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*Because of the multifocal nature
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Medullary Carcinoma of the Thyroid

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Medullary thyroid cancer (MTC) is a distinct C-cell tumor of the thyroid. We review the oncogenesis and management of both sporadic tumors and those tumors arising as part of specific inherited syndromes. The RET proto-oncogene plays a role in the development of inherited forms of MTC and has become important in the clinical management of patients and their families. The recognition of the high rate of regional nodal involvement has led to lymphadenectomy being strongly considered for patients undergoing thyroidectomy for MTC.

Introduction

Medullary carcinoma of the thyroid (MTC) represents a unique and complex surgical challenge. Although the mainstay of treatment remains total thyroidectomy and central neck dissection, recent work has suggested that in patients with palpable disease, bilateral neck dissections are important in controlling regional nodal micrometastasis. Calcitonin measurement allows for recognition of persistent and recurrent disease postoperatively. However, its elevation in patients with microscopic subclinical disease complicates postoperative treatment algorithms. Recent advances in the genet-

ic understanding of MTC have improved our ability to diagnose MTC subtypes, have promoted the development of familial screening programs, and have begun to supplant pathology in the fundamental identification of inherited MTC.

Medullary carcinoma of the thyroid represents approximately 4% of all thyroid cancers.¹ MTC arises not from thyroid follicular cells, but from parafollicular C cells. C cells and their malignant counterparts in MTC secrete calcitonin, a hormone that is important in both diagnosis and postoperative follow-up.² Hazard et al³ first described MTC in 1959. Steiner and colleagues⁴ in 1968 described the association among MTC, pheochromocytoma, and hyperparathyroidism as multiple endocrine neoplasia (MEN), type 2. Approximately 75% of medullary carcinoma occurs as a non-inherited, sporadic lesion, presenting typically in the fourth decade as a unifocal lesion without associated endocrinopathy. Inherited MTC accounts for the remaining 25% and may occur in three discrete inherited forms: MEN 2a, MEN 2b, and familial MTC (FMTC).

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Table 1. — The Spectrum of MEN Syndromes and Hereditary MTC

MEN Syndromes		Hereditary MTC	
MEN I	MEN 2a	MEN 2b	Familial MTC
Werner's syndrome	Sipple's syndrome	MTC	MTC
- Pituitary adenomas	- MTC	Pheochromocytoma 50%	
- Pancreatic islet cell tumor	- Pheochromocytoma 50%	Marfanoid habitus	
- Adrenal cortical adenomas	- Hyperparathyroidism 10-30%	Multiple mucosal intestinal ganglioneuromas 100%	
- Hyperparathyroidism			

MEN = multiple endocrine neoplasia, MTC = medullary carcinoma of the thyroid
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All inherited forms of MTC are autosomal dominant (Table 1). MEN 2a penetrance is age related and incomplete, with up to 30% of patients having no clinical expression of disease by age 70.⁵ Pheochromocytoma develops in approximately 50% of MEN 2a patients, and hyperparathyroidism develops in approximately 10% to 30%.⁴ In patients with multiple endocrinopathies in MEN 2a, MTC typically presents before pheochromocytoma and hyperparathyroidism. Variant forms of MEN 2a have been associated with cutaneous lichen amyloidosis, a pruritic skin lesion occurring on the upper back, or Hirschsprung's disease.⁶ Patients with MEN 2b have a marfanoid habitus and multiple mucosal and intestinal neuromata. Patients with MEN 2b have a marfanoid habitus and multiple mucosal and intestinal neuromata. Although such patients have a marfanoid habitus, characteristic ophthalmic and cardiac changes seen in Marfan's syndrome do not occur. MEN 2b patients have distinctive facial features, with thick lips and oral mucosal neuromas, high-arched palate, and prominent corneal nerves. Pheochromocytoma develops in approximately 50% of MEN 2b patients.

A distinct inherited non-MEN form of MTC has been described (FMTC).⁹ FMTC is inherited in an autosomal dominant pattern, and it occurs as isolated MTC without associated endocrinopathy. FMTC represents the most indolent form of MTC.

There are several reasons for preoperative diagnostic confusion between sporadic and inherited forms of MTC, with up to 30% of presumptive sporadic cases ultimately being diagnosed as familial.^{10,11} Family history may be unreliable. The patient may represent a proband of a new undiagnosed kindred or a de novo germline mutation. Because of this lack of diagnostic certainty and the multifocal nature of inherited disease, total thyroidectomy is the minimum surgical recommendation for all forms of MTC.

Calcitonin

Calcitonin is a 32 amino acid polypeptide hormone secreted by parafollicular C cells, which acts to depress serum calcium levels by inhibiting osteoclastic activity and increasing calcium renal excretion. The physiologic importance of calcitonin, however, is considered to be slight. Total thyroidectomy is not associated with increased calcium levels. Calcitonin does promote intestinal secretion of water and electrolytes. Extreme calcitonin elevations in patients with widely metastatic disease have been associated with chronic and severe diarrhea. Calcitonin elevation occurs in C-cell hyperplasia and all forms of MTC. However, patients with C-cell hyperplasia or early MTC may have normal basal calcitonin levels. Generally, basal calcitonin levels roughly correlate with tumor burden. Patients with palpable disease may have levels of greater than 1,000 pg/mL, while patients with metastatic disease may have levels greater than 100,000 pg/mL.¹² The infusion of calcium and/or pentagastrin can elevate basal calcitonin levels in patients with C-cell hyperplasia and frank MTC. Pentagastrin is believed to be the most efficient agent for provocative calcitonin stimulation. Provocative testing is considered to be positive when calcitonin levels are elevated to twice the basal level.¹⁰ Of gene carriers of inherited disease, 95% will convert to a positive calcitonin test by 35 years of age, with the average age of conversion being 13 years of age.^{6,11}

Oncogenesis

C cells, as adrenal medulla precursors, originate from the neural crest. In humans, these cells migrate not to the ultimobranchial body but to an intrathyroidal position.

In hereditary MTC, C-cell hyperplasia precedes the development of MTC and occurs multifocally through-

out the gland. Over time, these foci of premalignant C-cell clones evolve into multifocal, frankly malignant MTC. Pheochromocytoma occurring in MEN 2a and 2b is also predated by a diffuse, bilateral, multifocal proliferation termed “diffuse nodular hyperplasia” (Fig 1).¹¹

The “two-hit” mutational event theory of oncogenesis by Knudson et al¹³ has been used to explain the sequence of events leading to the development of hereditary MTC. The first event (or hit) in MEN MTC is thought to be the presence of a germline mutation in a neural crest precursor cell that is inherited as an autosomal dominant trait. As a result, the descendant neural crest tissues proliferate and become susceptible to malignant change. The second event (or hit) is believed to be a somatic mutation that occurs within the hyperplastic clone, resulting in the development of frank MTC. Recently, RET proto-oncogene germline mutations have been identified in all forms of hereditary MTC.^{14,15} It is not currently known whether the identified RET point mutations are sufficient for the development of frank MTC.

Genetic Advances

In the early 1990s, specific RET oncogene point germline mutations were identified on the centromeric region of chromosome 10 in patients with inherited MTC.^{14,16-18} Approximately 97% of patients with MEN 2a, 95% of patients with MEN 2b, and 86% of patients with FMTC have point mutations within a discrete set of RET codons (Table 2).

The RET oncogene codes for a transmembrane tyrosine kinase receptor, but it has an unclear physiologic role. RET has recently been shown to be part of a multiprotein complex that serves as a receptor for a neurotrophic molecule named GDNF (glial-derived neurotrophic factor).¹⁹ RET expression has a role in neural crest and neuroendocrine tissue development and migration and has been found in neural crest-derived tumors including neuroblastoma and pheochromocytoma.²⁰ Also, RET mutations have been found in patients with familial Hirschsprung’s disease, a disease of reduced or absent enteric ganglia.⁵

Studies suggest that RET mutations associated with inherited MTC convert RET to a dominant transforming gene with increased tyrosine kinase receptor activity.^{20,21} It is unknown whether the RET mutational changes are sufficient to produce MTC or whether they simply result in the development of C-cell hyperplasia, with secondary somatic events required for the development of frank malignancy.^{12,22,23} RET activation is associated with transforming potential in *in vitro* assays.²⁰ Somatic (ie, tumor) RET oncogene mutations have been found in codons 918, 768, and 883 in 23% to 85% of sporadic tumors, although mutations are not present in all tumor subpopulations.^{5,14,20,24}

RET Oncogene Testing

Because of autosomal dominant inheritance and age-related penetrance, offspring of patients affected with inherited MTC have a 35% chance of developing disease in their lifetime. Biochemical screening (pentagastrin-stimulated calcitonin levels) has been used

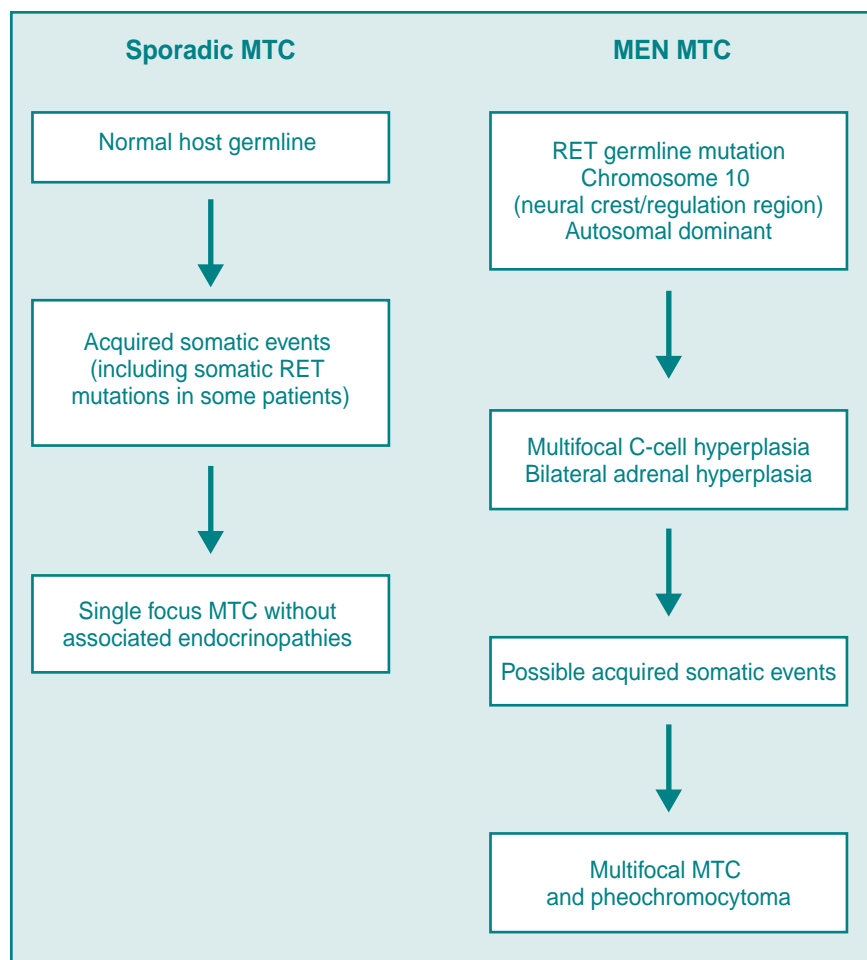


Fig 1. — Oncogenes in medullary carcinoma of the thyroid. MEN = multiple endocrine neoplasia, MTC = medullary carcinoma of the thyroid.

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Table 2. — Hereditary Medullary Carcinoma of the Thyroid

Syndrome	Cases With Known RET Mutations	Exon	Codons
MEN 2a	97%	10	609, 611, 618, 620
		11	630, 634
		13	768, 790
MEN 2b	95%	15	883
		16	918, 922
FMTC	86%	10	609, 611, 618, 620
		11	630, 634
		13	768, 790, 791
		14	804
		15	891

previously to allow diagnosis prior to clinical presentation. Such biochemical testing, which was formerly performed on all offspring of affected patients, must start in early childhood and continue every 6 to 12 months through the age of 35, by which time virtually all gene carriers will convert to a positive test. This testing is unpleasant, involving chest and abdominal pain, flushing, nausea, vomiting, and paresthesias. False-positive calcitonin testing has been estimated to occur in 1% to 10% of patients tested.^{6,12} In surgical series, the RET oncogene mutational testing has not been associated with either false-positive or false-negative results.^{25,27} Genetic testing also allows identification of disease at an earlier preclinical stage than even provocatively stimulated calcitonin levels. Approximately 80% of patients detected through biochemical screening have invasive medullary carcinoma present at surgery, with about 10% having frank metastatic disease.^{28,29} Wells et al³⁰ operated on 19 patients based on positive RET oncogene testing. Twelve of these patients had normal calcitonin testing. All patients at surgery had C-cell hyperplasia. Four had frank MTC, but none had nodal disease. All had normal postoperative provocatively stimulated calcitonin levels. RET oncogene testing has also been helpful in identifying inherited cases in approximately 1% to 5% of patients who were thought preoperatively to have sporadic disease. Therefore, RET mutation testing is recommended preoperatively for all MTC patients.^{14,31,32}

The management young children diagnosed with MEN 2a through oncogene testing in whom provocatively stimulated calcitonin levels are normal is controversial. Gagel and Cote⁶ note that waiting until the calcitonin level becomes abnormal has resulted in 90% of patients cured without evidence of postoperative calcitonin abnormality. Others have suggested a more aggressive approach with total thyroidectomy (without central neck dissection) in the second year of life for MEN 2a based solely on RET oncogene testing. Frank

MTC has been identified in a patient at 2 years of age.³³ Central neck dissection has been recommended if such patients demonstrate basal calcitonin elevations or they are 10 years of age or older.³⁴ Given the virulence of MEN 2b, most recommend thyroidectomy as early as possible — typically within the first year of life — regardless of the calcitonin level.²⁹

Once a patient's RET oncogene mutation has been identified, all family members should be tested for this mutation. Those whose testing is negative can be reassured and can forgo ongoing biochemical screening. If an MTC patient has not had a germline RET mutation identified, it is likely that sporadic disease is present. However, in 3% to 5% of patients with MEN 2a and in 15% of patients with FMTC, no RET oncogene mutations can be identified. Eng and colleagues³⁵ estimated that a patient without a known RET germline mutation has a 0.5% chance of MEN 2a and a 3% chance of FMTC. Family members of such patients can be studied with linkage analysis and need to be offered repetitive biochemical screening.³²

Pathology

Microscopically, MTC is similar in both sporadic and inherited forms with important distinguishing features, including C-cell hyperplasia and multifocal MTC in inherited forms. Microscopically, MTC classically consists of nests of eosinophilic argyrophilic polygonal cells with varying amounts of intracellular amyloid. Amyloid exhibits yellow-green birefringence under polarized light and is present in 80% of medullary tumors. Amyloid is believed to represent aggregated degenerate calcitonin gene products and is distributed unevenly.³⁶ Intracellular calcitonin secretory granules are a constant feature of MTC and are identified on immunohistochemical staining.

Clinical Presentation

Sporadic MTC presents in the fourth decade typically as a thyroid mass, emphasizing the importance of appropriate workup with fine-needle aspiration. Despite cytologic variability in MTC, fine-needle aspiration with calcitonin immunohistochemical staining is highly sensitive and specific for medullary carcinoma. Regional lymph nodes are positive in more than 50% of patients, with distant metastasis present in 10% to 20% of patients.¹¹ MTC of any type that presents as a palpable mass implies regional nodal involvement (Table 3).²

Table 3. — Medullary Thyroid Cancer Subtypes

	Mode of Transmission	Family History	Age at Presentation (decade)	Likelihood of Regional Lymph Node Involvement
Sporadic	-	Negative	4th	High
MEN 2a	Autosomal dominant	Positive or negative	3rd	High with clinical diagnosis Low with family screen diagnosis
MEN 2b	Autosomal dominant	Usually negative	1st or 2nd	High
FMTC	Autosomal dominant	Positive or negative	4th	Low

MEN = multiple endocrine neoplasia, FMTC = familial non-multiple endocrine neoplasia medullary carcinoma of the thyroid
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Compared with sporadic disease, MEN 2a presents in a younger age-group, typically in the third decade. If the diagnosis of MEN 2a is made through family screening, regional nodal involvement is less likely than if clinical presentation is through palpable mass. Although patients are at risk for development of pheochromocytoma and hyperparathyroidism, these associated endocrinopathies typically develop after MTC. In patients with MEN 2a presenting with a thyroid mass, regional nodes are positive in over 50% and distant metastasis present in approximately 20%.^{37,38} MEN 2b typically presents in childhood, usually through recognized marfanoid habitus, neuromas, or a thyroid mass. Regional nodes are positive in nearly 80%, and distant metastasis is present in up to 20% of patients. Family history is typically negative, as many patients with MEN 2b represent de novo mutations.^{11,39}

Familial MTC characteristically presents in the fourth decade and has a low incidence of regional adenopathy. FMTC represents the most indolent form of MTC and can be easily confused with sporadic disease.

Diagnostic Workup

The presence of symptoms associated with pheochromocytoma (nervousness, headache, and palpitations) and hypercalcemia, as well as symptoms of hoarseness, dysphagia, and diarrhea, should be discussed with the patient. Although some studies suggest that standard workup for patients with a solitary thyroid nodule should include calcitonin testing with up to 1.37% of patients showing elevations, most believe that because of the rarity of MTC, calcitonin represents a poor screening test.⁴⁰

Both basal and stimulated calcitonin levels should be obtained. Basal calcitonin levels are elevated in only approximately two thirds of patients who present with MTC.^{11,41} Carcinoembryonic antigen (CEA) levels should

be obtained preoperatively and have a role along with calcitonin testing in postoperative follow-up. In addition, calcium, parathyroid hormone, and 24-hour urine collection should be obtained for urinary catecholamines, vanillylmandelic acid, and metanephrines in all patients preoperatively.

Course and Prognosis

Medullary carcinoma tends to spread initially within the thyroid, metastasizing through regional lymphatics to cervical and mediastinal nodal groups and eventually hematogenously metastasizing to lung, liver, bone, and other sites.¹¹ Approximately one third of MTC recurs clinically after surgery, with up to 50% of patients having elevated calcitonin levels postoperatively.^{11,42} In patients presenting with palpable disease, 83% of inherited and 55% of sporadic cases have persistent calcitonin elevations postoperatively.⁴³ Metastatic disease may follow an indolent course over long periods of time, despite calcitonin elevations.⁴²

For all types of MTC, the 5-year survival rate is between 78% and 91%, and the 10-year survival is between 61% and 75%.^{11,39} Sporadic MTC, when corrected for stage, has a similar survival to MEN 2a. Within inherited MTC, survival is best for FMTC and worst in MEN 2b.^{36,44,45}

In general, the strongest prognostic variable is the extent of disease at presentation (see Table 1 on page 230 for MTC staging). Many other prognostic variables have been identified (Table 4). Bergholm et al³⁸ noted that regional metastasis was present in only 11% of patients who had thyroid primaries less than 1 cm and in 40% of patients with primaries greater than 3 cm. Presentation with a thyroid mass strongly correlates with regional nodal disease. Block² found that only 17% of patients who presented with palpable disease had normal calcitonin levels postoperatively. In a report by

Table 4. — Prognostic Variables of Medullary Thyroid Cancer

- Advanced stage (primary greater than 3 cm, positive nodes, distant metastasis)
- MTC subtype: MEN 2b (worst)
 - Sporadic
 - MEN 2a
 - FMTC (best)
- Age greater than 40 years
- Male gender
- Degree of preoperative calcitonin elevation
- Histologic factors: poor calcitonin immunoreactivity, absence of amyloid staining, and nondiploid DNA ploidy on pathology specimen

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van Heerden and colleagues,⁴² more than three positive lymph nodes at initial surgery increased the likelihood of recurrent disease. Saad et al¹¹ noted that stimulated calcitonin levels remained elevated in approximately 70% of patients with intrathyroidal disease and in 90% of patients with positive lymph nodes or local invasion. Wells and colleagues^{46,47} showed that preoperative calcitonin levels predicted the incidence of regionally involved nodes at surgery as well as postoperative calcitonin levels.

Treatment and Follow-up

Survival is optimized when disease is encompassed with the first surgical procedure. The predilection towards regional nodal metastasis with even small primaries, as well as the lack of suppressive or radioactive iodine postoperative options that are present with well-differentiated thyroid carcinoma, emphasizes the need for adequate initial surgical treatment.

Because of the tendency for nodal regional involvement, a prophylactic central neck dissection is required in all patients at the time of total thyroidectomy. The central neck dissection should extend from hyoid to innominate and laterally to the jugular veins and should include Delphian pre- and para-tracheal nodal groups as well as superior mediastinal nodes. The extent of the paratracheal dissection is controversial. The balance between aggressive nodal resection and parathyroid preservation should favor nodal resection. The inferior parathyroids during aggressive paratracheal dissection may not be able to be preserved. Nonetheless, a search should be made for the inferior parathyroid. Once histologically confirmed, it should be transplanted into the ipsilateral sternocleidomastoid muscle. An aggressive paratracheal dissection can occur with preservation of the superior parathyroid. Evans et al⁴⁸ recommend

mobilization of the sternohyoid muscles and resection of the sternothyroid muscles to improve the exposure of the thoracic inlet. As long as transcervical access to the upper mediastinum down to the level of the innominate is adequate, sternotomy is generally not required unless mediastinal adenopathy is identified by radiography preoperatively.⁴⁹

The inclusion of lateral neck lymphadenectomy has been shown to improve biochemical cure rate by more than 20%. In node-positive patients, systematic compartmental cervical lymphadenectomy vs selective lymphadenectomy also improved biochemical cure rate for some tumors.⁵⁰ Ellenhorn et al⁵¹ found the most frequently involved nodal regions in the neck, in order, were levels III, IV, II, VI (central), VII (mediastinal), and V.

The need for aggressive neck dissection at first surgery remains controversial.^{52,53} In their review of eight studies, Evans and coworkers⁴⁸ described a cervical lymph node recurrence rate of 45%. Recent work suggests that patients undergoing neck dissection for clinically evident nodal disease that developed after initial thyroid surgery infrequently have normal calcitonin levels postoperatively. This argues toward aggressive neck surgery at initial surgery.⁴⁹ It is also expected that surgical complications should be less when neck dissection is offered at initial surgery rather than in a reoperative setting. Extranodal soft tissue extension is more common when bulky cervical disease develops and is associated with ongoing postoperative calcitonin elevations.⁴⁹ Moley and DeBenedetti⁵² found that in patients with palpable, unilateral, intrathyroidal tumors (sporadic and familial cases), lymph node metastasis was found in 81% of central neck dissection specimens, in 81% of ipsilateral, lateral neck dissection specimens (II through V), and in 44% of contralateral neck dissection specimens (II through V). Intraoperative palpation was poor in the identification of nodal metastatic involvement (sensitivity 64%, specificity 71%). In another recent series,⁴⁹ sporadic disease (ie, unilateral thyroid disease) was associated with contralateral, lateral neck disease in 44% of patients. Contralateral neck disease occurred in up to 22% of patients even when the thyroid lesion was less than 1 cm. Thus, in patients with palpable thyroid disease with NO preoperative neck examinations, strong consideration should be made for bilateral functional neck dissections encompassing regions II through V. In patients with nonpalpable thyroid disease identified by screening, total thyroidectomy and central neck dissection should be adequate in most cases.

During thyroidectomy, all four parathyroid glands should be explored. Hyperparathyroidism associated with MEN 2a has a low recurrence when excision of grossly enlarged glands is performed.⁵⁴

A variety of chemotherapeutic agents including doxorubicin, dacarbazine, cyclophosphamide, bleomycin, cisplatin, fluorouracil, and vincristine have met with little success, with response rates between 15% and 30%.^{36,55} Limited success has also been found with radio-iodinated metaiodobenzyl guanidine (MIBG) and somatostatin analogs.^{56,57} Octreotide therapy can be considered for patients with metastatic disease or refractory diarrhea.^{56,58} Trials using ¹³¹I-labeled anti-CEA monoclonal antibodies have shown good tumor uptake and limited antitumor effect in up to 50% of patients for up to 26 months without significant toxicity.⁵⁹

External beam radiation therapy is generally considered for palliation in metastatic disease.⁶⁰ Some investigators have suggested that postoperative radiation therapy to the neck may help to control regional microscopic disease foci and may yield better survival rates.⁶¹ Brierley et al⁶² have recently shown that high-risk patients, defined as those with microscopic residual disease, nodal involvement, or extraglandular invasion, had local regional recurrence of only 14% with external beam radiation therapy postoperatively vs 48% without radiation therapy.

Calcitonin levels should be checked approximately 2 months postoperatively. Normal basal and stimulated calcitonin levels are excellent indications that resection has been curative.³⁷ Calcitonin and CEA levels should be followed postoperatively to help identify patients who are at risk for recurrence or metastasis.^{11,60} In patients with elevated calcitonin levels when examination of the head and neck is negative, a metastatic search is warranted. A regional search should include neck and mediastinal computed tomography (CT), magnetic resonance imaging (MRI), and sonography. A metastatic search should include lung, liver, and bone through chest CT, abdominal and liver MRI, and bone scanning. A variety of specific scans have been used, including ⁹⁹Tc-DMSA (dimercaptosuccinic acid), thallium chloride, ¹³¹I-MIBG, ¹³¹I-labeled CEA, or anticalcitonin antibodies, technetium sestamibi, and octreotide scans. All of these scans are generally poor in detecting small-volume microscopic disease.⁴⁸

Hepatic metastasis may occur early on in the course of MTC and may elude detection on MRI or CT scanning. Tung et al⁶³ have reviewed the usefulness of laparoscopic detection of MTC hepatic metastasis. Recent series suggest laparoscopic hepatic examination yield is low.⁴⁹ Selective venous catheterization is considered to be the most sensitive method for detecting hepatic metastasis.⁶⁴

In a patient with elevated calcitonin with a negative head and neck examination with a metastatic search that is negative, indolent cervical disease has

been presumed. In such a patient with elevated calcitonin and without obvious metastatic disease, the specific clinical course cannot be predicted.⁶⁵ Tisell et al⁶⁶ and later Buhr et al⁶⁷ and Moley et al⁶⁸ have recommended aggressive microsurgical neck dissection. Such surgery is typically offered bilaterally with sternotomy included only if mediastinal disease is imaged preoperatively.⁴⁸ The most recent work by Moley and colleagues⁶⁹ suggests that up to 38% of patients may have normal stimulated calcitonin levels after such neck reoperative surgery. Most studies suggest that approximately one third of patients may be cured with this technique if the remaining two thirds show either no change or decreased but still elevated calcitonin levels postoperatively. Gimm and Dralle⁷⁰ found that 28% of patients undergoing reoperative neck surgery for MTC had random lung biopsies showing pulmonary micrometastasis. A report by van Heerden et al⁴² noted good, long-term survival in patients without evidence of regional or metastatic disease despite elevated calcitonin levels, with an 86% 15-year survival. Patients who at first surgery had disease extending beyond the thyroid capsule or lymph node capsule typically failed cervical aggressive reoperative attempts.^{66,67} In patients without obvious metastatic disease with postoperative elevated calcitonin who initially presented with intrathyroidal disease, aggressive neck reoperation should be considered.

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