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Review Article EP12430.RA

MEDULLARY THYROID CARCINOMA

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ABSTRACT

Objective: This review outlines the advances in the diagnosis, genetic testing and the progress in medullary thyroid cancer (MTC) treatment in light of the most recent evidence.

Methods: English-language articles of medullary thyroid cancer published up to 2012 were reviewed. The pertinent articles and their references were obtained and those considered relevant were reviewed for inclusion.

Results: Medullary thyroid carcinoma (MTC), an uncommon neuroendocrine malignancy, accounts for 5% of thyroid cancers. MTC presents in the sporadic and also familial form (MEN 2A, MEN 2B or familial MTC syndromes). The familial forms are secondary to germline mutations in the RET proto-oncogene. Early diagnosis and treatment is paramount. Genetic testing has made possible early detection in asymptomatic carriers and high risk patients, with early or prophylactic surgery being curative in many. All carriers of a RET mutation should be evaluated and treated surgically for MTC. The primary treatment in all patients diagnosed with MTC is total thyroidectomy with central lymph node dissection. Calcitonin (Ct) and carcinoembryonic antigen (CEA) levels can be used as prognostic factors and as tumor markers. If elevated, further investigation including imaging modalities may be necessary for evaluation of metastatic disease. Surgery remains the main treatment for local and locally advanced disease.

Conclusion: MTC is rare but morbidity and mortality remain high if untreated. Genetic testing should be offered to all patients. Treatment of choice remains total thyroidectomy and central lymph node dissection. Palliative treatment for advanced disease includes surgery, radiation, standard chemotherapy, chemoembolization and, more recently, targeted therapies (tyrosine kinase inhibitors).

Key words: Medullary thyroid cancer; MEN 2; RET mutation; Exon & Codon; TKI

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Abbreviations:

ACTH = Adrenocorticotropic hormone; **ATA** = American Thyroid Association; **CEA** = Carcinoembryonic antigen; **CT** = Computed tomography; **Ct** = Calcitonin**; DT** = Doubling times; **EBRT** = External Beam Radiotherapy; **FDG-PET** = (18F)-fluorodeoxyglucose positron emission tomography; **FMTC** = Familial medullary thyroid carcinoma; **FNA** = Fine-needle aspiration; **MEN** = Multiple Endocrine Neoplasia; **MRI** = Magnetic resonance imaging; **MTC** = Medullary thyroid cancer; **TKI** = Tyrosine kinase inhibitors; **VIP** = Vasoactive intestinal peptide

INTRODUCTION

Medullary thyroid carcinoma (MTC) is a rare thyroid malignancy arising from the parafollicular C cells of the thyroid and occurs both in sporadic and familial forms. MTC accounts for approximately 5% of all thyroid cancers. (1-3) One important characteristic of this tumor is the production of calcitonin (Ct).

The majority of MTC are sporadic, but the familial form, responsible for about 25% of cases, is usually represented by multiple endocrine neoplasia (MEN) 2A or 2B or pure familial MTC syndrome (FMTC). (4) The hereditary disorders are caused by RET proto-oncogene germline mutations, located on chromosome 10 (5-7) and typically are bilateral and proceeded by premalignant C-cell hyperplasia. Sporadic cases have somatic RET mutations in 30-50%. C-cell hyperplasia is the initial stage of tumorigenesis in at least a fraction of sporadic MTC with subsequent progression to locoregional and distant metastases. (8)

The diagnosis of MTC is challenging and includes the differential between sporadic and hereditary disease, and the evaluation of disease extent that will impact therapeutic options. Early diagnosis and treatment is paramount and it is associated with more favorable outcomes;

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while late diagnosis is associated with reduced survival. (9, 10) Predictors of aggressiveness in MTC include certain specific RET mutations, as well as levels of calcitonin and carcinoembryonic antigen (CEA). (11, 12) Genetic testing has made possible early detection in asymptomatic carriers and high risk patients. (13) The use of routine ultrasound and calcitonin screening has improved early diagnosis and decreased mortality. MTC is primarily a surgical disease: cure may be achieved in hereditary MTC with complete surgical resection before progression to metastatic disease. (14, 15)

This review outlines advances in the diagnosis and genetic testing as well as progress in medullary thyroid cancer treatment.

Genetic Abnormalities

Germline mutations of the RET proto-oncogene occur in virtually all patients with hereditary MTC whereas somatic RET mutations are identified in only 30-50% of sporadic cases. (16) Genetic testing is now part of the routine evaluation in patients with MTC and when positive their family members, due to the high penetrance of MTC when associated with RET mutations. All patients should be counseled about possible familial disease and offered genetic testing.

The RET proto-oncogene germline mutations were identified in MEN 2A, MEN 2B and FMTC in 1993. The germline mutation responsible for the familial MTC syndromes is located in the proximal region of the long arm of chromosome 10, band q11.2 and encodes a receptor-like tyrosine kinase expressed primarily in neuroendocrine cells including thyroid C cells and adrenal medullary cells. (5, 6, 17, 18)

The majority of the mutations affecting MEN 2A syndrome are located in exon 10 (codons 609, 611, 618 and 620) and exon 11 (codon 634), the latter representing 80% of the

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mutations. Other mutations are also reported in exon 5 (codon 321), exon 8 (codons 515 and 533), exon 11 (codons 630, 634, 649, 666), exon 13 (codons 768, 776, 777, 790 and 791), exon 14 (codons 804), exon 15 (codons 866 and 891) and exon 16 (codon 912). These mutations may reflect new germiline mutations rather than somatic mutations. They are responsible for about 98% of all mutations in MEN 2A. In FMTC mutations are commonly found in exon 10 (codons 609, 611, 618, 620), exon 11 (codons 630, 631, 634, 649, 666), exon 13 (codon 768), exon 14 (codons 804, 819, 833, 844) and exon 15 (codons 866, 891). (5, 7, 19-21) New mutations are not common in patients with MEN 2A and FMTC and are usually found in less than 10% of the cases (table 1). (22, 23)

In MEN 2B syndrome a single mutation is found in exon 16 (codon 918) in about 95% of the cases (table 1). In 50% of the cases a de-novo germline mutation is seen, with evidence of genomic imprinting (allele inherited from patient's father). Rarely another mutation in exon 15 (codon 883) may also be found. (23-25)

Mutations were also identified in sporadic MTC (exon 13 and exon 16 at codon 918) but in only 30% of these patients. This mutation is associated with poor outcomes when compared to tumors without RET mutations (Table 1). (6, 26, 27) These mutations may represent new germline mutations rather than somatic mutations. The probability of an RET germline mutation in an individual with apparent sporadic MTC is 1-7% but screening is justified due to the heritable implications of this mutation. (28)

Clinical Syndromes

Most medullary thyroid carcinomas are sporadic but some are familial (25% of the cases). The following 4 types of MTC are recognized: sporadic MTC, MEN 2A, MEN 2B and FMTC.

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Sporadic

This accounts for the majority of the MTC cases (80%). The tumor is usually unifocal, with the peak onset between the fourth and sixth decades of life, being slightly more common in females than males. (29) Patients typically present with a palpable thyroid nodule or neck mass. In general there are no pathognomonic features on ultrasound, although frequently the lesions are solid, hypoechoic and contain coarse calcifications. Other features include cervical lymphadenopathy (can be detected in more than 50% of patients) and less common systemic symptoms like diarrhea and flushing, secondary to increased secretion of calcitonin, prostaglandins, serotonin or vasoactive intestinal peptide (VIP). Very rarely tumors may also secrete ACTH causing Cushing's syndrome.

Basal calcitonin (Ct) is elevated in almost all patients with medullary thyroid cancer. Carcinoembryonic antigen (CEA) is another useful tumor marker. Thyroid function is commonly normal. Fine needle aspiration (FNA) should always be performed but not infrequently cytology results are suspicious but inconclusive. When cytology is inconclusive but MTC is suspected, immunostains for Ct or Ct measurement in the washout fluid can be diagnostic. (30)

MEN 2A (Multiple Endocrine Neoplasia 2A) – Sipple Syndrome

This clinical syndrome includes medullary thyroid carcinoma, pheochromocytoma and primary hyperparathyroidism. (31) The genetic basis and mutations have already been mentioned. The syndrome is inherited in an autosomal dominant form with males and females equally affected. The risk of developing MTC is virtually 100% and is most often multifocal and bilateral, located in the upper third of the thyroid gland. There is also a 50% risk for pheochromocytoma and up to 30% risk for hyperparathyroidism. Almost all pheochromocytomas are benign, found in the

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adrenal gland, and are bilateral in up to 50% of the cases. Hyperparathyroidism usually will occur after the third decade of life. Other common associations of MEN 2A include Hirschsprung disease and cutaneous lichen amyloidosis. The peak incidence of MTC is in the 30s or early adulthood; prevalence is 25% at age of 13 and 70% at age of 70. (32)

MEN 2B (Multiple Endocrine Neoplasia 2B)

This clinical spectrum is very similar to patients with MEN 2A but MTC tumors usually have an early onset, are more aggressive, and may even be present at birth. Other common features include mucosal neuromas, ganglioneuromatosis of the gastrointestinal tract and Marfanoid body habitus. Hyperparathyroidism is almost never observed in this syndrome. The mucosal neuromas occur on the distal portion of the tongue, lips and throughout the intestinal tract. (33)

FMTC (familial medullary thyroid carcinoma)

These patients have exclusively MTC. To prove that a family member has FMTC it is imperative to demonstrate the absence of pheochromocytoma and hyperparathyroidism in two or more generations. Clinical presentation of MTC occurs at a later age and has a more favorable prognosis compared to other MTC types. Some consider FMTC a variant of MEN 2A. (34)

METHODS

In patients with thyroid nodules the initial evaluation begins with fine needle aspiration (FNA) and cytologic evaluation. If the clinical history or FNA is suspicious for MTC a calcitonin washout can also be performed. (30) Calcitonin screening in patients with thyroid nodules remains controversial and even though recommended in Europe, it is not part of standard of care in the United States, due to the rarity of MTC, unless there is a strong suspicious for MTC. (35,

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36). If pentagastrin stimulation testing was available in the United States and appropriate calcitonin cut-off points existed, routine evaluation would be more cost-effective. (36-38) Once the diagnosis of MTC is established, additional evaluation should include serum calcitonin, CEA, neck ultrasound, genetic counseling for RET proto-oncogene testing and biochemical investigation for other possible coexisting tumors, like pheochromocytoma and hyperparathyroidism. Plasma free metanephrines and normetanephrines or 24-hour urine for catecholamines, metanephrines and normetanephrines are the screening tests recommended the latter with lower false-positive rates. (39, 40) Calcitonin and CEA levels should be measured preoperatively, and are useful in the postoperative care as they can be used as evidence of biochemical cure or as prognostic factors. (41)

In patients presenting with calcitonin levels above 400 pg/mL the likelihood of distant metastasis is high and additional imaging including chest computed tomography (CT) or magnetic resource imaging (MRI), neck CT or MRI and liver protocol imaging should be performed (figure 1). (39)

Screening

Genetic screening for RET proto-oncogene mutations plays a role in the management of medullary thyroid cancer, not only facilitating the diagnosis but also the prognosis and in some cases the course of the disease. Depending on the location of the mutation the patient will be classified in different risk categories with different treatment options made available. (42) All patients diagnosed with medullary thyroid cancer or C-cell hyperplasia should undergo genetic testing, as even apparently sporadic MTC patients may have RET proto-oncogene mutations (4-10%). When a mutation exists, all first-degree relatives should ideally be screened for the same mutation. Patients with a family history of MEN 2 or FMTC should also be offered RET testing.

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In MEN 2B patients this should be performed right after birth, with MEN 2A and FMTC usually before age 5. (39)

Testing of exon 10 should be considered in patients with Hirschsprung disease. (39) MEN 2-specific exons of RET are the first to be tested. If initial testing is negative, the entire coding region of RET should be performed. In all patients with MEN 2B syndrome analysis to detect M918 in exon 16 and A993F in exon 15 mutations should be performed; if initial testing is negative for these mutations, the entire coding region of RET sequencing should be performed as well. (39)

In a family member who meets the criteria for MEN 2A, MEN 2B or FMTC, and the genetic testing of the entire regions turns out to be negative, all at-risk relatives should be periodically screened for MTC, including serial ultrasounds, calcitonin, evaluation for hyperparathyroidism and pheochromocytoma. Screening should be performed at 1 to 3 years intervals until age 50 years or 20 years beyond the oldest age of initial diagnosis in the family. (39)

Treatment

Prophylactic thyroidectomy in carriers (preventive treatment)

As the penetrance of familial MTC is almost 100%, all carriers of a RET mutation should be evaluated and treated surgically for MTC. The goal is to identify pre-symptomatic carriers with the mutation who will benefit from early thyroidectomy as this can prevent progression to clinically relevant disease.

The aggressiveness of MTC varies according to the mutations found; MEN 2B phenotype with mutations of codons 883, 918 and 922 can develop metastases even before the first year of life. Other mutations of codons 611, 618, 620, 634 and 891 require surgery by age 5 years.

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During the seventh international workshop on MEN a classification system was created depending of the RET mutation and patients were divided into different risk stratifications leading to different recommendations for the timing of prophylactic thyroidectomy. (15, 39) Recent ATA Guidelines classify risk as high (D), medium (B or C), and low (A). (39) Infants in the highest category risk (ATA-D) with MEN 2B mutations should undergo prophylactic total thyroidectomy in the first year of life; children with ATA-C mutations of codon 634 should undergo surgery before they are 5 years old. In the other two categories (ATA-A and ATA-B) prophylactic total thyroidectomy may be delayed beyond age 5 with annual surveillance including neck ultrasound, basal and stimulated calcitonin are performed (table 2). If these tests and imaging are abnormal surgery should be performed. (39)

Surgical Management

Total thyroidectomy and central neck dissection is the procedure of choice and it is recommended for all patients with MTC or those at risk of developing MTC, since the majority of familial syndromes and up to 30% of sporadic cases present with bilateral disease. (39) It is common for patients with MTC to present with metastatic disease to ipsilateral and contralateral cervical lymph nodes (80% and 40%, respectively) and less commonly with distant metastasis to the liver, lungs and bones. (43) From the surgical standpoint, usually these patients are divided in three categories: localized disease, metastatic disease limited to the neck and distant metastatic disease. In the latter group surgical cure is not possible. (44)

MTC patients without any clinical or imaging evidence of lymph node metastasis should undergo prophylactic central compartment (level VI) neck dissection. This category includes about 40% of patients with MTC. Patients with suspected lymph node metastasis limited to the central compartment and normal ultrasound of the lateral neck compartments should also

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undergo a level VI compartment dissection. Some favor the addition of an ipsilateral prophylactic lateral neck dissection. Patients with documented central and lateral neck metastases should undergo central and lateral neck compartmental dissection (levels IIA, III, IV and V). (39, 45) If the patient has more advanced disease (distant metastases), less aggressive neck surgery may be performed, mainly to preserve speech, swallowing and parathyroid function while maintaining locoregional disease control thus limiting central neck morbidity. Palliative surgery may be required in patients with extensive distant metastases primarily to relieve pain. (39)

The most common surgical complications include recurrent laryngeal nerve damage and hypoparathyroidism. Parathyroidectomy should be performed at the time of inial thyroidectomy if patient has established diagnosis of primary hyperparathyroidism (PHPT). PHPT in the hereditary syndromes is usually associated with parathyroid hyperplasia and surgery is directed at resection of the visibly enlarged glands. (39) All patients prior to surgery should also have a catecholamine secretion evaluation.

Long-Term Monitoring and Surveillance

Thyroxine therapy (T4) is given to maintain serum thyrotropin (TSH) level in the normal range. The appropriate starting dose is 1.6 mcg/kg of body weight. In contrast to well-differentiated thyroid cancer, suppressive TSH therapy form MTC is not recommended. Measurement of calcitonin (Ct) and CEA is an important part of follow up of patients with MTC as this reflects presence of persistent or recurrent disease. They are initially checked 2-3 months after surgery; patients with an undetectable basal Ct and normal CEA are considered biochemically cured and their recurrence rate is low, usually less than 3% on long-term follow-

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up. In these patients tests are repeated every 6 months for 2-3 years and annually thereafter (Figure 1). (39) Neck ultrasound is the imaging modality of choice in follow up of MTC patients.

Persistent or Recurrent Disease

Persistent Hypercalcitoninemia

Cure is not achieved if postop Ct levels are detectable. A neck ultrasound should be performed if levels are below 150 pg/ml; usually at these Ct levels distant metastases are very rare. Any suspicious lymph node(s) should be biopsied, and both cytology plus Ct measurement in the washout fluid should be studied. Additional imaging can be considered but these are usually negative. (39)

When calcitonin levels are above 150 pg/mL, patients should also undergo additional imaging techniques to evaluate for distant metastasis, including chest CT, neck CT, 3-phase contrast-enhanced liver CT or MRI, FDG-PET and bone scan. Surgical resection of locoregional recurrent or persistent MTC in patients without or with minimal distant metastases should include compartmental dissection of image or biopsy positive disease in the central and lateral neck compartments. (39) Figure 1 provides a schematic algorithm for follow up of these patients.

Surgery

When there is no anatomic evidence of disease despite detectable calcitonin, observation is warranted. Ct and CEA doubling time (DT) measures should be used to predict outcome and to help long-term follow-up.

When metastatic neck lymph nodes are small (< 1 cm) and without evidence of distant metastases, either observation or re-operative compartmental dissection is appropriate. When locoregional lymph nodes are <1 cm and the patient is asymptomatic with distant metastasis, observation rather than intervention is usually preferred. (39)

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In cases of symptomatic and/or progressive locoregional disease with lesions > 1 cm, surgery should be considered. Those with distant metastases may be candidates for clinical trials and palliative therapies, including chemotherapy, radiation, percutaneous interventions or hepatic chemoembolization. (39)

Radiation

The benefit of EBRT (external beam radiation therapy) in MTC remains controversial. Overall, external beam radiotherapy may be effective in preventing complications, relieving pain as well as improving locoregional control in patients at high risk of cervical relapse but there is no evidence that this therapy improves survival. (46-49) An analysis conducted by SEER (Surveillance Epidemiology and Results Program of the National Cancer Institute) showed no overall survival benefit when EBRT (external bean radiation therapy) was used except when increasing age and tumor size were considered. (50)

The American Thyroid Association recommends EBRT in patients with gross residual disease who underwent incomplete resection or have microscopic positive margins. Isolated brain metastases should be considered for surgical resection and EBRT may be indicated for the ones not amenable to surgery. (39) EBRT does not reduce calcitonin levels and has significant side effects on tissues, like radiation-induced scarring and fibrosis, making any additional surgical intervention more challenging. (51) In addition to that, radioactive iodine ablation has no benefit in MTC or its lymph nodes metastases. Overall, EBRT should be reserved for local control in high risk patients for neck recurrence that otherwise would require extensive surgery; however, survival however is not improved. (52, 53)

Targeted Therapies

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There is no curative therapy for patients with advanced medullary thyroid carcinoma. Patients with progressive, symptomatic disease who failed or cannot be treated by conventional therapy (surgery or radiation) may be candidates for systemic therapy. Ideally, patients with advanced MTC should participate in clinical trials with targeted therapies. (39) Targeted molecular therapies that inhibit RET and other tyrosine kinase receptors (TKI) have shown promise in the treatment of metastatic or locally advanced MTC. (11, 54) Tyrosine kinases are known to stimulate tumor proliferation and angiogenesis. Drugs that inhibit the tyrosine kinase function are novel molecular targets for treatment, such as vandetanib, sorafenib, sunitinib, pazopanib, cabozantinib and motesanib.

In 2011 vandetanib was the first agent approved by the FDA for treatment of adults with symptomatic and progressive MTC. Phase II studies showed partial response and some patients experienced stable disease for up to 24 weeks. (55, 56) A recent phase III study showed significant prolongation of progression-free survival. Some of the adverse events include diarrhea, rash, nausea, hypertension and headaches. (57)

Sorafenib, another oral TKI agent, was evaluated in two phase II studies and partial response was seen. (58, 59) Cabozantinib and Motesanib currently are in phase I (60) and phase II (61) studies, respectively; the first achieved partial response and the latter showed only 2% partial response. Cabozantinib was recently approved by the FDA for the treatment of patients with progressive metastatic medullary thyroid cancer as well.

Overall the results involving targeted therapies for MTC are encouraging but further investigation and trials are needed to evaluate their role in MTC treatment. Complete remission is very rare but TKIs can improve or stabilize metastatic disease, even though survival may not be affected.

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Other therapies include immunotherapy with antibody-based treatments targeting CEA in selected patients but results are very limited. (62) Traditional cytotoxic agents like dacarbazine, vincristine, 5-fluorouracil, cyclophosphamide, streptozocin and doxorubicin also provide limited benefit thus TKIs are now preferred. Chemoembolization with doxorubicin for hepatic metastases may also be attempted.

According to the ATA, in patients with asymptomatic metastatic tumors less than 2 cm with slow growth (less than 20% in diameter per year) observation is recommended. Imaging should be repeated every 6 to 12 months. Patients with progressive disease (tumors more than 2cm and growth of more than 20% in diameter per year) or with symptomatic disease not amenable to surgery or radiation, the preference is for systemic treatment as part of a clinical trial. If the patient cannot be enrolled in a clinical trial, an approved TKI is suggested. (39)

Prognosis

Overall the 10 year survival in patients with MTC can vary significantly depending on the study and tumor specifics (43-88%). (10, 29, 63-68) Some of the most important independent prognostic factors include age at onset, stage at diagnosis and completeness of the initial surgical resection. Mortality rates also increase as follows: familial MTC, MEN 2A, sporadic MTC and MEN 2B. Germline RET mutation codon 918 patients are more prone for invasive disease and have worse prognosis. Early treatment including total thyroidectomy and central neck lymph node clearance have nearly 100% cure rate. Even patients with postoperative hypercalcitoninemia but without clinical or radiologic evidence of residual tumor after curative surgery may have long term survival. (29) The calcitonin and CEA doubling times of less than two years are negative prognostic factors for MTC recurrence-free and overall survival in patients with persistent or recurrent disease. (69)

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CONCLUSIONS

Medullary thyroid cancer and familial syndromes are rare but morbidity and mortality remain high if untreated. Early diagnosis and treatment are paramount in the management of medullary thyroid cancer. Genetic testing introduction in the management of MTC has improved diagnosis and also prognosis and should be offered to all patients. Treatment of choice remains total thyroidectomy and central lymph node dissection. Calcitonin and CEA are excellent tumor markers and are as well important prognostic factors. Palliative treatment for advanced disease includes surgery, radiation, standard chemotherapy and chemoembolization. More recently new treatment modalities including targeted therapies (mainly tyrosine kinase inhibitors) are available. Preliminary results are encouraging; but further clinical trials are needed.

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Phenotype	Clinical Presentation	Exons	Codons	ATA risk
Sporadic MTC	MTC	13	768	A
		16	918	D
MEN 2A	MTC	5	321	A
	Pheochromocytoma	8	515, 533	A
	Hyperparathyroidism	10	609, 611, 618, 620	B
		11	630, 634, 649, 666	630 (ATA A) 634 (ATA B, C), 649, 666 (ATA A)
		13	768, 777, 790, 791	A
		14	804	ATA A, B and D
		15	866, 891	A
		16	912	A
MEN 2B	MTC	15	883	D
	Pheochromocytoma	16	918	D
	Hyperparathyroidism	10	609, 611, 618, 620	B
	Ganglioneuromatosis			
	Marfanoid Habitus			
FMTC	MTC	11	630, 631, 634, 649, 666	630, 631 (ATA B) 634 (ATA B, C), 649, 666

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			(ATA A)
	13	768	A
	14	804, 819, 833, 844	804 (ATA A, B and D), 819, 833, 844 (ATA A)
	15	866, 891	A

Table 1: Most common Genetic Mutations, Clinical Presentation and ATA risk

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ATA risk level	Age of RET testing	Age of required first US	Age of required first serum Ct	Age of prophylactic surgery
D	ASAP and within the 1st year of life	ASA and within the 1st year of life	6 months, if surgery not already done	ASAP and within the 1st year of life
C	< 3-5 years	> 3-5 years	> 3-5 years	Before age 5 years
B	< 3-5 years	> 3-5 years	> 3-5 years	Consider surgery before age 5. May delay surgery beyond age 5 years if stringent criteria are met
A	< 3-5 years	> 3-5 years	> 3-5 years	May delay surgery beyond age 5 years if stringent criteria are met

Table 2: American Thyroid Association Risk Level and Prophylactic Thyroidectomy testing and therapy

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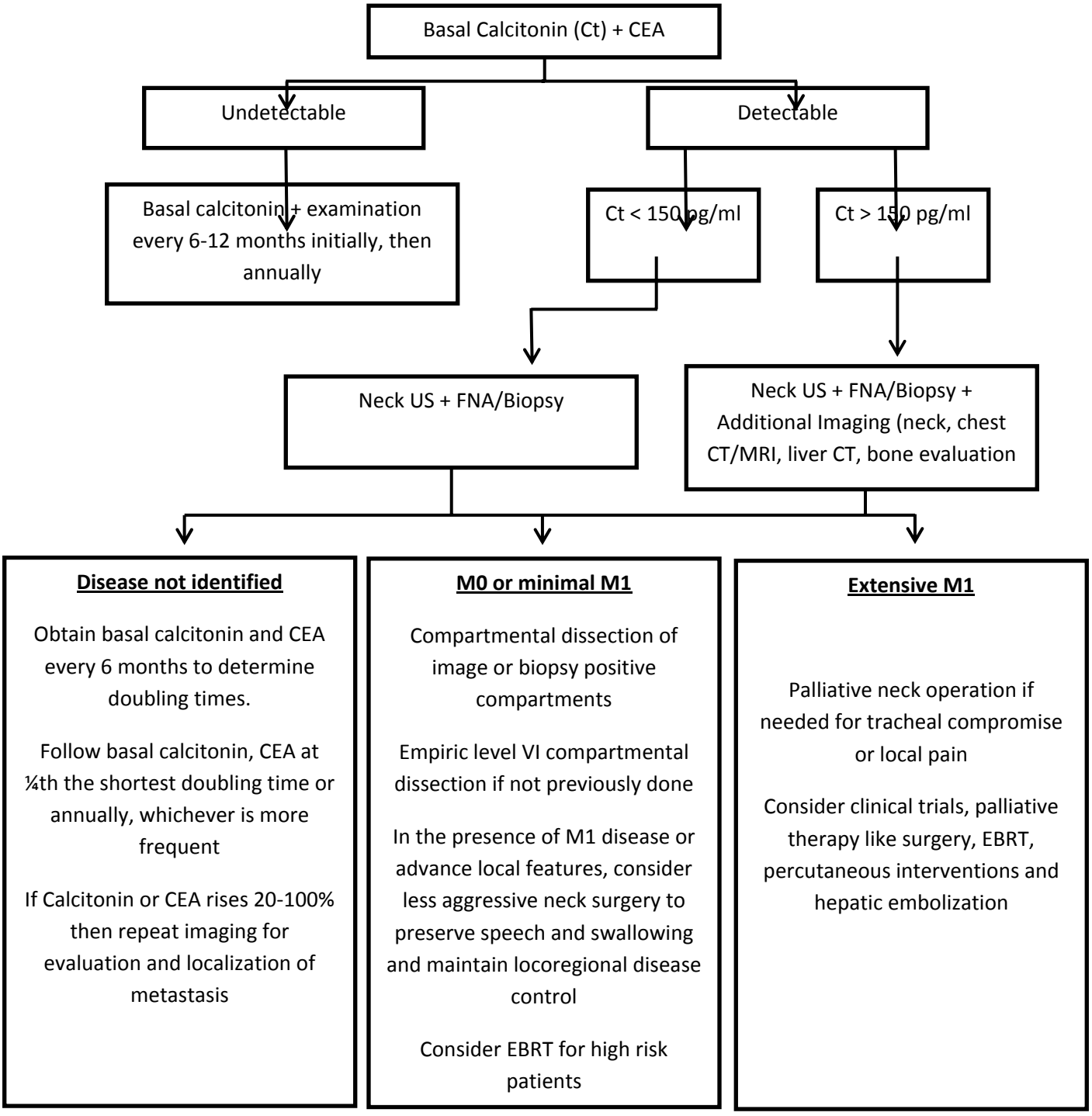

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Figure 1. Initial evaluation and treatment of post-operative patients and long-term surveillance. Adapted from the american Thryoid Association's medullary thyroid cancer guidelines. (39)

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