

TITLE: Medullary Thyroid Cancer

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Medullary thyroid cancer (MTC) is a cancer of the parafollicular C-cells of the thyroid, and is considered a neuroendocrine tumor since the C-cells are derived from neural crest cells. MTC is the 3rd most common thyroid cancer after papillary and follicular carcinoma, and is a secretory tumor known to secrete calcitonin, carcinoembryonic antigen (CEA), adrenocorticotropin hormone (ACTH), substance P, and gastrin. MTC has two forms, sporadic and familial.

Forms:

The Sporadic form of MTC represents roughly 75% of MTC cases, and typically carries a worse prognosis. Tumors of this type tend to be unifocal and unilateral. The typical age at presentation is around the 5th-6th decades, and there is usually no family history of MTC.

The familial form represents the other 25% of cases seen. These tumors are multifocal and bilateral at presentation, but tend to carry a better prognosis overall. This form is associated with autosomal dominant (AD) syndromes (Multiple Endocrine Neoplasia [MEN] IIA and IIB) as well as RET proto-oncogene missense mutations located on chromosome 10.

Presentation:

MTC typically presents as a slow growing neck mass. Nodal disease is common, with 50-60% of cases presenting with nodal metastasis at the time of presentation. Patients may also complain of compressive symptoms (dysphagia and/or dyspnea) and hoarseness (recurrent laryngeal nerve involvement). Diarrhea is another symptom that is commonly noted. This is because calcitonin, typically present in high amounts in MTC, causes an increased excretion of

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electrolytes into the intestine. Water then follows these electrolytes into the lumen, thus leading to the diarrhea

Syndromes:

As stated previously, MTC is associated with AD syndromes. The most common of these is MEN IIA, or Sipple Syndrome. The triad of features associated with this syndrome includes MTC, pheochromocytoma, and parathyroid hyperplasia. The RET mutations associated with Sipple syndrome typically involve codons 609, 611, 618, 620, and most commonly, 634. The 634 mutation is also responsible for cutaneous amyloidosis (Lichen amyloidosis) sometimes seen in this syndrome. Familial MTC is another AD disease associated with MTC. It is thought to be a subclass of MEN IIA as it shares similar mutations in the RET proto-oncogene (609, 611, 618, and 620). However, unlike MEN IIA, there is no history of pheochromocytoma or parathyroid hyperplasia. In addition, the 634 mutation is rarely seen in familial MTC. To officially make a diagnosis of familial MTC, there must be at least 2 or more family generations of MTC without any sign of pheochromocytoma or parathyroid hyperplasia. MEN IIB is another AD syndrome associated with MTC. The major features noted in this syndrome include MTC, pheochromocytoma, musculoskeletal manifestations (marfanoid habitus, pes cavus, pectus excavatum, proximal muscle weakness), mucosal neuromas, urinary and intestinal malformations. The MTC seen in this syndrome tends to be much more aggressive than in the other syndromes. Luckily, MEN IIB is very rare. The mutation involving codon 918 is the most notable mutation involving MEN IIB.

As the RET proto-oncogene mutation is strongly associated with MTC, the American Thyroid Association (ATA) has made multiple recommendations as to who should be screened for this mutation. Any patient with a diagnosis of MTC should be screened. In addition, any patient who has signs/features of MEN IIA, IIB, and familial MTC should be screened. Patients with family members with any of these syndromes should also undergo screening. If a patient has Lichen amyloidosis or Hirschsprung disease, they too should also be screened for this mutation.

When RET mutations are found, action must be taken to help prevent morbidity and mortality. First, all family members should be screened. Various recommendations as to the type of treatment that should be performed have been proposed by the ATA. The treatment typically involves performing a total thyroidectomy at minimum. The age at which to perform the thyroidectomy depends on the mutation involved. It has been discovered that some mutations are associated with a much more aggressive form of disease than others. For this reason, the ATA has grouped these mutations into four categories, A-D. D represents the most aggressive forms, while A is the least aggressive. The A category involves mutations in codons 768, 790, 791, 804, and 891. Category B has the 609, 611, 620, and 630 mutations while category C has the 634 mutation. Category D has the 918 and 883 mutations.

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Given that category D represents the most aggressive forms of the disease, the ATA recommends that patients with these mutations undergo total thyroidectomy prior to 1 year of age. Prior to removal, these patients should undergo ultrasound examination of their thyroid, central neck compartment, lateral neck compartments, and superior mediastinum. Serum calcitonin levels should be ordered as well, but it is much less reliable in this age group. Patients with category C mutations are recommended to undergo total thyroidectomy prior to age 5, but should have an ultrasound and serum calcitonin levels by age 3. Patients in categories A and B could potentially wait to have a thyroidectomy until after 5 years, thus helping to prevent complications as these children have been allowed to develop more. However, these children should be screened with ultrasound and serum calcitonin by age 3. In all cases, if the ultrasound reveals a thyroid nodule > 5mm or there is a serum calcitonin level > 40 pg/mL, the patient should undergo a thyroidectomy at the time of the discovery since these findings have been shown to be associated with a higher risk of MTC and metastasis. Neck dissections do not offer improved outcomes in the asymptomatic population and thus have not been recommended except in the cases where gross disease is noted.

In addition to the screening and treatment for MTC, patients with RET mutations must also undergo screening for pheochromocytoma and parathyroid hyperplasia. In patients who are noted to have mutations involving the 918 or 634 codons, it is recommended that they undergo screening for pheochromocytoma by the age of 10 and yearly thereafter with either a serum or 24 hour urine metanephrine/normetanephrine. With all other mutations, screening can occur at the age of 20 and annually thereafter. In patients noted to have mutations related to MEN IIA, they should undergo screening for hyperplastic parathyroid glands as well. If the mutation involves the 630 or 634 codon, screening should begin around age 8 and then annually thereafter with a serum calcium and intact parathyroid hormone (PTH). For all other mutations, patients can begin screening at age 20 and yearly thereafter.

In the event that an older patient is found to have mutations in the RET proto-oncogene (age > 1 in MEN IIB and age > 5 in MEN IIA and Familial MTC), it is recommended that these patients undergo immediate ultrasound examination and have a serum calcitonin checked. If the calcitonin level is less than 40 pg/mL, or any thyroid nodules are less than 5mm, total thyroidectomy is recommended. If the calcitonin is greater than 40 pg/mL or thyroid nodules are greater than 5mm, a total thyroidectomy along with a central neck dissection are recommended. If nodal disease is discovered in the lateral neck, then a formal neck dissection (levels IIA-V) is warranted. If during dissection, parathyroid glands are removed. These should be placed into the forearm and marked, especially if the patient has or may have MEN IIA. The reason for this is that these patients may require further neck treatments, thus the previously removed parathyroid glands could be injured in the neck upon re-operation leading to hypoparathyroidism and its complications.

In the symptomatic patient, once MTC is suspected, there are two primary tests that should be obtained; a serum calcitonin and a fine-needle aspiration (FNA) of the suspected nodule.

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Chang et al reviewed the pathology slides of 34 patients with known MTC. They found that 82% of the patients were correctly diagnosed by FNA alone. Three patients were diagnosed with follicular neoplasms, 1 with a desmoid tumor, and 2 others were suspicious for MTC. Overall, however, every patient underwent surgery and was correctly diagnosed. Pappavaskova et al reported that of the cases they reviewed with patients undergoing FNA biopsy in diagnosing MTC, 89% were diagnosed correctly by FNA alone. However, 99% of the patients underwent surgery, and were diagnosed correctly. Although FNA is considered a reliable test when it comes to diagnosing MTC, it typically discovers the disease in its later stages. Serum calcitonin levels are thought to be much better at detecting disease earlier, thus improving outcomes. Of all thyroid nodules, it is estimated that 0.3-1.4% are MTC. The controversy involves whether it is appropriate to order serum calcitonin levels on every patient with thyroid nodules, as cost may become an issue. Elisei et al examined 10,864 patients with thyroid nodules who had been screened by calcitonin levels and/or FNA biopsy. They found that 0.4% had MTC. Of the patients who were screened with serum calcitonin levels, the MTC was discovered earlier, and thus treated in an earlier stage. These patients had much better outcomes than those who were diagnosed by FNA alone; 59% complete remission rate versus 2.7% for patients who did not have MTC initially suspected by serum calcitonin. The next question to be asked is: what calcitonin level corresponds to likely disease? Costante et al reported that the positive predictive value of serum calcitonin in the detection of MTC was 8.3% for levels 20-50 pg/mL, 25% for 51-100 pg/mL, and 100% for levels greater than 100 pg/mL.

The next step in the process of diagnosing and treating MTC involves further laboratory studies. If a serum calcitonin has not yet been ordered, it should be done so now. In addition, the presence of a RET mutation must be known. A serum calcium is also important in this situation to assess for possible MEN IIA. Following the additional laboratory studies, an ultrasound of the thyroid, central neck compartment, lateral necks, and the super mediastinum should be performed. If a RET mutation discovered, the family members should be screened and treated as discussed above. In addition, the patient should undergo screening for pheochromocytoma. If any lymph nodes are detected on ultrasound, or if the serum calcitonin is greater than 400 pg/mL, the patient should undergo a CT scan of the neck and thorax as well as a triple phase CT scan of the liver to assess for metastatic disease. Machens et al found that distant metastasis began to appear when the measured calcitonin levels were 400 pg/mL or greater. They also found that when the serum calcitonin level was 15,000 pg/mL, or if there was a nodule that was 5cm in size, the metastatic rate was 50%. When the serum calcitonin level was 100,000 pg/mL or if a 6cm or larger nodule was discovered, the rate of metastasis was 100%.

Treatment Options:

The extent of treatment for MTC depends on the extent of the disease. Once MTC has metastasized, the chance for cure is very low. The first thing to consider if surgery is warranted is whether the patient has a pheochromocytoma. Treatment of the pheochromocytoma takes precedence as operating on a patient with an active pheochromocytoma could prove fatal. In

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many cases, the extent of the MTC will be limited, and surgical cure still remains a possibility. If the disease is confined to the thyroid or has spread to lymph nodes within the central neck compartment, the treatment involves a total thyroidectomy and central compartment neck dissection. If any lateral neck nodal disease is discovered, neck dissections involving levels IIa through V should be performed in addition to the above. When the MTC is deemed advanced (distant metastasis, invasion of the trachea, esophagus, or larynx) the treatment is palliative with the goal to maintain speech, swallowing and parathyroid function. Multiple studies have shown that the extent of surgery has no effect on patients with advanced MTC.

One question that arises when dealing with any thyroid malignancy is what to do with the recurrent laryngeal nerve if the tumor is encasing or invading it. The first assessment must be to determine whether the nerve is functional. For this reason, all patients should undergo flexible laryngoscopy prior to the operative procedure to properly document the functional status of the cords. If the nerve is out, and it is involved in tumor, the nerve should be taken with the tumor. If it is working, then the extent of the disease dictates what should be done. If the patient has limited disease, the nerve should be taken in an attempt to obtain proper oncological resection. If the patient has advanced disease, the nerve is not resected in order to preserve speech.

Postoperative Care:

In the post-operative period, it is important to assess whether all disease has been removed. The most commonly used post-operative screening test is the serum calcitonin. Following resection, it typically takes 1-2 months before the serum calcitonin levels normalize, if all disease has been removed. For this reason, it is recommended that the first post-operative calcitonin be drawn 2-3 months after resection. If it is undetectable, the patient should only be observed on a routine basis as the risk of recurrence is roughly 3% in this situation. Modigliani et al showed that when the post-operative calcitonin was undetectable, the 10 year survival rate was 97%. If the calcitonin level is detectable, but less than 150 pg/mL, persistent disease should be considered. In this scenario, a neck ultrasound should be ordered to assess for disease. Work-up for distant metastasis is to be considered, however, the likelihood of finding metastatic disease when the calcitonin is less than 150 pg/mL is very low. If the calcitonin level is greater than 150 pg/mL, then a full metastatic work-up should be performed, as the likelihood of finding distant disease is higher. This work-up should include a CT of the neck and thorax as well as a triple phase contrasted CT of the liver, along with a bone scan. The calcitonin doubling time can also be determined post-operatively, and will aid in two aspects. First, it should be used to help guide how often a patient should be re-evaluated, and second, it can predict future outcomes. For instance, if the calcitonin doubling time is < 6 months, these patients have 5 and 10 year survival rates of 25% and 8%, respectively, and thus these patients will need to be followed and monitored much more closely for disease recurrence than those with longer doubling times. If the doubling time is 6-24 months, the survival improves to 92% and 37%, respectively. If it is over 24 months, then the 10 year survival is close to 100%.

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If during the work-up, nodal disease greater than 1cm in size or other gross disease is discovered in the neck, the consensus is that formal resection should be performed in an attempt to remove the disease. How this is performed depends on the extent of the disease and previous treatments. If a formal neck dissection has not been performed previously, then the recommendation is that the patient undergoes formal neck dissection. However, if a formal resection has already occurred, then removal of the gross disease is adequate.

If the work-up for local and/or distant metastasis comes back negative with a detectable calcitonin, then observation is recommended. In the past, extensive neck dissections and mediastinal lymph node removal was performed in an attempt to locate and remove disease in this scenario. However, multiple studies have shown that this did not improve patient survival, and only increased patient morbidity. Another procedure that used to be performed in this scenario was a diagnostic laparoscopy with liver biopsies looking for disease. However, this is no longer recommended for two main reasons. First, when negative, the previously recommended treatment involved extensive neck and mediastinal dissections which have already been proven to not be beneficial in overall survival. Second, the imaging studies that are available today are much more reliable at detecting disease than they were in the past, thus diagnostic, invasive procedures would likely not reveal new information, and would just increase patient morbidity.

Radiation:

The role of radiation therapy in the treatment of MTC has also been studied. In these studies, it has been shown that the addition of external beam radiotherapy (EBRT) to the treatment of MTC has improved the relapse rate. However, it has not improved overall survival. Brierley et al used EBRT in patients with microscopic residual disease, cases where local soft tissue involvement occurred, and in cases with nodal positive disease. They found that the relapse rate was 86% at 10 years in patients treated post-operatively with EBRT compared to 52% in patients who were not treated with EBRT. In a smaller study, Chow et al treated patients with nodal positive disease with EBRT. Of the 4 patients who received post-operative EBRT, all were noted to have 10 year locoregional control. Of the 3 who did not receive EBRT, 1 had 10 year locoregional control. Because of these findings, the ATA has recommended that all patients with microscopic, nodal positive, or small amounts of macroscopic disease undergo post-operative treatment with EBRT. It is not recommended that patients with elevated calcitonin levels who are negative for nodal disease and had negative surgical margins undergo EBRT. This is because the exact location of disease is not known, and could potentially be at a different site than what would be irradiated. At this time, chemotherapy does not have a role in the treatment of MTC as these tumors have persistently shown to have a poor response to the chemotherapeutic agents.

Conclusion:

MTC is a rare, but potentially fatal malignancy. It is very important that this disease is recognized and treated early as distant metastasis carries a poor prognosis. In addition, the

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presence of a RET mutation needs to be determined as it will help to guide further work-up and treatment as well as trigger screening examinations for family members. Surgery is the primary treatment of MTC with EBRT being used in cases of residual and nodal disease to improve disease relapse rate. However, EBRT is not a substitute for proper oncologic resection as it has not been shown to improve survival.

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