

2012 European Thyroid Association Guidelines for Metastatic Medullary Thyroid Cancer

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Key Words

Medullary thyroid cancer • Metastases • Tyrosine kinase inhibitors • Rearranged during transfection mutation

Abstract

Distant metastases are the main cause of death in patients with medullary thyroid cancer (MTC). These 21 recommendations focus on MTC patients with distant metastases and a detailed follow-up protocol of patients with biochemical or imaging evidence of disease, selection criteria for treatment, and treatment modalities, including local and systemic treatments based on the results of recent trials. Asymptomatic patients with low tumor burden and stable disease may benefit from local treatment modalities and can be followed up at regular intervals of time. Imaging is usually performed every 6–12 months, or at longer intervals of time depending on the doubling times of serum calcitonin and carcinoembryonic antigen levels. Patients with symptoms, large tumor burden and progression on imaging should receive systemic treatment. Indeed, major progress has recently been achieved with novel targeted therapies using kinase inhibitors directed against RET and VEGFR, but further research is needed to improve the outcome of these patients.

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Methods of Development of Evidence-Based Guidelines

The European Thyroid Association (ETA) Executive Committee launched a taskforce to produce guidelines on the treatment of metastatic medullary thyroid cancer (MTC). A chairperson was selected to lead the task force (M.S.). M.S. then identified the other 5 members of the panel based on clinical expertise, scholarly approach and representation of endocrinology, nuclear medicine, oncology and surgery. Members of the task force were subsequently endorsed by the ETA Guidelines Board and the ETA Executive Committee, and each panel member declared whether he had any potential conflict of interest. The task force functioned without any financial or commercial support.

Relevant articles were identified by searching MEDLINE at Pubmed (NLM) using the following search terms: 'medullary carcinoma' OR 'medullary thyroid cancer' OR 'medullary thyroid carcinoma' before June 2011, and recommendations were developed based on the literature including the recent ATA guidelines [1] and expert opinion where appropriate. A preliminary document and a series of recommendations were generated by the chairperson and then critically reviewed by the members of the taskforce. The panel agreed recommendations

Table 1. Type of grading and definition of grades

Grading type	Definition
<i>Strength of the recommendation</i>	
Grade 1	Strong recommendation (for or against) Applies to most patients in most circumstances Benefits clearly outweigh the risk (or vice versa)
Grade 2	Weak recommendation (for or against) Best action may differ depending on circumstances or patient values Benefits and risks or burdens are closely balanced, or uncertain
<i>Quality of the evidence</i>	
+++	High quality; evidence at low risk of bias, such as randomized trials showing consistent results directly applicable to the recommendation
++	Moderate quality; studies with methodological flaws, showing inconsistent or indirect evidence
+	Low quality; case series or unsystematic clinical observations

would be based on consensus of the panel. Task force deliberations took place mostly through electronic communication. The draft guidelines were then posted on the ETA website for 6 weeks for all members to review. All suggestions and comments were considered for incorporation into the text.

The ETA Executive Committee elected to rate the recommendations according to the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Group (table 1) [2–4].

The strength of a recommendation is indicated by the number 1 or 2. Grade 1 indicates a strong recommendation (for or against). In contrast, grade 2 indicates a weak recommendation or a suggestion that may not be appropriate for every patient, depending on context, patient values and preferences.

Grading the quality of the evidence took into account study design, study quality, consistency of results and directness of the evidence. The quality of the evidence is indicated by plus signs at three levels [4].

Each recommendation is preceded by a description of the evidence.

The final document was approved by the ETA in December 2011.

Introduction

Medullary thyroid carcinoma (MTC) accounts for less than 5% of all thyroid cancers [1, 5]. Distant metastases are observed at presentation in 7–23% of MTC patients [1, 5] and can be imaged with standardized protocols [6]. Symptomatic clinical disease will occur in one to two thirds of MTC patients with any evidence of persistent disease after initial treatment at different time intervals during the subsequent 10 years after surgery, depending on the persistent tumor volume and progression rate [7–9]. Recurrent disease in the neck and mediastinum is frequently amenable to surgery, with either curative or palliative intent, and some patients may also benefit from external beam radiation therapy (EBRT). Distant metastases are the main cause of MTC-related death. In retrospective series, survival after the discovery of distant metastases was around 25% at 5 years and 10% at 10 years, but may be recorded higher in recent series due to earlier discovery of metastatic disease [1, 5].

The patients discussed in the present recommendations are those MTC patients with biochemical or imaging evidence of metastatic disease. This document does not address end-of-life discussions or palliative care.

Distant Metastases: Presentation and Diagnosis

Distant metastases often affect multiple organs including lungs, bones and liver, and more rarely brain, skin and breast, and are frequently associated with persistent disease in the neck [6]. In patients with recurrent disease, an acceptable quality of life can usually be maintained for months or even years, but diarrhea may be debilitating. Slow tumor growth is common, and distant metastases limited to a single organ may be considered for curative surgical resection or another local treatment modality. Patients with distant metastases and persistent/recurrent disease in the neck may benefit from treatment of neck disease depending on the extent of both neck and distant disease and of disease progression rate. Only patients with significant tumor burden and those with symptomatic or progressive disease according to the RECIST (Response Evaluation Criteria in Solid Tumor) criteria are candidates for systemic treatment.

Distant metastases may be discovered at presentation or during follow-up of patients with persistent elevated serum calcitonin (Ct) or carcinoembryonic antigen (CEA) levels. In fact, serum markers remain detectable after initial treatment in a significant percentage of patients, and

more frequently in those with large thyroid tumors, tumor extension beyond the thyroid capsule and extensive lymph node involvement. Distant metastases are rarely detected in patients with a serum Ct level <150 pg/ml, and the risk increases with higher serum Ct levels [1, 6]. However, patients with poorly differentiated and aggressive metastatic MTC may have low Ct levels or discrepantly high serum CEA levels. Imaging should identify all clinically relevant sites of disease, including those tumors large enough to be serially assessed to determine response to therapy, as well as those that may require additional local interventions prior to systemic treatment. Patients who have only biochemical disease (elevation of serum Ct and/or CEA levels) and no demonstrable tumor foci may have a long life expectancy with a good quality of life and do not require systemic treatment [7–9]. They are followed with serum tumor marker measurements, and imaging is repeated at regular time intervals, depending on the serum marker level and doubling time [1, 10–14].

Imaging procedures in metastatic MTC patients may include contrast-enhanced spiral CT scan or MRI of the brain, ultrasonography of the neck and liver, contrast-enhanced spiral CT scan of the neck and chest, triple-phase CT scan or preferably contrast-enhanced MRI of the liver (because liver metastases may be difficult to visualize with CT scan during treatment with antiangiogenic agents), bone scintigraphy and contrast-enhanced MRI of the spine and pelvis [6]. Fluorodeoxyglucose (FDG)-uptake on PET scan is usually low, and for this reason FDG-PET scan usually is poorly sensitive and cannot be used to assess tumor progression or response to treatment [6, 15, 16]. PET scan with F-DOPA may provide additional information on tumor localization and differentiation; however, it is expensive and there is no general agreement for its routine use [17, 18].

In the absence of indication for treatment, standardized imaging (CT scan of the neck, chest and abdomen and other imaging modalities according to known abnormalities) is repeated every 6–12 months or either at longer intervals of time in patients with long doubling times of Ct and CEA or more frequently in patients with short doubling times of serum Ct and CEA (<6 months), and the progression rate is assessed using RECIST [19, 20]. Patients with measurable lesions and documented progression on imaging, defined as at least a 20% increase in the sum of the longest diameters of measured lesions or the appearance of one or more new lesions in a given time interval (between 6 and 12 months) should be considered candidates for systemic treatment. Progression rate can be evaluated by serum Ct and CEA doubling

times, which are usually related to tumor progression on imaging [10–14], but disease progression should always be confirmed by imaging before initiation of any treatment [19, 20].

Recommendation 1

(a) Imaging should use multiple imaging modalities to identify all clinically relevant sites of disease. Grade: quality of evidence (QOE) = ++; strength of recommendation (SOR) = grade 1.

(b) Progression rate may be assessed by determining doubling times of tumor markers (Ct and CEA), but progression should be confirmed by imaging using RECIST. Grade: QOE = +++; SOR = grade 1.

(c) Patients with elevated serum marker levels with no tumor foci on imaging should undergo repeated serum marker measurements every 6–12 months, or either at longer intervals of time or more frequently depending on doubling times of serum Ct and CEA, without medical intervention. When biochemical progression is observed, imaging should be repeated. Grade: QOE = ++; SOR = grade 1.

(d) Patients with known metastases who do not receive any systemic treatment because metastases are asymptomatic or small in size and have no demonstrated progression should undergo repeated imaging every 6–12 months and either at longer intervals of time or more frequently according to doubling times of serum Ct and CEA. Grade: QOE = ++; SOR = grade 1.

(e) Patients with small volume distant metastases with no evidence of progression and with neck tumor foci should be considered for treatment of neck disease (surgery and/or external beam radiation therapy). Decision can only be made on an individual basis. Grade: QOE = +; SOR = grade 2.

(f) Only patients with significant tumor burden and those with symptomatic or progressive disease according to RECIST are candidates for systemic treatment. Grade: QOE = +++; SOR = grade 1.

Local Treatment Modalities for Distant Metastases

Because progression rate is often low, local treatment procedures targeting predominant lesion(s), although not curative, may provide benefits in terms of quality of life for long periods of time and may delay the initiation of systemic treatments. This is the reason why local treatment modalities of metastases are first reviewed for each potential site of distant metastases.

Brain Metastases

Clinically overt brain metastases from MTC are uncommon (about 1–5% of MTC patients with local or metastatic disease), but brain metastases are probably more prevalent than has been reported due to the lack of routine imaging of the central nervous system. Brain metastases are most often suspected in patients with residual or recurrent MTC and neurologic symptoms in the setting of extensive distant metastases; brain imaging should be performed before initiation of systemic therapy [21–23]. The discovery of small asymptomatic lesions without edema may not necessarily indicate active treatment, but rather clinical and imaging follow-up. In retrospective studies in thyroid carcinoma and nonthyroid carcinoma, it has been suggested that surgical resection in patients with solitary or limited number of brain metastases may be associated with improved quality of life [21–24].

Recommendation 2

Brain imaging should be performed in patients with neurologic symptoms and also before initiation of any systemic treatment. Patients with isolated or limited brain metastases should be first considered for surgical resection or stereotactic radiosurgery. Whole brain EBRT is indicated for clinically overt brain metastases. Grade: QOE = ++; SOR = grade 1.

Bone Metastases

Bone metastases occur in 45% of MTC patients with local or metastatic disease [6]. Bone metastases may be found on anatomic or functional tumor imaging. Some patients present with painful bone lesions, fracture, or spinal cord compression. Experience with bone metastases from tumors other than MTC have demonstrated that percutaneous methods of treatment such as cementoplasty (image-guided injection of polymethyl metacrylate cement in bones), thermal ablation (radiofrequency or cryotherapy) and arterial embolization followed by surgery, or a combination of these methods, have been associated with pain reduction and bone consolidation [25–32]. Isolated bone metastases may be surgically resected or treated with percutaneous methods, but it is extremely uncommon for these patients to be rendered free of disease. In some studies in differentiated thyroid carcinoma, it has been suggested that surgery is worthwhile when 5 or less bone metastases are present [33, 34]. It is not known if these results can be expanded to MTC. EBRT may lead to considerable reduction in pain in 80% of patients, which may last for months [35].

Intravenous bisphosphonates are prescribed by many specialists for painful bony metastases and to prevent progression of existing osseous metastases from other primary malignancies with some success, but there is no substantial experience in MTC [36]. In addition, concerns about side effects from high doses of bisphosphonates, like osteonecrosis of the jaw, in particular during treatment with an antiangiogenic drug, may restrict its use.

Recommendation 3

(a) Patients with spinal cord compression require urgent glucocorticosteroid therapy and surgical evaluation, and postoperative EBRT should be considered. If not amenable to surgery, primary EBRT should be performed. Grade: QOE = +++; SOR = grade 1.

(b) Surgery is indicated in weight-bearing bone metastases with fracture or impending fracture. Adjuvant EBRT is indicated for incompletely resected bone metastases. Grade: QOE = ++; SOR = grade 1.

(c) Minimally invasive percutaneous treatments (alone or in combination) should be considered to treat painful bone metastases and may be an alternative to surgery and EBRT on bone lesion with impending fracture. Grade: QOE = +; SOR = grade 1.

(d) EBRT should be considered to treat painful bone metastases and is indicated for clinically significant lesions that are not candidates for surgery or percutaneous treatment, especially if they are widespread/extended, demonstrate progression or may threaten adjacent structures in case of progression. Grade: QOE = ++; SOR = grade 1.

(e) Limited/small bone metastases that are asymptomatic and are not an immediate threat may be followed. Grade: QOE = +; SOR = grade 2.

(f) No recommendation is made for the use of bisphosphonates in the setting of MTC with bone metastases.

Lung Metastases

Lung metastases occur in 33% of MTC patients with local or metastatic disease [6]. They are usually multiple (miliary) and often associated with mediastinal lymph node metastases. In rare cases, dominant mediastinal lesions may be considered for surgical resection. More often, lung and mediastinal lesions are left untreated or considered for systemic treatment if the lesions are progressive. Lung or mediastinal lesions causing local compression of an airway or bleeding may be considered for surgery or EBRT, and lesions with central airway invasion may be amenable to the addition of photodynamic ther-

apy or airway stenting (when the tumor is >15 mm from the vocal cord) to improve quality of life [37]. Radiofrequency ablation may be indicated in patients with few (<5, ideally <3) predominantly peripheral lung metastases of <40 mm in size [38].

Recommendation 4

Patients with respiratory symptoms may benefit from local treatment modalities; patients with few predominant lung metastases may be treated with radiofrequency ablation when the metastases are peripheral, <40 mm in diameter and slowly progressive; lung or mediastinal lesions that are progressive should be considered for systemic therapy. Grade: QOE = ++; SOR = grade 1.

Liver Metastases

Liver metastases occur in 45% of MTC patients with local or metastatic disease [6]. When liver metastases are large or progressive, or associated with symptoms such as diarrhea or pain, there is a need for treatment. Single or limited large metastases may be surgically resected or treated with percutaneous radiofrequency ablation that may lead to prolonged symptom reduction in 90–95% of patients, including reduction of diarrhea. Radiofrequency ablation is less effective in lesions >50 mm [39]. However, liver metastases are usually multiple and not amenable to surgery and may be best treated with chemoembolization or systemic treatment [40, 41]. In a series of 11 patients, chemoembolization induced symptomatic improvement in all, with transient remission or stabilization in 60%. In another series of 12 MTC patients, 42% had partial response and another 42% had stabilization, while diarrhea improved in 40% [42, 43]. The extent of liver involvement was the main predictive factor, with partial responses being observed only in patients with liver involvement <30% and when metastases were <30 mm. Following a single cycle (1 or 2 courses), the duration of partial responses and stabilizations was longer than 1 year. When disease progression occurred, an additional cycle of chemoembolization provided an additional partial tumor response, but of shorter duration. Despite these favorable responses, chemoembolization did not downstage patients enough to allow for subsequent curative surgery. Only patients with preserved liver and renal function, without major bile duct dilatation or portal vein thrombosis are candidates for chemoembolization. Toxicity was mild and transient, but care must be taken to exclude the presence of a pheochromocytoma.

Recommendation 5

Liver metastases that are progressive, large or associated with symptoms such as diarrhea or pain should be considered for active treatment. In case of isolated or few liver metastases, surgery is considered when the lesions are limited to one or two lobes; radiofrequency ablation (when there are few lesions <30 mm) or chemoembolization (when lesions are disseminated in the liver) should also be considered. In other cases, patients should be considered for systemic treatment. Grade: QOE = ++; SOR = grade 1.

Systemic Treatment: Chemotherapy and Clinical Trials

Among cytotoxic drugs, the most frequently used tested agent in MTC patients is doxorubicin, used either alone or in combination with cisplatin. Response rates ranged from 0 to 22%, with all responses being partial and only lasting a few months [44, 45]. As MTC is a well-differentiated endocrine tumor, various combinations of 5'-fluorouracil, dacarbazine, streptozocin, cyclophosphamide and vincristine have been used, leading to response rates of approximately 20%, with symptomatic improvement in a limited number of patients [46–51]. Newer cytotoxic drugs, such as taxanes, gemcitabine or irinotecan have not been evaluated in significant series of MTC patients. Dendritic cell immunotherapy may be effective, but is still under evaluation [52].

In the limited experience with radiolabeled molecules, only few responses have been reported with [⁹⁰yttrium-DOTA]-TOC in MTC patients with rising Ct levels and tumor uptake on ¹¹¹In-Octreoscan [53]. With pretargeted radioimmunotherapy with bispecific monoclonal anti-CEA antibody and a ¹³¹I-labeled bivalent hapten in patients with metastatic progressive MTC (defined with Ct doubling time <2 years), overall survival was significantly longer compared to high-risk untreated historical controls (median overall survival: 110 vs. 61 months; *p* < 0.03). Toxicity was mainly hematological and was associated with bone or bone-marrow tumor spread [54]. Treatment with ¹³¹I-MIBG is generally regarded as ineffective for MTC [55].

A germline rearranged during transfection (RET) mutation is found in most familial forms of MTC [56]. The proto-oncogene encoded Ret protein is a membrane receptor with tyrosine kinase activity, and activating RET mutations activate its kinase function that triggers downstream mitogenic and survival signaling. Somatic muta-

tions in RET are also found in 30–50% of sporadic MTC tumors, and among these mutations, more than 80% are in codon 918 (exon 16) and about 10% are in codon 634 (exon 11), with the other mutations being located in exons 10, 13, 14 or 15. It should be noted that mutations have been sought mostly in primary tumors and little is known on the RET status in metastatic tissue that may require treatment intervention some decades after the treatment of the primary tumor.

Angiogenesis is critical in the development of these hypervascularized tumors, and provides another set of potential molecular targets for therapy. Various vascular endothelial growth factors (VEGF) and VEGF receptors [VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1, KDR)] are often overexpressed in MTC, both in tumor cells and in supporting vascular endothelium [57]. Many agents that target the VEGFR-2 kinase also target the Ret kinase.

In recent years, several kinase inhibitors have been evaluated in phase I and II clinical trials, including axitinib, cabozantinib (XL-184), lenvatinib (E7080), motesanib, pazopanib, sorafenib, sunitinib and vandetanib [58–68]. In phase II trials, several of these agents have demonstrated partial response rates in the range of 20–50% with a larger number of patients demonstrating prolonged stable disease. In these patients, the drug may decrease the production of Ct and CEA in blood and this may occur even in the absence of beneficial effects on tumor masses, and for this reason serum marker levels cannot be used to assess the antitumor efficacy of the drug. Two of these agents, vandetanib and cabozantinib have entered phase III clinical trials.

A phase II trial with vandetanib, targeting the kinases of Ret, EGFR and VEGFR, was evaluated at a maximal tolerated dose (300 mg/day) in 30 hereditary MTC patients. Partial response was observed in 10 patients, among whom 6 had a confirmed partial response and stable disease longer than 24 weeks was established in another 16 patients [67]. Another phase II trial with vandetanib (100 mg/day) included 19 hereditary MTC patients, and a partial response was observed in 3 patients and stable disease longer than 24 weeks in another 10 patients, demonstrating antitumour activity in this setting. However, it is not clear whether there is a relationship between dose and efficacy, as well as between dose and toxicity [68]. A large randomized phase III trial comparing progression-free survival (PFS) in patients treated with vandetanib (300 mg/day) or placebo has been completed in 331 patients with locally advanced or metastatic MTC [69]. The median PFS was significantly prolonged from 19.3 months in the placebo arm to a predicted median of

30.5 months (median not yet reached) in the vandetanib arm (HR: 0.46; $p < 10^{-4}$); partial responses were observed in 45% of patients treated with vandetanib, with a predicted median duration of response of 22 months. The improvement of pain and diarrhea allowed a number of patients in the vandetanib arm to resume a normal social life. All subgroups of patients, according to tumor burden, progression rate or symptoms, experienced significant PFS benefits from treatment. Also, PFS benefits were observed in both patients with RET mutation and in those with no demonstrated somatic RET mutation; however, the number of RET-negative patients in whom all RET exons could be sequenced was limited. Adverse events, including diarrhea, fatigue, rash and folliculitis, photosensitization, hypertension, and prolongation of the QTc interval, were mainly grade 1 or 2. However, 12% of patients receiving vandetanib discontinued treatment due to toxicity and 35% required dose reduction because of an adverse event. Vandetanib was approved by the FDA in April 2011 and by the EMA in February 2012 for the treatment of aggressive and symptomatic MTC in patients with unresectable locally advanced or metastatic disease. However, further data are needed to quantify drug benefits in patients with no RET mutation in their metastatic tissue.

A phase I trial with cabozantinib, targeting the kinases of Ret, c-Met and VEGFR, included 34 evaluable MTC patients. Seventeen patients had a partial response, among whom 10 had a confirmed partial response, and another 15 patients had stable disease [65, 66]. Partial responses were observed regardless of somatic RET mutation status and in both treatment-naïve patients and in those who had previously been treated with another kinase inhibitor, suggesting the absence of cross-resistance with other compounds. Based on these favorable results, a randomized phase III trial of cabozantinib (175 mg/day) versus placebo is ongoing in patients with progressive MTC (NCT00704730).

These agents have shown the potential to provide high rates of disease control with durable responses and improved quality of life, and a highly significant improvement of PFS in the only phase III trial thus far completed [69]. However, these treatments have to be given to patients as long as tumor control persists, and short-term toxicity is significant, with dose reduction or treatment withdrawal in a significant proportion of patients; long-term toxicity needs to be investigated. There is currently no evidence for a higher treatment efficacy at an earlier than later stage when the tumor has progressed. This should lead to initiating these treatments only in patients

with significant tumor burden and documented tumor progression. In contrast, patients with elevated serum marker levels or with minimal disease on imaging may be followed-up at regular intervals of time. An unresolved issue is what should be done in patients with progressive disease after a first-line treatment, and second-line trials are needed for these patients.

Additionally, it is possible that other new agents, or combination or sequential therapy with these targeted agents or with conventional cytotoxic chemotherapy will eventually prove more effective than a single targeted therapy alone [70, 71].

Recommendation 6

(a) In patients with significant tumor burden and symptomatic or progressive disease according to RECIST, the use of standard chemotherapeutic agents should not be considered as first-line therapy for patients with persistent or recurrent MTC. Grade: QOE = ++; SOR = grade 2.

(b) Inhibitors of both Ret and VEGFR tyrosine kinases appear to be the most effective treatment modality in these MTC patients. Grade: QOE = +++; SOR = grade 1.

(c) Treatment with radiolabeled molecules may be considered in selected patients, ideally in the setting of a well-designed clinical trial. Grade: QOE = +; SOR = grade 2.

Symptoms, Evaluation and Treatment of Hormonally Active Metastases

Diarrhea [72, 73], ectopic corticotropin-releasing hormone and ectopic adrenocorticotrophic hormone production that can result in Cushing syndrome [74] are the main hormonally mediated complications of MTC, most frequently in the setting of advanced disease and usually in patients with hepatic metastases.

The diarrhea may be hypersecretory or due to enhanced gastrointestinal motility, or a combination of both. The diarrhea can be debilitating both in terms of quality of life and nutrition and should be treated with antimotility agents (such as loperamide, diphenoxylate/atropine and codeine) [1]. Somatostatin analogue therapy either alone or in combination with interferon- α produced no more than a modest improvement of diarrhea in some MTC patients [75, 76]. Local treatment of large hepatic metastases using selective artery chemoembolization [42, 43] and treatment with tyrosine kinase inhibitors may improve diarrhea in some patients.

Cushing syndrome can be severe and debilitating, and is associated with poor patient survival due to the extended and progressive MTC [74]. Even in the setting of widely metastatic MTC, control of cortisol hypersecretion may be achieved by debulking of large hepatic metastases (surgery or chemoembolization); by medical therapy using ketoconazole, mifepristone or mitotane; and/or by bilateral adrenalectomy [77].

Recommendation 7

(a) Therapy to reduce the frequency and amount of diarrhea in the setting of MTC should be employed. Initial therapy should include antimotility agents. Alternative therapies may include surgery or chemoembolization of liver metastases in selected cases and systemic treatment with tyrosine kinase inhibitors in patients with progressive and bulky disease. Grade: QOE = ++; SOR = grade 1.

(b) Clinicians should maintain a heightened vigilance for Cushing syndrome due to paraneoplastic production of adrenocorticotrophic hormone and/or corticotropin-releasing hormone from MTC. While MTC patients with Cushing syndrome typically have a poor prognosis, treatment should be considered even in the setting of widely metastatic MTC because the syndrome can be severe and debilitating. Grade: QOE = ++; SOR = grade 1.

(c) Cushing syndrome from MTC may be treated in a multimodality manner with therapy directed towards the tumor and medical therapy directed towards Cushing syndrome, or whenever feasible with bilateral adrenalectomy. Grade: QOE = ++; SOR = grade 1.

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