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The NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors: Pheochromocytoma, Paraganglioma & Medullary Thyroid Cancer

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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, pre-operative 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, 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 patients longitudinally for recurrence. MTC 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. Genetic testing for RET mutations has allowed identification of familial cases and prophylactic thyroidectomy for cure. The only curative treatment is complete surgical resection.

PHEOCHROMOCYTOMA AND PARAGANGLIOMA

Introduction

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, about 80% of pheochromocytomas are located in the adrenal medulla[1]. Extra-adrenal sympathetic paragangliomas in the abdomen most commonly arise from chromaffin tissue

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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. Head and neck paragangliomas, however, rarely produce significant amounts of catecholamines (less than 5%).

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 (e.g. 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 about 0.05% to 0.1% of patients with sustained hypertension. However, this probably accounts for only 50% of people harboring pheochromocytoma or paraganglioma because about half the 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 US of 500 to 1600 cases per year.

Pathology and molecular genetics

All pheochromocytomas and paragangliomas display similar basic histopathological characteristics although some differences between familial tumors have been described. According to the 2004 WHO criteria[3], 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[4]. At present it is estimated that at least 24–27% of pheochromocytomas or paragangliomas are associated with known genetic mutations, in children this prevalence may be as high as 40%[5–10].

Pheochromocytomas may occur sporadically or as part of hereditary syndrome. According to the latest studies, among patients with non-syndromic pheochromocytoma, up to about *24% of tumors may be hereditary*[5, 10, 11]. 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 1,2). In general, the traits are inherited in an autosomal dominant pattern[11].

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[12]. Some studies suggested that more than 2/3 of patients with SDHB-related pheochromocytoma or paraganglioma will develop metstatic disease[13, 14]. 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 for pheochromocytoma or paraganglioma[13] (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 intra-tumoral process occurs independently of catecholamine release. In line with these concepts, numerous independent studies have now confirmed that measurements of fractionated metanephrines (i.e. normetanephrine and metanephrine measured separately) in urine or plasma provide superior diagnostic sensitivity over measurement of the parent catecholamines (Table 3)[15–17]. However, to preserve high diagnostic sensitivity it is strongly recommended to obtain blood samples in the supine position[18].

Therefore, current recommendations are that initial testing for pheochromocytoma or paraganglioma must include measurements of fractionated metanephrines in plasma, urine, or both, as available[21]. Blood sampling should be performed at a supine position after about 15–20 mins of i.v. catheter insertion. Food, caffeinated beverages, strenuous physical activity, or smoking are not permitted at least about 8–12 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[22]. 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 (e.g. blood sampling while seated) should first be considered and eliminated[22]. 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[22].

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 due to concerns regarding radiation exposure. Recent data suggest that adrenergic blockade in pheochromocytoma or paraganglioma patients as a specific precautionary measure prior to intravenous nonionic contrast enhanced CT imaging is not necessary (unpublished observations). CT 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 [^{123}I]-labeled meta-iodobenzylguanidine scintigraphy ([^{123}I]-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 [^{18}F]-fluorodopamine ([^{18}F]-FDA), [^{18}F]-fluoro-dihydroxyphenylalanine ([^{18}F]-FDOPA), and [^{18}F]-fluoro-2-deoxy-D-glucose ([^{18}F]-FDG) have emerged for use in positron emission tomography (PET). The superiority of [^{18}F]-FDA PET imaging over [^{131}I]-MIBG scintigraphy, especially in malignant tumors, has been reported[29]. [^{18}F]-FDOPA PET imaging has been described to outperform [^{123}I]-MIBG scintigraphy in the detection of pheochromocytoma[30]. However, the sensitivity of [^{18}F]-FDOPA for metastatic paragangliomas is limited[31]. Studies have revealed that most pheochromocytomas show uptake of [^{18}F]-FDG in PET imaging[32, 33]. Recently, [^{18}F]-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 adrenal and extra-adrenal tumors. Observational studies have clearly shown that the laparoscopic procedure decreases postoperative morbidity, hospital stay, and expense as compared to the conventional transabdominal technique for tumor removal. Due to 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 life-long risk for development of recurrent disease, contralateral disease or malignant dedifferentiation and thus affect follow-up protocols.

Management of hormonal syndromes

Intra-operative risks must be kept to a minimum by appropriate pre-operative medical treatment to block the effects of catecholamines for at least 10–14 days before surgery[36, 37]. Adequate pre-operative α-blockade has been proven to reduce the number of peri-operative 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 (Dibenzyline), an α-adrenoceptor blocker, is most commonly used for preoperative control of blood pressure. The drug is initially administered orally at a dose of 10–20 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) that 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 employed without first blocking α-adrenoceptor mediated vasoconstriction. Volume contraction associated with chronic vasoconstriction can be seen in patients with pheochromocytoma and paraganglioma. Therefore, pre-operative volume expansion achieved by saline infusion or increased water intake is recommended to reduce post-operative hypotension[39].

Management of advanced disease

Palliative surgery is usually performed in order 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 alpha and beta 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 or cryoablation are current attractive options.

[^{131}I]-MIBG is used for patients in whom [^{123}I]-MIBG scintigraphy is positive (only about 1/3 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 [^{131}I]-MIBG and of monotherapy versus combination with other radionuclides or modes of chemotherapy. In patients with rapidly growing tumors, even if [^{123}I]-MIBG scintigraphy shows positive lesions, chemotherapy is a preferable treatment option (only about 1/3 of patients will respond).

Chemotherapy, with a combination of cyclophosphamide, vincristin and dacarbazine (CVD), 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 [^{123}I]-MIBG scintigraphy and in those with rapidly progressing tumors.

The effect of [^{177}-Lu-DOTA]-Octreotate in malignant paragangliomas or pheochromocytomas has only been described 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 [^{131}I]-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

Introduction

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, 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 patients longitudinally for recurrence. MTC 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

The majority of MTCs are sporadic and these patients most commonly present in the fifth or sixth decade 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*) proto-oncogene[44]. Hereditary MTCs occur in the setting of the multiple endocrine neoplasia (MEN) syndrome type 2 (2A or 2B) or as familial MTC (FMTC) without associated endocrinopathies[45].

MTC is present in virtually all of cases of MEN2A and is typically multifocal and bilateral[46]. The age of onset varies with the specific genetic mutation, but it 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 prior to definitive surgery for MTC. Pre-operative alpha blockade should be utilized and laparoscopic adrenalectomy is the preferred operation for pheochromocytoma (as mentioned in the previous section). Hyperparathyroidism occurs in 20–35% of patients with MEN2A. Diagnosis of hyperparathyroidism is performed with serum calcium and intact parathyroid hormone (PTH) 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 MEN2A will have single gland disease and intraoperative PTH testing can help guide the extent of surgery[47]. Some variants of MEN2A are also associated with either cutaneous lichen amyloidosis or Hirschsprung's disease. Patient prognosis in MEN2A is predominantly based upon successful treatment of the MTC[48].

In MEN2B, almost 100% of patients will develop MTC[49]. MTC occurs at a very young age and has a very aggressive course. Because of this, patients with MEN2B are rarely rendered disease free. Pheochromocytomas occur in 50% of patients. Other associated features of MEN2B 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. Due to the aggressive nature of the MTC in these patients, many die at a young age. Therefore, most of the MEN2B diagnoses are de-novo germline mutations.

In familial MTC (FMTC), patients develop isolated MTC without other endocrinopathies. There is significant overlap in the genetic mutations that lead to either FMTC or MEN2A. In order to consider a family to have FMTC and not MEN2A, there must be no evidence of either pheochromocytoma or hyperparathyroidism in more than ten carriers and multiple members need to be affected after the age of 50. Since MTC is often the first manifestation

of MEN2A, with pheochromocytomas lagging significantly behind, distinguishing between MEN2A and FMTC can be difficult

Pathology and molecular genetics

Pathologically, MTC lesions are whitish-gray in color and firm to palpation. MTC 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 (REarranged during Transfection) proto-oncogene, which in 1991 was mapped to chromosome 10q11.2[50]. 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 germline. In sporadic MTC cases, somatic mutations of RET have been discovered in 25–45% of cases. The most common germline mutation in MEN2A is in codon 634 (80% of patients). The most frequently associated germline mutation with MEN2B 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 germline 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 6–10% chance of an occult germline RET mutation. Therefore, most recommend that all patients with a diagnosis of MTC should undergo RET mutation genetic analysis.

The aggressiveness of the MTC in hereditary disease is dependent upon the specific RET mutation[48,51]. Currently RET mutations are classified into 3 groups based aggressiveness of MTC or level of risk as shown in Table 4[52]. 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 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. 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. Since MTC is these patients is rarely reported prior to 10 years of age, many recommend waiting until that time to perform the thyroidectomy. However, since thyroidectomy can be cured if performed early and that there remains variability and unpredictability in some families, hence many suggest treating all patients with MEN2A the same and perform their prophylactic operation by age 5 whenever possible.

Imaging and biochemical markers

The ability to genetically diagnose hereditary MTC with RET testing has virtually eliminated the need for biochemical and radiologic tests to determine which family members are at risk to develop MTC. Thus, genetic testing offers potential surgical intervention prior to the development of MTC. However, physicians still rely on biochemical and radiology tests to diagnoses sporadic MTC, and to follow patients with both hereditary and sporadic MTC for recurrent disease. C-cells elaborate a number of peptides and hormones. Calcitonin is the most common while other substances secreted by the C-cells include: carcino-embryonic antigen (CEA), corticotrophin, somatostatin, vasoactive intestinal peptide, and

serotonin. Calcitonin has proven to be the most useful biochemical marker, because levels correlate with tumor burden[53]. 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[54]. Calcitonin levels may be slightly elevated in a small percent of normal patients, but most patients with an elevation >100 pg/ml (normal range <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 10–40 pg/ml. Distant metastases are seen with calcitonin levels of greater than 150 pg/ml and frequently > 1000 pg/ml. CEA is also used as a marker of disease, and may be preferentially expressed in less differentiated tumors. A preoperative serum CEA level>30 ng/ml is often suggests disease that has progressed outside of the thyroid. CEA levels>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 (FNA) can then be performed under ultrasound guidance of any thyroid mass or enlarged lymph nodes. MTC is characterized by the presence of small cells with minimal cytoplasm and abundance of stromal amyloid on cytology. To confirm the diagnosis of MTC, FNA 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 10–15% 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 which are not seen on imaging. These small liver metastases are best visualized by laparoscopy[55,56].

Management of local-regional disease

Prophylactic Surgery—Prophylactic surgery removes the at risk organ prior to it developing 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 amongst the RET mutations, we will be better able to predict when disease is likely to develop and therefore plan operative intervention prior to 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[52]. In general it is reasonable to intervene in children with MEN2A and FMTC by age 5, while patients with MEN2B 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 MEN2A who was operated on under the age of 7 has had evidence of recurrent disease, with over 5 years of follow-up[57]. If a family does not want to proceed with prophylactic surgery in a young child, then it is reasonable to follow the patient closely with stimulated plasma calcitonin levels, and then proceed with operation when there is a rise 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 or not 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 their 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 while nodal disease has been seen in the occult setting, it is very rare in children under ten. They suggest that a more selective approach can be performed utilizing 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 (2.4%) patients with nodal disease and 3 patients with permanent hypoparathyroidism (3.5%)[57]. While 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. In order to minimize the risks of this prophylactic operation, it is essential that these procedures be performed only by experienced surgeons.

Since 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 prior to age 10[57]. However, since the long-term outcomes are not known, it is recommended that after a prophylactic thyroidectomy patients be followed every 1–2 years with plasma calcitonin and CEA levels. In addition, patients at risk for MEN2 need to be screened for the development of both pheochromocytoma (MEN2A and 2B) and hyperparathyroidism (MEN2A 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[58]. Addition of a central neck dissection improves cure rates over a thyroidectomy alone in patients with clinically evident MTC[59]. 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, familial MTC, or MEN2B then the autotransplant can be performed in the sternocleidomastoid. In patients with MEN2A, due to the risk of hyperparathyroidism in the remnant, the parathyroid tissue should be autotransplanted to the non-dominant forearm. Placement of the

autograft in the forearm facilitates the work-up and management of any hyperparathyroidism that may develop. Autotransplanted parathyroid glands usually do not function for 4–8 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 metastasis are present in 14–80% of patients[60] and contralateral lateral nodal metastasis have been reported in 19%–49% of patients. Since there is a high incidence of lymph node disease, even in tumors <1 cm, some surgeons advocate a bilateral lateral neck dissection for all patients with MTC[61]. Unlike papillary thyroid cancer, where microscopic nodal disease may be effectively treated with radioactive iodine, the only effective treatment for MTC is surgical resection. While many patients with MTC have an indolent course, some patients suffer from 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 persist disease based on the presence of an elevated calcitonin after primary operation. Despite an aggressive surgical resection of all neck lymph nodes, only 32% of patients with nodal disease at the time of there operation have undetectable calcitonin levels post-operatively.

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 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. 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 SEER database, over 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[62]. 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[63].

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 side effect profile of traditional chemotherapy is often substantial, making this an unappealing option for many patients. Recently, tyrosine kinase inhibitors targeting RET, EGFR, and VEGF have been utilized in clinical trials for patients with metastatic MTC. Limited efficacy was seen with imitanib mesylate (Gleevac)[64]. The RET inhibitor Vandetanib (Zactima), a RET inhibitor, has shown some initial encouraging results in patients with hereditary MTC including a few partial responses and many stable responsse by CT imaging, with a dramatic decrease in tumor markers (Wells SA, Jr.,

Gosnell, J.E., Gagel, R.F., Moley, J.F., et al. Vandetanib in metastatic hereditary medullary thyroid cancer: Follow-up results of an open-label phase II trial. Journal of Clinical Oncology 2007; 25(18S):6018.). Initial results with motesanib diphophate (AMG 706), a multikinase inhibitor that targets VEGF, PDGF, RET, and Kit receptors, may also shown promise (Sherman SI, Schlumberger, M.J., Droz, J., Hoffman, M, et al. Initial results from a phase II trial of motesanib diphophate (AMG 706) in patients with differentiated thyroid cancer (DTC). Journal of Clinical Oncology 2007; 25(18S):6017.)

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. Since 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 since 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 are very sensitive ways for detecting either residual or recurrent disease. When the post-operative biochemical markers are elevated, a careful metastatic evaluation should be performed prior to proceeding with operative exploration. Since neck re-operations are associated with significant risks, reoperation should only be pursued 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[63]. Several studies have confirmed that reoperative neck operations can normalize calcitonin levels in about a third of patients[65,66].

Conclusion and future looking statements

MTC is a NE cancer for which surgery is the only curative therapy. Genetic testing for RET mutations have allowed potential cure for the 25% of patients with hereditary MTC. However, for the majority of patients with sporadic MTC, the disease cannot be controlled with current therapies. Thus, future treatment will likely exploit knowledge about the mechanisms and pathways which regulate the growth and metastatic phenotype of MTC. Several signaling pathways, such as the phosphatidyl-inositol 3-kinase (PI3K)/Akt, glycogen synthase kinase-3, mitogen activated protein kinases (MAPKs), and Notch/Hairy Enhancer of Split-1 (HES-1)/achaete-scute complex like-1 (ASCL1) signaling pathway, have also been shown to play important roles in regulating the growth of MTC[67–73]. Drugs which modify these signaling pathways are currently in clinical trials for patients with MTC.

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Table 1

Characteristics in various pheochromocytomas

Tumor and clinical characteristics	Sporadic	SDHB	MEN, VHL, NF1
Malignancy rate	10 – 36%	High but to be determined	< 5%
Most common location of primary tumor	Extra-adrenal	Extra-adrenal	Adrenal
Biochemical phenotype	NE	NE, DA	NE, EPI
Most common sites of metastatic lesions	Bones, LNs, liver, lungs	Bones,	Bones, LNs
Unfavorable prognostic factors	Younger age, large tumor, low NE levels	Younger age, large tumor, low NE and high DA levels	Large tumor

Abbreviations: NE: norepinephrine; EPI: epinephrine; DA: dopamine; LNs: lymphatic nodes.

Table 2

Presence of various tumors in hereditary syndromes associated with pheochromocytomas or paragangliomas

Paraganglioma syndromes (SDH)	
SDHD	Head and neck paraganglioma
	Intra-adrenal pheochromocytoma
	Extra-adrenal pheochromocytoma[#]
SDHB	Head and neck paraganglioma
	Intra-adrenal pheochromocytoma
	Extra-adrenal pheochromocytoma[#]
	Renal carcinoma
Multiple Endocrine Neoplasia type 2	
Type 2a.	Medullary thyroid carcinoma
	Pheochromocytoma
	Hyperparathyroidism
	Cutaneous lichen amyloidosis
Type 2b.	Medullary thyroid carcinoma
	Pheochromocytoma
	Multiple neuromas
	Marfanoid habitus
FMTC	Familial medullary thyroid carcinoma
Von Hippel-Lindau syndrome type 2	
Type 2a.	Retinal and central nervous system haemangioblastomas
	Intra-adrenal pheochromocytoma
	Endolymphatic sac tumors
	Epididymal cystadenomas
Type 2b.	Renal-cell cysts and carcinomas
	Retinal and central nervous system haemangioblastomas
	Pancreatic neoplasms and cysts
	Intra-adrenal pheochromocytoma
	Endolymphatic sac tumors
	Epididymal cystadenomas
Type 2c.	Intra-adrenal pheochromocytoma
Neurofibromatosis type 1	
	Neurofibromas (multiple)
	Café-au-lait spots
	Intra-adrenal pheochromocytoma

Adapted from Lenders *et al.*[1], officially extra-adrenal paraganglioma, more frequent in SDHB (~80%).

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

Children: Adapted from Weise *et al.*[19] (based on 45 children studied, 12 pheochromocytomas). Adult patients: Adapted from Zelinka *et al.*[20] and Lenders *et al.*[15].

Table 4

RET Mutations associated with Hereditary MTC

Risk Level for MTC	**Most Common Codon mutations**	Age of prophylactic surgery
Level 3 (Highest)	883 918 922	Within first 6 months of life (preferably in the first month)
Level 2 (Higher)	611 618 620 634	By age 5
Level 1 (High)	609 630 768 790 791 804 891	By age 5–10

Table 5

TNM Staging of Medullary Thyroid Cancer

	Tumor Size	Tumor Invasion	Node Positive Status	Metastasis
Stage 1	< 2cm	limited to thyroid	NO	NO
Stage 2	2–4 cm	limited to thyroid	NO	NO
Stage 3	>4 cm	minimal extrathyroidal invasion	YES, level 6 nodes	NO
Stage 4	Any size	Extends beyond the perithyroidal soft tissues	YES lymph nodes outside of level 6	YES