

The North American Neuroendocrine Tumor Society Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors

Pheochromocytoma, Paraganglioma, and Medullary Thyroid Cancer

Herbert Chen, MD,* Rebecca S. Sippel, MD,* M. Sue O'Dorisio, MD, PhD,† Aaron I. Vinik, MD, PhD,‡
Ricardo V. Lloyd, MD, PhD,§ and Karel Pacak, MD, PhD, DSc||

Abstract: Pheochromocytomas, intra-adrenal paraganglioma, and extra-adrenal sympathetic and parasympathetic paragangliomas are neuroendocrine tumors derived from adrenal chromaffin cells or similar cells in extra-adrenal sympathetic and parasympathetic paraganglia, respectively. Serious morbidity and mortality rates associated with these tumors are related to the potent effects of catecholamines on various organs, especially those of the cardiovascular system. Before any surgical procedure is done, preoperative blockade is necessary to protect the patient against significant release of catecholamines due to anesthesia and surgical manipulation of the tumor. Treatment options vary with the extent of the disease, with laparoscopic surgery being the preferred treatment for removal of primary tumors. Medullary thyroid cancer (MTC) is a malignancy of the thyroid C cells or parafollicular cells. Thyroid C cells elaborate a number of peptides and hormones, such as calcitonin, carcinoembryonic antigen, and chromogranin A. Some or all of these markers are elevated in patients with MTC and can be used to confirm the diagnosis as well as to follow patients longitudinally for recurrence. Medullary thyroid cancer consists of a spectrum of diseases that ranges from extremely indolent tumors that are stable for many years to aggressive types associated with a high mortality rate. Genetic testing for *RET* mutations has allowed identification of familial cases and prophylactic thyroidectomy for cure. The only curative treatment is complete surgical resection.

Key Words: neuroendocrine tumors, pheochromocytoma, paraganglioma, medullary thyroid cancer

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PHEOCHROMOCYTOMA AND PARAGANGLIOMA

In 2004, the World Health Organization defined a pheochromocytoma as an intra-adrenal paraganglioma, whereas closely related tumors of extra-adrenal sympathetic or parasympathetic paraganglia are classified as extra-adrenal paragangliomas. In general, approximately 80% of pheochromocytomas are located in the adrenal medulla.¹ Extra-adrenal sympathetic paragan-

gliomas in the abdomen most commonly arise from chromaffin tissue around the inferior mesenteric artery (the organ of Zuckerkandl) and aortic bifurcation, less commonly from any other chromaffin tissue in the abdomen, pelvis, and thorax.² Extra-adrenal parasympathetic paragangliomas are most commonly found in the neck and head.

Pheochromocytomas and sympathetic extra-adrenal paragangliomas almost all produce, store, metabolize, and secrete catecholamines or their metabolites. Recent studies have found that approximately 20% of head and neck paragangliomas also produce significant amounts of catecholamines.³

Main signs and symptoms of catecholamine excess include hypertension, palpitations, headache, sweating, and pallor. Less common signs and symptoms are fatigue, nausea, weight loss, constipation, flushing, and fever. According to the degree of catecholamine excess, patients may present with myocardial infarction, arrhythmia, stroke, or other vascular manifestations (eg, any organ ischemia). Similar signs and symptoms are produced by numerous other clinical conditions, and therefore, pheochromocytoma is often referred to as the “great mimic.”

Epidemiology

Pheochromocytomas and paragangliomas are rare and occur in approximately 0.05% to 0.1% of patients with sustained hypertension. However, this probably accounts for only 50% of people harboring pheochromocytoma or paraganglioma because approximately half of patients with pheochromocytoma or paraganglioma have paroxysmal hypertension or normotension. The prevalence of pheochromocytoma and paraganglioma can be estimated to lie between 1:6500 and 1:2500, with the annual incidence in the United States of 500 to 1600 cases per year.

Pathology and Molecular Genetics

All pheochromocytomas and paragangliomas display similar basic histopathologic characteristics, although some differences between familial tumors have been described. According to the 2004 World Health Organization criteria,⁴ malignancy is defined by the presence of metastases, not local invasion (although a significant invasion is considered by some pathologists as the sign of malignancy). There is currently no consensus on the adoption of a formal scoring system for these tumors.

Improvements in genetics, diagnosis, and treatment of pheochromocytomas have changed the approaches to these tumors in recent years. The formerly used rule of 10% for pheochromocytoma (10% malignant, 10% bilateral, and 10% extra-adrenal) has been increasingly challenged.⁵ At present, it is estimated that at least 24% to 27% of pheochromocytomas or paragangliomas are associated with known genetic mutations; in children, this prevalence may be as high as 40%.^{6–11}

Pheochromocytomas may occur sporadically or as part of hereditary syndrome. According to the latest studies, among

From the *Department of Surgery, University of Wisconsin, Madison, WI; †Department of Pediatrics, University of Iowa, Iowa City, IA; ‡Eastern Virginia Medical School, Strelitz Diabetes Research Center, Norfolk, VA; §Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI; and ||Section on Medical Neuroendocrinology, Reproductive and Adult Endocrinology Branch, National Institute of Child Health and Human Development, National Institute of Health Bethesda, MD. Reprints: Herbert Chen, MD, Department of Surgery, University of Wisconsin, H4/722 CSC, 600 Highland Ave, Madison, WI 53792-7375 (e-mail: chen@surgery.wisc.edu); or Karel Pacak, MD, PhD, DSc, Section on Medical Neuroendocrinology Reproductive and Adult Endocrinology Branch NICHD, Bldg 10, CRC, 1-East Room 1-3140, 10 Center Dr, MSC-1109 Bethesda, MD 20892-1109 (e-mail: karel@mail.nih.gov).

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TABLE 1. Characteristics in Various Pheochromocytomas or Paragangliomas

Tumor and Clinical Characteristics	Sporadic	SDHB	MEN, VHL, NF-1
Malignancy rate	10%–36%	High (>50%) but to be determined	<5%
Most common location of primary tumor	Adrenal	Extra-adrenal	Adrenal
Biochemical phenotype	NE	NE, DA	NE EPI
Most common sites of metastatic lesions	Bones, LNs, liver, lungs	Bones, LNs, liver, lungs	Bones, LNs
Unfavorable prognostic factors	Younger age, large tumor, low NE levels	Younger age, large tumor, low NE and high DA levels	Large tumor

NE indicates norepinephrine; EPI, epinephrine; DA, dopamine; LNs, lymphatic nodes.

patients with nonsyndromic pheochromocytoma, up to approximately 24% of tumors may be hereditary.^{6,11,12} Hereditary pheochromocytoma is associated with multiple endocrine neoplasia type 2 (MEN-2A or MEN-2B), neurofibromatosis type 1 (NF-1), von Hippel-Lindau (VHL) syndrome, and familial paragangliomas and pheochromocytomas due to germ-line mutations of genes encoding succinate dehydrogenase subunits B, C, and D (SDHB, SDHC, SDHD) (Tables 1 and 2). In general, the traits are inherited in an autosomal dominant pattern.¹²

The panel at the First International Symposium on Pheochromocytoma recommended that it is neither appropriate nor currently cost-effective to test every disease-causing gene in every patient with a pheochromocytoma and paraganglioma. To choose a proper genetic test, the biochemical profile of catecholamine secretion, age of the patient, localization of the primary tumor, and previous family history must be carefully evaluated and included in the genetic algorithm. Specifically, MEN-2– and NF-1–related pheochromocytoma always secrete epinephrine; VHL-related pheochromocytomas always secrete norepinephrine; and elevation of dopamine together with norepinephrine is seen in some SDHB-related paragangliomas. In contrast to MEN-2, VHL, and NF-1 tumors that are almost always found in the adrenal gland, SDHB-related tumors are found in extra-adrenal localizations. In those patients with malignant disease secondary to an extra-adrenal paraganglioma, almost 50% had SDHB mutations.¹³ Some studies suggested that more than two thirds of patients with SDHB-related pheochromocytoma or paraganglioma will develop metastatic disease.^{14,15} Family history is often helpful in MEN-2, VHL, and NF-1 tumors, but only 10% of the currently investigated patients with SDHB mutations have a positive family history of pheochromocytoma or paraganglioma¹⁴ (Table 1).

Imaging and Biochemical Markers

Diagnosis of pheochromocytoma and paraganglioma relies on biochemical evidence of catecholamine production by the tumor. Biochemical testing should be performed in symptomatic patients, patients with an adrenal incidentaloma, and those who have a hereditary risk for developing a pheochromocytoma or paraganglioma.

Catecholamines are metabolized within chromaffin cells to metanephrines (norepinephrine to normetanephrine and epinephrine to metanephrine, respectively), and this intratumoral process occurs independently of catecholamine release. In line with these concepts, numerous independent studies have now confirmed that measurements of fractionated metanephrines (ie, normetanephrine and metanephrine measured separately) in urine or plasma provide superior diagnostic sensitivity over measurement of the parent catecholamines (Table 3).^{16–18} However, to preserve high diagnostic sensitivity, it is strongly recommended to obtain blood samples in the supine position.¹⁹

TABLE 2. Presence of Various Tumors in Common Hereditary Syndromes Associated With Pheochromocytoma or Paraganglioma

Paraganglioma syndromes (SDH)	
SDHD	Head and neck paraganglioma Pheochromocytoma Extra-adrenal paraganglioma*
SDHB	Head and neck paraganglioma Pheochromocytoma Extra-adrenal paraganglioma* Renal carcinoma
MEN-2	
Type 2A	Medullary thyroid carcinoma Pheochromocytoma Hyperparathyroidism Cutaneous lichen amyloidosis
Type 2b	Medullary thyroid carcinoma Pheochromocytoma Multiple neuromas Marfanoid habitus Familial medullary thyroid carcinoma
FMTC	
VHL syndrome type 2	
Type 2A	Retinal and central nervous system hemangioblastomas Pheochromocytoma Endolymphatic sac tumors Epididymal cystadenomas
Type 2B	Renal-cell cysts and carcinomas Retinal and central nervous system hemangioblastomas Pancreatic neoplasms and cysts Pheochromocytoma Endolymphatic sac tumors Epididymal cystadenomas
Type 2C	Pheochromocytoma
NF-1	Neurofibromas (multiple) Café au lait spots Pheochromocytoma

Adapted with permission from *Lancet*.¹

Data on children were adapted with permission from *The Journal of Clinical Endocrinology and Metabolism*¹⁶ (based on 45 children studied, 12 pheochromocytomas) and data on adult patients from *Stress*⁷⁷ and *The Journal of the American Medical Association*.¹⁶

*More frequent in SDHB (~80%). SDHC SDH5 mutations are rare and therefore not listed.

TABLE 3. Sensitivity and Specificity of Biochemical Tests for the Detection of Pheochromocytoma or Paraganglioma

Biochemical Test	Sensitivity, %		Specificity, %	
	Children	Adults	Children	Adults
Plasma normetanephrine and metanephrine	100	99	94	89
Plasma norepinephrine and epinephrine	92	84	91	81
Urinary normetanephrine and metanephrine	100	97	95	69
Urinary norepinephrine and epinephrine	100	86	83	88
Urinary vanillylmandelic acid	—	64	—	95

Therefore, current recommendations are that initial testing for pheochromocytoma or paraganglioma must include measurements of fractionated metanephrines in plasma, urine, or both, as available.²⁰ Blood sampling should be performed at a supine position after approximately 15 to 20 minutes of intravenous catheter insertion. Food, caffeinated beverages, strenuous physical activity, or smoking are not permitted at least approximately 8 to 12 hours before the testing. The elevation of plasma metanephrines of more than 4-fold above the upper reference limit is associated with close to 100% probability of the tumor.²¹ The actual level of the abnormal result should therefore be used to determine the need for immediate tumor localization studies versus additional biochemical investigations.

Should additional biochemical testing be necessary, the possibility of false-positive results due to medications, clinical conditions (as described above), or inadequate sampling conditions (eg, blood sampling while seated) should first be considered and eliminated.²¹ In patients with plasma metanephrine values above the upper reference limit and less than 4-fold above that limit, the clonidine suppression test combined with measurements of plasma catecholamines and normetanephrine may prove useful.²¹

Either computed tomography (CT) or magnetic resonance imaging (MRI) is recommended for initial tumor localization, with MRI preferred in children and pregnant or lactating women because of concerns regarding radiation exposure. Recent data suggest that adrenergic blockade in pheochromocytoma or paraganglioma patients as a specific precautionary measure before intravenous nonionic contrast-enhanced CT imaging is not necessary.²² Computed tomography and MRI have excellent sensitivity for detecting most catecholamine-producing tumors; these anatomical imaging approaches lack the specificity required to unequivocally identify a mass as a pheochromocytoma or paraganglioma.²³ The specificity of functional imaging using [¹²³I]-labeled metaiodobenzylguanidine scintigraphy ([¹²³I]-MIBG) offers an approach that overcomes the specificity limitations of anatomical imaging. Reduced sensitivity of MIBG scans in familial paraganglioma syndromes, malignant disease, and extra-adrenal paragangliomas has been described.^{24–28} Newer compounds such [¹⁸F]-fluorodopamine ([¹⁸F]-FDA), [¹⁸F]-fluorodihydroxyphenylalanine ([¹⁸F]-FDOPA), and [¹⁸F]-fluoro-2-deoxy-D-glucose ([¹⁸F]-FDG) have emerged for use in positron emission tomography (PET). The superiority of [¹⁸F]-FDA PET imaging over [¹²³I]-MIBG scintigraphy, especially in malignant tumors, has been reported.²⁹ [¹⁸F]-FDOPA PET imaging has been described to outperform [¹²³I]-MIBG scintigraphy in the detection of pheochromocytoma and head and

neck paragangliomas (unpublished observations and Hoegerle et al³⁰). However, the sensitivity of [¹⁸F]-FDOPA for metastatic paragangliomas is limited.³¹ Studies have revealed that most pheochromocytomas show uptake of [¹⁸F]-FDG in PET imaging.^{32,33} Recently, [¹⁸F]-FDG was demonstrated to be a superior tool in the evaluation of metastatic SDHB-associated adult pheochromocytoma and paraganglioma.³⁴ It is recommended that functional imaging be used on all pheochromocytomas and paragangliomas, except adrenal pheochromocytomas, that are less than 5 cm in size and associated with elevations of plasma or urine metanephrine (practically all epinephrine-producing pheochromocytomas are found in the adrenal gland or are recurrences of previously resected adrenal tumors).

Management of Local-Regional Disease

Surgery is the primary treatment of pheochromocytoma and paraganglioma, and laparoscopic surgery is now the technique of first choice for resection of adrenal and extra-adrenal tumors. Observational studies have clearly shown that laparoscopic procedure decreases postoperative morbidity, hospital stay, and expense as compared with the conventional transabdominal technique for tumor removal. Because of the high incidence of bilateral adrenal disease in hereditary pheochromocytoma, partial adrenalectomies are advocated in these patients, thereby avoiding morbidity associated with medical adrenal replacement. It remains controversial whether partial adrenalectomies should be considered in patients with a sporadic unilateral pheochromocytoma. However, open surgical approaches could still be necessary in selected patients with locally invasive or malignant disease.³⁵

Although follow-up is especially important for patients identified with mutations of disease-causing genes, there is currently no method based on pathological examination of a resected tumor to rule out potential for malignancy or recurrence. Thus, long-term periodic follow-up remains recommended for all cases of pheochromocytoma and paraganglioma. Genetic testing will increasingly be the key factor in estimating the lifelong risk for development of recurrent disease, contralateral disease, or malignant dedifferentiation and thus affect follow-up protocols.

Management of Hormonal Syndromes

Intraoperative risks must be kept to a minimum by appropriate preoperative medical treatment to block the effects of catecholamines for at least 10 to 14 days before surgery.^{36,37} Adequate preoperative α -blockade has been proven to reduce the number of perioperative complications to less than 3%.³⁸ All patients with pheochromocytoma or paraganglioma (even those with apparent normal levels of catecholamines) should receive appropriate preoperative medical management to block the effects of released catecholamines. Phenoxybenzamine (Dibenzylamine), an α -adrenoceptor blocker, is most commonly used for preoperative control of blood pressure. The drug is initially administered orally at a dose of 10 to 20 mg twice daily. Alternatives to phenoxybenzamine for preoperative blockade of catecholamine-induced vasoconstriction include calcium-channel blockers and selective competitive α_1 -adrenoceptor blocking agents, such as terazosin (Hytrin) and doxazosin (Cardura), which have shorter half-lives and lower the risk for postoperative hypotension. A β -adrenoceptor blocker may be used for preoperative control of tachyarrhythmias or angina. However, loss of β -adrenoceptor-mediated vasodilatation in a patient with unopposed catecholamine-induced vasoconstriction can result in dangerous increases in blood pressure. Therefore, β -adrenoceptor blockers should never be used without

first blocking α -adrenoceptor-mediated vasoconstriction. Volume contraction associated with chronic vasoconstriction can be seen in patients with pheochromocytoma and paraganglioma. Therefore, preoperative volume expansion achieved by saline infusion or increased water intake is recommended to reduce postoperative hypotension.³⁹

Management of Advanced Disease

Palliative surgery is usually performed to release tumor pressure on surrounding tissues or to decrease tumor mass. Decreased tumor burden can lead to a significant decrease in catecholamine secretion and organ damage as well as α - and β -blockade dosage. Reduced tumor burden can also facilitate subsequent radiotherapy or chemotherapy. However, a survival advantage of surgical debulking is not proven. In some patients with organ metastatic lesions (not if numerous or very small), radiofrequency ablation and cryoablation are current attractive options.

[¹³¹I]-MIBG is used for patients in whom [¹²³I]-MIBG scintigraphy is positive (only approximately one third of patients will respond). Biochemical or symptom response rates as high as 67% and 89%, respectively, have been published.⁴⁰ Multicenter studies are required to reach consensus on the efficacy of high-dose versus fractionated usually medium doses of [¹³¹I]-MIBG and of monotherapy versus combination with other radio-nuclides or modes of chemotherapy. In patients with rapidly growing tumors, even if [¹²³I]-MIBG scintigraphy shows positive lesions, chemotherapy is a preferable treatment option (only approximately one third of patients will respond).

Chemotherapy, with a combination of cyclophosphamide, vincristine, and dacarbazine, can provide tumor regression and symptom relief in up to 50% of patients, but the responses are usually short and in only 30% of patients.⁴¹ Chemotherapy is preferred in patients with negative [¹²³I]-MIBG scintigraphy and in those with rapidly progressing tumors.

The effect of [¹⁷⁷-Lu-DOTA]-octreotate in malignant paragangliomas or pheochromocytomas has been described only in case reports.⁴² External-beam irradiation of bone metastases or radiofrequency and cryoablation may provide additional treatment alternatives in selected cases only. External radiation therapy may represent an appropriate approach to treat some bone lesions, especially those that are rapidly growing.

Conclusions and Future Looking Statements

Future studies will have to investigate the different genotype-phenotype associations with consequent varying imaging performances and provide head-to-head comparisons of these methods in specific subsets of patients.

Clinical trials comparing high-dose [¹³¹I]-MIBG with smaller repeated doses or combinations with chemotherapeutic regimens are awaited. Treatment results, however, might vary considerably between patients with different underlying genetic mutations. This important observation of possible specific genotype-phenotype relationships is subject to further prospective and retrospective studies and will lead to more tailor-made treatment and follow-up approaches in the future.

MEDULLARY THYROID CANCER

Medullary thyroid cancer (MTC) is a malignancy of the thyroid C cells or parafollicular cells. Thyroid C cells elaborate a number of peptides and hormones, such as calcitonin, carcinoembryonic antigen (CEA), and chromogranin A. Some or all of these markers are elevated in patients with MTC and can be used to confirm the diagnosis as well as to follow up patients longitudinally for recurrence. Medullary thyroid cancer consists

of a spectrum of disease that ranges from extremely indolent tumors that are stable for many years to aggressive types associated with a high mortality rate.

Epidemiology

Most MTCs are sporadic, and these patients with MTC most commonly present in the fifth or sixth decade of their lives with a palpable cervical lymph node or a solitary thyroid nodule.⁴³ However, up to 25% of MTC cases result from a germ-line activating mutation in the rearranged during transfection (*RET*) protooncogene.⁴⁴ Hereditary MTCs occur in the setting of the MEN syndrome type 2 (2A or 2B) or as familial MTC (FMTC) without associated endocrinopathies.⁴⁵

Medullary thyroid cancer is present in virtually all of cases of MEN-2A and is typically multifocal and bilateral.⁴⁶ The age at onset varies with the specific genetic mutation, but MTC usually presents in early adulthood. Pheochromocytomas can be seen in up to 50% of cases, and they are frequently multifocal and associated with adrenal medullary hyperplasia. Pheochromocytomas can be detected by using either plasma or urine metanephrines levels. It is important to recognize and diagnose pheochromocytomas, because they should be resected before definitive surgery for MTC. Preoperative α -blockade should be used, and laparoscopic adrenalectomy is the preferred operation for pheochromocytoma (as mentioned in the previous section). Hyperparathyroidism occurs in 20% to 35% of patients with MEN-2A. Diagnosis of hyperparathyroidism is made with serum calcium and intact parathyroid hormone levels. Parathyroidectomy is usually performed at the time of thyroidectomy. Although 4-gland hyperplasia necessitating a subtotal parathyroidectomy or total parathyroidectomy with forearm implantation often occurs, some patients with MEN-2A will have a single gland disease, and intraoperative parathyroid hormone testing can help guide the extent of surgery.⁴⁷ Some variants of MEN-2A are also associated with either cutaneous lichen amyloidosis or Hirschsprung disease. Patient prognosis in MEN-2A is predominantly based on successful treatment of MTC.⁴⁸

In MEN-2B, almost 100% of patients will develop MTC.⁴⁹ Medullary thyroid cancer occurs at a very young age and has a very aggressive course. Because of this, patients with MEN-2B are rarely rendered disease-free. Pheochromocytomas occur in 50% of patients. Other associated features of MEN-2B include development of diffuse ganglioneuromas of the lips, tongues, eyelids, and gastrointestinal tract. These patients have a characteristic appearance including a marfanoid habitus, everted eyelids, and thick lips. These patients also have problems with megacolon, skeletal abnormalities, and markedly enlarged peripheral nerves. Because of the aggressive nature of MTC in these patients, many die at a young age. Therefore, most of the MEN-2B diagnoses are de novo germ-line mutations.

In FMTC, patients develop isolated MTC without other endocrinopathies. There is significant overlap in the genetic mutations that lead to either FMTC or MEN-2A. To consider a family to have FMTC and not MEN-2A, there must be no evidence of either pheochromocytoma or hyperparathyroidism in more than 10 carriers, and multiple members need to be affected after the age of 50 years. Because MTC is often the first manifestation of MEN-2A, with pheochromocytomas lagging significantly behind, distinguishing between MEN-2A and FMTC can be difficult.

Pathology and Molecular Genetics

Pathologically, MTC lesions are whitish gray in color and firm to palpation. Medullary thyroid cancer appears microscopically as nests of uniform cells that have stromal amyloid. In

sporadic MTC, the thyroid lesions are usually unifocal, but in hereditary disease, tumors are frequently multifocal and bilateral. C cell hyperplasia can be present in many patients with hereditary disease and is a precursor lesion. C cell hyperplasia is defined as more than 6 C cells per follicle or more than 50 C cells per low-power field.

Familial MTC is inherited in an autosomal dominant pattern, with variable expressivity and penetrance. The genetic mutation is found in the RET protooncogene, which in 1991 was mapped to chromosome 10q11.2.⁴⁹ The RET gene encodes a transmembrane tyrosine kinase receptor: a single point mutation is required for malignant transformation. In patients with hereditary disease, this point mutation is in the germ line. In sporadic MTC cases, somatic mutations of RET have been discovered in 25% to 45% of cases. The most common germ-line mutation in MEN-2A is in codon 634 (80% of patients). The most frequently associated germ-line mutation with MEN-2B is in codon 918. Most patients with hereditary disease are now identified through genetic testing of at-risk family members. Family members of patients with a germ-line mutation of the RET gene have a 50% chance of inheriting the mutation. In patients harboring a RET mutation, their lifetime risk of malignancy approaches 100%. Even in those with perceived sporadic MTC, there is a 6% to 10% chance of an occult germ-line RET mutation. Therefore, most recommend that all patients with a diagnosis of MTC undergo RET mutation genetic analysis.

The aggressiveness of MTC in hereditary disease is dependent on the specific RET mutation.^{48,50} Currently, RET mutations are classified into 3 groups based on aggressiveness of MTC or level of risk, as shown in Table 4.⁵¹ Level 3 mutations (RET codons 883, 918, and 922) are the most aggressive. These patients can have metastasis in the first years of life.⁴⁶ Because of the high risk of malignant progression at a very young age, thyroidectomy is recommended within the first 6 months and preferably within the first month of life. Level 2 mutations (RET codons 611, 618, 620, and 634 mutations) are considered high risk for aggressive MTC. Patients with level 2 RET mutations should undergo thyroidectomy before age 5 years. Level 1 mutations (RET codons 609, 768s, 790, 791, 804, and 891) are the lowest risk for aggressive MTC of all the RET mutations. In

patients with level 1 RET mutations, MTC usually develops later in life and is more indolent. Because MTC in these patients is rarely reported before 10 years of age, many recommend waiting until that time to perform the thyroidectomy. However, because thyroidectomy can be cured if performed early and there remain variability and unpredictability in some families, many suggest treating all patients with MEN-2A the same and perform their prophylactic operation by age 5 years whenever possible.

Imaging and Biochemical Markers

The ability to genetically diagnose hereditary MTC with RET testing has virtually eliminated the need for biochemical and radiological tests to determine which family members are at risk to develop MTC. Thus, genetic testing offers potential surgical intervention before the development of MTC. However, physicians still rely on biochemical and radiology tests to diagnose sporadic MTC, and to follow up patients with both hereditary and sporadic MTC for recurrent disease. C cells elaborate a number of peptides and hormones. Calcitonin is the most common, whereas other substances secreted by the C cells include CEA, corticotrophin, somatostatin, vasoactive intestinal peptide, and serotonin. Calcitonin has proven to be the most useful biochemical marker, because levels correlate with tumor burden.⁵² An elevated or rising calcitonin level is often the first sign of recurrent or persistent disease. Calcitonin doubling time has been shown to be accurate for determining prognosis.⁵³ Calcitonin levels may be slightly elevated in a small percentage of normal patients, but most patients with an elevation of greater than 100 pg/mL (reference, <10 pg/mL) have a diagnosis of MTC. The degree of calcitonin elevation correlates well with tumor volume. Lymph node metastases are seen at calcitonin levels of 10 to 40 pg/mL. Distant metastases are seen with calcitonin levels of greater than 150 pg/mL and frequently greater than 1000 pg/mL. Carcinoembryonic antigen is also used as a marker of disease and may be preferentially expressed in less differentiated tumors. A preoperative serum CEA level of greater than 30 ng/mL often suggests disease that has progressed outside the thyroid. Carcinoembryonic antigen levels of greater than 100 are highly associated with extensive lymph node involvement and distant metastasis. An increasing CEA level in the presence of a stable calcitonin is usually a sign of dedifferentiation of MTC and is associated with a worse prognosis. Chromogranin A is also elevated in patients with MTC and can be used to follow tumor progression.

Imaging studies are critical in the management of patients with sporadic MTC. Most patients with sporadic MTC will present with a thyroid mass. A neck ultrasound can be used to characterize the mass as well as to look for additional thyroid lesion as well as the presence of suspicious lymph nodes. Fine-needle aspiration can then be performed under ultrasound guidance of any thyroid mass or enlarged lymph nodes. Medullary thyroid cancer is characterized by the presence of small cells with minimal cytoplasm and abundance of stromal amyloid on cytology. To confirm the diagnosis of MTC, fine-needle-aspiration slides can undergo immunostaining for calcitonin, chromogranin A, or CEA. Once the diagnosis of MTC is made, CT scans of the chest, mediastinum, and abdomen are usually performed as part of the metastatic workup. Distant metastases are present in 10% to 15% of patients at the time of diagnosis, with the most common locations being the mediastinum, liver, lungs, and bone. Metastatic lesions may be large and calcified and readily apparent on imaging, but can also display a military pattern of small micrometastases that are not seen on imaging. These small liver metastases are best visualized by laparoscopy.^{54,55}

TABLE 4. RET Mutations Associated With Hereditary MTC

Risk Level for MTC	Most Common Codon Mutations	Age at Prophylactic Surgery
Level 3 (highest)	883	Within first 6 mo of life (preferably in the first month)
	918	
	922	
Level 2 (higher)	611	By age 5 y
	618	
	620	
	634	
Level 1 (high)	609	By age 5–10 y
	630	
	768	
	790	
	791	
	804	
	891	

Management of Local-Regional Disease

Prophylactic Surgery

Prophylactic surgery removes the at-risk organ before it develops a clinically significant disease. When determining the timing of prophylactic surgery, it is important to balance the risk of clinically significant disease with the risks of operative intervention. In hereditary MTC, there is a clear age-related progression from C cell hyperplasia to MTC and ultimately to nodal spread. However, the optimal timing of prophylactic thyroidectomy is not clear. Hopefully, as we gain a better understanding of the phenotype-genotype relationships among the RET mutations, we will be better able to predict when disease is likely to develop and therefore plan operative intervention before that time.

The RET mutations associated with hereditary MTC are listed in Table 4 with guidelines as to when to perform a prophylactic thyroidectomy for each mutation.⁵¹ In general, it is reasonable to intervene in children with MEN-2A and FMTC by age 5 years, whereas patients with MEN-2B should be operated on during infancy whenever feasible. In a recent study looking at long-term follow-up of patients who have undergone prophylactic thyroidectomy, no patient with MEN-2A who was operated on at younger than 7 years has had evidence of recurrent disease, with more than 5 years of follow-up.⁵⁶ If a family does not want to proceed with prophylactic surgery in a young child, then it is reasonable to follow up the patient closely with stimulated plasma calcitonin levels and then proceed with operation when there is an increase in the stimulated calcitonin levels.

The extent of surgery that is necessary in the prophylactic setting has been debated. Everyone agrees that at a minimum all patients should undergo a total thyroidectomy. The debate involves whether a central neck lymphadenectomy should be performed. Advocates of routine central neck dissection argue that even in screened patients clinically occult disease with nodal metastasis can be present in 6% of patients. They argue that the best opportunity to cure a patient is at his/her initial operation. With the use of routine autotransplantation of the parathyroid glands, the long-term complications of a central neck dissection can be minimized. Opponents of routine central neck dissection argue that although nodal disease has been seen in the occult setting, it is very rare in children younger than 10 years. They suggest that a more selective approach can be performed using preoperative ultrasound and tumor markers to further risk stratify patients. With a normal preoperative ultrasound and serum calcitonin (basal and/or stimulated) and CEA level, the risk of occult nodal disease is very low, and the potential benefits of a prophylactic neck dissection are outweighed by the risks of permanent hypoparathyroidism. In a recent series from Washington University where they have performed 85 prophylactic total thyroidectomies with bilateral central neck dissections (with routine parathyroidectomy with autotransplantation), they found 2 patients (2.4%) with nodal disease and 3 patients with permanent hypoparathyroidism (3.5%).⁵⁶ Although the incidence of nodal disease is low, those patients who have nodal disease at the time of their prophylactic dissection often end up having persistently elevated calcitonin levels and are not cured of their disease. To minimize the risks of this prophylactic operation, it is essential that these procedures be performed only by experienced surgeons.

Because the first prophylactic thyroidectomies were performed in the early 1990s, the risk of recurrence after a prophylactic thyroidectomy is still unknown. Preliminary results suggest that the risk of recurrence is very low, especially when surgery is performed before age 10 years.⁵⁶ However, because

the long-term outcomes are not known, it is recommended that, after a prophylactic thyroidectomy, patients be followed every 1 to 2 years with plasma calcitonin and CEA levels. In addition, patients at risk for MEN-2 need to be screened for the development of both pheochromocytoma (MEN-2A and 2B) and hyperparathyroidism (MEN-2A only), which can occur decades later.

Clinically Evident Disease

Patients who have clinically evident disease are best treated with a minimum of a total thyroidectomy and bilateral central neck dissection. Ipsilateral lateral neck dissection should be added if the primary tumor is greater than 1 cm in size or there is evidence of positive nodes in the central neck. A contralateral lateral neck dissection should be considered in patients with bilateral tumors or extensive lateral adenopathy on the side of the tumor.

Central neck nodal disease is present in up to 81% of patients with palpable tumors.⁵⁷ Addition of a central neck dissection improves cure rates over a thyroidectomy alone in patients with clinically evident MTC.⁵⁸ A central neck dissection consists of a complete clearing of all lymph nodes and fibrofatty tissue from the level VI compartment. Level VI extends from the hyoid bone superiorly to the innominate vessels inferiorly; laterally, it is bound by the carotids. A level VI lymphadenectomy requires careful dissection of the recurrent laryngeal nerve along its entire length; it also requires meticulous dissection of the parathyroid glands. Many surgeons argue that it is impossible to do a complete central neck dissection without removing the parathyroids and/or their blood supply. Some surgeons routinely remove the parathyroid glands with the specimen and then carefully dissect them free from the nodal tissue and autotransplant them. If patients have sporadic MTC, FMTC, or MEN-2B, then the autotransplant can be performed in the sternocleidomastoid. In patients with MEN-2A, because of the risk of hyperparathyroidism in the remnant, the parathyroid tissue should be autotransplanted to the nondominant forearm. Placement of the autograft in the forearm facilitates the workup and management of any hyperparathyroidism that may develop. Autotransplanted parathyroid glands usually do not function for 4 to 8 weeks, so calcium and vitamin D replacement is required during this time.

The role of a lateral dissection in MTC is less clear. Ipsilateral nodal metastases are present in 14% to 80% of patients,⁵⁹ and contralateral lateral nodal metastases have been reported in 19% to 49% of patients. Because there is a high incidence of lymph node disease, even in tumors of less than 1 cm, some surgeons advocate a bilateral lateral neck dissection for all patients with MTC.⁶⁰ Unlike papillary thyroid cancer, where microscopic nodal disease may be effectively treated with radioactive iodine, the only effective treatment for MTC is surgical resection. Although many patients with MTC have an indolent course, some patients have a much more aggressive variant of disease, and early surgical intervention gives them the best chance for a long-term cure. The significance of microscopic disease in the lymph nodes is not fully known, but a significant number of patients will have recurrent or persistent disease based on the presence of an elevated calcitonin level after primary operation. Despite an aggressive surgical resection of all neck lymph nodes, only 32% of patients with nodal disease at the time of their operation have undetectable calcitonin levels postoperatively.

The morbidity of a bilateral neck dissection can be significant, and because of this, many surgeons advocate a more selective approach to the lateral neck. Preoperative neck ultrasound

TABLE 5. TNM Staging of Medullary Thyroid Cancer

	Tumor Size, cm	Tumor Invasion	Node Positive Status	Metastasis
Stage 1	<2	Limited to thyroid	No	No
Stage 2	2–4	Limited to thyroid	No	No
Stage 3	>4	Minimal extrathyroidal invasion	Yes, level 6 nodes	No
Stage 4	Any size	Extends beyond the perithyroidal soft tissues	Yes, lymph nodes outside level 6	Yes

is highly sensitive for detecting lateral lymphadenopathy. An ipsilateral lateral lymphadenectomy is advocated when ultrasound or physical exam suggests the presence of lateral lymphadenopathy, when central compartment lymph nodes are involved, or when the primary tumor is 1 cm or greater. Contralateral lateral neck dissections are then added when patients have bilateral tumors or there is extensive lymphadenopathy on the primary tumor side. Contralateral lymph node involvement is almost never seen in the absence of ipsilateral lymph node disease; therefore, in patients with a unifocal tumor and no ipsilateral lymph node disease, there is likely no benefit to a contralateral neck dissection. Lateral neck dissections can be performed at the time of the initial total thyroidectomy and central neck dissection or can be done in a staged procedure after the initial operation. Interestingly, according to the Surveillance, Epidemiology, and End Results database, more than half of patients treated for MTC over the last several decades had less than the recommendation operation, suggesting that many patients with persistent calcitonin elevations may have had an inadequate initial operation.⁶¹ The staging of MTC is shown in Table 5.

Management of Hormonal Syndromes

Calcitonin levels, if marked elevated, can also cause symptoms including flushing, diarrhea, and weight loss. Patients with hormonal symptoms may benefit from medical treatment with somatostatin analogs. These patients may also benefit from cytoreductive surgery of unresectable disease. Surgery has been demonstrated to effectively palliate patients with incurable MTC.⁶²

Management of Advanced Disease

Systemic Chemotherapy

Conventional chemotherapy has shown limited efficacy in patients with MTC. Complete responses are very rare, and partial responses have been seen in less than a third of patients. The adverse effect profile of traditional chemotherapy is often substantial, making this an unappealing option for many patients. Recently, tyrosine kinase inhibitors targeting RET, epidermal growth factor receptor, and vascular endothelial growth factor have been used in clinical trials for patients with metastatic MTC. Limited efficacy was seen with imatinib mesylate (Gleevec).⁶³ Vandetanib (Zactima), a RET inhibitor, has shown some initial encouraging results in patients with hereditary MTC including a few partial responses and many stable response by CT imaging, with a dramatic decrease in tumor markers.⁶⁴ Initial results with motesanib diphosphate (AMG 706), a multikinase inhibitor that targets vascular endothelial growth factor, platelet-derived growth factor, RET, and Kit receptors, may also show promise.^{65,66}

Radiation Therapy

Radiation therapy can palliate local disease when surgery is not feasible. Radiation therapy is effective in treating pain from

bony metastases. However, the role for radiation to treat MTC in the neck is questionable. External-beam radiation causes extensive scarring and fibrosis within the neck, making future surgical interventions both difficult and potentially dangerous. Because the benefits of radiation therapy are not clear, and its use limits future surgical intervention, its use should be reserved for cases of known residual disease in which complete surgical resection is not possible. Radioactive iodine treatment is part of the standard treatment for papillary thyroid cancer; it has no role in the management of MTC because C cells are not of thyroid follicular origin; radioactive iodine is not taken up in the C cells.

Surgery

Approximately 50% of patients with MTC will develop recurrent disease. Calcitonin, CEA, and/or chromogranin A testing is a very sensitive way for detecting either residual or recurrent disease. When the postoperative biochemical markers are elevated, a careful metastatic evaluation should be performed before proceeding with operative exploration. Because neck reoperations are associated with significant risks, reoperation should be pursued only if there is significant likelihood of benefit. Patients with inadequate initial operations or those with only locoregional disease in the neck, surgical resection can and should be considered. Palliative operations in the neck can relieve local compression and other associated symptoms.⁶² Several studies have confirmed that reoperative neck operations can normalize calcitonin levels in approximately a third of patients.^{67,68}

Conclusions and Future Looking Statements

Medullary thyroid cancer is a neuroendocrine cancer for which surgery is the only curative therapy. Genetic testing for RET mutations has allowed potential cure for 25% of patients with hereditary MTC. However, for most patients with sporadic MTC, the disease cannot be controlled with current therapies. Thus, future treatment will likely exploit knowledge about the mechanisms and pathways that regulate the growth and metastatic phenotype of MTC. Several signaling pathways, such as the phosphatidylinositol 3-kinase/Akt, glycogen synthase kinase-3, mitogen activated protein kinases, and Notch/Hairy Enhancer of Split-1/achaete-scute complex like 1 signaling pathway, have also been shown to play important roles in regulating the growth of MTC.^{69–75} Drugs that modify these signaling pathways are currently in clinical trials for patients with MTC.

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