Indication and Timing of Thyroid Surgery for Patients with Hereditary Medullary Thyroid Cancer Syndromes

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Key Words
Familial medullary thyroid cancer, MEN 2A, MEN 2B, FMTC, RET, prophylactic thyroidectomy

Abstract
Hereditary medullary thyroid cancer syndromes comprise familial medullary thyroid cancer (FMTC) and multiple endocrine neoplasia types 2A and 2B. Hereditary medullary thyroid cancers have an autosomal dominant pattern of inheritance and are caused by activating germline point mutations in the RET proto-oncogene. Evaluation of the onset, extent, and progression of hereditary medullary thyroid cancer associated with specific RET mutations has enabled clinicians to treat patients based on the level of risk associated with their specific mutation. Children identified by RET screening to be at risk for the development of medullary thyroid cancer can be treated with prophylactic thyroidectomy before developing the disease. This review covers the diagnosis, evaluation, timing of surgical management, and optimal follow-up of patients with hereditary medullary thyroid cancer syndromes. (JNCCN 2006;4:139–147)

Hereditary medullary thyroid cancer (MTC) accounts for 25% of MTC, or 1% to 3% of all thyroid cancers. MTC is a neuroendocrine tumor of the calcitonin-producing parafollicular C cells derived from the embryonic neural crest. Hereditary MTC is one of the best understood inherited neuroendocrine tumors because the 3 patterns of autosomal dominant inheritance result from germline point mutations in the RET proto-oncogene. The RET (REarranged during Transfection) proto-oncogene was identified in 1985. It encodes a receptor tyrosine kinase and is located on chromosome 10q11.2. In 1993, RET was identified as the susceptibility gene for familial MTC (FMTC) and multiple endocrine neoplasia type 2A (MEN 2A). In 1994, mutations in the RET proto-oncogene were also found to be responsible for MEN type 2B (MEN 2B). RET screening is now used to identify family members at risk for developing MTC and to help determine the optimal treatment approach. The genotype and phenotype features of the 3 hereditary MTC syndromes are summarized in Table 1.

Diagnosis and Workup of Familial Medullary Thyroid Cancer

Index cases of hereditary MTC commonly present like sporadic cases, with a palpable thyroid mass or enlarged cervical lymph nodes and sometimes with pheochromocytoma or hyperparathyroidism. The highest density of parafollicular C cells is in the posterior upper third of each thyroid lobe. Most medullary thyroid cancers occur in this region. Associated symptoms of hoarseness, dysphagia, or shortness of breath are seen in up to 15% of patients and often indicate aggressive tumors that have invaded the recurrent laryngeal nerve, trachea, or esophagus. Any patient presenting with these symptoms should undergo direct laryngoscopy to assess the function of the recurrent laryngeal nerve. Additional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) should also be considered to define the extent of tumor invasion.

Regional cervical lymph node involvement is seen in up to 80% of patients with primary tumor size 1 cm or...
larger and 100% of patients with tumors that have invaded through the thyroid capsule. Lymph node metastases occur most commonly in the central cervical compartment (56%), followed by the ipsilateral (49%) and contralateral (22%) cervical compartments. The central and lateral cervical lymph node compartments are shown in Figure 1. Distant metastases of MTC to the liver, lung, and bone are seen in 12% to 15% of patients and can be associated with flushing and diarrhea from tumor production of calcitonin, calcitonin gene-related peptide, or other vasoactive substances. Occasionally, patients with MTC present with hypertensive crises or other complications of pheochromocytoma. Rarely, MTC produces ectopic adrenocorticotropic hormone (ACTH), causing Cushing’s syndrome or hyperparathyroidism.

To establish the diagnosis of medullary thyroid cancer in a patient with a neck mass, fine-needle aspiration (FNA) biopsy should be performed. The diagnosis can be confirmed with positive immunohistochemical staining for calcitonin, carcinoembryonic antigen (CEA), and amyloid, and negative staining for thyroglobulin. After the diagnosis of MTC has been established, serum basal or calcium-stimulated calcitonin and CEA levels should be measured. Calcium-stimulated calcitonin has replaced pentagastrin stimulation (no longer available in the United States), and involves the intravenous administration of calcium (2 mg/kg) over 1 minute, with serum calcitonin levels measured at 2, 5, and 10 minutes after administration. A positive test is defined as calcitonin at least 2 times the upper limit of normal after calcium stimulation. Preoperative calcitonin levels directly correlate with tumor size, and preoperative calcitonin levels less than 50 pg/mL are associated with postoperative calcitonin normalization in 98% of patients (compared with only 42% of patients with preoperative calcitonin greater than 50 pg/mL). Falsely elevated calcitonin can be caused by autoimmune (Hashimoto’s) thyroiditis and multinodular goiter. All patients should have genetic testing for germline mutations in the RET proto-oncogene.

The physical examination of patients with MTC should include complete neck ultrasound, including careful examination of the thyroid gland for additional nodules, and examination of all cervical lymph node compartments for enlarged or suspicious lymph nodes. All patients with MTC should also have preoperative

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Incidence of MTC</th>
<th>Youngest Age at Presentation of MTC</th>
<th>Associated Tumors</th>
<th>RET Codon Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level 1</td>
</tr>
<tr>
<td>FMTC</td>
<td>100%</td>
<td>&lt; 6 y</td>
<td>None</td>
<td>768 790 791</td>
</tr>
<tr>
<td>MEN 2A</td>
<td>95%</td>
<td>&lt; 1 y</td>
<td>Pheochromocytoma, 40% Hyperparathyroidism, 20% Cutaneous lichen amyloidosis, 9% +/- Hirschsprung’s</td>
<td>790 791</td>
</tr>
<tr>
<td>MEN 2B</td>
<td>100%</td>
<td>&lt; 9 mo</td>
<td>Pheochromocytoma, 70% Intestinal/mucosal ganglioneuromatosis Marfanoid features</td>
<td>883 918 922</td>
</tr>
</tbody>
</table>

Abbreviations: FMTC, familial medullary thyroid cancer syndrome; MEN 2A, multiple endocrine neoplasia, type 2A; MEN 2B, multiple endocrine neoplasia, type 2B; MTC, medullary thyroid cancer; RET, REarranged during Transfection.
biochemical testing for pheochromocytoma. Approximately 40% of patients with MEN 2 have a pheochromocytoma.\textsuperscript{11} Pheochromocytomas in MEN 2 are more often bilateral, are confined to the adrenal gland, and have a lower risk of malignancy than sporadic pheochromocytomas.\textsuperscript{10,14} Patients with elevated urinary or serum catecholamine and metabolites should undergo an abdominal CT scan with fine cuts through the adrenal glands to localize a pheochromocytoma. Patients with a pheochromocytoma should be treated with an alpha blocker (phenoxybenzamine, 10 mg 3 times a day, titrated up to 40 mg 3 times a day) for at least 2 weeks before surgical intervention. Surgery in a patient with an undiagnosed pheochromocytoma without alpha blockade can be fatal. In patients with MTC and a pheochromocytoma, the adrenalectomy should be performed before total thyroidectomy and after appropriate alpha blockade.

A complete family history is essential to identify cases of hereditary MTC syndromes. All patients should be questioned about a family history of thyroid cancer, pheochromocytomas, hyperparathyroidism, or clinical manifestations such as neck mass, hoarseness, hypertension, anxiety, sweating, palpitations, headache, fatigue, weakness, memory loss, depression, musculoskeletal aches and pains, kidney stones, and osteoporosis. Serum calcium should be measured to rule out hyperparathyroidism. Finally, all patients with MTC should undergo germline RET screening, because 6\% to 24\% of patients with apparently sporadic MTC have germline RET mutations.\textsuperscript{15,16} Patients and families with germline RET mutations should undergo appropriate genetic counseling before genetic testing.

**RET Screening**

Germline RET proto-oncogene mutations have been identified in exons 10, 11, 13, 14, 15, and 16 through direct DNA sequence analysis. The most common mutation is in exon 11, codon 634, which is seen in two thirds of patients with hereditary MTC syndromes (FMTC and MEN 2A). RET screening identifies index cases of hereditary MTC syndromes and can identify which family members are at risk for developing MTC, eliminating the need for yearly routine calcitonin screening. Early identification of patients at risk for MTC using RET screening resulted in a 95\% biochemical cure rate at 6-year follow-up in 1 study, compared with a 33\% biochemical cure rate in patients who were diagnosed clinically with hereditary MTC.\textsuperscript{9}

Certain RET mutations are associated with an earlier age of onset and more aggressive tumors. This genotype–phenotype relationship should be used to determine the optimal timing of prophylactic thyroidectomy in families with hereditary MTC (Table 1). To date, no false-negative or false-positive RET tests have been reported in family members of a patient with MEN 2 with a detectable RET mutation. An estimated 5\% to 10\% of families with hereditary MTC do not have a described RET mutation and thus may have a false-negative result. These family members should be followed up with yearly basal and calcium-stimulated calcitonin levels.

**Surgical Treatment of Medullary Thyroid Cancer**

The only effective treatment for MTC is surgical resection. Parafollicular C cells do not trap iodine like thyroid follicular cells. Therefore, radioiodine ablation is not effective. MTC is generally more aggressive than differentiated thyroid cancers, and local recurrence in the thyroid bed or cervical lymph nodes occurs in more than 50\% of patients after surgical resection of established palpable tumors. Hereditary MTC is almost always multicentric and bilateral, with pre-malignant diffuse C-cell hyperplasia present even in the absence of ultrasound abnormalities.\textsuperscript{17,18} Overall, central neck lymph node metastases occur in at least 50\% of patients with hereditary MTC that present with a palpable mass, with ipsilateral lymph node involvement in 28\% and contralateral lymph node involvement in 19\%.\textsuperscript{19}

Patients with a diagnosis of MTC should undergo total thyroidectomy with central cervical lymph node (levels VI, VII) and ipsilateral functional modified radical lymph node (levels II, III, IV, V) resection. If abnormal contralateral lymph node nodes are noted using ultrasound or palpation or if bilateral primary tumors are found, a contralateral functional modified radical neck lymph node dissection should also be performed. Total thyroidectomy involves the extracapsular removal of the thyroid lobes, isthmus, and pyramidal lobe, sparing the recurrent laryngeal nerve and parathyroid glands. If the blood supply to the parathyroid glands appears to be compromised or if recurrence in the region of the parathyroid glands is a concern, the
parathyroid glands may be transplanted into the sternocleidomastoid muscle (sporadic, FMTC, or MEN 2B) or the nondominant forearm brachioradialis muscle (MEN 2A). Complete central neck lymph node dissection includes removal of all lymphatic and fibrofatty tissue between the 2 carotid arteries laterally, and from the hyoid bone superiorly down to the anterior superior mediastinum. A functional modified radical lymph node dissection involves the removal of all lymphatic and fibrofatty tissue along the jugular chain from the angle of the mandible superiorly to the innominate vessels inferiorly and from the anterior border of the trapezius muscle laterally to the anterior scalene muscles. The jugular vein, sternocleidomastoid muscle, and phrenic, spinal accessory, vagus, cervical sensory, and brachial plexus nerves are left intact.

Patients with a germline RET mutation and a thyroid nodule or elevated calcitonin should undergo total thyroidectomy with central neck lymph node resection, plus an ipsilateral lateral function neck dissection if the central lymph nodes are positive for MTC. Patients with a germline RET mutation and no other evidence of MTC should undergo prophylactic total thyroidectomy. The timing of prophylactic thyroidectomy is based on the risk level of each specific RET mutation (Table 1).

Recurrent or residual MTC should be suspected when serum calcitonin is detectable after complete resection. Calcitonin levels greater than 1,000 pg/mL may indicate distant metastases in the liver or lungs.20 The workup of recurrent MTC should start with a review of the initial surgery and pathologic findings to ensure that an appropriate surgical resection was performed. A recent review of over 1,000 patients with MTC in the Surveillance, Epidemiology, and End Results (SEER) database between 1973 and 2000 showed that even over the past 8 years, 15% of patients had only a subtotal or thyroid lobectomy, and 41% had no lymph node dissection.21 Subsequent evaluation should include complete neck ultrasound, direct laryngoscopy, and chest and abdominal CT. Hepatic metastases of MTC are often too small (< 3 mm) to be visualized with a CT scan, and a laparoscopic examination of the liver may be helpful for adequate staging before a redo neck operation. Nuclear medicine evaluation of MTC includes positron-emission tomography (PET) scan, octreotide scan and bone scans.22,23 If all evaluations are negative, selective venous catheterization for stimulated calcitonin measurement to localize the recurrence may be helpful.24 Observation alone is appropriate for patients with elevated calcitonin levels and no detectable disease.

Metastatic MTC to the liver with symptomatic diarrhea and flushing can be treated with resection or radiofrequency ablation.7 Lung metastases of MTC may be resectable thoracoscopically or through open thoracotomy. In general, isolated metastases of MTC should be resected whenever possible.

Prognosis
Many clinicopathologic tumor staging systems have been proposed to predict prognosis and risk of recurrence for MTC. The American Joint Committee on Cancer (AJCC) and Union International Contre le Cancer (UICC) pTNM, the European Organization for Research and Treatment of Cancer (EORTC), the National Thyroid Cancer Treatment Cooperative Study (NTCTCS), and SEER staging systems for MTC are shown in Table 2. The overall 10-year survival for patients with MTC is approximately 75% (range, 61%–88%).25,26 In addition to stage, multivariate analysis has identified age at diagnosis as one of the most important independent predictors of survival, with 10-year survival rates of 75% in patients younger than 40 years and only 50% in patients over age 40 at diagnosis.8,27 All the staging systems have been shown to be accurate predictors of survival. Poor prognostic pathologic features include strong CEA or galectin-3 staining, weak calcitonin staining, and cellular heterogeneity.28-30

Adjuvant Treatment for Medullary Thyroid Cancer
Chemotherapy
Despite meticulous surgical resection, at least 50% of patients presenting with clinically evident MTC will have local recurrence or distant metastases. Many patients survive for years with detectable levels of calcitonin or metastatic disease.11 Adjuvant chemotherapy with cytotoxic single agents such as doxorubicin produces a partial, short-lived response in less than 40%.32,33 Small trials using combination chemotherapy (dacarbazine, 5-FU, epirubicin, vincristine, cyclophosphamide, and cisplatin) have also produced only
partial responses or short-term disease stabilization.\textsuperscript{34–39}
A phase II clinical trial of irinotecan in patients with metastatic MTC is ongoing. A preclinical study in nude mice of combrestatin A-4 phosphate (CA4P) with doxorubicin showed significant antitumor activity against human MTC in a xenograft model.\textsuperscript{40}

Somatostatin analogues, including octreotide and lanreotide, used alone or with interferon \textsuperscript{2b} improve symptoms of flushing and diarrhea in over 60% of patients, and lower calcitonin and CEA levels in a few patients, but have not been shown to reduce tumor volume.\textsuperscript{41,42} Arylidene-2-indolinone (RPI-1), a small molecule inhibitor, reverses the constitutive tyrosine phosphorylation caused by the \textit{RET} 634 mutation in \textit{MEN} 2A and is a novel approach to the treatment of hereditary MTCs.\textsuperscript{43} Other studies using tyrosine kinase inhibitors in vitro have shown promising results,\textsuperscript{44,45} and phase II clinical trials are underway.

Gene therapy using dominant negative \textit{RET} mutants or RNA interference to block \textit{RET} expression is another potential treatment approach being investigated.\textsuperscript{46,47} A phase I trial using \textsuperscript{131}I-labeled anti-CEA monoclonal antibodies (\textsuperscript{131}I-MN-14) with autologous hematopoietic stem cell rescue in 12 patients reported 1 partial response.\textsuperscript{48} Another study used vaccination with calcitonin-pulsed dendritic cells as immunotherapy in 7 patients with 1 partial response.\textsuperscript{49} A different immunotherapeutic approach would be to develop monoclonal antibodies against the

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### Table 2 Medullary Thyroid Cancer Staging Systems

<table>
<thead>
<tr>
<th>Staging System</th>
<th>Definition</th>
<th>Cause-Specific Mortality (%)</th>
<th>PVE (%)</th>
<th>Rank</th>
<th>P Values</th>
</tr>
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<tbody>
<tr>
<td><strong>TNM</strong>\textsuperscript{*}</td>
<td>T1, N0, M0</td>
<td>0</td>
<td>13.118</td>
<td>2</td>
<td>.0017</td>
</tr>
<tr>
<td>I</td>
<td>T1, N0, M0</td>
<td>0.0</td>
<td>10.0</td>
<td>3</td>
<td>.0017</td>
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<tr>
<td>II</td>
<td>T2-4, N0, M0</td>
<td>14.5</td>
<td>44.5</td>
<td>4</td>
<td>.0017</td>
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<tr>
<td>III</td>
<td>Any T, N1, M0</td>
<td>40.0</td>
<td>40.0</td>
<td>5</td>
<td>.0017</td>
</tr>
<tr>
<td>IV</td>
<td>Any T, Any N, M1</td>
<td>100.0</td>
<td>100.0</td>
<td>6</td>
<td>.0017</td>
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<tr>
<td>EORTC Scoring System:</td>
<td></td>
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<tr>
<td>Group I: &lt; 50</td>
<td>+12 male</td>
<td>0</td>
<td>15.147</td>
<td>1</td>
<td>.0001</td>
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<tr>
<td>Group II: 50–65</td>
<td>+10 less differentiated</td>
<td>8.7</td>
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<tr>
<td>Group III: 66–83</td>
<td>+45 anaplastic</td>
<td>33.3</td>
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<tr>
<td>Group IV: 84–108</td>
<td>+10 extrathyroidal</td>
<td>40.0</td>
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<tr>
<td>Group V: &gt; 109</td>
<td>+15 distant metastasis</td>
<td>100.0</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NTCTCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>C-cell hyperplasia</td>
<td>0</td>
<td>12.715</td>
<td>3</td>
<td>.0012</td>
</tr>
<tr>
<td>II</td>
<td>Tumor &lt;1 cm</td>
<td>5.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Tumor &gt;1 cm or positive cervical lymph nodes</td>
<td>10.5</td>
<td></td>
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</tr>
<tr>
<td>IV</td>
<td>Extrathyroidal invasion or extracervical metastases</td>
<td>38.9</td>
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<td>SEER</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Local</td>
<td>Confined to thyroid</td>
<td>10.8</td>
<td>12.131</td>
<td>4</td>
<td>.0007</td>
</tr>
<tr>
<td>Regional</td>
<td>Extrathyroidal invasion or positive cervical lymph nodes</td>
<td>10.8</td>
<td></td>
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</tr>
<tr>
<td>Metastasis</td>
<td>Extracervical metastases</td>
<td>29.6</td>
<td></td>
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</tbody>
</table>

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; NTCTCS, National Thyroid Cancer Treatment Cooperative Study; SEER, Surveillance, Epidemiology and End Results; PVE, proportion of variance explained.

*Tumor size: T1 \( \leq 1 \) cm; T2 > 1 cm but \( < 4 \) cm; T3 \( \geq 4 \) cm; T4 extrathyroidal invasion.

Lymph node: N0 = no regional lymph node metastases; N1 = positive cervical lymph node metastases. Metastasis: M0 = no distant metastases; M1 = positive distant metastases.
ectodomain of RET, analogous to the use of trastuzumab against ErbB2 in the treatment of breast cancer.47

**Radiation**

No survival benefit has been documented with external beam radiation in the treatment of MTC, although more recent retrospective studies have suggested an improvement in local control, especially in patients with locally invasive tumors or positive tumor margins. One small cohort study of patients with residual microscopic MTC in the neck showed that locoregional control at 10 years was 86% in the group treated with postoperative external beam radiation versus 52% in the group that did not receive postoperative radiation.31 An important consideration in the use of external beam radiation for the treatment of MTC is that radiation-induced fibrosis and vasculitis may make repeat neck surgery much more difficult. Complications of radiation include myelitis (0.5%), esophagitis, laryngitis, and late esophageal stricture (5%).32 External beam radiation therapy may be useful in patients with very aggressive or unresectable tumors.

**Multiple Endocrine Neoplasia Type 2A**

**Presentation**

Multiple endocrine neoplasia 2A is associated with MTC in over 95% of patients, pheochromocytoma in 40%, and multiple gland parathyroid hyperplasia in 20%. Cutaneous lichen amyloidosis may be present in some patients (9%) with MEN 2A and is characterized by a pigmented, scaly rash in the interscapular area or on the extensor surfaces of the extremities.33 Cutaneous lichen amyloidosis also occurs sporadically and as a familial disease in patients without MEN 2A or identified RET mutations. Patients with MEN 2A usually develop MTC by the third decade of life, although patients developing MTC before the age of 2 have been reported.

**Screening**

Over 95% of MEN 2A index patients have identified RET mutations on germline screening.35 MEN 2A RET mutations are usually located in the extracellular cysteine residues on exons 10 and 11, most commonly at codon 634. Patients with higher-risk level II mutations (609, 611, 618, 620, 634) should undergo total prophylactic thyroidectomy before 5 years of age. The appropriate time for thyroidectomy in patients with low-risk level I mutations (790, 791) is more controversial because the penetrance is highly variable, but these patients should probably also undergo thyroidectomy before 5 years of age (Table 1).

**Prophylactic Surgical Intervention**

Patients with MEN 2A MTC or a thyroid nodule and elevated calcium-stimulated calcitonin levels should undergo total prophylactic thyroidectomy, central neck lymph node dissection, and ipsilateral lateral functional neck lymph node dissection. Patients with palpable or ultrasound evidence of contralateral disease should also undergo contralateral lymph node dissection. Prophylactic thyroidectomy for patients with MEN 2A and no evidence of MTC should be performed before age 5, especially for patients with higher-risk level II mutations.
Intraoperative management of the parathyroid glands is controversial, because 20% of patients with MEN 2A have multiple gland parathyroid hyperplasia. Some surgeons advocate routine total parathyroidectomy with autotransplantation into the nondominant forearm brachioradialis muscle.55 Advocates of this approach suggest that it permits a more complete lymph node dissection and avoids the risk of repeat neck dissection for hyperparathyroidism in the future. Other surgeons advocate leaving the parathyroid glands in situ with their vascular pedicles intact, marked with a surgical clip for future identification.55,56 If the parathyroid’s vascular supply appears to be compromised, the gland should be confirmed by frozen section, then autotransplanted into the forearm.

Multiple Endocrine Neoplasia Type 2B

Presentation
Medullary thyroid cancer associated with MEN 2B presents within the first 2 decades of life and tends to be the most aggressive form of hereditary MTC. Researchers have reported metastatic MTC in patients as young as 1 year of age.57,58 Other features of MEN 2B include pheochromocytoma, marfanoid body habitus, mucosal neuromas of the lips and oral cavity, intestinal ganglioneuromas, and occasionally chronic constipation associated with colonic motility disorders and megacolon.

Screening
RET proto-oncogene mutations in codon 833 or 918 cause MEN 2B.59 This high-risk level III mutation may cause MTC as early as 6 months of age and is present in about 25% of patients with sporadic MTC as a somatic mutation (Table 1).

Prophylactic Surgical Intervention
Because of the aggressive nature of MTC associated with MEN 2B, all patients with identified RET mutations should undergo prophylactic thyroidectomy before 1 year of age, ideally in the first month of life. Prophylactic central neck lymph node dissection should be performed if suspicious lymph nodes are seen on physical examination or ultrasound, or a thyroid nodule or elevated calcitonin level is detected preoperatively.6 Central neck lymph node dissection in children should always be performed by skilled endocrine surgeons who can identify and preserve or transplant the parathyroid glands.

Recommendations
Appropriate RET screening, diagnosis, and timing and approach of surgical treatment of hereditary MTC is critical in the management of this often challenging disease. Complete surgical resection, including total thyroidectomy, central neck lymph node dissection, and, when indicated, lateral ipsilateral or bilateral functional modified radical lymph node dissection offers the only chance of cure in both sporadic and hereditary syndromes. Careful follow-up in the postoperative period, with serial calcitonin levels at 6 months and then annually, is important to detect recurrent or persistent disease.

Identification and appropriate surgical treatment of hereditary MTC syndromes at an early age result in an excellent long-term prognosis. Prophylactic thyroidectomy in children can be performed with minimal morbidity and up to a 96% biochemical cure.60,61 Early diagnosis of FMTC, MEN 2A, and MEN 2B with RET screening and prophylactic thyroidectomy timed according to the risk level of individual RET mutations may allow treatment before MTC develops.

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