Artistic creativity and a careful study of emotions are synthesized with refinement in presentation, as shown in this illustration of Japanese art.

**Medullary Thyroid Cancer**

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**Etiology, diagnosis, treatment options, and testing for medullary thyroid cancer are reviewed.**

**Background:** Medullary thyroid cancer, a tumor of the parafollicular C cells, accounts for approximately 10% of all thyroid malignancies. An estimated 75% of cases are sporadic, and the remaining 25% are familial.

**Methods:** The author reviews the clinical features and diagnostic tests for this entity, as well as the surgical treatment of recurrent or persistent medullary carcinoma.

**Results:** Sporadic medullary thyroid cancer typically presents as an isolated unilateral mass. Familial tumors tend to be multifocal and bilateral. In patients with multiple endocrine neoplasia type 2A, pheochromocytomas and parathyroid hyperplasia also may develop. Care is taken to avoid operating on a patient with occult pheochromocytoma. Total thyroidecomy and central lymph node dissection are the keys for successful surgical treatment.

**Conclusions:** Surgery is the cornerstone of treatment for medullary carcinoma of the thyroid. Genetic testing using the ret oncogene allows identification of individuals who are at risk for the disease or those with early-stage disease.

**Introduction**

Medullary thyroid cancer (MTC) is a tumor of the parafollicular C cells that accounts for approximately 10% of all thyroid malignancies. An estimated 75% of MTC cases are sporadic, and the remaining 25% are familial. Embryologically, these cells originate within the neural crest and function similarly to other neuroendocrine cells within the amine precursor uptake and decarboxylation system. C cells are distributed throughout the entire thyroid gland, although they tend to predominate in the upper poles. Calcitonin, a hormone active in calcium metabolism, is synthesized and secreted by C cells and therefore serves as a useful serum marker for the presence of MTC. Calcitonin levels are most useful in screening individuals who are genetically predisposed to the disease and in following patients who already have been treated. The recent identification of the gene responsible for heritable forms of MTC has allowed earlier identification of individuals at risk for the disease.[1-4]

Sporadic MTC usually presents as a unifocal clonal population of tumor cells, while the heritable forms are typically multifocal. In its most aggressive form, MTC is capable of vascular and lymphatic invasion, as well as penetration of the thyroid capsule. Subsequent regional lymphatic involvement occurs to the parathyroidal, paratracheal, jugular chain and upper mediastinal lymph nodes. Adjacent structures that are often invaded include the trachea, jugular vein, and strap muscles. Impingement on the recurrent laryngeal nerve may result in the new clinical finding of hoarseness. Although MTC may remain locally contained in the neck, metastases to the liver, lungs and bone can occur in advanced cases.

**Clinical Features and Diagnostic Tests**

Sporadic MTC typically presents as an isolated, unilateral mass. By the time sporadic MTC is clinically obvious, regional lymphatic spread usually has occurred. In hereditary forms of MTC, tumors tend to be multifocal and bilateral with an autosomal dominant inheritance pattern. Hereditary MTC also is frequently accompanied by C-cell hyperplasia, which is thought by some to represent a precursor lesion. In patients with multiple endocrine neoplasia (MEN) type 2A, pheochromocytomas and parathyroid hyperplasia may develop in addition to MTC. The most aggressive MTCs are those that occur as part of the MEN 2B syndrome. MEN 2B patients develop MTC in association with pheochromocytomas but not parathyroid hyperplasia. Instead, the MEN 2B phenotype includes multiple mucosal neuromas, intestinal ganglioneuromas, and megacolon. MEN 2B also is inherited in an autosomal dominant pattern, although spontaneous mutations have been known to occur. Familial MTC (FMTC) is the most indolent form of MTC, which again is inherited in an autosomal dominant manner. Individuals with FMTC develop MTC alone and usually at a later age than MEN 2A or 2B (Table).
The striking phenotype of MEN 2B enables diagnosis by physical examination alone. A marfanoid habitus, coarse facies, thick lips, and a prominent jaw are characteristic. Patients with MEN 2A or FMTC, however, appear outwardly normal. Classically, individuals at risk for MEN 2A and FMTC have been screened by measuring stimulated serum calcitonin levels. Associated pheochromocytomas are detected by measuring urinary catecholamines, metanephrines, and vanillylmandelic acid. Serum calcium levels are measured to screen for hyperparathyroidism. The recent characterization of the gene responsible for these syndromes has made genetic testing possible in order to identify mutant gene carriers. Although not yet proven, the earlier identification of individuals at risk for these syndromes is expected to allow more effective surgical intervention before biochemical or clinical evidence of tumor develops. Furthermore, accurate genetic identification of individuals not carrying the mutation will eliminate the need for lifelong biochemical testing.

Fine-needle aspiration cytology allows for the diagnosis of MTC in patients presenting with a mass in the neck, although thyroid lobectomy for histologic determination is sometimes necessary. Whenever MTC is suspected, a thorough physical examination is indicated to disclose signs of MEN 2B. Also, an extensive family history should be recorded, with particular attention to instances of thyroid, adrenal, or parathyroid tumors, as well as sudden unexplained deaths suggestive of undiagnosed pheochromocytoma. Local extension of tumor is suggested by symptoms of hoarseness, dysphagia, stridor, and hemoptysis.

Patients being considered for operation should have calcitonin and carcinoembryonic antigen (CEA) levels measured preoperatively. The most sensitive method reported for determining plasma calcitonin levels is a provocative test using calcium and pentagastrin.[5] After obtaining basal calcitonin levels, intravenous calcium is infused (2 mg/kg/min), followed immediately by pentagastrin (0.5 µg/kg/5 sec) and completed by drawing blood for measurements of plasma calcitonin at one, two, three, and five minutes. Serum calcium is measured to screen for hyperparathyroidism. Finally, screening for pheochromocytoma is mandatory with 24-hour urine collection for catecholamines, vanillylmandelic acid, and metanephrines. The consequences of operating on a patient with occult pheochromocytoma can be catastrophic. Patients with sporadic MTC also should be screened since nearly 20% eventually prove to be cases of MEN 2A. The algorithm summarizes the approach to patients with suspected MTC.

**Surgical Treatment**

Regardless of the form in which MTC presents, the primary treatments for MTC are total thyroidectomy and central lymph node dissection. This includes the removal of all thyroid tissue, as well as all nodal tissue extending from the hyoid bone superiorly to the innominate vessels inferiorly. When the primary thyroid mass is large (>2.0 cm) or when jugular and paratracheal lymph nodes are involved, an ipsilateral functional neck dissection should be completed. Most experts believe that adequate thyroidectomy and nodal clearance cannot be achieved without total parathyroidectomy as well, thus necessitating parathyroid autografting.[6]

A persistently elevated calcitonin level following resection suggests residual or recurrent MTC. Most studies, however, observe that despite elevated calcitonin levels following thyroidectomy and node dissection, patients continue to do well without evidence of disease for many years.[7-9] Consequently, most recommend close surveillance of these patients in the absence of obvious clinical disease.

Several modalities may be used to detect occult residual or recurrent disease in patients with persistently elevated calcitonin levels postoperatively. Physical examination to evaluate for enlarged nodes along the jugular or paratracheal chain is extremely important. Helpful imaging studies include ultrasonography and computed tomography scanning, with fine-needle biopsy when possible. Raue et al[10] compared ultrasound examination of the neck along with physical examination, computed tomography scanning, selective venous sampling, and fine-needle biopsy in a study of 47 patients with elevated calcitonin levels following primary surgery for MTC. This study concluded that ultrasound was the most sensitive and reliable method for the detection of recurrent disease. Other studies, however, support the use of
selective venous sampling to correctly localize recurrent or persistent disease.[11-13]

The role of nuclear imaging studies in the detection of persistent or recurrent MTC is less clear. $^{131}$I-metaiodobenzylguanidine (MIBG) is known to be absorbed by MTC cells.[14-16] It also frequently concentrates in pheochromocytomas and neuroblastomas. Occult or metastatic MTC also has been effectively localized using $^{99}$Tc-dimercaptosuccinate.[17] Radioimmunoguided surgery has been described for MTC. Following the preoperative administration of a radiolabeled monoclonal antibody specifically for CEA, a hand-held probe is used to detect metastases in the operative field. Immunoscintigraphy identified all previously recognized tumors in five patients and detected additional tumor deposits in three of the five patients.[18] Trials using an anticalcinonin antibody are currently underway.

**Treatment of Recurrent or Persistent MTC**

Several centers have reported their experiences with reoperation for persistent or recurrent MTC confined to the neck. Because MTC is often an indolent disease, it is generally believed that operative debulking may retard its course. Eleven patients at the Mayo Clinic underwent reoperation for persistent hypercalcitoninaemia following clinical or radiographic demonstration of recurrent disease.[19] Although calcitonin levels did not return to normal levels in any patient, they clinically did very well with five- and ten-year survivals of 90% and 86%, respectively. Only two patients in this study died of MTC. Norton et al[12] reported a series of seven patients who underwent reoperation for persistent hypercalcitoninaemia following localization of the tumor by selective venous sampling. The postoperative calcitonin level normalized in one patient, and levels decreased in the remaining six. Extensive "micro-dissection" of all lymphatic and fatty tissue within the central and lateral zones of the neck for recurrent or persistent disease also has been described. In a report by Tisel et al[20] on 11 patients with persistent hypercalcitoninaemia following presumptive adequate primary surgery, calcitonin levels were normalized in four patients and were reduced in three. Using a similarly aggressive reoperative approach, Buhr et al[21] reported reductions in plasma calcitonin levels in all 28 patients studied.

Nonsurgical treatment of patients with persistent hypercalcitoninaemia has met with inconsistent results. Radioactive iodine is not useful in patients with metastatic or persistent MTC because the C cells are not derived from thyroid follicles and therefore do not concentrate iodine. External beam radiation has proven effective in some studies and not in others, although most were retrospective in design. In a report by Samaain et al[22] on 202 patients, those treated with radiation therapy had worse outcomes. The authors concluded that treatment failure was primarily due to recurrence of disease outside of the field of radiation. Nguyen et al[23] recently reported a series of 59 patients with MTC who received adjuvant radiation therapy following surgery. Local recurrences occurred in 18 (30%) patients following a mean dose of 5400 cGy, while 24 patients were free of disease after five years. Although these results are encouraging, they are not much different from surgery alone and warrant further study to more clearly define the role of radiation therapy in this disease.

No large series exists evaluating the efficacy of chemotherapy for MTC. In summary, doxorubicin (alone or in combination) appears to have resulted in several responses and is the drug of choice for patients without a surgical option.[24,25] Immunotherapy with interferon-alpha resulting in at least a partial response in two patients also has been described.[26]

**Genetic Testing**

Perhaps the most dramatic recent development in the management of patients with MTC is the identification of defects in the ret proto-oncogene as being responsible for MEN 2A, MEN 2B, and familial non-MEN MTC.[1-4] This 480-kb region localizes to chromosome 10q11.2[1,2] and encodes a transmembrane tyrosine kinase. In MEN 2A and familial non-MEN MTC, nonconservative point mutations are found within codons specifying cysteine residues within the extracellular binding domain of the ret gene product. This results in the disruption of normal disulphide bridge formation and subsequent abnormalities in tertiary protein structure. Questions still remain about the nature of the genetic abnormality in MEN 2B. Mutations occur, however, within the sequence that encodes the intracellular tyrosine kinase domain. The availability of probes specific for these abnormal sequences now make it possible to identify carriers of the germine mutations before they develop overt neoplasms. Patients with MEN 2A, for example, are virtually certain to develop MTC during their lives and usually before 30 years of age. At-risk family members who are found to have inherited the ret gene mutation are, therefore, candidates for prophylactic thyroidectomy. Family members who did not inherit the mutation will not develop MTC and can be spared a lifelong experience of stimulated calcitonin testing. Theoretically, the genetic testing of peripheral blood lymphocyte DNA will be necessary only once in the lifetime of an at-risk individual.

The largest study reported to date evaluating the effectiveness of preventive surgery for MEN 2A gene carriers was conducted by the Department of Surgery at Washington University in St. Louis.[27] Of the 132 individuals studied, 48 carried a diagnosis of MEN 2A, and 58 had an affected parent or sibling (50% at-risk carriers). Twenty-six unaffected spouses served as controls. Mutations in the ret gene were detected by direct sequencing and/or by simple polymerase chain reaction analysis. Twenty-one individuals were identified who had inherited the ret mutation. All 26 unaffected control individuals had normal ret alleles. Total thyroidectomy, lymph node dissection, and parathyroid autoimplantation were offered to all 21 mutant carriers following genetic counseling. To date, 13 have undergone operation; of these, seven had elevated calcitonin levels and six did not. All elevated plasma calcitonin levels returned to normal following resection. All patients with preoperatively elevated calcitonin levels had microscopic evidence of MTC on histologic evaluation. A total of 212 lymph node specimens were obtained, and none contained metastases.

Prophylactic thyroidectomy for patients carrying ret proto-oncogene mutations appears to be a major advance in the approach to individuals with MEN 2A and FMTC. Furthermore, the precise identification of individuals at risk— or not at risk— eliminates the need for life-long screening. Whether this approach will result in improved long-term outcomes is not yet known, but the early data are promising. Work is currently underway to identify similar or unique genetic mutations active in the more frequent cases of sporadic MTC.

**References**


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