patients receiving surgery which was discordant from the 2009 ATA recommendations had significantly shorter survival than those undergoing surgery according to recommendations ($p < 0.014$). Among 2033 patients with MTC, 41% did not receive appropriate surgical treatment—most commonly receiving total thyroidectomy without central

lymphadenectomy (25%), partial thyroidectomy (13%), or no surgery at all (3%) [15].

The purpose of this review is to discuss the latest updates in the surgical treatment of MTC, as well as the management of locally advanced, recurrent, and metastatic disease based on the most recent data and expert consensus guidelines.

Molecular biology

Medullary thyroid cancer occurs either sporadically (approximately 75%) or in a hereditary form [16]. For hereditary forms, it is transmitted in an autosomal dominant fashion caused by germline mutations in the receptor tyrosine kinase re-arranged during transfection (RET) proto-oncogene, and is expressed as type 2 multiple endocrine neoplasia (MEN) syndromes MEN 2A and MEN 2B, or familial MTC (FMTC) [17]. MEN 2A represents the majority (approximately 80%) of inherited MTC cases, and it is associated with multifocal and bilateral MTC, pheochromocytoma, and primary hyperparathyroidism [18]. Patients with MEN 2B develop early-onset MTC and pheochromocytoma, as well as mucosal neuromata, a marfanoid habitus, and digestive problems stemming from intestinal ganglioneuromas. FMTC represents a clinical variant of MEN 2A in which MTC is the only feature [2]. FMTC patients should have at least four affected family members with MTC alone, with none being diagnosed with pheochromocytoma or primary hyperparathyroidism [19]. Individuals with hereditary MTC initially develop primary C-cell hyperplasia (CCH), which progresses to early invasive medullary microcarcinoma, and ultimately to macroscopic MTC [20, 21]. Overall, clinicians caring for patients with a diagnosis of MTC need to consider genetic testing for the RET proto-oncogene for all incident cases, and if positive, genetic counseling should be done. The broader clinical implication of the inherited forms mandate screening for pheochromocytoma and primary hyperparathyroidism prior to any intervention.

Diagnostic evaluation

The initial diagnostic evaluation should begin with a detailed medical history and physical examination of the patient. History should include questions about symptoms associated with pheochromocytoma, primary hyperparathyroidism, calcitonin excess such as diarrhea, and ectopic ACTH production. A detailed family history of any thyroid, parathyroid, or adrenal disease and surgery should be included, followed by an ultrasound of the thyroid gland and neck to evaluate for any lymphadenopathy. Clinicians who perform or interpret a neck ultrasound as part of the diagnostic evaluation should keep in mind that MTC may present as a thyroid nodule with variable features on ultrasound. The sonographic findings associated with the more common thyroid malignancy papillary thyroid cancer (PTC) are often also presented with MTC. These "high risk" features include marked hypoechogenicity, microcalcifications, increased intra-nodular vascularity, and irregular margins (Fig. 1) [22, 23]. However, 28% of cases of MTC can feature low-risk sonographic characteristics, such as an ovoid or round appearance, cystic changes, smooth edges, and circumscribed margins [24]. Given this, ultrasound alone cannot be used to definitively diagnose MTC.

The clinical suspicion of a possible sporadic MTC is most often raised following fine-needle aspiration (FNA) of a new thyroid nodule. There are several histologic variants of MTC that can present with morphologic heterogeneity on aspiration cytology, sometimes mimicking other tumors. Classic cytologic features include a dispersed cell pattern with epithelioid, plasmacytoid, polygonal, or spindle cells [25]. In addition, the presence of stromal amyloid in the background and absence of thyroid follicles can be highly suggestive. As aspiration cytology cannot always distinguish MTC based on the morphologic features of the cells alone, any thyroid tumor with features suggestive of MTC on cytology should be confirmed through the use of immunohistochemistry verifying a paucity of thyroglobulin staining and positivity for calcitonin, chromogranin, and carcinoembryonic antigen (CEA) [2]. The calcitonin level in the washout from an FNA sample can be measured and is typically found to be >15,000 pg/mL, with benign nodules typically being <10 pg/mL [26]. For cases with indeterminate background material and MTC is suspected, Congo Red stain of an FNA aspirate can confirm background material as consistent with amyloid.

Measurement of serum calcitonin, with or without the administration of pentagastrin, in patients with thyroid nodules is done routinely in Europe, but not in the United States [27]. It has been shown in some studies to have a higher diagnostic sensitivity and specificity for MTC compared with FNA findings, and at least one study has demonstrated serum calcitonin screening potentially to be cost effective in the US [27–30]. While most patients with elevated plasma calcitonin levels >100 pg/mL have a diagnosis of MTC [31], elevated serum calcitonin can also be found in other patients for reasons unrelated to MTC, such as chronic renal failure, primary hyperparathyroidism, or autoimmune thyroiditis [32, 33]. As a result, routine use of serum calcitonin in patients with thyroid nodules remains controversial, and current ATA guidelines do not recommend its routine use for screening [2]; more studies are needed to further delineate the clinical utility of this test in patients with thyroid nodules.

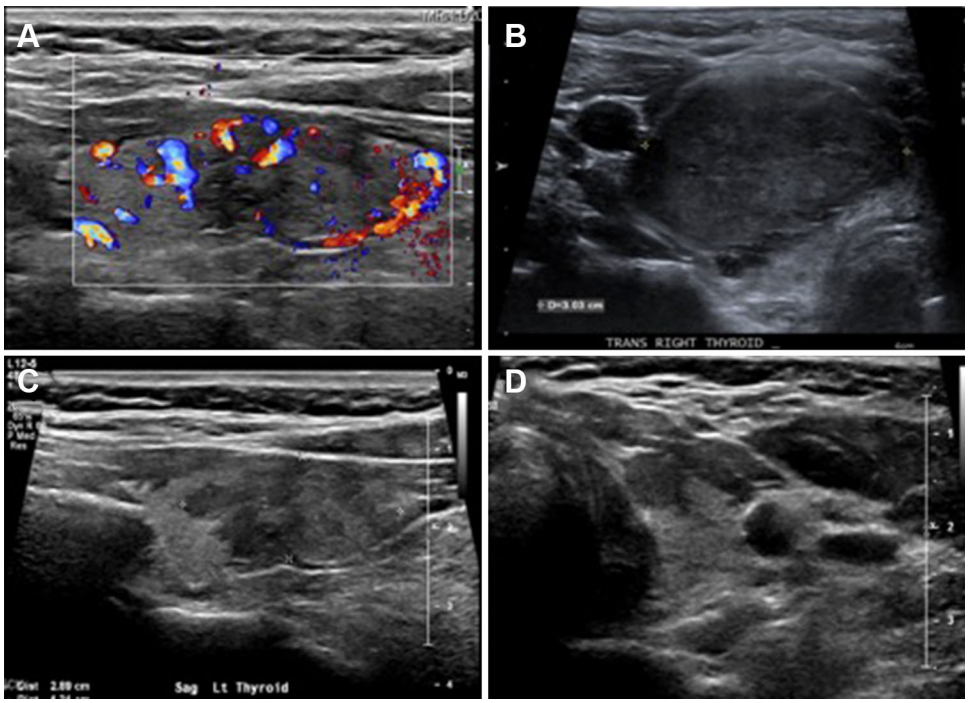

Fig. 1 Ultrasound features suspicious for medullary thyroid carcinoma. **a** Intra-nodular vascularity, **b** microcalcifications, **c** irregular borders, **d** hypoechogenicity

The degree of calcitonin elevation in patients with MTC correlates well with tumor volume, degree of nodal metastasis, distant metastasis, and ability to achieve biochemical cure with surgery. Nodal metastases can be present in the setting of basal calcitonin levels as low as 20 pg/mL (normal <10 pg/mL) and the risk of nodal and distant metastatic disease escalates with successive higher calcitonin levels [34]. At 500 pg/mL, the rate of lymph-node metastasis in the neck approaches 50% and the likelihood of distant metastasis is >5% [34]. A preoperative serum calcitonin level >10,000 pg/mL is ominous and highly predictive of the inability to biochemically cure a patient with operative intervention [34]. CEA is a secondary useful tumor marker in patients with MTC and should be part of the initial laboratory evaluation of incident cases. Although not as sensitive or specific as calcitonin, it can be found elevated in approximately 70% of cases and likewise correlates with disease progression [35]. CEA levels >30 ng/mL (normal <4.6 ng/mL) are associated with lymph-node metastasis >70% of the time and levels >100 ng/mL are associated with a risk of distant metastasis of 75% [35].

Moley et al. demonstrated that up to 81% of patients with palpable MTC tumors have metastatic lymph nodes in the central compartment [36]; therefore, evaluation of all patients with suspected MTC must include a dedicated comprehensive neck ultrasound with meticulous lymph-node mapping of the central and lateral cervical lymph-node compartments with FNA biopsy of any lymph node having indeterminate or suspicious morphology [2, 14, 36]. If bulky nodal metastases are documented, or the serum calcitonin level is >500 pg/mL, more extensive evaluation for locally advanced and distant metastatic disease should be pursued [2, 34]. Contrast-enhanced computed tomography (CT) of the neck and chest should be performed to identify extension of neck and mediastinal disease beyond what is identified by ultrasound. Since distant metastases of MTC frequently present in the liver and bone, tri-phasic contrast CT or contrast-enhanced magnetic resonance imaging (MRI) of the liver should be done with axial MRI or bone scintigraphy. Based on the most recently revised ATA and NCCN guidelines, 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) scan is not recommended as part of the initial metastatic work-up [2, 14].

Surgical management of sporadic MTC

Localized and locally advanced MTC

Central compartment (level VI) nodal disease is presented in a significant number of patients with MTC [36]. The addition of routine central neck lymph-node dissection in MTC patients results in a higher cure rate than thyroidectomy alone. This was demonstrated by Greenblatt et al. in a retrospective study comparing patients with MTC who underwent total thyroidectomy with central lymph-node dissection (CLND) and patients who had total thyroidectomy alone. Despite a small sample size, the authors were able to show that the CLND group had a lower incidence of

residual disease (0 vs. 89%, $p = 0.018$) and fewer re-operations (0 vs. 78%, $p = 0.045$) [37]. Accordingly, the current ATA and NCCN guidelines recommend that patients with sporadic MTC confined to the thyroid gland, and without evidence of cervical or distant metastases by ultrasound examination and no distant metastases should have a total thyroidectomy and bilateral CLND (level VI) [2, 14]. A comprehensive level VI compartmental dissection consists of a complete clearing of all lymph nodes and fibrofatty tissue from the hyoid bone superiorly to the sternal notch inferiorly and to the carotid sheaths laterally. It requires a meticulous dissection along the course of the recurrent laryngeal nerve, with preservation of the parathyroid glands along with their blood supply. Adult patients with MTC found to have germline RET mutations are managed in a fashion analogous to sporadic MTC with respect to extent of surgery once pheochromocytoma has been biochemically excluded in most cases. However, surgeons can account for and tailor the extent of surgery for patients identified with certain inherited forms, most notably M918T and A883F mutations, by considering more extensive node dissection for any tumor >0.5 mm [14].

Patients with MTC confined to the neck and biopsy-proven metastatic lymph nodes in the lateral neck should undergo therapeutic simultaneous total thyroidectomy, bilateral CLND (level VI), and selective neck dissection of the, respectively, involved lateral compartments, at a minimum inclusive of levels II–V, with preservation of the sternocleidomastoid muscle, internal jugular vein, and spinal accessory nerve [2, 14]. What is less clear and remains that controversial is the role of prophylactic lateral neck dissection for patients with sonographically normal-appearing lymph nodes or those without biopsy-proven lymph-node metastases, but with significant elevation of the serum calcitonin level. Given the significant potential complications associated with a lateral compartment dissection, including injury to the spinal accessory nerve with subsequent shoulder dysfunction, brachial plexus, phrenic nerve, and lymphatic/thoracic duct leak, the most recent ATA guidelines recommend that a lateral neck dissection be reserved for cases of documented disease; it can be considered under those circumstances where the likelihood of metastatic disease in the lateral neck is high enough to outweigh the risks of surgery based on patient preference [2].

The 2016 NCCN guidelines recommend that a prophylactic ipsilateral selective neck dissection should be considered for patients who harbor high-volume and gross metastatic nodal disease in the adjacent central neck [14]. In a series of 195 consecutive patients with MTC who underwent a total thyroidectomy with central and ipsilateral lateral neck dissection from 1994 to 2007, Machens et al. demonstrated that with one-to-three positive central lymph nodes, involvement of the ipsilateral lateral neck increased from 10.1% (with no central node involvement) to 77% ($p < 0.001$), and with ≥4 positive central nodes, the rate was 98% [7]. The ATA Guidelines Taskforce on MTC could not achieve consensus and neither recommended for nor against prophylactic ipsilateral lateral compartment lymph-node dissection in patients with normal-appearing lymph nodes on ultrasound [2].

In a retrospective study of 300 patients with MTC who underwent total thyroidectomy with central compartment lymphadenectomy as well as ipsilateral compartment lymphadenectomy in 227 patients (76%) and contralateral lateral neck dissection in 217 patients (72%), Machens and colleagues demonstrated with every increment of basal calcitonin levels that there was a successive increase risk of metastatic lymph-node disease of the ipsilateral and contralateral neck compartments [34]. Lymph-node metastases were presented in 9% of cases in the ipsilateral lateral neck beyond a basal calcitonin threshold of 20 pg/mL [34]. Occult lymph-node metastases were presented in the contralateral lateral neck 14% of the time when the basal calcitonin level was >200 pg/mL [34]. Accordingly, the ATA guidelines allow for consideration of a prophylactic ipsilateral lateral neck dissection in patients with basal serum calcitonin levels >20 pg/mL [2]. Prophylactic contralateral lateral compartment neck dissection should be considered when preoperative imaging is positive in the ipsilateral lateral neck and the basal serum calcitonin level is >200 pg/mL [2].

In the presence of locally advanced or metastatic disease at initial presentation, the goals of surgery are more palliative in nature with attention given to minimizing complications. In the presence of MTC that invades the trachea, thyroid cartilage, or esophagus, the extent of extirpative surgery (palliative debulking, laryngectomy, esophagectomy, or laryngopharyngectomy) is determined by an assessment of the ability to maintain speech and swallowing and the patient's life expectancy based on the extent of disease and other medical comorbidities [2]. In these patients, less aggressive surgery in the central and lateral neck may be appropriate to preserve speech, swallowing, parathyroid function, and shoulder mobility. External beam radiotherapy (EBRT), systemic medical therapy, and other nonsurgical therapies should be considered to achieve local tumor control [2].

Persistent and recurrent disease

Reoperative surgery

In experienced hands, reoperative surgery for loco-regional disease can achieve long-term biochemical cure in up to one-third of patients [38, 39]. In a report by Fialkowski

et al. on 54 patients with reoperation for recurrent or persistent MTC with a mean follow-up of 9 years, 43 (80%) had no evidence of disease on subsequent imaging. Of those, 14 patients (33%) had unstimulated postoperative calcitonin levels <10 pg/mL at 8–10 years and 11 patients (26%) had levels between 10 and 100 pg/mL [38]. In a retrospective study of 241 MTC patients which had undergone reoperative cervical lymph-node dissection, Machens and colleagues found that 73 of 241 patients (30.2%) attained biochemical cure. The success of such remedial surgery, however, was largely dependent on the burden of disease at the original surgery as evidenced by 59 of 133 patients (44%) demonstrated cure when no metastatic lymph nodes were found at the primary surgery, while only 12 of 65 patients (18%) had biochemical cure when 1–5 metastatic lymph nodes were found at initial surgery and 2 of 43 patients (5%) who had >5 positive lymph nodes at the time of initial resection could achieve biochemical cure [40].

For patients with persistent or recurrent loco-regional MTC without distant metastases, surgical resection and lymph-node dissection performed in a compartment-directed fashion should be considered for biopsy-proven disease [2, 38, 39]. Reoperation does carry a higher risk of complications, including thoracic duct leak, injury to the phrenic nerve, brachial plexus and spinal accessory nerve, hypoparathyroidism, and injury to the recurrent laryngeal nerve [41], and the potential benefit of reoperative surgery needs to be weighed against these potential complications. In these cases, obtaining prior operative and pathology reports along with a preoperative assessment of the vocal cords with laryngoscopy is of paramount importance. For cases of central neck recurrence, remedial central neck dissection can be facilitated by a lateral approach, during which strap muscles are mobilized laterally off the carotid, and the space between the carotid and the trachea is entered through an intact tissue plane [42]. In general, limited dissection, such as resection of only grossly metastatic lymph nodes and "berry picking", should be avoided unless there was a prior compartment-oriented dissection [2].

Adjunctive treatments

Adjuvant radioactive iodine (RAI) is not indicated following thyroidectomy for MTC [43]. The benefits of EBRT in patients with MTC remain controversial and difficult to evaluate due to lack of randomized prospective trials [44–48]. Overall, adjuvant EBRT has not been shown to provide for any survival benefit in MTC patients with lymph-node metastases. Utilizing the SEER database, Martinez et al. examined 534 patients with MTC who underwent total thyroidectomy and lymphadenectomy between 1988 and 2004. EBRT was given to 66 patients (12.4%), while 468 (87.6%) received none. With 12 years of follow-up, the addition of postoperative EBRT did not show a significant improvement in overall survival in multivariable analysis (hazard ratio (HR) 1.39 for no EBRT treatment, 95% confidence interval (CI) 0.57–3.37; $p = 0.47$) [45]. Radiation has been unitized more for local tumor control in those patients at high risk for recurrence (i.e., grossly positive surgical margins). The published data regarding effectiveness of EBRT in loco-regional control are limited and demonstrate mixed results. In a retrospective study of 51 patients with MTC treated with postoperative EBRT between 1960 and 1992, Fife et al. demonstrated only a trend towards improved local control in patients who received radiation dose of ≥60 Gy over 6 weeks ($p = 0.23$) [46]. In a study by Brierley et al., records of 73 patients with MTC were reviewed between 1954 and 1992. Overall, 46 patients were irradiated postoperatively with the dose of radiation ranging from 20 to 75.5 Gy (median 40 Gy). With a median treatment time of 28 days, the overall survival in radiated patients was 70 and 57% at 5 and 10 years, respectively. When patients who received external radiation postoperatively were compared to those who did not, there was no difference in the survival over a period of 20 years ($p = 0.66$) [48]. On univariate analysis, the authors examined only the patients who were considered to be at high risk of local/regional relapse (40 patients) who had microscopic residual disease, lymph-node involvement, or extraglandular extension. Of those, 25 patients received external radiation and 15 did not. At 10 years, the local/regional recurrence-free rate for the group that received external radiation was 86% compared with 52% in those with no postoperative radiation ($p = 0.049$) [48]. Guideline recommendations allow for consideration of adjuvant EBRT to the neck and mediastinum for patients at high risk for local recurrence and those at risk for airway obstruction [2, 14]. The potential benefits must be weighed against the acute and chronic toxicity associated with treatment; these include skin erythema and desquamation, mucositis, esophagitis, and laryngeal edema, hoarseness, odynophagia, and dysphagia sometimes requiring a temporary gastrostomy tube [2]. MTC adjacent to more radiosensitive tissue such as the spinal cord should be approached with intensity-modulated radiation therapy (IMRT).

Prophylactic thyroidectomy and genetic testing in children and adults with MEN2A, MEN2B, and FMTC

The term prophylactic thyroidectomy has been used to describe early removal of the thyroid gland in children or adults who have inherited a mutation in the RET proto-oncogene without clinically evident of disease for the

purpose of minimizing long-term risk of MTC-related cancer death. Guidelines now employ a mutation-directed approach with regard to timing of a prophylactic thyroidectomy [49]. The 2009 ATA guidelines used a stepwise increasing risk classification system from A to D to define categories of RET mutations and the associated aggressiveness of the MTC [2, 50]. The more recent iteration of the ATA guidelines now assigns new categories, including "highest risk" (HST), which encompasses patients with MEN2B and the RET mutation M918T; "high risk" (H) for patients with RET mutations C634F/G/R/S/W/Y and A883F; and "moderate risk" (MOD) for patients with mutations other than the ones listed above [2]. Children with the highest risk mutations in codons M918T associated with MEN 2B should be considered for a total thyroidectomy with central neck dissection in the first 12 months of life [2]. Children with MEN2A and ATA-H category mutations should undergo annual physical examination, cervical ultrasound, and measurement of serum calcitonin levels starting at 3 years of age. These patients should have a total thyroidectomy at or before 5 years of age. Children in the ATA-MOD category may have their prophylactic thyroidectomy postponed until later childhood or young adulthood, as long as they continue to have normal serum calcitonin levels during surveillance [2]. In children with MEN2A, central (Level VI) neck dissection should accompany the total thyroidectomy when the preoperative basal serum calcitonin is >40 pg/mL, given the potential risk of harboring micrometastatic disease [2].

Genetic counseling and genetic testing for RET germline mutations should be offered to first-degree relatives of patients found to have hereditary MTC [2]. It is vital that clinicians properly inform MTC patients prior to gene testing what identification of a RET germline mutation may mean in the context of inherited risk of a serious disease for other family members and the importance of identifying at risk family members and notifying them that they may be at risk [2]. Screening family members for hereditary MTC is relatively straightforward when one knows the RET germline mutation identified in the index case as a targeted approach can detect the specific mutated RET allele in at-risk family members. The recommended method of initial testing for germline RET mutation is a single or multi-tiered analysis to detect RET mutations in exon 8, 10, 11, and 13–16 [2, 51]. In patients with a more aggressive phenotype and suspicion of MEN2B, genetic testing should initially test for the RET M918T mutation (exon 16), and if negative, the RET A883F mutation (exon 15) with consideration of full gene sequencing if negative. All adult family members identified with RET germline mutations (MEN2A, 2B or FMTC) should undergo a prophylactic total thyroidectomy with bilateral central lymphadenectomy [2].

Management of medullary thyroid microcarcinoma

Medullary thyroid microcarcinoma (microMTC) is defined as MTC that measures ≤1 cm [52, 53]. There has been some debate about the clinical significance of microMTCs and whether these tumors should be managed as aggressively as larger MTC tumors >1 cm [54–58]. An analysis by Kazaure et al. used the SEER database and showed a substantial rate of advanced disease in 310 patients with microMTC. Among patients who had lymph nodes removed, 37% had nodal metastases; for example, a 5-mm microMTC was associated, on average, with a 23% risk of lymph-node metastases [57]. This was in accordance with an earlier study by Beressi et al. demonstrating a 31% incidence of lymph-node metastases in 80 patients with microMTC [58]. As a result, most experts agree that thyroidectomy with bilateral central lymphadenectomy should be considered for patients with known MTC ≤1 cm [56, 57].

Long-term surveillance

Postoperatively, serum calcitonin and CEA levels should be measured 3 months after the initial surgery, and if undetectable, they should be measured every 6 months for 1 year, and annually thereafter [2, 14, 59, 60]. Patients who have normal serum CEA and undetectable serum calcitonin values are considered biochemically cured and have an excellent prognosis, with a likelihood of disease recurrence over 5–10 years ranging from <1 to 8.5%, and a 5-year survival of 97–99% [60–64]. In a retrospective analysis of calcitonin and CEA levels postoperatively in 360 patients with MTC treated at a single institution from 1973 to 2013, Lindsey et al. demonstrated that patients with undetectable postoperative calcitonin levels were associated with disease-specific survival rates at 5, 10, and 20 years of 100, 95, and 87.1%, respectively [61].

Patients with elevated postoperative serum calcitonin levels that are <150 pg/mL should have a physical examination and ultrasound of the neck every 6 months [2]. If the neck ultrasound is negative, the patient should be followed with physical examination, measurement of serum calcitonin and CEA levels, and ultrasounds at 6-month intervals to estimate the calcitonin doubling time. Calcitonin doubling time has been shown to be a significant predictor of survival in patients with MTC [64]. Barbet et al. published a retrospective study of 65 MTC patients with a mean follow-up of 16 years after surgery. The 5- and 10-year survival rates in those patients with serum calcitonin doubling times <6 months were 25 and 8%,

respectively, compared to 92 and 37%, respectively, for those with doubling times between 6 and 24 months [64]. The ATA provides a calculator to determine doubling times of serial serum calcitonin and CEA measurements (http://www.thyroid.org/thyroidphysiciansprofessionals/calculators/thyroid-cancer-carcinoma) [2]. If the postoperative serum calcitonin level exceeds 150 pg/mL, there should be concern for distant metastatic disease and patients should be evaluated with chest CT, contrast-enhanced MRI or three-phase contrast-enhanced CT of the liver, and bone scintigraphy or MRI of the pelvis and axial skeleton [2, 14]. This recommendation stems from work by Pellegriti et al., where the authors reviewed the experience of 63 patients with MTC treated with surgery who were followed with serum calcitonin levels and extensive imaging over a period of 5 years. Of the 18 patients that developed imageable disease recurrence, 7 had calcitonin level >150 postoperatively, and 4 of 7 (57%) where later found to have distant metastatic disease [65].

Metastatic MTC

Improved understanding of the molecular oncogenesis of MTC has resulted in identification of novel molecular targets for treatment of locally advanced and/or metastatic disease. The relatively recent focus on systemic treatment has been around using compounds that inhibit receptors of intracellular (tyrosine) kinases which primarily target angiogenesis. Different agents that target the vascular endothelial growth factor receptors (VEGFRs) with focus on tyrosine kinase inhibitors such as motesanib diphosphate, vandetanib, sorafenib, and sunitinib have been tried. To date, only vandetanib and cabozantinib which target both RET and VEGFR have been approved by the US Food and Drug Administration for the treatment of progressive and/or symptomatic MTC that can be locally advanced or metastatic [66–69]. Both drugs have shown the potential to provide high rates of disease control with durable responses and a highly significant improvement in progression-free survival. A prospective, randomized, double blind, phase III trial with vandetanib (300 mg/day) demonstrated prolonged progression-free survival from 19.3 months in the placebo arm to a predicted median of 30.5 months in the vandetanib arm (hazard ratio (HR) 0.46; $p < 0.0001$) [66]. Similarly, a prospective phase III trial of cabozantinib (140 mg/day) in 330 patients with progressive, metastatic, or locally advanced MTC showed significantly improved progression-free survival from 4.0 months with placebo to 11.2 months cabozantinib (HR 0.28; $p < 0.0001$) [69]. Despite these promising early findings, there has been no statistically significant improvement in overall survival with either drug [66, 69].

Systemic therapy for advanced metastatic disease with multikinase inhibitors requires daily or twice daily doses taken long-term to maintain tumor control. The short-term toxicity can be substantial; patients who receive vandetanib frequently experience diarrhea, fatigue, rash and folliculitis, photosensitization, hypertension, and prolongation of the QTc interval. Twelve percent require discontinuation of treatment due to toxicity, and 35% require dose reductions because of an adverse event [66]. Side effects of cabozantinib include diarrhea, abdominal discomfort, fatigue, hypertension, palmo-plantar erythrodysesthesia, and gastrointestinal fistulas; 16% of patients receiving cabozantinib will require discontinuation of treatment due to toxicity, and 79% will require dose reductions because of an adverse event [69]. As there is a paucity of data on long-term toxicity, and so far, no data demonstrating improved overall survival, indications for using these drugs [70, 71] are limited to those who have significant tumor burden, symptomatic disease, and documented tumor progression [2].

Palliative surgery has a role in the treatment of patients with metastatic disease who experience space-occupying metastases that cause acute spinal cord compression, or airway and esophageal obstruction [2]. Considering that metastatic MTC is incurable, the surgical management goal in these patients is to provide palliative symptomatic relief, such as in cases of refractory pain, and control metastases that are life threatening, such as bronchial obstruction or spinal cord compression.

Conclusion

The low incidence of MTC has made the study of this disease difficult. Both the ATA and NCCN have established guidelines for the diagnosis and treatment of patients with MTC. It is important for physicians who manage this disease to be aware of the most updated recommendations. Currently, surgery is the only means of cure for MTC, and thyroidectomy with at least central compartment lymphadenectomy is the mainstay of treatment. Any patient with a new diagnosis of MTC should have a physical examination, determination of serum levels of calcitonin and CEA, a dedicated neck ultrasound, and genetic testing for a RET germline mutation. Novel small molecule therapies for locally advanced and metastatic disease are evolving, and the question about neo-adjuvant approaches has been raised.

Compliance with ethical standards

Conflict of interest Julie Ann Sosa M.D., M.A, F.A.C.S discloses that she is a member of the Data Monitoring Committee of the Medullary Thyroid Cancer Consortium Registry supported by

NovoNordisk, GlaxoSmithKline, Astra Zeneca, and Eli Lilly. All other authors report no financial or other form of interests or potential conflicts of interest.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Hazard JB, Crile G Jr (1959) Medullary [solid] carcinoma of the thyroid: a clinicopathologic entity. J Clin Endocrinol Metab 19:152–161
2. Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF et al (2015) Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 25:567–610
3. Roman S, Lin R, Sosa JA (2006) Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1252 cases. Cancer 107(9):2134–2142
4. Veiga LH, Neta G, Aschebrook-Kilfoy B, Ron E, Devesa SS (2013) Thyroid cancer incidence patterns in Sao Paulo, Brazil, and the U.S. SEER program. Thyroid 23(6):748–757
5. Machens A, Schneyer U, Holzhausen HJ et al (2005) Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level. J Clin Endocrinol Metab 90:2029–2034
6. Scollo C, Baudin E, Travagli J et al (2003) Rationale for central and bilateral lymph node dissection in sporadic and hereditary medullary thyroid cancer. J Clin Endocrinol 88:2070–2075
7. Machens A, Hauptmann S, Dralle H (2008) Prediction of lateral lymph node metastases in medullary thyroid cancer. Br J Surg 95:586–591
8. Bumming P, Ahlman H, Nilsson B, Nilsson O, Wangberg B, Jansson S (2008) Can the early reduction of tumour markers predict outcome in surgically treated sporadic medullary thyroid carcinoma? Langenbecks Arch Surg 393:699–703
9. Pelizzo MR, Boschin IM, Bernante P et al (2007) Natural history, diagnosis, treatment and outcome of medullary thyroid cancer: 37 years experience on 157 patients. Eur J Surg Oncol 33:493–497
10. Chen H, Sippel RS, O'Dorisio MS, Vinik AI, Lloyd RV, Pacak KDS (2010) The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer. Pancreas 39:775–783
11. Schlumberger M, Bastholt L, Dralle H, Jarzab B, Pacini F, Smit JWA (2012) European Thyroid Association guidelines for metastatic medullary thyroid cancer. Eur Thyroid J 1:5–14
12. Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, Gilbert J, Harrison B, Johnson SJ, Giles TE, Moss L, Lewington V, Newbold K, Taylor J, Thakker RV, Watkinson J, Williams GR (2014) British Thyroid Association. Guidelines for the management of thyroid cancer. Clin Endocrinol 81(Suppl 1):1–122
13. Grande E, Santamaría Sandi J, Capdevila J, Navarro González E, Zafón Llopis C, Ramón Y, Cajal Asensio T, Gómez Sáez JM, Jiménez-Fonseca P, Riesco-Eizaguirre G, Galofré JC (2016) Consensus on management of advanced medullary thyroid carcinoma on behalf of the Working Group of Thyroid Cancer of the Spanish Society of Endocrinology (SEEN) and the Spanish Task Force Group for Orphan and Infrequent Tumors (GETHI). Clin Transl Oncol 18(8):769–775
14. NCCN Clinical Practice Guidelines in Oncology (2016) Medullary thyroid carcinoma. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf
15. Panigrahi B, Roman SA, Sosa JA (2010) Medullary thyroid cancer: are practice patterns in the United States discordant from American Thyroid Association guidelines? Ann Surg Oncol 17:1490–1498
16. Leboulleux S, Baudin E, Travagli JP, Schlumberger M (2004) Medullary thyroid carcinoma. Clin Endocrinol Oxf 61(3):299–310
17. Mulligan LM, Eng C, Healey CS, Clayton D, Kwok JB, Gardner E, Ponder MA, Frilling A, Jackson CE, Lehnert H et al (1994) Specific mutations of the RET proto-oncogene are related to disease phenotype in MEN 2A and FMTC. Nat Genet 6(1):70–74
18. Howe JR, Norton JA, Wells SJ (1993) Prevalence of pheochromocytoma and hyperparathyroidism in multiple endocrine neoplasia type 2A: results of long-term follow-up. Surgery 114:1070–1077
19. Eng C, Clayton D, Schuffenecker I, Lenoir G, Cote G, Gagel RF, van Amstel HK, Lips CJ, Nishisho I, Takai SI, Marsh DJ, Robinson BG, Frank-Raue K, Raue F, Xue F, Noll WW, Romei C, Pacini F, Fink M, Niederle B, Zedenius J, Nordenskjöld M, Komminoth P, Hendy GN, Mulligan LM et al (1996) The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2 International RET mutation consortium analysis. JAMA 276(19):1575–1579
20. Machens A, Niccoli-Sire P, Hoegel J et al (2003) Early malignant progression of hereditary medullary thyroid cancer. N Engl J Med 349:1517–1525
21. Machens A, Holzhausen HJ, Thanh PN, Dralle H (2003) Malignant progression from C-cell hyperplasia to medullary thyroid carcinoma in 167 carriers of RET germline mutations. Surgery 134(3):425–431
22. Zhou L, Chen B, Zhao M, Zhang H, Liang B (2015) Sonographic features of medullary thyroid carcinoma according to tumor size: comparison with papillary thyroid carcinoma. J Ultrasound Med 34(6):1003–1009
23. Kim SH, Kim BS, Jung SL, Lee JW, Yang PS, Kang BJ, Lim HW, Kim JY, Whang IY, Kwon HS, Jung CK (2009) Ultrasonographic findings of medullary thyroid carcinoma: a comparison with papillary thyroid carcinoma. Korean J Radiol 10:101–105
24. Lee S, Shin JH, Han BK, Ko EY (2010) Medullary thyroid carcinoma: comparison with papillary thyroid carcinoma and application of current sonographic criteria. Am J Roentgenol 194:1090–1094
25. Pusztaszeri MP, Bongiovanni M, Faquin WC (2014) Update on the cytologic and molecular features of medullary thyroid carcinoma. Adv Anat Pathol 21(1):26–35
26. Kudo T, Miyauchi A, Ito Y, Takamura Y, Amino N, Hirokawa M (2007) Diagnosis of medullary thyroid carcinoma by calcitonin measurement in fine-needle aspiration biopsy specimens. Thyroid 17(7):635–638
27. Elisei R, Bottici V, Luchetti F, Di Coscio G, Romei C, Grasso L, Miccoli P, Iacconi P, Basolo F, Pinchera A, Pacini F (2004) Impact of routine measurement of serum calcitonin on the diagnosis and outcome of medullary thyroid cancer: experience in 10,864 patients with nodular thyroid disorders. J Clin Endocrinol Metab 89:163–168
28. Vierhapper H, Raber W, Bieglmayer C, Kaserer K, Weinhausl A, Niederle B (1997) Routine measurement of plasma calcitonin in nodular thyroid diseases. J Clin Endocrinol Metab 82:1589–1593

29. Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S, Crocetti U, Attard M, Maranghi M, Torlontano M, Filetti S (2007) Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab 92:450–455
30. Cheung K, Roman SA, Wang TS, Walker HD, Sosa JA (2008) Calcitonin measurement in the evaluation of thyroid nodules in the United States: a cost-effectiveness and decision analysis. J Clin Endocrinol Metab 93(6):2173–2180
31. Niccoli P, Wion-Barbot N, Caron P, Henry JF, de Micco C, Saint Andre JP, Bigorgne JC, Modigliani E, Conte-Devolx B (1997) Interest of routine measurement of serum calcitonin: study in a large series of thyroidectomized patients. The French Medullary Study Group. J Clin Endocrinol Metab 82:338–341
32. Borchhardt KA, Horl WH, Sunder-Plassmann G (2005) Reversibility of 'secondary hypercalcitoninemia' after kidney transplantation. Am J Transplant 5:1757–1763
33. Schuetz M, Duan H, Wahl K, Pirich C, Antoni A, Kommata S, Kletter K, Dudczak R, Karanikas G, Willheim M (2006) T lymphocyte cytokine production patterns in Hashimoto patients with elevated calcitonin levels and their relationship to tumor initiation. Anticancer Res 26:4591–4596
34. Machens A, Dralle H (2010) Biomarker-based risk stratification for previously untreated medullary thyroid cancer. J Clin Endocrinol Metab 95:2655–2663
35. Machens A, Ukkat J, Hauptmann S, Dralle H (2007) Abnormal carcinoembryonic antigen levels and medullary thyroid cancer progression: a multivariate analysis. Arch Surg 142(3):289–293
36. Moley JF, DeBenedetti MK (1999) Patterns of nodal metastases in palpable medullary thyroid carcinoma: recommendations for extent of node dissection. Ann Surg 229:880–887
37. Greenblatt DY, Elson D, Mack E et al (2007) Initial lymph node dissection increases cure rates in patients with medullary thyroid cancer. Asian J Surg 30:108–112
38. Fialkowski E, DeBenedetti M, Moley J (2008) Long-term outcome of reoperations for medullary thyroid carcinoma. World J Surg 32:754–765
39. Kebebew E, Kikuchi S, Duh QY, Clark OH (2000) Long-term results of reoperation and localizing studies in patients with persistent or recurrent medullary thyroid cancer. Arch Surg 135:895–901
40. Machens A, Dralle H (2013) Benefit-risk balance of reoperation for persistent medullary thyroid cancer. Ann Surg 257(4):751–757
41. Tufano RP, Bishop J, Wu G (2012) Reoperative central compartment dissection for patients with recurrent/persistent papillary thyroid cancer: efficacy, safety, and the association of the BRAF mutation. Laryngoscope 122(7):1634–1640
42. Dackiw APB (2010) The surgical management of medullary thyroid cancer. Otolaryngol Clin N Am 43:365–374
43. Meijer JA, Bakker LE, Valk GD, de Herder WW, de Wilt JH, Netea-Maier RT, Schaper N, Fliers E, Lips P, Plukker JT, Links TP, Smit JA (2013) Radioactive iodine in the treatment of medullary thyroid carcinoma: a controlled multicenter study. Eur J Endocrinol 168:779–786
44. Brierley JD, Tsang RW (2008) External beam radiation therapy for thyroid cancer. Endocrinol Metab Clin N Am 37:497–509
45. Martinez SR, Beal SH, Chen A, Chen SL, Schneider PD (2010) Adjuvant external beam radiation for medullary thyroid carcinoma. J Surg Oncol 102:175–178
46. Fife KM, Bower M, Harmer CL (1996) Medullary thyroid cancer: the role of radiotherapy in local control. Eur J Surg Oncol 22:588–591
47. Terezakis SA, Lee NY (2010) The role of radiation therapy in the treatment of medullary thyroid cancer. J Natl Compr Cancer Netw 8:532–540 **(quiz 541)**
48. Brierley J, Tsang R, Simpson WJ, Gospodarowicz M, Sutcliffe S, Panzarella T (1996) Medullary thyroid cancer: analyses of survival and prognostic factors and the role of radiation therapy in local control. Thyroid 6(4):305–310
49. Zenaty D, Aigrain Y, Peuchmaur M et al (2009) Medullary thyroid carcinoma identified within the first year of life in children with hereditary multiple endocrine neoplasia type 2A [codon 634] and 2B. Eur J Endocrinol 160:807–813
50. Kloos RT, Eng C, Evans DB et al (2009) Medullary Thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 19:565–612
51. Romei C, Tacito A, Molinaro E, Agate L, Bottici Valeria et al (2015) Twenty years lesson learning: how does the RET gene screening test impact clinical management of medullary thyroid cancer. Clin Endocrinol (Oxford) 82(6):892–899
52. Baloch ZW, LiVolsi VA (2006) Microcarcinoma of the thyroid. Adv Anat Pathol 13:69–75
53. Ogilvie JB, Patel KN, Heller KS (2010) Impact of the 2009 American Thyroid Association guidelines on the choice of operation for well-differentiated thyroid microcarcinomas. Surgery 148:1222–1226
54. Hamy A, Pessaux P, Mirallie E et al (2005) Central neck dissection in the management of sporadic medullary thyroid microcarcinoma. Eur J Surg Oncol 31:774–777
55. Pillarisetty V, Katz S, Ghossein R, Tuttle R, Shaha A (2009) Micromedullary thyroid cancer: how micro is truly micro? Ann Surg Oncol 16:2875–2881
56. Peix JL, Braun P, Saadat M, Berger N, El Khazen M, Mancini F (2000) Occult micro medullary thyroid carcinoma: therapeutic strategy and follow-up. World J Surg 24:1373–1376
57. Kazaure HS, Roman S, Sosa JA (2012) Medullary thyroid microcarcinoma. A population-level analysis of 310 patients. Cancer 118:620–627
58. Beressi N, Campos JM, Beressi JP et al (1998) Sporadic medullary microcarcinoma of the thyroid: a retrospective analysis of 80 cases. Thyroid 8:1039–1044
59. Ismailov SI, Piulatova NR (2004) Postoperative calcitonin study in medullary thyroid carcinoma. Endocr Relat Cancer 11:357–363
60. Elisei R, Pinchera A (2012) Advances in the follow-up of differentiated or medullary thyroid cancer. Nat Rev Endocrinol 8:466–475
61. Lindsey SC, Ganly I, Palmer F, Tuttle RM (2015) Response to initial therapy predicts clinical outcomes in medullary thyroid cancer. Thyroid 25:242–249
62. Tuttle RM, Ganly I (2013) Risk stratification in medullary thyroid cancer: moving beyond static anatomic staging. Oral Oncol 49(695–701):12
63. Yang JH, Lindsey SC, Camacho CP, Valente FO, Germano-Neto F, Machado AL et al (2015) Integration of a postoperative calcitonin measurement into an anatomical staging system improves initial risk stratification in medullary thyroid cancer. Clin Endocrinol [Oxf] 83:938–942
64. Barbet J, Campion L, Kraeber-Bodéré F, Chatal JF, GTE Study Group (2005) Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. J Clin Endocrinol Metab 90:6077–6084
65. Pellegriti G, Leboulleux S, Baudin E, Bellon N, Scollo C, Travagli JP, Schlumberger M (2003) Long-term outcome of medullary thyroid carcinoma in patients with normal postoperative medical imaging. Br J Cancer 88:1537–1542
66. Wells SA Jr, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M et al (2012) Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol 30:134–141

67. Elisei R, Schlumberger MJ, Muller SP, Schoffski P, Brose MS, Shah MH et al (2013) Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol 31:3639–3646
68. Deshpande HA, Sheth K, Sosa JA, Roman S (2012) Efficacy and tolerability of pharmacotherapy options for the treatment of medullary thyroid cancer. Clin Med Insights Oncol 6:355–362
69. Schoffski P, Elisei R, Muller S et al (2012) An international, double-blind, randomized, placebo-controlled phase III trial [EXAM] of cabozantinib [XL-184] in medullary thyroid carcinoma [MTC] patients [pts] with documented RECIST progression at baseline. J Clin Oncol 30:5508
70. Cabanillas ME, Hu MI, Jimenez C (2014) Medullary thyroid cancer in the era of tyrosine kinase inhibitors: to treat or not to treat-and with which drug-those are the questions. J Clin Endocrinol Metab 99:4390–4396
71. Grande E, Kreissl MC, Filetti S, Newbold K, Reinisch W, Robert C et al (2013) Vandetanib in advanced medullary thyroid cancer: review of adverse event management strategies. Adv Ther 30:945–966