Medullary Thyroid Cancer

www.thyca.org
ThyCa: Thyroid Cancer Survivors' Association, Inc.
Phone Toll Free 1-877-588-7904 • Fax 1-630-604-6078
E-mail: thyca@thyca.org

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Medullary Thyroid Cancer

This *handbook* *provides an overview of medullary thyroid cancer, its diagnosis, and typical treatment options, advances in research, and how to find a specialist experienced with this rare type of thyroid cancer. We also tell you about free support services, educational events, and more resources. Our goal is help patients and caregivers cope with the emotional and practical impacts of this disease.*

While this handbook contains important information about medullary thyroid cancer, your individual course of testing, treatment, and follow-up may vary for many reasons.

This free handbook is one in a series, for people with all types of thyroid cancer. Others now available from ThyCa are ***Thyroid Cancer Basics*** *(about all types of thyroid cancer) and* ***Anaplastic Thyroid Cancer.*** *More handbooks are in development.*

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Please note: The information in this handbook is intended for educational purposes and is for general orientation. It is not intended, nor should it be interpreted, as medical advice or medical instructions or to replace your doctor's advice. You are advised to consult your own medical doctor(s) for all matters involving your health and medical care.

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Invitation: Your suggestions for ThyCa publications—
E-mail to publications@thyca.org

You Are Not Alone

A medullary thyroid cancer (MTC) diagnosis can be difficult. Please be reassured that you are not alone.

Our goal is to offer help, hope, and support to:

- Strengthen your knowledge through education about this rare type of thyroid cancer
- Help you feel part of a community of MTC survivors as you cope with emotional and practical concerns
- Introduce you to the many free services, information resources, and educational events that can help you

This handbook is for anyone coping with a medullary thyroid cancer diagnosis.

This handbook gives you:

- Basic facts and helpful tips for coping with **medullary thyroid cancer**
- More details about treatment, follow-up, and research advances
- Suggestions on finding a specialist in medullary thyroid cancer, either directly or else through your physician

This handbook was developed by medullary thyroid cancer specialist physicians and researchers and medullary thyroid cancer survivors and caregivers who participate in the Medullary Thyroid Cancer E-Mail Discussion and Support Group sponsored by ThyCa: Thyroid Cancer Survivors' Association, Inc., in cooperation with other ThyCa volunteers and ThyCa medical advisors.

In addition to the medical information …

In addition to the medical information, we will also share strategies that have helped when it comes to coping, whether we are the patients or the families who are coping with medullary thyroid cancer.

We want to provide a place not only for information, but also for emotional support.

So, if you or someone in your family is coping with MTC, we invite you to join the MTC e-mail group. Instructions for joining this group can be found at www.thyca.org/sg/email/#medullary.

Many of the "meddies" in this e-mail group have been living with MTC for many years, sometimes decades.

The participants hope that the shared experiences and knowledge of living with MTC will be helpful and encouraging to anyone looking for answers and support.

Among the benefits of joining are that all the group's messages, going back more than 12 years, are in a convenient archive. They continue to share survivors' and caregivers' experiences, support, and understanding. Many members also take part in the ThyCa Inspire Online Support Community and on Facebook or other social media. Visit www.thyca.org for more information.

Meeting Online and In Person

Because of the rare nature of this disease, it is natural to feel a sense of urgency and a fear of the unknown, especially when first diagnosed.

When MTC patients meet another meddie, whether on-line or at one of the ThyCa conferences or workshops, we experience an instant kinship. The cascade of questions and information exchange that follows creates a very special bond.

We hope that everyone reading this handbook and taking part in the MTC e-mail group will experience this bond as we share, learn from and support one another.

If you would like to speak one-to-one with an MTC support person in ThyCa, we encourage you to contact ThyCa's Person-To-Person Network at www.thyca.org/sg/tppn/. Or you may call the ThyCa toll-free number at 1-877-588-7904.

Understanding Our Disease

All too often MTC patients and their families start their MTC journey with little or no knowledge of this rare disease.

By reading this handbook and communicating with this worldwide group, we can have more confidence that we are staying informed and, hopefully, one step ahead of our disease.

Even though MTC is rare and we are labeled as having an "orphan" disease, we are still very much a part of the greater medical community. The intriguing science and research surrounding MTC overlaps and contributes to the knowledge and understanding of other cancers as well.

We hope this MTC handbook encourages others by helping them appreciate that MTC is not just a footnote in a medical textbook, but an actively researched disease.

1. Medullary Thyroid Cancer: Basic Facts

- Medullary thyroid carcinoma or cancer (MTC) is uncommon. It accounts for only 3-4% of all thyroid cancers.

- Medullary thyroid cancer is different from the much more common differentiated thyroid cancer (papillary, follicular and variants), which are treated differently from medullary thyroid cancer.

- Medullary thyroid cancer affects people of all ages, from young children to seniors.

MTC is different from other types of thyroid cancers (which are derived from follicular cells), because it is a neuroendocrine tumor. This means that it happens in cells that function in some ways like cells in the nervous system. This makes it easy for a doctor experienced with MTC to tell MTC from other thyroid cancers.

- Unlike the more common differentiated thyroid cancers that produce thyroglobulin and thyroid hormone, the cells from which MTC is derived are hybrids – they have features of both neurons and endocrine cells.

- MTC develops in the parafollicular C cells (commonly called "C cells") of the thyroid gland. These cells have features of both neurons and endocrine cells.

  - C cells make a different protein called **calcitonin** (sometimes referred to as thyrocalcitonin), which affects the regulation of calcium levels in the body.

- The earliest stage, before a tumor develops, appears microscopically as localized cell proliferation. It is called "C cell hyperplasia."

- MTC often presents as a thyroid nodule. Like all thyroid cancer, MTC is easier to treat and control if found before it spreads to other parts of the body. However, it frequently spreads before the thyroid nodule is discovered.

- C cells are different from the more common thyroid follicular cells because they do not make either thyroid hormone (also called thyroxine) or the protein thyroglobulin. C cells are not responsive to thyroid stimulating hormone (TSH).

Types of MTC

The two types of medullary thyroid cancer are **sporadic** (non-inherited) and **familial** (hereditary or inherited):

- **Sporadic** MTC (sometimes called "spontaneous MTC") is diagnosed in approximately 75-80% of all MTC cases and occurs in individuals without an identifiable family history of MTC. It usually occurs in patients over the age of 20 years.

- **Familial (hereditary)** MTC occurs in approximately 20-25% of all MTC cases, and comes with a 50% risk of each related family member developing MTC, which can appear at any time from infancy to adulthood. There are 3 types of familial MTC:

  - **Multiple endocrine neoplasia (MEN) 2A**, a syndrome of MTC with possible association with parathyroid hyperplasia (which causes elevation of calcium levels or hypercalcemia) or adrenal gland tumors, called pheochromocytomas;
  - **MEN2B,** a syndrome associated with MTC and pheochromocytoma, and
  - f**amilial medullary thyroid carcinoma (FMTC).**
  - Some forms of MTC may be associated with other endocrine tumors, including parathyroid adenomias causing elevated calcium levels (hypercalcemia), and adrenal gland tumors (which are also called "pheochromocytoma").

- MTC is very rare in children and adolescents, and is diagnosed in fewer than one child per million per year.

  - When MTC is diagnosed in children and adolescents, it is almost always the hereditary type.

- A later section of this handbook has some points about finding physicians with expertise in MTC.

More About Medullary Thyroid Cancer

- **Genetic testing to analyze the RET proto-oncogene, the cause of a high percentage of familial MTCs, should be done for all people diagnosed with medullary thyroid cancer even if there is no family history suggestive of MTC, parathyroid tumors, or pheochromocytoma.**

- At the time of initial diagnosis, genetic testing is needed to determine whether the MTC is sporadic or familial (hereditary).

- Genetic testing is considered the standard of care and is not an experimentalal test.

- If it is determined that the patient has familial (hereditary) medullary thyroid cancer, then first-degree relatives (parents, siblings and children) should all be tested to determine whether there are DNA changes (mutation) in the RET proto-oncogene that predicts the development of MTC. The testing focuses on the RET proto-oncogene.

- In some cases, hereditary mutations may not be found in either parent. These ‘de novo” mutations occur most commonly in MEN2B.

- In individuals with these RET proto-oncogene genetic changes, including infants and children, this test allows early removal of the thyroid gland before cancer develops or while it is still confined to the thyroid gland. This surgery has a very high probability of preventing future development of MTC in affected individuals.

- Nearly 100% of patients who are found to have a mutation (an abnormal sequence in the RET proto-oncogene), and therefore are at risk of hereditary MTC, will eventually develop MTC. The specific mutation can be used to determine when (at what age) the thyroid gland should be removed.

- Medullary thyroid cancers usually make the proteins calcitonin and carcinoembryonic antigen (CEA), which can be measured by blood tests. These tests can be used as tumor markers as part of the long-term monitoring process to detect any recurrent or persistent disease.

- **Medullary thyroid cancer does not have the ability to concentrate iodine. Because of this, radioactive iodine treatment is not effective and should NOT be used to treat MTC.** (*Note:* Rarely, a patient has, at the same time, both MTC and differentiated thyroid cancer (papillary, follicular, or one of their variants). In this situation, the nature and timing of treatment for the other type of cancer will be determined in discussions with the physicians. Treatments for differentiated thyroid cancer are discussed in ThyCa's free handbook **Thyroid Cancer Basics**, downloadable from www.thyca.org or available from ThyCa by mail.)

The primary treatment for MTC is surgery to completely remove the thyroid (total thyroidectomy). If there is evidence of involved lymph nodes in the neck, these are removed as well. Locally advanced disease that might affect the aero-digestive tract is also removed surgically. If there is widely disseminated disease, the benefits and risks of surgery need to be weighted carefully, and surgery is often bypassed in this situation.

- Research for MTC treatment is ongoing, and newer medicines have been tested and recently approved by the U.S. Food and Drug Administration (FDA) for treating advanced or progressive MTC that is not able to be completely removed or has spread.

- Two drugs, vandetanib (Caprelsa®) and cabozantinib (Cometriq®), have recently been approved for selected patients with medullary thyroid cancer that is rapidly growing outside of the thyroid gland and that cannot be effectively treated with standard treatment modalities. These drugs have significant side effects and should only be given after thorough consultation with a physician experienced in treating MTC with these drugs or else a physician working with other expert clinicians.

2. Prognosis in Medullary Thyroid Cancer

- Although MTC can metastasize (spread throughout the body) early, it often progresses relatively slowly.
- The long-term prognosis for medullary thyroid cancer is not as favorable as for differentiated thyroid cancers (papillary and follicular), However, the prognosis is generally much better than for undifferentiated thyroid cancer (anaplastic thyroid cancer), as well as the prognosis for many other types of cancer.
- The long-term survival rate often depends on the stage of the cancer at the time of diagnosis.
- For all types of MTC, the 5-year survival rate is 80-90%, and the 10-year survival rate is 60-75%. The long-term survival rate often depends on the stage of the cancer at the time of diagnosis.
  - If the disease is localized (has not spread outside the thyroid) the prognosis is better, with a 10-year survival rate of approximately 90%.
  - If the disease has spread only to regional/local lymph nodes or has invaded the regional soft tissue or muscle of the neck, the ten-year survival rate is about 75%.
  - If the disease has spread to the liver, lungs, or bone, the 10-year survival rate drops to 40%.
  - Tumors with a codon 918 RET proto-oncogene mutation may be more likely to be aggressive and associated with a poorer outcome, according to current thinking and the available peer-reviewed data,
  - **It is important to note that these statistics pre-date new drug therapies that are now available.** These promising drug therapies are specifically for patients with advanced, metastatic MTC and the overall prognosis may be improving, but it is too soon to tell.
  - A final important point: These statistics reflect observations from large groups of thyroid cancer patients and cannot be used to predict your survival, as an individual patient. Some people do better than the trends shown above.
- Approximately one third of MTC patients will have a recurrence.

- Those with high levels of calcitonin at the time of diagnosis are more likely to have persistent disease, or are more likely to experience a recurrence.
  - Almost one half of the patients with high calcitonin or CEA levels after surgery may experience persistent or recurrent disease.
  - Even with persistent disease, MTC patients can live a very long life.
  - Additionally, the amount of change of calcitonin or CEA produced over the period of 1 year can help predict patient survival. The rate of increase often correlates with the rate of tumor growth.
  - The rate of change of the serum calcitonin and of CEA can be used to predict long-term survival. Those individuals who have a doubling time (the time it takes the serum calcitonin or CEA to double as assessed over a several year period) of less than 2 years are at greatest risk of dying from metastatic disease, whereas those with a doubling time of greater than 2 years have a much more favorable course. The American Thyroid Association has a tool to help with the doubling time calculation at: www.thyroid.org/thyroid-physicians-professionals/calculators/thyroid-cancer-carcinoma/

Therefore, it is important that you have regular follow-up examinations by an MTC expert physician (or a local physician working as part of team with an MTC expert either by phone, e-mail, or other communication) to detect whether the cancer has recurred, and whether you should be considered for starting treatment with vandetanib or cabozantinib.

Health monitoring should continue throughout your lifetime.

3. Diagnosis of Medullary Thyroid Cancer

- MTC can come to the attention of a patient or health care professional in several ways.

- First, as a thyroid nodule, detected by the patient or a health care provider.
- Second, the patient or physician could detect an enlarged lymph node or nodes in the neck (often to one side), which may actually grow to a larger size than the primary tumor.
- Third, the patient might present with persistent, chronic diarrhea that cannot be attributed to any other cause. This usually indicates that the tumor had spread beyond the neck, although not 100% of the time. This type of presentation is quite uncommon and represents only 1-2% of MTC.

- In patients with hereditary MTC the disease could present as bumpy lips and tongue, which is specific to MEN-2B, or hypertension associated with the presence of a pheochromocytoma. There is also the chance that an asymptomatic person could be identified by genetic testing.
- MTC is usually painless and without symptoms in its early stages.

Symptoms Associated with a Thyroid Nodule

- Some symptoms that may appear include:
  - Hoarseness that has no known cause and does not go away
  - Difficulty breathing or shortness of breath
  - Difficulty swallowing or an unusual sensation (a “lump”) when swallowing
  - Nodule (lump) or growth at the base of the neck
  - An abnormally large lymph node (a “swollen gland”) that fails to spontaneously shrink over a few weeks/ time.

Evaluating a Nodule and Diagnosing Cancer

Steps in evaluating a thyroid nodule may include:

- Physical examination. This should include a laryngeal exam (checking the vocal cords).
- Neck ultrasound
- Fine needle aspiration (FNA) biopsy, often under ultrasound guidance

- Thyroid function lab tests—blood tests
- Chest X-ray
- CT (computerized tomography) —or other imaging techniques
- Thyroid scan with low-dose radioactive iodine or technetium
- Other blood or FNA testing involving molecular markers (calcitonin and CEA), for patients with indeterminate thyroid nodules

Points to keep in mind:

- Your doctor will determine the diagnostic methods to use for you. Don't hesitate to ask questions about the merits of each method.
- The fine needle aspiration (FNA) is the most reliable way to determine whether a nodule is benign, possibly cancerous, or definitely cancerous. It is frequently used to decide if more advanced testing, such as an evolving number of molecular tests, is necessary.
- The FNA cannot always determine whether cancer is definitely present or the specific type of thyroid cancer. Because of this, the tissue analysis after thyroid surgery is used to determine the diagnosis.

4. Progression of Medullary Thyroid Cancer

- The cause of most MTCs is a **gene mutation** (a change in genetic or DNA sequence) in the RET proto-oncogene.
  - The DNA change or mutation modifies the protein sequence of the RET receptor, a change that activates it, turning on a number of cellular processes that promote cell growth and suppress cell death. This combination of increased growth and a failure of normal cell death leads to development of cancer. Activation of the RET gene also leads to increased production of calcitonin.

- RET is a normal and necessary part of C cell function. But certain mutations of the RET gene cause this gene to stay switched "on." This leads to abnormal proliferation of C cells, and, in many cases, subsequent development of MTC.

- Overproduction of C cells leads to what is called "Nodular C-cell Hyperplasia," a precursor to development of medullary thyroid cancer. This condition was first observed in hereditary MTC, because thyroidectomy can be performed in asymptomatic individuals. This condition allows monitoring of these hereditary MTC patients by a blood test for calcitonin, as described later.
  - At this stage small nodules (1-2 millimeters, also called microlesions) are present, but they are not cancerous. This will generally develop into MTC over a variable period of time, so it is **very important** to continue health monitoring.

- Early detection of MTC in children or other close relatives of a patient with hereditary cancer is important, because early intervention through thyroidectomy in individuals with germline RET mutation can result in a cure.

- Early detection in children and close relatives can be done through genetic testing, discussed in sections below.

5. Sporadic Medullary Thyroid Cancer

Most patients with MTC (75-80%) will have sporadic MTC. Unlike hereditary MTC, sporadic MTC usually arises from a single C cell within the thyroid when a mutation or DNA abnormality develops.

Mutation or DNA changes of two genes, RET and less commonly RAS, have been identified in sporadic medullary thyroid cancer.

Up to 50-60% of patients with sporadic MTC will have a somatic RET mutation, similar to those seen in patients with familial MTC, but these mutations are seen only in the tumor and are therefore not inherited or passed on to children. An additional 15-20% have been found to have mutations of the RAS oncogene.

The other sporadic MTC cases are likely caused by other gene mutations, but right now many of these causes are unknown.

Testing your tumor for DNA mutations is a relatively new concept that it still finding its way into clinical practice. Some studies suggest that the detection of a mutation in your tumor may allow better individualization of your treatment. For example, finding a RET 918 mutation has been associated with a more aggressive MTC tumor. In fact, the frequency of RET 918 mutation is greatest in patients taking drug therapy and on clinical trials, but may also predict the greatest likelihood of responding to drug therapy.

With more experience, it is possible that detection of mutations within MTC tumors may play a greater role in treatment selections.

For now, the only accepted recommendation is to conduct more rigorous screening in order to find tumor recurrence at the earliest stage possible.

Note: When the genetic test for RET first became available, some studies found that roughly 6% of individuals who had been classified as having Sporadic MTC in fact had the hereditary variety.

This means their children and other family members are also at risk for MTC.

Therefore:

- It is important, if you have been diagnosed with Sporadic MTC, to still insist that your physician do an RET analysis (on a blood sample) on you to determine whether this could be hereditary.

- If you or a family member are an MTC survivor and underwent genetic tests more than 10-15 years ago, you may want to talk to your doctor about getting tested again, because there have been many advances in the testing for genetic mutations causing MTC.

6. Hereditary Medullary Thyroid Cancer and Genetic Testing

Just as it sounds, **Hereditary (Familial) MTC** is inherited and genetic testing can determine whether a patient with MTC has one of several gene mutations that have been shown to occur in inherited MTC.

Although only about 20-25% of MTC cases are Familial MTC, it is recommended that *EVERYONE* diagnosed with MTC undergo germline or blood genetic testing to determine whether the MTC is inherited, because of the implications for other family members.

Early identification of an MTC gene can, in many instances, prevent family members from ever developing MTC.

This genetic testing will determine whether the patient with MTC carries one of the RET mutations that have been shown to occur in hereditary MTC.

The identification of a mutation in you may affect your treatment plan and monitoring.

Genetic testing also gives doctors a more complete picture of an MTC patient's prognosis.

If a RET mutation is found in the patient's germline DNA, close family members of the patient (parents, siblings, children) should also be tested.

The presence or absence of a RET mutation specifically determines follow-up treatment and provides an important tool in family planning decisions.

If close relatives, especially children, are found to have the RET mutation, the thyroid gland can be removed before the MTC has a chance to develop. This is important, because in people with the RET mutation it is not so much a question as to whether MTC will develop or not, but rather "when."

Without surgery, nearly all of those with the mutation will develop MTC. With surgery, however, MTC often can be prevented in people with the mutation. So, early removal of the thyroid gland is highly recommended.

Our understanding of MTC has increased greatly over the past 20 years since the discovery of RET mutations.

While doctors have found gene mutations in about 99% of patients with familial MTC, there are a few families with proven hereditary transmission where a mutation has not been identified. Work continues to identify the mutations in these few families.

7. Multiple Endocrine Neoplasia (MEN)

Familial medullary thyroid cancer can occur by itself (FMTC), or, most commonly, as a part of a syndrome called Multiple Endocrine Neoplasia type 2 (MEN 2).

MEN2 and FMTC are caused by a mutation in the RET gene on chromosome 10.

There are 3 types of MEN 2: FMTC, MEN 2A, and MEN2B. MEN 2A is also sometimes called Sipple Syndrome, named for John Sipple, who first described it. Familial medullary thyroid cancer, a variant of MEN2A, usually is not associated with other endocrine tumors.

Genetic testing is used to uncover the specific type of RET mutation. With this information, doctors can tell you what other manifestations of this syndrome you are at risk to develop.

Familial Medullary Thyroid Cancer (FMTC)

- Patients with FMTC are at risk to develop MTC. The diagnosis of FMTC can be tricky even for an experienced doctor. Several RET mutations have been found in families that were first thought to be FMTC, but later were reclassified to MEN 2A. Only a subset of RET mutations appear to be associated with true FMTC.

- FMTC is often thought to be the least aggressive of the MEN2 syndromes. This makes the development of a treatment plan challenging. Potential problems may include:
  - MTC tumors that can occur very late in life
  - Difficulty in establishing hereditary MTC based on family history alone
  - Uncertainty regarding the best time to perform thyroidectomy
  - The unpredictable potential for rare appearance of adrenal tumors

MEN 2A

- Patients with MEN 2A are at risk for MTC, parathyroid hyperplasia (a nonmalignant growth of the parathyroid glands that causes hypercalcemia), and adrenal tumors. MEN 2A is most commonly caused by a mutation of the RET proto-oncogene, most commonly changing the amino acid that occurs at position 634.
- Genetic testing is often used to predict the clinical features of MEN2. You can get genetic testing done to help doctors figure out your prognosis and the best treatment options available, and treatment options for family members who also have this mutation.
  - For example, a family member who has a RET 634 mutation may require a total thyroidectomy at a young age. Other mutations that are statistically associated with a later development of MTC and these patients may be able to safely delay their thyroidectomy, while having frequent calcitonin monitoring.
- MEN 2A may be associated with:
  - Pheochromocytoma, a rare tumor of one or both adrenal glands that may need to be surgically removed.
  - Hyperparathyroidism, caused by excessive production of parathyroid hormone by the parathyroid glands. Hyperparathyroidism may lead to hypercalcemia.
  - Cutaneous Lichen Amyloidosis, which causes itchy skin lesions on the upper back.
  - Hirschsprung's disease, a condition associated with intestinal abnormalities or obstructions caused by missing nerve cells in the colon that are required for normal bowel movement.

MEN 2B

MEN 2B is associated with specific RET mutations, most commonly at amino acids 883 or 918.

- Individuals with these mutations often have distinctive physical characteristics. Patients with MEN 2B may have very thick lips caused by the development of benign tumors and they may develop benign tumors, called neuromas, on the tip of the tongue or in the gastrointestinal tract.
- Some patients with MEN 2B may have distinct features, such as long limbs and an altered growth state in which the lower body is much longer than the upper body.
- There is also an absence of parathyroid adenoma in these patients. The reason is unclear.
- MTC associated with MEN 2B in patients with the RET 918 mutation is often a more aggressive disease, with earlier onset and worse prognosis.
- Because of the rare nature of RET 883 associated MEN 2B the prognosis remains unclear. For this reason both MEN 2B mutations are currently treated in a similar manner.

8. Staging Medullary Thyroid Cancer

Your doctor needs to know the stage of the disease to plan your treatment. This staging will most commonly be performed following thyroid surgery, but may be done before.

The stage refers to the cancer's size, type, and whether and where it has spread at the time of diagnosis. Specific stages are used for MTC.

Medullary Thyroid Cancer Staging

Staging of cancer is a general technique for describing the location and behavior of a type of cancer and has been applied to most types of cancer.

The standard staging approach is from the American Joint Commission on Cancer (AJCC), using what is commonly referred to as TNM staging. The American Thyroid Association guidelines for medullary thyroid cancer recommend use of the AJCC approach. This staging is based on tumor size (T in TNM), spread to local or regional lymph nodes (N in TNM), and presence of distant metastases (M in TNM).

Stages

Stage I
Tumor is 2 cm in diameter (0.8 inch) or smaller, and limited to the thyroid gland with no metastases to the lymph node or any other part of the body.

Stage II
Tumor is larger than 2 cm (0.8 inch) but smaller than 4 cm (1.6 inches), and limited to the thyroid gland with no metastases to lymph nodes or any other part of the body.

Stage III
Tumor may be larger than 4 cm (1.6 inches), with no metastases to lymph nodes or any other part of the body, OR can be anywhere from smaller than 2 cm (0.8 inch) to larger than 4 cm, with regional lymph node metastases (regional refers to the neck) but no metastases to any other part of the body.

Stage IVA
Tumor may be anywhere from smaller than 2 cm (0.8 inch) to larger than 4 cm (1.6 inches), or extending outside of the thyroid gland, with metastasis to lymph nodes deep within the neck, and no distant metastasis, OR large tumor that has invaded the vertebrae of the neck or encased the artery or blood vessels in the neck, with no lymph node metastases or regional lymph node metastases, and no distant metastases.

Stage IVB
Large tumor that has invaded the vertebrae of the neck or encased the artery or blood vessels in the neck, with or without lymph node metastases, and no distant metastasis.

Stage IVC
Any tumor size or lymph node metastases, with the presence of distant metastasis.

9. Treatments for Medullary Thyroid Cancer

Your treatment will be tailored to your own circumstances, including the size of the tumor or tumors and whether the cancer has spread to local lymph nodes or distant sites (lung, bone, or liver most likely), as well as other factors.

Because of the rarity of MTC it is very important to seek out a medical team that has specific experience in the treatment of this cancer.

MTC treatments include:

- **Surgery**—usually the first step for treating any thyroid cancer. In patients with MTC diagnosed before surgery, a total thyroidectomy as well as a prophylactic central neck dissection, recommended by most experts, should be performed in patients even if the tumor has been found only inside the thyroid gland. The central neck dissection is performed because MTC often has lymph node metastases, which cannot always be detected before the initial surgery. Surgery may also be used as the primary treatment for recurrence, particularly in the neck.

- **External beam radiation**—to the neck or to solitary distant sites of spread may be considered for some patients depending upon the extent of the tumor in the neck or to localized areas of growth.

- **Chemotherapy**—especially newly approved **targeted therapies**, are sometimes used. Others may be used as part of a clinical trial for selected patients.

Points to keep in mind:

- Treatment aims to remove all or most of the cancer and help prevent the disease from recurring or spreading.

- Treating medullary thyroid cancer may use two or more of these treatment approaches.
- Discuss your treatment options with your physician so that you understand what is recommended and why. And always remember, you have the final decision. You need to be your own advocate.
- Note that common treatments for differentiated thyroid cancer (papillary and follicular), most notably radioactive iodine ablation, are NOT effective in the treatment of MTC, because C cells do not absorb iodine.
- Additionally, while thyroid hormone replacement medication must be taken daily for the rest of the patient's life, there is no benefit to taking a "suppressive" dose (a dose of thyroid hormone to suppress the TSH below the bottom of the normal range) for those with MTC. This is only appropriate for therapy for those with differentiated thyroid cancers. Therefore, in MTC the goal is to keep the blood level of TSH within the normal range.
- Treatment for patients with persistent MTC will depend on whether the cancer is localized to the neck or has spread to other parts of the body. If the cancer has spread to other parts of the body, treatment will also depend on whether the cancer is growing and/or causing symptoms.
- Patients with widespread, rapidly growing disease that is causing symptoms affecting their quality of life and ability to function will require the most intensive treatment, which may include chemotherapy.

10. Medullary Thyroid Cancer Treatment by Disease Stage

The treatment your doctor will recommend depends on the stage of your MTC. Please remember that the treatment recommended for you may differ from the general statements below, for reasons related to your individual circumstances or the experience of your doctor.

It is very important to discuss your individual treatment plan with your doctor.

Stage I or II

- Surgical removal via a near-total/total thyroidectomy.
- A central compartment neck dissection. This means surgical removal of lymph nodes in the thyroid bed area around the thyroid gland.

Stage III and IV

- Surgical removal via a near-total/total thyroidectomy, plus a central compartment neck dissection or further neck dissection (surgical removal of lymph nodes next to the thyroid or other neck locations).

Types of neck dissections

- If the cancer has spread to other lymph nodes in the side part of the neck, farther away from the thyroid, a modified lateral neck dissection is often done.
- "Lateral" refers to the side region of the neck.
- Sometimes this dissection is done only on the same side of the neck as the thyroid cancer, and sometimes it is "bilateral," done on both sides of the neck.
- Modified lateral neck dissection is a more extensive surgery than a central neck dissection because more lymph nodes are removed and more critical anatomy structures are present in the area that needs to be protected.
- A procedure referred to as a radical neck dissection is the most extensive, but is rarely needed, as it potentially removes blood vessels, muscles, and nerves when they are invaded by the cancer.

Nonsurgical treatments

- Some patients may receive **external beam radiation**.
- Some patients may receive **chemotherapy** in the form of the drugs called **vandetanib**, or **cabozantinib**. Both have been FDA approved for the treatment of progressing MTC.

- If tumor markers are increasing but there is no evidence of measurable disease progression, your doctor usually would not recommend vandetanib or cabozantinib. The physician guidelines from the National Comprehensive Cancer Network recommend these drugs only for patients with structural disease progression, not just increasing tumor markers such as calcitonin and/or CEA. The American Thyroid Association MTC Guidelines were produced prior to the FDA approval of either vandetanib or cabozantinib and address these agents only in the context of a clinical trial. These guidelines are currently being updated.
- Some patients may participate in a clinical trial for other drugs that are being investigated, or may be treated with other drugs with efficacy in MTC that have been approved for the treatment of other kinds of cancer. Most typically this occurs if they cannot take vandetanib or cabozantinib because of side effects or their tumors become resistant to both drug treatments.

11. Medullary Thyroid Cancer Surgery and Management

Surgery is generally the first and most common treatment for all stages of MTC. It is sometimes the only treatment.

As noted earlier, a surgeon will remove as much of the thyroid cancer as possible, generally through a near-total thyroidectomy, and will also do a central neck dissection.

The surgery is done to remove the cancerous cells and protect the airway, or trachea, that is right behind the thyroid gland. Tumors that grow into the airway can cause difficulty with breathing.

Sometimes it is necessary to leave a very small part of the thyroid gland behind in order to prevent damage to the parathyroid glands and the nerves that control the sound of your voice (“recurrent laryngeal nerves”).

The central neck dissection is done in MTC because of the possibility of lymph node metastases that are undetectable prior to surgery.

If there are enlarged lymph nodes, further lymphadenectomy or neck dissection (removal of lymph nodes in additional parts of the neck) will also be performed.

Points to keep in mind:

- The best outcomes and fewest complications are achieved when surgery is performed by a very experienced thyroid surgeon who has extensive experience with MTC surgery or at least very extensive experience with thyroid and thyroid cancer surgery in general.
- This means that it is best to find a surgeon who does numerous MTC surgeries each year. Keep in mind that few thyroid surgeons are dedicated to treating only patients with MTC because of how rare it is.
- A later section of this handbook has some points about finding a physician with expertise in MTC specifically and thyroid cancer and thyroid surgery in general.
- When you meet with the surgeon, ask how often he or she performs thyroid cancer surgery.
- While not all patients may have access to a surgeon who performs a large number of these surgeries per year, it is considered important that your surgeon have some kind of recent experience with MTC if at all possible. If the only surgeon in your area does not have this experience, it will be helpful if he or she consults with an expert in MTC prior to doing the surgery. You may also want to consider traveling to a specialized center to have your surgery performed.
- **The initial surgery is the most important part of your treatment.** It is standard practice to perform neck ultrasonography for all patients prior to surgery, to carefully inspect the lymph node compartments in the lateral and central neck for metastases. Some surgeons also use other imaging techniques such as CT or MRI scans, although these often do not show MTC lesions unless calcitonin is in the thousands.

- Initial MTC surgery is usually more extensive than surgery for other types of thyroid cancer. The surgeon removes lymph nodes in the central neck compartment in most people with medullary thyroid cancer when the diagnosis is made preoperatively.
- The surgeon may alter the extent of the initial surgery, depending on the tumor size and whether or not there are lymph node metastases and/or extension of tumor into nearby neck tissues. Tumor in the soft tissues of the neck can usually be removed without injuring neck muscles or the recurrent laryngeal nerve, which powers the vocal cords.
- The surgeon will remove any abnormal-appearing or biopsy-proven metastatic lymph nodes. It is recommended that the surgeon remove entire groups of lymph nodes within one or another neck compartment if at least one malignant lymph node is found.
- After the thyroid gland is surgically removed, a mutation analysis of the tumor should be performed on the tumor tissue. The tumor can be evaluated for the presence of certain mutations, particularly the RET 918 mutation. This is an important prognostic factor. and play a role in the follow up management of your disease. This test is different from genetic RET testing done to determine whether you carry a germline mutation.

After initial thyroidectomy and lymph node dissection, the role of repetitive surgery to remove additional lymph nodes is debated. Additional lymph node dissection may result in a surgical cure in no more than 5-10% of cases.

Whether to perform additional surgery after the primary surgery is an issue that should be discussed carefully with your doctor.

After Surgery— Possible Risks

The more experienced a surgeon is at performing thyroid surgery, the lower the risk of complications.

However, complications can occur even with the most experienced surgeon. There is general agreement that these risks are lower for surgeons with more experience in the management of thyroid cancer. That's why finding an experienced surgeon is considered so important.

Some Risks:

- Temporary or permanent hoarseness or loss of voice, resulting from damage to the laryngeal nerves that are located next to the thyroid gland.
  - A change in the voice quality that may be temporary or rarely permanent.
  - A number of corrective measures to improve the quality of speech are possible if the nerve is damaged. These include surgery to change the position of the affected vocal cord, or injecting the vocal cord with a substance to add bulk.
  - If both nerves are injured, some patients will have breathing problems and require a tracheotomy (placement of a permanent breathing opening in the trachea or windpipe below the voicebox), although this is extremely rare.
  - See www.thyca.org for a free webinar you can watch relating to surgery for voice issues.

- Damage to the parathyroid glands results in a condition called hypoparathyroidism, characterized by the presence of a low serum calcium concentration.
  - There are 4 parathyroid glands that are located adjacent to the thyroid gland. These glands produce a hormone (parathyroid hormone, PTH) that maintains the serum calcium in the normal range. During your thyroidectomy, the surgeon will carefully locate the glands and try to leave them in place without damaging them.
  - Symptoms of low calcium levels are muscle spasms as well as tingling and numbness, especially around your mouth in your hands or feet.

  - Hypoparathyroidism is treated with oral calcium supplementation and one of several vitamin D preparations. Generally the dose of vitamin D is higher than used for normal dietary supplementation and will be adjusted by your doctor based on the level of calcium in the blood.
  - Most frequently, the condition is temporary (transient) and treatment with calcium and calcitriol is often only needed for a period of 2 to 4 weeks.
  - In a small percentage of patients, this complication of surgery can result in lifelong hypoparathyroidism and the lifelong need for calcium and vitamin D replacement.
- Infection. This is a very rare complication. It is treated with antibiotics.
- Bleeding. This is rare and is controlled at the time of the operation or afterward.
- Neuropathy, including some pain and tightness in the neck and arms after surgery are common, but some people experience longer-lasting pain or buzzing sensations related to post-surgical nerve damage (neuropathy). Massage, physical therapy, and stretching may help. Other treatments may include pain-relieving drugs.
- Lymphedema, particularly after extensive lymph node dissections, is also a possibility. Your doctor will give you instructions regarding what helps.

Recovery from Surgery

- Most thyroid surgery requires only one night's stay in the hospital.
- Your doctor will give you instructions for the care of your incision, as well as what activities are appropriate during recovery and when you can resume your normal activities. Some patients leave the hospital with a drain coming out of their neck for a few days until the swelling goes down and no additional fluid drains.
- Your doctor will also give instructions for when you should call if there should be a problem. Before you leave the hospital, you should be given the time and date of your post-surgery appointment or at least how to arrange that by a phone call from home.

- Pillows in the hospital, during your ride home, and at home will aid your comfort.
- Rest, good nutrition, plenty of fluids, and brief walking times will also aid your recovery.
- Physical therapy may be recommended to help with tightness and weakness after surgery.
- For more information about surgery, visit www.thyca.org.
- Also, the reference book *Thyroid Cancer: A Guide for Patients,* has chapters by two thyroid surgeons on thyroid surgery and re-operative thyroid surgery.
- ThyCa's free support groups and one-to-one support are helpful resources for discussing experiences and tips for coping before and after your surgery, with others who are coping with MTC. Many support group participants are long-term MTC survivors.
- Support is available both one-to-one and in groups —in person, by phone, and online. All of ThyCa's free support services are available through our web site www.thyca.org.

12. Long-Term Monitoring

After your surgical treatment, you will receive life-long monitoring. This is for two main reasons.

- First, long-term monitoring is important to make sure that your dose of thyroid hormone replacement is appropriate—neither too low nor too high for your specific needs.
- Second, you will need testing to determine whether there is persistent disease or possible recurrence. About one in three people with medullary thyroid cancer have persistent disease or a recurrence, sometimes years after the initial treatment. The prognosis for any person with a recurrence is better if it is discovered early. This is why life-long monitoring is important.
- The exact type of monitoring, and how often it takes place, depends on the size of the original tumor and whether the cancer had spread locally or distantly, as well as other factors.

- People free of disease receive less frequent monitoring or testing than those with evidence of persistent disease.
- In those with no evidence of recurrence, testing will become less frequent as the years pass. You and your doctor should discuss a plan to fit your situation.

Monitoring will most likely include:

- **Physical neck examination,** including feeling the thyroid bed area under your scar and also the side portion of the neck where lymph nodes are located. Typically, this is done every 3 to 6 months for the first 2 years, and at least once a year thereafter.
- **Thyroid hormone and TSH Blood tests** will determine if you are on the right dosage of thyroid hormone replacement. Your medication dose may change over time.
- **Blood testing** is also important to monitor for cancer recurrence. For MTC patients, the blood tests typically performed measure **two specific tumor markers**: **calcitonin** and **CEA**.
  - It is always a good idea to discuss with your doctor any other prescription or over-the-counter medications you may be taking.
  - In particular, it is important to discuss the use of proton pump inhibitors – for example, (omeprazole), Nexium (esomeprazole) or other members of this class of drugs for gastroesophageal reflux disease (GERD) or dyspepsia – as they may affect your body's production of calcitonin. Drugs you may be using such as liraglutide (Victoza) and other GLP-1 therapies are also ones to discuss with your doctor.
- **Neck ultrasound** is increasingly used because it is a very sensitive way to find potential disease in the neck. It involves moving an instrument along your neck, without any pain, and there is no radiation exposure associated with it.

Your doctor may recommend imaging tests, such as a CT or MRI scan, in addition to blood work and ultrasound.

Each time you are tested, discuss the results and your future testing or treatment needs with your doctor.

Calcitonin and CEA Blood Tests

After surgery has been performed, there are two other indicators (known as tumor markers) that are helpful in determining how well a patient is doing.

- Calcitonin levels normally drop, sometimes to an "undetectable" level, following surgery. It generally takes 6-8 weeks for the calcitonin level to drop, but in some patients elevation may persist for as long as 4-6 months after surgery.
- Similarly, it is not uncommon for it to take 4-5 months for elevated CEA levels to go back to normal after surgery.
- A complete surgical cure is difficult to achieve for patients who have lymph node involvement in the neck at the time of diagnosis, even if the lymph nodes are removed. So, many of these patients will most likely have elevated levels of calcitonin after surgery.
- It is a good idea to get multiple calcitonin and CEA measurements 3 and 6 months after surgery in order to establish a new baseline.
- Thereafter, additional serum calcitonin and CEA measurements at 6-12 month intervals will allow the calculation of a calcitonin or CEA doubling time (the amount of time it takes for either measurement to double).
- In general, calcitonin and CEA should be measured every 6 months.
- The rate of increase for the amount of calcitonin and CEA your body produces are important prognostic factors, and may influence your course of treatment.
  - Tracking these values every 6-12 months over a period of several years is useful in determining the rate of growth or spread of the cancer. Tumors with a shorter doubling time (less than 2 years) are more likely to behave aggressively.
- Patients should fast overnight before any measurement of calcitonin to help minimize normal fluctuations in levels.
- Additionally, any patients on H2-blockers (e.g. Pepcid) or proton pump inhibitors (e.g., Prilosec, Nexium) should have their calcitonin tested after these agents have been discontinued (if possible) as they can cause elevations.

- Discuss with your doctor any prescription or over-the-counter medications you are taking, as well as any dietary factors (such as spicy food and alcohol consumption) that may affect calcitonin production.

Other Blood Tests

After surgery to remove your thyroid gland, you will be placed on thyroid hormone replacement pills, known generically as levothyroxine, which will be taken daily for the rest of your life.

During the first year after your treatment, your physician may order blood tests (thyroxine or free T4 and TSH) several times to make sure you are on the right dosage of thyroid hormone replacement. After a correct dosage of thyroid hormone has been established, yearly testing is generally adequate.

Among events that may affect your dosage of thyroid hormone replacement are new medications or supplements, weight gain or loss, pregnancy, and menopause. However, you will generally be on the same dosage for long periods of time.

For MTC patients who have had their thyroid gland removed, blood testing for the thyroid-stimulating hormone (TSH) is also done with a goal of maintaining the serum TSH in the normal range.

In addition to these tests, some doctors will also recommend the measurement of free T4, which is the actual measurement of levothyroxine levels in your blood.

If You Have Hypoparathyroidism

If you experienced parathyroid damage or loss during your thyroid surgery, maintaining proper calcium levels will be an ongoing concern. You will have your blood calcium levels monitored. You may also have levels of parathyroid hormone (PTH) and vitamin D monitored. You will receive specific instructions from your doctor regarding calcium and vitamin D supplementation.

13. Treatment of Recurrent MTC

- If MTC is not completely removed by surgery or comes back, the treatment generally depends on where the cancer is, as well as its size and extent.
- Doctors will often take a “watch and wait” approach.
- Surgery is usually the first choice if the cancer appears to be operable. However, once MTC has spread to lymph nodes, repeat surgery will usually not result in cure. Surgery to remove the lymph nodes may nevertheless be necessary, but you will need to discuss with your physician what the goals and expectations are for your situation.
- External beam radiation (EBR) may be warranted if the cancer is localized in the neck area. It should be noted that this rarely produces a “cure,” but it can be effective in suppressing the re-growth in the neck area, particularly if the patient has already undergone more than one surgery.
- The disadvantages of EBR are that it makes further surgery in that area more difficult and can lead to significant scarring to the esophagus, causing swallowing problems, and may also increase the risk associated with certain new chemotherapies.
- Targeted chemotherapy is treatment with agents directed to disrupt growth pathways in the cancer cells. Two examples are vandetanib and cabozantinib.
- Rarely, cytotoxic chemotherapy may be appropriate, or patients may receive experimental treatments in the setting of a clinical trial.
- This clinical trial option is typically reserved for situations in which other treatments fail.

External Beam Radiation

External beam radiation is sometimes given:

- As an added treatment in addition to the primary treatment (which is generally surgery), or
- As a treatment when the cancer cannot be removed by surgery, or
- As a palliative approach to relieve symptoms and improve quality of life.

It is most often used for cancer that returns after initial treatments, or to treat cancer that has spread to bone (bone metastases) or brain (brain metastases).

More about External Beam Radiation Therapy:

- External beam radiation therapy uses high-energy rays to destroy cancer cells. A machine directs a carefully focused beam of radiation at the cancer.
- This therapy usually involves treatments 5 days a week for about 6 weeks if it is to the neck, or 2 weeks if it is to a painful or solitary lesion that has spread.
- Although each treatment takes only a few minutes, the preparation before the treatment takes longer, because of the precision required to direct the beam of radiation to the appropriate area.
- The side effects depend mainly on how much radiation is given and which part of your body is treated. The radiation can destroy nearby normal tissue as well. Ask the physician supervising the administration to outline your potential side effects.
- Radiation to the neck may cause oral symptoms including a dry and sore mouth and throat, hoarseness, and difficulty swallowing. Many patients will have skin irritation similar to a sunburn – the skin in the treated area may become red, dry, and tender.
- Fatigue, especially in the later weeks of treatment, is also a common side effect.
- The side effects usually go away after the treatment ends.

Chemotherapy, Including Targeted Therapies

A newer kind of chemotherapy called “targeted chemotherapy” or “targeted therapy” is used for people with advanced medullary thyroid cancer.

Two oral, targeted chemotherapy drugs are currently available. These medications show great promise for extending the amount of time patients can live without their cancer worsening (called “progression-free survival”). As with many medications, there are potential side effects associated with treatment that should be discussed with your doctor before starting treatment.

- **vandetanib:** Approved by the FDA for treatment of progressing, locally advanced or metastatic medullary thyroid cancer in April 2011.
- **cabozantinib:** Approved by the FDA for treatment of progressing, advanced, metastatic medullary thyroid cancer in November 2012.

If tumor markers are increasing but there is no evidence of structural disease progression (that is, your tumors are not growing bigger), your doctor may not recommend vandetanib or cabozantinib. The National Comprehensive Cancer Network guidelines only recommend these drugs for patients with structural disease progression. Structural disease progression means that the disease can be detected both by blood markers, and also with an imaging method such as CT or MRI.

- **General Points about Chemotherapy**
- Chemotherapy involves the use of drugs to destroy cancer cells or to stop the pathways or mechanisms that allow them to grow and divide.
- These drugs act in a systemic fashion. This means that they enter the bloodstream and are circulated throughout the body, reaching cancer cells or pathways to cancer, wherever they may be.
- Some treatments slow disease progression, while others stop it or reduce it.
- Chemotherapy drugs are given by injection into a vein, by injection into a muscle, or as a pill that is taken by mouth.

- The new targeted therapy drugs vandetanib and cabozantinib are in pill form and are taken by mouth, usually every day. The new targeted therapy drugs are usually used at home.
- Other chemotherapy drugs may be given by injection into a vein or by injection into a muscle.
- Chemotherapy that is given by injection may be received in an outpatient clinic, in the hospital, at the doctor's office, or at home. Some people may need to stay in the hospital following treatment.
- During treatment you will be monitored for side effects and to determine the effectiveness of the chemotherapy. Your dose may be adjusted during your treatment.
- Side effects depend mainly on which drugs are given, and the dose. Your doctor can suggest ways to prevent or control many of these side effects. Ways can include lowering the dose of the chemotherapy or reducing the frequency of the treatments.
- Most side effects go away or are reduced in severity after the treatment ends. Many will go away or get better after the first few months of treatment.
- Side effects of the approved chemotherapies may diarrhea, high blood pressure (hypertension), changes in blood levels of thyroid hormones or calcium, skin changes (e.g. rash, acne, sun sensitivity, hand-foot syndrome), fatigue, increased chance of infections due to low blood counts, loss of appetite, weight loss, changes in your EKG, mouth sores or other sores, rash, nausea, neuropathy, and others.
- The length of treatment varies, depending on the drug and how effective it has been for a particular person. Most people treated with vandetanib or cabozantinib receive a maintenance dose of a drug on a long-term basis, until they lose tolerance to the medication or develop progressive disease.

- Be aware that many of the new therapies are given as pills and for the most part can be very expensive (sometimes exceeding $10,000 a month). As such, they may be covered by your prescription drug coverage, and not your medical insurance plan. It may be advisable to get the best coverage you can get for prescription drugs, because co-pays for these drugs may be considerable and limit your ability to get them. All patients with MTC and spread outside of the neck should investigate what their co-pays would be in the event that they need one of these medications. In many cases it will be better to pay a higher monthly rate for an increased level of insurance than the co-pays for these medications later. Also, check with the manufacturer of the drug for any income-based program they may have to assist patients with the co-payment.
- The U.S. Food and Drug Administration requires that information regarding an individual drugs effectiveness and side effects be readily available. Detailed information on vandetanib and cabozantinib can be found on package inserts and is available for download at manufacturer websites.

Coping with Possible Side Effects

Side effects can occur with all treatments, including newer targeted therapies

1. Surgery, external beam radiation, and chemotherapy including the newer chemotherapies, can all involve side effects. In some forms of MTC, the disease itself may involve symptoms and side effects that need to be addressed.
2. Side effects range from none to mild to moderate to severe in any given person. Most people experience moderate side effects.
3. Some side effects can be reduced, some may be able to be prevented, and for all, tips from other survivors who have experienced them can be very helpful in coping.

    - For example, gastrointestinal side effects such as diarrhea or constipation may be reduced or prevented through modifying your diet as recommended by your medical professionals.
    - Medications can help prevent some side effects, such as nausea.

- Some medications are helpful for dealing with diarrhea, which can be a symptom of MTC and/or a side effect of targeted therapy drugs.
- Certain creams and other topical treatments may be helpful for the rashes and skin lesions that develop with chemotherapy.

4. Your physician may give you written instructions regarding side effects that may occur with the specific treatments that you receive, as well as how to help prevent or cope with them.
5. For oral and intravenous medications and clinical trials, you will receive a sheet listing potential side effects. You will also receive information to call your physician if a particular side effect occurs.
6. If you are taking any nonprescription medications or dietary supplements, be sure to tell your physician. Some of these may interfere with your treatment, or interact with prescription medications and affect side effects.
7. People to ask about how to reduce or prevent side effects:

Medical Professionals

- Your physicians
- Your nurses
- Your pharmacist
- An oncology dietitian

Peer Support and More Resources

- Other survivors and caregivers in ThyCa's online support communities. They're linked from the ThyCa Home page www.thyca.org.
- Peer roundtable discussions at ThyCa Conferences and other events. Some roundtables bring together people coping with different types of thyroid cancer, because they often are coping with similar issues regarding side effects.
- Speakers at ThyCa Conferences, workshops, and seminars.
- Speakers at general cancer education events.
- Web sites such as the National Cancer Institute (www.cancer.gov) at the National Institutes of Health. See ThyCa's Links list.

- Books by physician specialists, such as: Mario Lacouture, M.D., Dermatologist, Memorial Sloan-Kettering Cancer Center: *Dr. Lacouture's Skin Care Guide for People Living with Cancer* (Harborside Press, 2012). It gives details and checklists for care of skin, hair, and nails, including potential side effects of each type of therapy and medication, and how to handle side effects.
- Wellness and Survivorship. Coping with MTC also includes emotional support, stress management, nutrition, and other aspects of self care. Find out more about these topics through ThyCa's web site, support groups, and special events.

14. Clinical Trials

If conventional treatments are not successful, you might discuss participating in a clinical trial with your doctor.

Recent advances in understanding MTC, particularly in RET proto-oncogene signaling, are now being translated into promising new therapies.

Also, a number of other therapeutic strategies are being developed that could be appropriate specifically for patients who lack RET mutations in their tumors.

Some new drugs currently in various clinical trial phases show some promise. They may be used if vandetanib and cabozantinib have already been used and are no longer effective.
They include:

- Sunitinib (Sutent) – has been approved by the FDA for kidney cancer and may be beneficial for thyroid cancer patients.
- Lenvatinib (E7080) – is an experimental drug that may be beneficial for thyroid cancer patients.
- Pazopanib (Votrient) – has been approved by the FDA for kidney cancer and may be beneficial for thyroid cancer patients.
- Everolimus (Afinitor) – has been approved by the FDA for several forms of cancer, and is in clinical trial in combination with vandetanib.

Careful thought should be given before deciding on a clinical trial.

- A clinical trial is a research study where physicians try treatment that has theoretical promise, but has not been proven to work. During clinical trials physicians systematically collect information to find out whether the treatment works.
- Making the decision about participation is not easy. On the one hand, it offers hope of increased longevity or a cure. Clinical trials also result in knowledge that might help others. On the other hand, clinical trials often involve drug side effects, and travel and expense. Some of these expenses are covered by the clinical trial. You should ask about this. These can affect a person's quality of life.
- During a clinical trial you will be monitored closely for progression and any side effects of the drug.
- This is a personal decision best reached by consideration and discussion with your doctors, family, and friends.
- Clinical trials take place in many different locations—in cancer centers, other major medical centers, community hospitals and clinics, physicians' offices and veterans' and military hospitals.
- Clinical trials usually involve travel to one or more research centers funded for the trial. The cost of the trial drug itself is usually free. However, care that is considered routine and would be normally provided outside of a trial is covered in the same way your care would be provided by your regular physician and is usually billed to insurance. You would be responsible for any normal co-pays your insurance requires (just as you would if you were not in a clinical trial). Costs for travel, and lodging may be reimbursed and you should ask about this at the time of your visit. In addition, there are often hotels with special patient/caregiver rates. Some areas have special residences that are supported by charitable donations and they may ask only for a small fee from the patient.
- **More Information:** You will find more information about clinical trials in the Clinical Trials section of ThyCa's web site www.thyca.org. Included are links to the National Cancer Institute Clinical Trials Web page, plus helpful tips from ThyCa volunteers who have participated in clinical trials.

15. Thyroid Hormone Replacement Therapy

If your thyroid was removed surgically, you will receive thyroid hormone replacement therapy (levothyroxine) for the rest of your life.

- **If you have medullary thyroid cancer,** you will receive a dose to keep your thyroid stimulating hormone (TSH) within the normal range.
- Your doctor will order blood tests periodically to ensure that you are on the proper dose of thyroid hormone replacement.

Know Your Pills

- **Levothyroxine** is the generic name for synthetic thyroid hormone prescribed for people who have been treated for thyroid cancer. Several brand-name synthetic levothyroxine preparations are currently available. Although all of these medications are synthetic levothyroxine, they are not identical. The manufacturing processes differ, as do the fillers and dyes. These differences may affect the absorption of the drug.
- For this reason, thyroid cancer specialist physicians recommend that thyroid cancer patients consistently take levothyroxine from the same manufacturer. If you need to change manufacturers for some reason, you should have your thyroid levels checked 6-8 weeks later, because your TSH may have changed and no longer be at the level recommended by your physician.
- **Wherever you obtain your prescriptions, always double check your pills when you receive them** to be sure that you are getting what your doctor prescribed.
- Another point to remember is that levothyroxine is temperature-sensitive, especially if stored above room temperature. Picking up pills at a local pharmacy may help avoid temperature extremes.
- **Store your levothyroxine pills away from heat, humidity, and light.** When the weather is warm or sunny, don't leave them in a parked car, because it can become too hot. When traveling, keep your pills from becoming exposed to heat.

- **Take your levothyroxine every day at the same time, under similar circumstances.** Most people take their pill first thing in the morning. It is best to take it with a full glass of water, an hour before eating anything or drinking any other beverage. This will ensure proper absorption, because food, minerals, vitamins, and other medications can interfere with absorption.
- After taking your levothyroxine, it is also recommended that you wait about 4 hours before taking any calcium supplements and/or vitamins containing iron. Other medications may interfere with the absorption of levothyroxine—check with your doctor or pharmacist.
- Read the information provided by your pharmacist and tell your physician if you experience any of the symptoms noted on the bottle.
- Following your thyroidectomy it may take one or more dosage changes to find the dosage level that is correct for you.

For more information, visit the Know Your Pills page of www.thyca.org or ask us for a free handout.

16. Finding the Right Doctor for You

Specialized expertise is important. MTC patients need treatment based on current knowledge about medullary thyroid cancer. Since this is a relatively rare form of cancer, there is somewhat limited direct clinical expertise in this area.

This section gives general comments about physician selection, together with some specific points to consider, plus lists of sources for finding physicians for consultation with you or your doctor, or for your treatment.

Treating thyroid cancer often involves a team of physicians, with one physician as the team leader. You will likely see several doctors in addition to your family doctor.

General Comments
We want to emphasize the importance of benefiting from the expertise of specialists, either by receiving your treatment from a specialist, or through having your physician consult with a specialist. **We cannot overemphasize the importance of this point.**

In many cases, only an endocrinologist or endocrine surgeon or medical oncologist who has treated large numbers of people with medullary thyroid cancer will have the kind of experience needed to help you maneuver through the treatment decisions regarding this disease.

It is also critically important to consider the advantages of being cared for by, or being in consultation with, physician(s) who are part of or who have access to multidisciplinary care centers rather than physicians who function in isolation from other specialists. The physicians at or with access to these multidisciplinary centers can include endocrinologists, surgeons, medical and radiation oncologists, radiologists, and clinical genetics services.

Finally, a successful initial treatment plan provides the greatest possibility of transitioning you back to your primary physician or endocrinologist for routine annual check ups. A correct diagnosis coupled with early and complete surgical intervention offers the best chance of MTC cure.

The specialists involved in MTC treatment may include:

- Endocrine Surgeons. Most perform thyroid, parathyroid, and adrenal surgery. Surgical specialists can be either Head/Neck Surgeons or Surgical Oncologists, and can specialize as endocrine surgeons.
- Endocrinologists. These are experts in diagnosis of MTC and the longterm follow-up of MTC patients after surgery. Some endocrinologists are also trained to use the new systemic chemotherapies.
- Medical Oncologists. Those who run clinical trials or have participated in running clinical trials for thyroid cancer are most likely to have experience in treating these cancers.
- Radiologists
- Clinical genetics services

Plus other physicians who are specialists in:

- Pediatric MTC
- Pheochromocytoma
- Vocal Cord Surgery

Here are some points to consider:

- If you have MTC, it's important that the physician be willing to answer questions about their experience with this particular type of thyroid cancer. Many physicians (surgeons, endocrinologists, oncologists, and radiologists) have extensive knowledge and experience with the common types of thyroid cancer, though not necessarily with MTC.
- Because of limitations associated with FNA testing in some cases you may not receive your MTC diagnosis until after your thyroid surgery. It remains important to involve a specialist to evaluate the effectiveness of your surgery and long-term treatment strategy.
- If you are not located in an area close to a center with extensive expertise in MTC, then it is important to find a doctor who is willing to consult with the expert specialists. MTC patients need physicians who are willing to consult with MTC specialists who know how to stay ahead of the disease. It may mean recommending that you travel to a distant treatment center at least for a consultation visit.
- A doctor treating MTC must be open to reviewing the latest treatment guidelines and research literature, as well as discussing treatment options with researchers and experienced clinicians, including (if needed) those involved in clinical trials of new treatment.
- ThyCa's web site (www.thyca.org) has links to professional associations with lists of their member physicians involved in thyroid cancer care.
- Many MTC specialists have spoken at ThyCa conferences and workshops. Their names can be found at www.thyca.org/support/conferences/.

- ThyCa's Medical Advisory Council Members include specialists in MTC, as do some of their colleagues at their institutions and other centers. Their names can be found at www.thyca.org/about-us/medical-advisors/.
- Participants in online support groups also share names of specialists involved in their own care. We encourage all MTC patients to join ThyCa's Medullary Thyroid Cancer E-Mail Support Group. The group invites patients and caregivers to contact other survivors and caregivers through the MTC E-mail Support Group list if they have any questions or just need support. To receive messages from this free group, follow the instructions for joining on this page: www.thyca.org/sg/email/#medullary

17. Tips for Preparing for Appointments

(Adapted from material from Washington Hospital Center in DC)

1. Bring a picture ID, your health insurance card if you have one, and your referral, if required by your insurance.
2. Bring a summary of your health history, including reports from all thyroid cancer doctors. Examples: pathology report from FNA, scan/imaging results, surgical report, with related pathology report.
3. Bring a list of medications you are taking. This includes prescription medications, over-the-counter medications, and nutritional supplements, including dose (strength) and frequency (number of times you take it each day).
4. Cancer treatment may be a very stressful process. It is helpful to write down your questions so that you don't forget to ask about anything that is important to you. You may also find it helpful to make notes of the doctors' answers/instructions.
5. Keep your notes and records in a binder or in file folders to help organize them.
6. Plan to arrive 15 minutes before your appointment.
7. Bring something to keep you busy and calm while you wait.

18. Tips for Communicating and Remembering What Your Doctor Says

- Having good communication with your doctors is one of the keys to getting good medical care.
- You want the best care. You are coming to the doctor for medical care; it should be a professional relationship.
- Take a family member or friend to the appointment. Two sets of ears are better than one.
- Take notes. Bring a notebook (or an electronic device such as a tablet computer) to write down questions as they occur to you.
- Ask for an explanation of unfamiliar terms and definitions.
- Ask for a visual aid. Seeing what your doctor is talking about on a chart or visual aid will help you remember.
- Ask if the doctor has any printed information to give you.
- Ask questions. Be your own advocate. Let your doctor know what is most helpful.

  (Adapted from tips at ThyCa support group meetings and from Teamwork: The Cancer Patient's Guide to Talking With Your Doctor by L.R. Brusky and others.)

19. Questions You May Want To Ask

For more questions to ask during your appointments, go to www.thyca.org and put "questions to ask" in the Search box.

Remember also, every patient's treatment is different. The answers will depend on your individual situation.

About the Cancer

- What kind of medullary thyroid cancer do I have? Sporadic or familial?
- What is the stage of my medullary thyroid cancer?

About Any Treatment Being Discussed

- What testing will be done? What do the results mean?
- What are my treatment options? What are the advantages and disadvantages of the treatment recommended?
- How will I know if the treatment is working?
- What are possible short-term side effects? What are the possible long-term side effects? What can help prevent side effects? What will help me cope with them if they occur?
- What happens when my treatment is over?
- How will the treatment change my day-to-day life?

More Possible Topics to Discuss:

- Surgery
- Other Treatments
- Long-Term Follow-Up Care
- Thyroid Hormone Replacement
- About my prognosis

Points to keep in mind:

- Ask questions. The medical visits are for you. Also remember, you do not have to find all answers immediately.
- Some answers may change over time, based on changes in your personal medical situation and research advances.

20. Recordkeeping Tips

It is very helpful to keep copies of all lab tests and medical reports. You may want to keep paper copies, store them on your computer, or use a medical history app on your smartphone or tablet. Use the system that makes sense for you.

Keep a notebook such as a loose-leaf 3-ring binder, or else file folders, with your medical records, notes from appointments, and other helpful information.

At home, a box or a file cabinet can store your past records, insurance papers, and other materials. Your materials will probably become extensive. You also can scan your records and keep them on a flashdrive.

Many people keep files on their computers, or use a smartphone or tablet app. Many hospitals are moving to electronic records and will provide you with copies of lab reports and tests on a web site that you can access.

On your computer, a log or journal, updated after each test or appointment, is helpful. You can print it out and add it to your paper files and 3-ring binder.

Make copies of printed forms you fill out, such as the medical history form that you complete at your first visit with a new physician.

Take your most recent records to your appointments. You may need a tote bag. You may receive new materials at your visit.

MTC Topics on which to keep records

Your calcitonin and CEA levels, with dates measured. List all you know about over time.

- Be aware of factors unrelated to MTC that may cause calcitonin levels to fluctuate or increase. Examples include some of the common drugs used for acid reflux, beta blockers for cardiac issues, Contrast dye used in CT scanning, the lab testing technique used if not the same each time, other tumors or conditions, and poor kidney function.
- Discuss changes in test results with your physician to determine the possible cause or causes.

21. Living with Medullary Thyroid Cancer

Each person's journey with medullary thyroid cancer is unique.

Please remember, you are not alone. All of us connected through ThyCa are here to help you cope with the challenges of all the aspects of this disease.

Many patients and caregivers have found it helpful to consider these questions, suggested by oncologist A. B. Weir, M.D., in *"When Your Doctor Has Bad News."*

- How will I learn to live with my illness?
- Who am I now? How can I matter?
- Do I have a new mission?
- What gifts can I give?
- How do I best prepare my loved ones to live with my illness?
- Can this type of life be my finest hour?

We invite you to find support and education from ThyCa's free local support groups, free online groups, and special events.

What Helps Most in Coping:
From MTC Patients in ThyCa's E-Mail Group

- Knowledge is power, and we hope that that power will help to ease your fears.
- Be strong when you can and cry when you can't. Showers are a particularly good place for a GOOD cry.
- The most important thing to fight your illness: your will to keep fighting.
- Well-wishes, prayers, e-mails, e-hugs, phone calls, and socks! Just remember to collect rubber duckies and wear colorful socks!

22. Coping with Metastatic Disease

Please know that many “meddies” live for many, many years with MTC that has metastasized to their liver. It is not uncommon for it to spread there. Although it is not a good thing, it is not as bad as when most other types of cancers spread to the liver.

That is why it is so important to see a true specialist. They will be able to assess the cancer and help to evaluate the risks in the near future and in the distant future. If you are in one of the higher risk categories (which is not automatic just because it has spread to the liver), or you have metastatic disease that is growing, there may be options such as chemotherapies or newer investigational drugs in clinical trials.

In general, it is thought that any cancer in the neck that can be removed surgically should be, hopefully during the initial surgery. This goes for people even if their cancer has spread. That is because the neck is the most likely place for it to cause problems, if it grows into or pushes on the trachea, threatening the airway. It is also the easiest place to operate on.

However, many doctors who don't know MTC either leave some cancer in lymph nodes behind because they didn't do a thorough preoperative neck ultrasound or neck MRI. Others are surprised by the tenacious adherence of the cancer to healthy tissues, including important nerves, etc.

Experts know how to scrape it and they know just how far to go without damaging the nerves. You want someone who truly knows how to make that judgment call while doing the operation. You don't want a surgeon who will be surprised and you don't want one who is aggressive at the expense of quality of life.

Regarding choosing between chasing the new tumor or waiting and watching, there is no clear answer. You need to get the facts from your doctor(s) and then make the decision that best fits your personality.

Ask others you trust for help/input if you need it. You are the one living with the cancer and the surgeries.

23. Success Stories

While it is devastating to come out of surgery to find out that a cure wasn't possible, it is very uplifting to read that many people go on for many years living with MTC—even those who didn't have access to newer treatments now becoming available.

We all love the success stories — those who were cured and those who weren't.

Our web site's Medullary section on www.thyca.org, has MTC Journey Stories. We also publish MTC stories in our newsletter. We invite you to share your story with ThyCa.

24. Coping and Mood Swings

We are surrounded by good people who have normal energy and "ordinary" life problems, and we forget why we are so tired and why, some days, simply getting up and putting in a full day is the most courageous of acts.

We are surrounded by well-intentioned people who, in repeatedly asking how we're doing, remind us of what we try daily to put out of our minds; or people who forget entirely, and cannot understand why we can't keep up with them, why our battle is different.

We face the daily knowledge that there may not be a happy ending at all, except in whatever glory is to be found in our daily struggle to control our own lives—and there is, it should be noted, substantial (if often unnoticed) glory in that effort.

Maybe our mood swings aren't so mysterious. Part of it really is hormones. The emotions trigger physical effects. Don't be afraid to seek physical causes and medical solutions.

But we should be gentle on ourselves and recognize that part of these mood swings are not mysterious at all. In part, at least, they are just another side effect of what we battle every day.

25. Will I be able to work full time with MTC?

Each person is different. Depending on when your cancer was discovered, the extent of the disease, your general state of health outside of your cancer, your age, and many other factors, MTC can be a "small bump" on the road of life, or a major detour.

The type of work that you do, including the work schedule, physical and mental requirements, and possibilities for flexibility in hours and duties, also affects your possibilities for work.

Many MTC patients take short-term disability leave from work during their initial treatment to allow their body to heal and adjust to life without a thyroid. They then return to work part time or full time, depending on their financial needs and their speed of recovery.

Others may change from full time to part time employment. Some who are self-employed may be able to adjust their schedules and work.

For others, MTC signals the time to retire, focus on health, and enjoy family time.

26. For more information about MTC

- **Visit our web site www.thyca.org, including our Medullary Thyroid Cancer section on the site.** Our web site receives review and input from more than 50 experts. It has more than 800 pages of information, support, plus a Calendar of Events and links to free support services and numerous helpful organizations and additional resources. The Medullary Thyroid Cancer site on www.thyca.org also includes MTC journey stories written by MTC patients and caregivers.
- Watch and listen to the free Webinars with MTC experts, also available **free** on our web site www.thyca.org.

- Watch and listen to the videos of MTC patient and caregiver experiences, as well as physician perspectives on coping with the practical and emotional impacts of thyroid cancer, including MTC.
- Join ThyCa's free **Medullary Thyroid Cancer E-Mail Discussion and Support Group** for ongoing communication, information, and support from other MTC patients and caregivers. This group's members include long-term survivors of MTC, as well as caregivers. Participants share experiences, strength, and hope, offering encouragement and understanding to each other. The group's past messages are all archived for reference by participants. Instructions for joining this free group are in this handbook and on www.thyca.org.
- Follow ThyCa on Facebook and Twitter and the ThyCa Inspire online community, all linked on our web site's home page www.thyca.org. We post news updates on these sites as well as in the MTC E-Mail Group.
- Attend the annual **International Thyroid Cancer Survivors' Conference**, sponsored by ThyCa. MTC specialist physicians lead sessions and answer questions about the latest advances in MTC treatment and research. In addition, numerous other specialists cover issues important to people with any type of thyroid cancer. Additional roundtable discussion sessions give opportunities for MTC survivors and caregivers to share experiences and coping tips and give and receive support. Details are on www.thyca.org.
- Read the MTC Guidelines for Physicians, published by the American Thyroid Association, as well as the MTC guidelines for physicians from the National Comprehensive Cancer Network. These guidelines are written by MTC experts for use by other physicians. The guidelines provide technical discussions of options and recommendations on the care of Medullary Thyroid Cancer. Remember, these documents are written for medical professionals, so may not be completely understandable to patients and caregivers.

27. Thyroid Cancer? ThyCa can help.

We are an internationally recognized, medically advised organization providing **free** support services to people with thyroid cancer.

- **For patients and caregivers** — We offer information and understanding to patients and their families when they need it most.
- **For the public** — We promote awareness for early detection, and provide outreach and education year-round. We sponsor Thyroid Cancer Awareness Month each September.
- **For professionals** — We provide this free handbook, patient brochures and wallet cards, free downloadable Low-Iodine Cookbook for patients with differentiated thyroid cancer, and other materials to give to patients. Plus research funding, with grant recipients selected by an expert panel of the American Thyroid Association.

Free Services & Resources: Award-winning web site • Person-to-person support • Local support groups • E-mail support groups • Awareness brochures • Regional workshops • Annual International Conference • Online newsletter • Handbooks • Downloadable Low-Iodine Cookbook • and more

Please contact us for more information and free materials:

ThyCa: Thyroid Cancer Survivors' Association, Inc.
www.thyca.org · thyca@thyca.org
Toll-free 877-588-7904 • Fax 630-604-6078
P.O. Box 1102, Olney, MD 20830-1102

ThyCa: Thyroid Cancer Survivors' Association, Inc., is a nonprofit 501(c)(3) organization of thyroid cancer survivors, family members, and health care professionals, advised by distinguished thyroid cancer specialists and dedicated to support, education, communication, awareness for early detection, and thyroid cancer research fundraising and research grants.

Medullary Thyroid Cancer

This handbook is available free of charge in these formats:

- You may download it in 8 ½ x 11 inch format, for a loose-leaf binder or other binding.
- In its compact handbook form (5 ½ x 8 ½ inches), we mail individual copies to patients, caregivers, and anyone interested in thyroid cancer.
- We also mail the handbook in bulk, free of charge, to physicians and other health care professionals, and to thyroid cancer support groups and related organizations.

Courtesy of

ThyCa: Thyroid Cancer Survivors' Association, Inc.
Support • Education • Communication • Hope Through Research

Serving people with thyroid cancer, and their families, friends,
health care professionals, and the public,
since 1995

www.thyca.org