Cancer--Medullary thyroid

The thyroid is a gland at the base of the throat near the trachea (windpipe). It is shaped like a butterfly, with a right lobe and a left lobe. The isthmus, a thin piece of tissue, connects the two lobes. A healthy thyroid is a little larger than a quarter. It usually cannot be felt through the skin. The thyroid uses iodine, a mineral found in some foods, to help make several hormones. Thyroid hormones do the following:

- Control heart rate, body temperature, and how quickly food is changed into energy (metabolism).
- Control the amount of calcium in the blood.

There are three ways that cancer spreads in the body.

The three ways that cancer spreads in the body are:

- Through tissue. Cancer invades the surrounding normal tissue.

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• Through the lymph system. Cancer invades the lymph system and travels through the lymph vessels to other places in the body.
• Through the blood. Cancer invades the veins and capillaries and travels through the blood to other places in the body.

When cancer cells break away from the primary (original) tumor and travel through the lymph or blood to other places in the body, another (secondary) tumor may form. This process is called metastasis. The secondary (metastatic) tumor is the same type of cancer as the primary tumor. For example, if breast cancer spreads to the bones, the cancer cells in the bones are actually breast cancer cells. The disease is metastatic breast cancer, not bone cancer.

_Medullary thyroid cancer (MTC)_ is a distinct form of thyroid carcinoma which originates from the _parafollicular cells_ (C cells) of the thyroid gland. These C cells produce calcitonin.

Medullary carcinoma of the thyroid (MTC) constitutes approximately 4% of all thyroid cancers.

Approximately 25% of medullary thyroid cancer is genetic in nature, caused by a mutation in the RET proto-oncogene. This form is classified as familial MTC. When MTC occurs by itself it is termed sporadic MTC. When it coexists with tumors of the parathyroid gland and medullary component of the adrenal glands (pheochromocytoma) it is called multiple endocrine neoplasia type 2 (MEN2).

Sporadic, or isolated, MTC accounts for 75% of cases, and inherited MTC constitute the rest. Inherited MTC occurs in association with multiple endocrine neoplasia (MEN) type 2A and 2B syndromes, but non-MEN familial MTC also occur.

It was first characterized in 1959.

_Markers_
While the increased serum concentration of calcitonin is not harmful, it is useful as a marker which can be tested in blood.

A second marker, carcinoembryonic antigen (CEA), also produced by medullary thyroid carcinoma, is released into the blood and it is useful as a serum or blood tumor marker. In general measurement of serum CEA is less sensitive than serum calcitonin for detecting the presence of a tumor, but has less minute to minute variability and is therefore useful as an indicator of tumor mass.

**Genetics**

Mutations (DNA changes) in the RET proto-oncogene, located on chromosome 10, lead to the expression of a mutated receptor tyrosine kinase protein, termed RET. RET is involved in the regulation of cell growth and development and its mutation is responsible for nearly all cases of hereditary or familial medullary thyroid carcinoma. Its mutation may also be responsible for the development of hyperparathyroidism and pheochromocytoma. Hereditary medullary thyroid cancer is inherited as an autosomal dominant trait, meaning that each child of an affected parent has a 50/50 probability of inheriting the mutant RET proto-oncogene from the affected parent. DNA analysis makes it possible to identify children who carry the mutant gene; surgical removal of the thyroid in children who carry the mutant gene is curative if the entire thyroid gland is removed at an early age, before there is spread of the tumor. The parathyroid tumors and pheochromocytomas are removed when they cause clinical symptomatology. Hereditary medullary thyroid carcinoma or multiple endocrine neoplasia (MEN2) accounts for approximately 25% of all medullary thyroid carcinomas.

Seventy-five percent of medullary thyroid carcinoma occurs in individuals without an identifiable family history and is assigned the term ‘sporadic’. Individuals who develop sporadic medullary thyroid carcinoma tend to be older and have more extensive disease at the time of initial presentation than those with a family history (screening
is likely to be initiated at an early age in the hereditary form). Approximately 25-60% of sporadic medullary thyroid carcinomas have a somatic mutation (one that occurs within a single ‘parafollicular’ cell) of the RET proto-oncogene. This mutation is presumed to be the initiating event, although there could be other as yet unidentified causes.

Medullary thyroid cancer is sometimes caused by a change in a gene that is passed from parent to child.

The genes in cells carry hereditary information from parent to child. A certain change in a gene that is passed from parent to child (inherited) may cause medullary thyroid cancer. A test has been developed that can find the changed gene before medullary thyroid cancer appears. The patient is tested first to see if he or she has the changed gene. If the patient has it, other family members may also be tested. Family members, including young children, who have the changed gene can decrease the chance of developing medullary thyroid cancer by having a thyroidectomy (surgery to remove the thyroid).

Pathophysiology

Medullary thyroid cancer (MTC) is usually diagnosed on physical examination as a solitary neck nodule, and early spread to regional lymph nodes is common. Distant metastases occur in the liver, lung, bone, and brain.

Sporadic MTC usually is unilateral. In association with multiple endocrine neoplasia (MEN) syndromes, it is always bilateral and multi-centric. MTC typically is the first abnormality observed in both MEN 2A and 2B syndromes.

In addition to producing calcitonin, MTC cells can produce several other hormones, including corticotropin, serotonin, melanin, and prostaglandins; moreover, para-neoplastic syndromes (eg, Carcinoid syndrome, Cushing syndrome) can occur in these patients.
Mutations have been classified into discrete subtypes, which confer varying degrees of risk; prophylactic thyroidectomy can now be offered to specific types of patients with this genetic abnormality.

**Clinical features**

A specific constellation of symptoms of medullary thyroid carcinoma (MTC) is not usually noted; however, one or more of the following symptoms may be observed:

- Patients may describe a lump at the base of the neck, which may interfere with or become more prominent during swallowing.
- Patients with locally advanced disease may present with hoarseness, dysphagia (difficulty in swallowing), and respiratory difficulty.
- Although uncommon, patients may present with various paraneoplastic syndromes, including Cushing or carcinoid syndrome.
- Diarrhea may occur from increased intestinal electrolyte secretion secondary to high plasma calcitonin levels.
- Distant metastases (eg, lung, liver, bone) may produce symptoms of weight loss, lethargy, and bone pain.
- Physical examination may demonstrate a dominant thyroid nodule at the base of the neck.
- Palpable cervical lymphadenopathy signifies disease that has progressed locally.
- Abdominal pain, jaundice, and rarely, bone tenderness may occur in patients with systemic metastases.

The major clinical symptom of metastatic medullary thyroid carcinoma is diarrhea; occasionally a patient will have flushing episodes. Both occur particularly with liver metastasis. Occasionally, diarrhea or flushing will be the initial presenting complaint. The flushing that occurs in medullary thyroid carcinoma is indistinguishable from that associated with carcinoid syndrome. The
presumed cause of flushing and diarrhea is the excessive production of calcitonin gene products (calcitonin or calcitonin gene-related peptide) and differs from the causation of flushing and diarrhea in carcinoid syndrome.

Diarrhoea is present in roughly one third of cases of medullary carcinoma of the thyroid. Excessive loss of water and electrolytes in the stools was the major factor. Steatorrhoea (excess of fat in the stools) was mild or absent, and intestinal absorption of glucose and vitamin B₁₂ was normal; the histological appearance of the small intestinal mucosa was normal or subnormal. Water and sodium diarrhoea seems to be linked to a sometimes considerable increase in the rate of transit through the small intestine and colon, and may be relieved by codeine or codethyline.

The link between the tumour and the disordered motility seems definite in view of certain cases in which removal of the tumour caused the diarrhoea to disappear immediately.

Production by the tumour of serotonin or other derivatives of tryptophan or of kallikrein, which activates bradykinin, is rare. With regard to prostaglandins, high concentrations have been observed in the tumours and in the venous blood draining the tumours, but their presence in systemic blood is inconstant. The only hormonal substance, concentration of which seems to be definitely increased in the systemic blood of patients with a medullary carcinoma of the thyroid, is thyro-calcitonin but this hormone does not seem to have any effect on the motor activity of the digestive tract.

The frequent increase in the maximum blood sugar level during an oral tolerance test should not be interpreted as evidence of a para-diabetic condition. In fact, the intravenous glucose tolerance test is usually normal and the excessive rise in blood sugar after oral administration seems to be the consequence of the increased rate of transit through the small intestine.
Sites of spread of medullary thyroid carcinoma include local lymph nodes in the neck, lymph nodes in the central portion of the chest (mediastinum), liver, lung, and bone. Spread to other sites such as skin or brain occurs but is uncommon.

*Treatment*

Surgery can be effective when the condition is detected early, but a risk for recurrence remains.

Unlike differentiated thyroid carcinoma, there is no role for radioiodine treatment in medullary-type disease.

External beam radiotherapy should be considered for patients at high risk of regional recurrence, even after optimum surgical treatment. Brierley et al., conducted a retrospective study and found that external beam radiation was beneficial in some patients.

After a long period during which surgery and radiation therapy formed the major treatments for medullary thyroid carcinoma, clinical trials of several new tyrosine kinase inhibitors are now being studied. Preliminary results show clear evidence of response 10-30% of patients, providing hope for future advances. In the majority of responders there has been less than a 30% decrease in tumor mass yet the responses have been durable; responses have been stable for periods exceeding 3 years.

The major side effects of this class of drug include hypertension, nausea, diarrhea, some cardiac electrical abnormalities, and thrombotic or bleeding episodes. Long-term safety of drugs effective for treatment of medullary thyroid carcinoma has not been established. None of the agents that show promise for treatment of medullary thyroid carcinoma have been approved by the US Food and Drug Administration for this purpose and most are available only through clinical trials.
Advances in genetic testing in have revolutionized the management of this disease.

**Prognosis**

Peak incidence of isolated medullary carcinoma of the thyroid (MTC) occurs in the fifth or sixth decade of life, and the peak incidence of MTC associated with multiple endocrine neoplasia (MEN) 2A or 2B occurs during the second or third decade of life.

Outcome depends on extent of disease, nature of tumor biology, and overall efficacy of surgical or any other treatment.

The prognosis of MTC is poorer than that of follicular and papillary thyroid cancer when it has metastasized (spread) beyond the thyroid gland.

The prognostic value of measuring calcitonin and carcinoembryonic antigen (CEA) concentrations in the blood in patients with abnormal calcitonin levels post-surgery has been recently published (2005) in a retrospective study of 65 MTC patients; see Barbet, *et al.* The postsurgical times ranged from 2.9 years to 29.5 years; all 65 patients continued to have abnormal calcitonin levels after total thyroidectomy and bilateral lymph node dissection. The prognosis of surviving MTC appears to be correlated with the rate at which a patient’s postoperative calcitonin concentration doubles, rather than the pre- or postoperative absolute calcitonin level.

Isolated medullary carcinoma of the thyroid (MTC) typically demonstrates a relatively indolent biologic progression. While regional lymph node metastases are possible, the lesion may not spread outside of the cervical region until several months later. MTC associated with multiple endocrine neoplasia (MEN) syndromes may have a more aggressive course, which also depends on associated comorbidity (eg, pheochromocytoma).
Despite advances in genetic screening for the RET proto-oncogene, preliminary population studies have yet to show a definitive impact on disease prognosis.

Approximately 86% of those with medullary carcinoma of the thyroid live at least 5 years after diagnosis. The 10-year survival rate is 65%.

The result of the 65 patient studies can be summarized with respect to the calcitonin doubling time (CDT):

**CDT < 6 months:** 3 patients out of 12 (25%) survived 5 years. 1 patient out of 12 (8%) survived 10 years. All died within 6 months to 13.3 years.

**CDT between 6 months and 2 years:** 11 patients out of 12 (92%) survived 5 years. 3 patients out of 8 (37%) survived 10 years. 4 patients out of 12 (25%) survived to the end of the study.

**CDT > 2 years:** 41 patients out of 41 (100%) were alive at the end of the study. These included 1 patient whose calcitonin was stable, and 11 patients who had decreasing calcitonin levels.

The 65 patients had a median age of 51 (range was 6 to 75), with 24 age 45 years or younger and 41 older than 45 years. The gender representation was 31 males and 34 females. All patients shared the following characteristics: 1) had total thyroidectomy and lymph node dissection; 2) had non-zero calcitonin levels after surgery; 3) had at least 4 serum calcitonin measurements after surgery; 4) had a status that could be confirmed at the conclusion of the study.

The same study noted that calcitonin doubling time is a statistically better predictor of MTC survival, compared with CEA.

**Risk of developing thyroid cancer**

Anything that increases your risk of getting a disease is called a risk factor. Having a risk factor does not mean that you will get cancer;
not having risk factors doesn’t mean that you will not get cancer. People who think they may be at risk should discuss this with their doctor. Risk factors for thyroid cancer include the following:

- Being between 25 and 65 years old.
- Being female.
- Having a history of goiter (enlarged thyroid).
- Having a family history of thyroid disease or thyroid cancer.
- Having certain genetic conditions such as familial medullary thyroid cancer (FMTC), multiple endocrine neoplasia type 2A syndrome, and multiple endocrine neoplasia type 2B syndrome.
- Being Asian.

Complications may include:

- Cancer spreads to other areas of the body
- Parathyroid glands are accidentally removed during surgery.

1. DIAGNOSTIC EVALUATION:

Clinical Evaluation:

- Complete history and physical examination

_The history should document presence/absence and duration of symptoms referable to hypercalcitonemia (diarrhea and flushing), pheochromocytoma (headache, palpitations/tachycardia, hypertension, diaphoresis (perspiration), nausea/vomiting, tremulousness/anxiety), or hyperparathyroidism (renal stones, bone abnormalities, etc.) as well as the presence or absence of hoarseness, dysphagia and stridor (sound caused by obstruction of air passage). The history should also indicate whether or not there is a family history of non-MEN medullary carcinoma (FMTC), multiple endocrine neoplasia (MEN) 2A or 2B. History of previous or current mucosal neuromata (a tumor or mass growing from a nerve) of the oral cavity or GI tract should be noted._
• Complete head and neck exam

Consists of inspection and palpation of the head and neck; the presence or absence of neuromata of the tongue, thickened lips or marfanoid facies should be documented. Attention should focus on the characteristics of the palpable thyroid mass such as size, consistency, number and fixation to trachea or larynx. Extrathyroidal extension to involve soft tissues in the central compartment of the neck or the skin should also be documented. The larynx should be visualized and vocal cord function documented.

If enlarged lymph nodes are present, their location (Group or Level I - VI), number, size, mobility, relationship to adjacent structures and staging should be documented.

Imaging Studies:

• Chest radiograph
  To evaluate for metastatic disease

• CT scan of neck with contrast or MRI
  It is indicated when there is suspicion of tumor extending into the larynx or trachea or into the mediastinum. MRI is preferable if well-differentiated thyroid neoplasm remains in the differential at this point (The iodine contrast used for CT scanning may delay postoperative radioactive iodine therapy).

Laboratory Tests:

Should include:

• Serum calcitonin levels Serum calcium (If elevated, obtain parathyroid hormone level).
• Serum albumin levels
• Alkaline Phosphatase 24-hour urine catecholamine (especially if symptoms suspicious for pheochromocytoma or if known familial MTC).
• Preoperative laboratory tests as required by institutional guidelines.
II. BIOPSY:

Fine needle aspiration has likely preceded suspicion of medullary carcinoma if sporadic MTC. If sporadic MTC suspected from elevated calcitonin alone, FNA is optional, depending on clinical presentation. (Increased calcitonin is present occasionally in other malignancies, bone disorders, renal failure, hemorrhagic disorders or thyroiditis.)

FNA of thyroid not necessary when there is a family history of MTC and RET gene mutation or increased pentagastrin stimulated calcitonin level have been documented.

III. TREATMENT:

Primary tumor:

- Surgery
  Total thyroid-ectomy recommended in all cases.

- Radiation
  Not indicated as primary treatment.

- Chemotherapy
  Not indicated

Neck:

- Surgery

$N_0$: Medial compartment neck dissection should be performed in all cases; it includes lymph nodes from the level of the hyoid bone to the innominate vein and from one carotid sheath to the other. In addition, all cases merit intraoperative palpation of the jugular nodes and neck dissection if palpable nodes are present.

$N_+$: In cases with clinical or radiologic suspicion of nodal metastases, a neck dissection should be performed which includes levels II-V and may preserve uninvolved structures (e.g., spinal accessory nerve). It should be recognized during
the course of neck treatment that no effective adjunctive treatment has been established for medullary carcinoma

- Chemotherapy
  
  *No role established*

Other:

In MEN 2A parathyroid hyperplasia occurs in 10-20% of the cases and subtotal parathyroidectomy or total parathyroidectomy and autotransplantation should be considered at the time of primary operation to avoid the potential risk of recurrent laryngeal nerve injury in reoperation of the central compartment. Cryopreservation of one or more removed parathyroid glands may be considered for later reimplantation should hypo-parathyroidism result from the initial surgery.

IV. ADJUVANT TREATMENT:

Preoperative

Pheochromocytoma discovered during pre-operative work-up should be resected prior to treatment of MTC.

Postoperative

Radiation therapy:

Extra-capsular extension of tumor has been associated with poor prognosis in MTC. There is limited information in the literature suggesting that radiation therapy may be beneficial in patients with multiple, large nodal metastases with extra-capsular extension. It may also be beneficial when there is gross or microscopic residual tumor.

V. FOLLOW UP:
The follow up schedule depends on the patient’s clinical course and individual risk for recurrence. In general, patients should be examined every 3 to 6 months for three years, thereafter every 6 - 12 months for up to ten years, and then once a year for life.

Follow up evaluations should include:

- Examination of the head and neck area.
- Chest x-ray, yearly.
- Calcitonin levels, yearly, in all patients
- Serum calcium levels and urine catecholamines, yearly, in patients with familial MTC.
- Serum Carcinoembryonic antigen (CEA) may be useful as a secondary tumor marker.
- CT scan of the neck and upper mediastinum after completion of treatment may be useful as a baseline study.
- When calcitonin levels are elevated following treatment, the following modalities may be useful in localizing residual disease: CT scans, octreotide scintigraphy, and selective venous catheterization.

VI. FAMILY SCREENING:

A sporadic case of MTC may represent the index case of familial MTC kindred. Bilateral tumors or evidence of C-cell hyperplasia may indicate such a situation. Family history of thyroid surgery, a poorly differentiated carcinoma or sudden death may also indicate a familial MTC. Available members of familial MTC kindreds should be screened for MTC. For FMTC and MEN 2A, assessment of peripheral blood for evidence of RET gene mutation can be performed. No such gene mutation has been defined for MEN 2B and these kindreds must be screened using baseline and pentagastrin stimulated serum calcitonin measurements.

The following stages are used for medullary thyroid cancer:

Stage 0
Stage 0 medullary thyroid cancer is found only with a special screening test. No tumor can be found in the thyroid.

**Stage I**

Stage I medullary thyroid cancer is found only in the thyroid and is 2 centimeters or smaller.

**Stage II**

Stage II medullary thyroid cancer is only in the thyroid and is larger than 2 centimeters but not larger than 4 centimeters.

**Stage III**

In stage III medullary thyroid cancer:

- the tumor is larger than 4 centimeters or cancer has spread to tissues just outside the thyroid, but not to lymph nodes; or
- the tumor is any size and cancer may have spread to tissues just outside the thyroid and has spread to lymph nodes near the trachea or the larynx (voice box).

**Stage IV**

Stage IV medullary thyroid cancer is divided into stages IVA, IVB, and IVC.

In stage IVA, it may be possible to remove the tumor by surgery; either of the following is found:

- cancer has spread out of the thyroid to tissues under the skin, the trachea, the esophagus, the larynx (voice box), and/or the recurrent laryngeal nerve (a nerve with 2 branches that go to the larynx); cancer may have spread to lymph nodes; or
• cancer may have spread to tissues just outside the thyroid and has spread to lymph nodes on one or both sides of the neck or between the lungs.

In stage IVB, the tumor cannot be removed by surgery; cancer has spread to tissue in front of the spinal column or has surrounded the carotid artery or the blood vessels in the area between the lungs. Cancer may have spread to lymph nodes.

In stage IVC, cancer has spread to other parts of the body, such as the lungs and bones.

Anaplastic thyroid cancer is considered stage IV thyroid cancer.

Anaplastic thyroid cancer grows quickly and has usually spread within the neck when it is found.

Stage IV anaplastic thyroid cancer is divided into stages IVA, IVB, and IVC.

In stage IVA, cancer is found in the thyroid and may have spread to lymph nodes. The cancer can be removed by surgery.

In stage IVB, cancer has spread outside the thyroid and may have spread to lymph nodes. The cancer cannot be removed by surgery.

In stage IVC, cancer has spread to other parts of the body, such as the lungs and bones.

Recurrent thyroid cancer is cancer that has recurred (come back) after it has been treated. Thyroid cancer may come back in the thyroid or in other parts of the body.