Medullary Thyroid Carcinoma: Management of Lymph Node Metastases

Jeffrey F. Moley, MD, St. Louis, Missouri

Key Words
Thyroid gland, cancer, malignancy, medullary thyroid cancer, multiple endocrine neoplasia, lymph node metastasis, thyroidectomy, neck dissection

Abstract
Medullary thyroid carcinoma (MTC) is a neuroendocrine malignancy of the thyroid C cells. Metastatic spread commonly occurs to cervical and mediastinal lymph nodes. MTC cells do not concentrate radioactive iodine and are not sensitive to hormonal manipulation. Surgery is currently the only therapy that can reliably lead to cure, reduction in tumor burden, or effective palliation. In patients with hereditary MTC, central lymph node dissection should be considered in preventative operations if the calcitonin level is elevated. Systematic surgical removal of at-risk or involved lymph node basins (compartmental dissection) should be performed in all patients with palpable primary tumors and recurrent disease. A “berry-picking” approach is discouraged. Although data are limited, standard chemotherapy and radiation therapy have not been shown to be effective in the treatment of MTC. Newer targeted drug therapies are promising and are being examined in therapeutic clinical trials. (JNCCN 2010;8:549–556)

Medullary Thyroid Carcinoma
Medullary thyroid carcinoma (MTC) comprises 3% to 9% of all thyroid cancers and arises from thyroid C cells. MTC has several distinctive features. First, MTC may be sporadic (75% of cases) or hereditary, occurring in all patients with multiple endocrine neoplasia type 2 (MEN 2) syndromes (25% of cases). Second, although MTC is more aggressive than differentiated thyroid carcinoma, it is still an indolent malignancy, with reported 10-year survival rates from 69% to 89%. Finally, unlike differentiated thyroid cancer, no known effective systemic therapy exists for MTC, although recent trials with small molecule inhibitors are promising. MTC cells do not concentrate radioactive iodine and are not sensitive to manipulation of thyroid stimulating hormone (TSH). These features must be considered when planning therapy for a patient with MTC.

Calcitonin is produced by thyroid C cells and MTC. It is a sensitive and specific tumor marker that may be measured in blood in the basal state, or after the administration of the secretagogues calcium and pentagastrin (no longer available in the United States). Calcitonin levels are almost always elevated in patients with MTC. Measurement of calcitonin levels is helpful in screening patients who are at risk for MTC and in following up those who have been treated. After thyroidectomy for MTC, elevated blood levels of calcitonin indicate persistent regional nodal metastasis or distant metastasis. Some MTCs also secrete carcinoembryonic antigen (CEA), but its long half-life and lower specificity make it a less useful marker.

Most patients with sporadic and some with hereditary MTC present with a thyroid nodule. In these patients, the rate of clinical cervical lymph node involvement is as high as 75%, and additional occult metastases may be present. Clinical complaints, including respiratory difficulty, hoarseness, and dysphagia, are present in approximately 15% of patients with palpable disease, and approximately 10% to 15% will have evidence of distant metastases at presentation.

MTC does not concentrate iodine and presents as a cold nodule on thyroid scintigraphy scans. CT scans...
may show nodules with areas of characteristic calcifications within the thyroid and possibly extrathyroidal disease. Fine-needle aspiration of the palpable thyroid nodule or cervical lymph node metastasis is a sensitive means for establishing the diagnosis of MTC. Ultrasound examination of the neck is a sensitive technique for identifying cervical lymph node metastases.

Primary MTC tumors may invade adjacent structures, including larynx, trachea, recurrent laryngeal nerve, and esophagus. In familial forms, tumors are usually bilateral and multifocal. Once the primary tumor is established, metastasis to regional lymph nodes is an early event. Nodes in the central compartment (levels VI and VII) are most often involved, followed by levels II through V on the ipsilateral, and frequently the contralateral, side (Figures 1, 2). Metastatic spread to the upper and anterior mediastinum may be observed. Hematogenous spread occurs variably in the course of MTC, generally to the liver, lungs, and bone. Distant metastases often occur in a fine miliary pattern that is not well visualized on CT scans or other anatomic imaging.

Lymph node involvement in MTC affects prognosis, and nodal status is incorporated into the American Joint Committee on Cancer MTC staging classification, in addition to tumor size, invasion, and distant metastases. In several studies, 10-year cause-specific survival was most influenced by age, stage, and postoperative basal calcitonin levels. This was confirmed in a recent review, which again showed that the most sensitive predictors of survival were age at diagnosis and tumor stage. In this series, differences in survival time were correlated with biochemical and radiographic remission. In those who did not, 10-year survival was slightly reduced to 73%. These observations confirm the indolent nature of the disease and suggest the benefit of therapeutic interventions that keep tumor burden at a minimum (reoperative surgery when technically possible, cytostatic agents, selective use of external-beam radiation therapy [EBRT]).

**Initial Treatment**

Surgical treatment of MTC is influenced by several factors: 1) the clinical course of MTC is usually more aggressive than that of differentiated thyroid cancer, with higher rates of recurrence and mortality, especially in young patients; 2) MTC cells do not take up radioactive iodine; 3) hormone suppression is ineffective; 4) MTC is multifocal and bilateral in 90% of patients with hereditary forms of the disease and in 20% of patients with the sporadic form; 5) nodal

---

**Figure 1** Lymph node groups in the neck. From Fialkowski EA, Moley JF. Current approaches to medullary thyroid carcinoma, sporadic and familial. J Surg Oncol 2006;94:737–747; with permission.
metastases are present in more than 70% of patients with palpable disease; and 6) the ability to measure postoperative calcitonin levels allows adequacy of surgical extirpation to be assessed.

Because of the high likelihood of a familial component and the effectiveness of early surgery, all patients with or at risk for MTC should undergo genetic screening for germline RET mutations. Several groups have published recommendations regarding genetic testing. Additionally, because of the prominence of pheochromocytoma in MEN 2, the diagnosis of pheochromocytoma must be excluded in all cases of MTC before surgery, either through a negative genetic screen or measuring plasma metanephrines or urine catecholamines. If a pheochromocytoma is present, it should be removed before thyroidectomy.

Recently published guidelines for clinicians include recommendations for managing MTC in multiple relevant clinical settings.

Management of Lymph Nodes During Operations for Palpable MTC

In patients with palpable MTC (sporadic or hereditary), total thyroidectomy is the appropriate treatment for the primary tumor, accompanied by a central node dissection. Calcitonin levels are virtually always elevated in these patients. Classification and methods of central neck lymph node dissection have been described by several groups. In this operation, all thyroid and nodal tissue is removed from the level of the hyoid bone superiorly to the innominate vessels inferiorly. A systematic (compartment-oriented) approach to the removal of all nodal tissue in the central neck has been reported to improve recurrence and survival rates when compared retrospectively with procedures that remove only grossly involved nodes. Preoperative ultrasonographic evaluation of neck nodes is helpful, and suspicious nodes may be marked (skin marking is usually adequate) and removed at operation. CT and fluorodeoxyglucose PET may be useful in these patients, however, ultrasound allows a more detailed evaluation of nodal architecture and enables easier localization, biopsy, and marking in the perioperative setting.

The likelihood of lateral compartment lymph node involvement (levels II–IV) is related to the presence and extent of nodal disease in the central compartment, although “skip metastases” have been reported. In one study, the presence of 0; 1 to 3; or 4 or more central lymph node metastases was correlated with a 10.1%, 77%, and 98% risk for metastatic involvement of ipsilateral level II through IV nodes, respectively. For contralateral lateral compartment involvement, the rates were 4.9%, 28%, and 77% with the presence of 0; 1 to 9; and 10 or more central lymph node metastases, respectively.

In a report from the author’s institution, the surgeon’s ability to detect lymph node metastases intraoperatively was evaluated in 73 patients. In this series, metastases were present in 80% of central nodes, 75% of ipsilateral jugular nodes (levels II–IV), and 47% of contralateral jugular nodes. Notably, intraoperative palpation of nodes was not an accurate
predictor of the presence or absence of metastases in a nodal compartment. The sensitivity of intraoperative assessment by the surgeon was only 64% and the specificity was 71%. Therefore, reliance on intraoperative assessment would miss involved nodes 36% of the time. Preoperative imaging, particularly with ultrasound, is helpful in delineating the extent of nodal spread and in planning the extent of node dissection, as has been described in differentiated thyroid carcinoma.24

Patients with established MTC (palpable or present on imaging studies, with elevated calcitonin levels) should undergo total thyroidectomy and central neck dissection, and unilateral or bilateral dissection of levels II through V nodes should be considered. The decision to resect lateral nodes depends on the extent of central neck node involvement and results of preoperative imaging4,10,18,24 (Figure 3). In patients with central lymph node metastases and negative imaging of the lateral neck, however, performing at least an ipsilateral level II through IV compartment lymph node dissection should be done because of the high likelihood of microscopic nodal involvement.10,23 If the contralateral neck is also negative on imaging, however, most surgeons, including the author, would not perform an immediate dissection because of increased morbidity, scarring, and the unproven therapeutic benefit.

Controversy exists over the optimal management of the parathyroid glands. In the past, the author’s group routinely performed 4-gland parathyroidectomy with autotransplantation, arguing that adequate bilateral central node dissection is not possible if the parathyroid glands are left in place with sufficient blood supply. Reported rates of long-term hypoparathyroidism are low with this approach.25 Since 2005, the author’s approach has been to resect and autotransplant the 2 parathyroids on the side of the primary tumor and the contralateral lower parathyroid, leaving the contralateral upper parathyroid in situ on a vascular pedicle if possible. All removed parathyroids should be carefully minced into 1 x 3 mm fragments, and fragments transplanted into individual muscle pockets (2–3 fragments per pocket) that are then closed with a suture.26 Transplantation of whole minced glands into a single pocket is discouraged. Parathyroid fragments may be transplanted into individual muscle pockets in the sternocleidomastoid muscle in cases of sporadic disease, familial MTC, or MEN 2B. They may be transplanted into the nondominant forearm in cases of MEN 2A in patients who have a significant risk for future hyperparathyroidism (e.g., codon 634 RET mutation carriers). The reason for this difference is the risk for subsequent graft-dependant hyperparathyroidism in some patients with MEN 2A, which is more easily localized and treated if the grafts are in the forearm.

Hereditary MTC

MTC is a sporadic malignancy in 75% of cases and hereditary in 25%. Hereditary forms of MTC occur as part of MEN 2A and related syndromes. These include MEN 2A, characterized by MTC, pheochromocytoma, and hyperparathyroidism; MEN 2B, characterized by MTC, pheochromocytoma, mucosal ganglioneuromatosis, megacolon, and a distinct marfanoid habitus; and familial MTC, characterized by MTC alone. Patterns of inheritance in these syndromes are autosomal dominant, and all known MEN 2 variants are caused by mutations in the RET proto-oncogene. MEN 2A is caused by mutations at extracellular cysteine residues, MEN 2B is usually caused by a methionine to threonine mutation at codon 918 in the tyrosine kinase catalytic domain, and familial MTC is caused by the same mutations as MEN 2A and by less common mutations in the intracellular portion of the protein.16,27

MTC is the hallmark of these syndromes, with nearly 100% penetrance, but its aggressiveness and clinical course vary among clinical subtypes. MTC in
the setting of MEN 2B is generally most aggressive, with invasive carcinoma often presenting in the first year of life. Patients with codon 634 (level II) mutations have an increasing risk for lymph node metastasis beginning in the mid-teens, with more than 40% cumulative risk by 20 years of age. MTC in the setting of familial MTC or codon 609, 768, 790, 791, 804, or 891 mutations is least aggressive, commonly presenting in the second or even third decade of life. The surgical approach in older RET mutation carriers should be individualized based on calcitonin level, presence of palpable disease, imaging results, RET mutation, and family history.

**Management of Lymph Nodes During Preventative Operations for Hereditary MTC**

The author’s group at Washington University reported long-term follow-up on a series of 50 young patients with MEN 2A after total thyroidectomy, central node dissection, and total parathyroidectomy, with autotransplantation of all of the parathyroid tissue into the muscle of the nondominant forearm during the primary surgical procedure. Long-term disease control was excellent. Long-term parathyroid function was normal (no supplementation) in 47 of 50 patients. Other groups reported good results with selective removal of lymph nodes and parathyroids in young, at-risk patients. Recent follow-up studies indicate that the likelihood of nodal metastases is extremely low in patients younger than 8 years with MEN 2A and familial MTC, and in those with basal calcitonin level less than 40 pg/mL. Because of this, the group’s practice is now to perform total thyroidectomy, leaving the parathyroids in situ, if possible, in children with low calcitonin levels. In patients with an elevated calcitonin level, the group performs total thyroidectomy, central node dissection, and parathyroid autotransplantation. In either case, these operations should only be performed by surgeons experienced in thyroid and parathyroid operations in children.

Patients with MEN 2B require a different approach; thyroidectomy should be performed in infancy because MTC is often already established at birth. Central neck dissection should be performed if the calcitonin level is elevated. This procedure requires that the surgeon has identified and preserved the parathyroids, either through autotransplantation or on an intact pedicle. If the parathyroids cannot be identified and preserved, only the thyroid should be removed. The consequences of hypoparathyroidism in infants are disastrous, and all possible steps must be taken to avoid this. These operations should only be performed by surgeons experienced in identifying parathyroid glands in children and infants. These parathyroids are extremely small and may be translucent, often obscured by prominent cervical thymic tissue, making identification difficult for even the most experienced parathyroid surgeon.

**Postoperative Follow-Up**

All patients with MTC should be followed up with postoperative serial serum calcitonin levels to survey for persistent or recurrent disease. Serum calcitonin is very useful in the follow-up of postoperative patients with MTC, and elevated levels indicate residual or recurrent disease. Provocative calcitonin testing with calcium and pentagastrin stimulation is more sensitive for small amounts of disease, but pentagastrin is not currently available in the United States.

The author’s group recommends that patients who have undergone prophylactic total thyroidectomy and central lymph node dissection for MTC have serum calcitonin measured postoperatively and then semi-annually thereafter. The postsurgical reduction of calcitonin level indicates degree of success in eradicating the tumor and serves as a baseline. The expression *biochemical cure* has been used to describe a patient treated for MTC who has a normal calcitonin level. Basal calcitonin values usually decline sharply after adequate surgical treatment. Measuring calcitonin doubling times over months and years of follow-up is recommended, and higher doubling times correlate with more aggressive progression.

Patients with elevated but stable calcitonin levels over time often do very well clinically, and follow-up and treatment should not be overly aggressive.

**Management of Persistent or Recurrent Disease**

Reoperation should be considered in patients with elevated calcitonin levels in the setting of inadequate initial operation, imaging evidence of recurrent or persistent disease, and threat of compression...
or invasion of the trachea and major vessels. In experienced hands, reoperative surgery for locoregional disease can achieve long-term control and biochemical cure in up to one third of patients.\textsuperscript{17,36,38–41} Before proceeding with neck reoperation with curative intent, a metastatic workup is necessary to evaluate the lungs, liver, and bones. Patients who have systemic symptoms from a metastatic tumor (e.g., pain, flushing, diarrhea) may benefit from a palliative tumor debulking procedure.

Re-exploration of the neck to remove metastatic lymph nodes carries a higher risk for complications, including thoracic duct leak, injury to a recurrent laryngeal nerve, and hypoparathyroidism. Central neck reoperations in children are especially dangerous because of the small size of the parathyroids, and should be avoided unless absolutely necessary (e.g., bulky central disease threatening the airway or great vessels).

Redo central neck dissection may be facilitated by a “back-door” or lateral approach, in which the strap muscles are mobilized laterally off of the carotid, and the space between the carotid and the trachea is entered through a previously unoperated tissue plane\textsuperscript{42} (Figure 4). The recurrent laryngeal nerve and parathyroids may then be identified, allowing for safe removal of recurrent or residual central disease and lymph nodes. In a series of 100 redo central neck operations by the author’s group, no recurrent nerve injuries occurred using this approach.\textsuperscript{43} Lateral neck dissections (levels II–V) are performed as necessary based on preoperative imaging and whether central nodes are involved.

Radioactive iodine ablation has not been shown to be beneficial in MTC, because the tumor cells do not take up iodine. A “bystander effect” has been suggested for radioactive iodine treatment of small intra-thyroidal tumors, but this has only been reported anecdotally.\textsuperscript{44} Radioactive iodine certainly has no role in the treatment of lymph node metastases from MTC.

Published studies investigating the role of EBRT in MTC have been retrospective and used small patient cohorts. The benefit of EBRT in MTC remains controversial. In a study by Brierley et al.,\textsuperscript{45} 46 of 73 patients underwent EBRT at a median dose of 40 Gy, with no overall benefit shown. Subgroup analysis of 40 patients with “high-risk features,” however, showed a higher local/regional relapse-free rate in irradiated compared with nonirradiated patients. Unlike published surgical series, calcitonin levels were not reduced by EBRT. The added disadvantage of EBRT is its effect on tissues (i.e., radiation-induced scarring and fibrosis), which makes subsequent surgical intervention more difficult and risky.

The use of immunotherapy antibody-based treatments targeted at CEA in selected patients with MTC showed limited promise in clinical trials. A single study using the humanized anti-CEA monoclonal antibody labetuzumab showed significant inhibition of MTC tumor growth in vivo, but a phase

---

**Figure 4** “Back door” approach to recurrent metastatic nodal disease in the left central neck of a young patient with multiple endocrine neoplasia type 2B. There is a node replaced by tumor that is abutting the recurrent laryngeal nerve (RLN).
Management of Lymph Node Metastases

I trial using labetuzumab only showed limited benefit in patients with advanced MTC. The authors expressed that the lack of a significant treatment response could be related to the relationship between pharmacokinetics and tumor burden, suggesting that the drug would probably be more successful in patients with early-stage disease.

Previous clinical response rates for chemotherapy have been disappointing in patients with locally advanced or metastatic MTC. Understanding of MTC molecular oncogenesis, however, has resulted in identification of novel molecular targets for treatment. Most current targeted molecular therapies fall under the classification of tyrosine kinase inhibitors. Vandetanib (ZD6474, Zactima, AstraZeneca Pharmaceuticals) is a novel anilinoquinazoline compound engineered to selectively inhibit vascular endothelial growth factor receptor, endothelial growth factor receptor, and RET tyrosine kinases. In a study of 30 patients with advanced hereditary MTC, Wells et al. reported a 20% partial response rate and a greater than 50% reduction of calcitonin levels in 24 of 30 patients. Several other institutional and multi-institutional phase II drug trials are ongoing or completed for MTC patients with unresectable, measurable, and locally advanced MTC.

Conclusions

The propensity for MTC to metastasize to cervical lymph nodes is a defining feature of this disease that informs surgical management in all clinical settings: prophylactic surgery in RET mutation carriers, primary operations for established tumors, reoperations for persistent and recurrent disease, and palliative procedures for symptomatic tumors. Eradication of involved nodes can result in long-term cure or disease control. A working knowledge of cervical lymph node anatomy and the natural history of MTC spread within these nodal groups is important to surgeons managing these patients. The parathyroid glands are intimately related to the central nodes. Careful, correct management of the parathyroid glands in these situations will minimize the risk for hypoparathyroidism, which especially must be avoided in young children.

References

Moley


