The Surgical Management of Medullary Thyroid Cancer

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Medullary thyroid cancer (MTC), accounts for approximately 5% to 10% of all thyroid cancers and arises from the parafollicular thyroid C cells, neuroendocrine cells that produce calcitonin, and carcinoembryonic antigen. MTC may occur either as a sporadic event (75%) or secondary to a germline mutation of the RET proto-oncogene (25%) with an autosomal dominant pattern of inheritance and almost complete penetrance. Critical to treatment of this disease is complete surgical resection because MTC cells do not take up iodine and thus iodine-131 therapy is ineffective. Total thyroidectomy is the recommended treatment in all patients with MTC. Because lymph node metastases frequently occur in the central compartment of the neck, central neck dissection, defined as removal of all fibrofatty and lymphatic tissue from the hyoid bone to the innominate vessels, between the internal jugular veins is indicated.

Over the last decade, significant advances in the understanding of the biology and clinical outcomes of MTC have been made, culminating most recently in the publication of treatment guidelines by the American Thyroid Association. The MTC expert panel followed an evidence-based approach because the lack of randomized clinical trial data for MTC limits the ability to form strong consensus recommendations on key issues.

Recommendation levels followed by this esteemed panel include;

“A” STRONGLY RECOMMENDS

The recommendation is based on good evidence that the service or intervention can improve important health outcomes. Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.
“B” RECOMMENDS

The recommendation is based on fair evidence that the service or intervention can improve important health outcomes. The evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

“C” RECOMMENDS

The recommendation is based on expert opinion alone.

Among the most important, recommendations 61 to 64 address the extent of surgery in typical cases of MTC.

RECOMMENDATION 61

Patients with known or highly suspected MTC with no evidence of advanced local invasion by the primary tumor, no evidence cervical lymph node metastases on physical examination and cervical ultrasound, and no evidence of distant metastases should undergo total thyroidectomy and prophylactic central compartment (level VI) neck dissection (Grade B recommendation).

Prophylactic lateral neck dissection was omitted (Recommendation 61, Grade B). In discussion, the panel recognized a minority view that considers prophylactic ipsilateral modified neck dissection as a possible option. The data supporting this treatment recommendation are discussed later in further detail. Results of preoperative neck ultrasound and biopsy strongly influence the extent of surgery.

RECOMMENDATION 62

Patients who have MTC with suspected limited local metastatic disease to regional lymph nodes in the central compartment (with a normal ultrasound examination of the lateral neck compartments) in the setting of no distant (extracervical) metastases or limited distant metastases should typically undergo a total thyroidectomy and level VI compartmental dissection. A minority of the Task Force favored prophylactic lateral neck dissection when lymph node metastases were present in the adjacent paratracheal central compartment (Grade B recommendation).

Hence, the finding of positive central and negative lateral nodes typically would be treated with total thyroidectomy and level VI dissection only (Recommendation 62, Grade B).

There is some controversy as to the recommended extent of lymph node dissection in patients presenting with a palpable nodule diagnosed on fine needle aspiration (FNA) cytology to be MTC. In a recent report, more than 80% of patients referred with persistent or recurrent MTC were judged to have had an inadequate initial operation. More than 50% of patients have persistently elevated calcitonin levels after initial surgery for MTC. As noted earlier, standard surgical treatment for patients diagnosed with MTC is total thyroidectomy and central compartment lymph node dissection. Controversy exists as to the requirement for a unilateral lateral neck lymph node dissection or bilateral lateral neck lymph node dissection.

In general, for patients with familial or sporadic MTC with clinical evidence of regional metastatic disease, compartment-oriented neck dissection in a systematic fashion is advocated. In patients with familial MTC and an elevated basal calcitonin level or a thyroid nodule palpable on physical examination or visualized on ultrasonography, total thyroidectomy with central compartment lymphadenectomy and bilateral
lateral neck dissection may be performed. In patients with presumed sporadic MTC, and importantly when the primary mass is large (> 2 cm) or when paratracheal nodes are involved, an ipsilateral lateral neck dissection on the side of the lesion may also be indicated. In patients with palpable cervical lymphadenopathy a bilateral lateral neck dissection may also be performed. This approach maximizes local regional tumor control while minimizing the need for reoperation. With improvement in preoperative imaging, specifically high sensitivity ultrasound, operation in the contralateral lateral neck may be performed when cytologically proven disease by FNA is documented.

Moley recently analyzed the distribution of nodal metastases in patients where MTC presented as a palpable thyroid mass. These data indicate a significant incidence of disease in the contralateral lateral neck when patients presented with palpable MTC. In patients with unilateral palpable primary tumors, there was a 47% incidence of positive contralateral nodes in Levels II, III, and IV. These authors recommend a bilateral modified neck dissection in patients with palpable MTC. If this can indeed be performed safely, bilateral neck dissection would seem to maximize local tumor control even further. This dissection is controversial as noted earlier in the ATA recommendations.

RECOMMENDATION 63

Patients who have MTC with suspected limited local metastatic disease to regional lymph nodes in the central and lateral neck compartments (with ultrasound-visible lymph node metastases in the lateral neck compartments) in the setting of no distant metastases or limited distant metastases should typically undergo a total thyroidectomy, central (level VI), and lateral neck (levels IIA, III, IV, V) dissection (Grade B recommendation).

Thus, the presence of abnormal central and lateral nodes typically would lead to total thyroidectomy with central compartment dissection, and lateral neck dissection involving levels IIa, III, IV, and V.

RECOMMENDATION 64

In the presence of distant metastatic disease, less aggressive neck surgery may be appropriate to preserve speech, swallowing, and parathyroid function while maintaining locoregional disease control to prevent central neck morbidity (Grade C recommendation).

Thus, less aggressive neck surgery may be appropriate in the setting of extensive metastatic disease (Recommendation 64, Grade C).

TECHNICAL DETAILS OF CENTRAL AND MODIFIED NECK DISSECTION

The extent of central neck dissection includes all thyroid tissue and all nodal tissue from the hyoid bone superiorly to the innominate vessels inferiorly. Central nodal tissue on the anterior surface of the trachea is resected and the superior surface of the innominate vein behind the sternal notch is exposed. Fibrofatty tissue between the carotid sheaths and trachea is removed including the paratracheal nodes along the recurrent laryngeal nerves. This dissection is continued inferiorly on the right to the point at which the junction of the innominate artery and carotid is exposed and to a comparable level on the left behind the head of the clavicle. This systematic compartment oriented lymphadenectomy approach to the surgical management of medullary thyroid cancer has been shown to improve local-regional control and suggested to improve survival (Fig. 1).
A lateral neck lymph node dissection involves removal of lymph nodes anterior and posterolateral to the jugular vein. Defined limits are the posterior belly of the digastric muscle superiorly, the spinal accessory nerve posterolaterally, and the thoracic inlet and clavicle inferiorly. The sternocleidomastoid muscle, jugular vein, carotid artery, and vagus nerve are preserved (see Fig. 1). If the jugular vein or sternocleidomastoid

muscle are involved with tumor, these are resected as a part of the specimen. If a bilateral dissection is indicated and the jugular vein has been resected on one side, this is best done as a two-stage procedure. If flow in the jugular vein is interrupted on the contralateral side, severe facial edema will result.

There is also some controversy as to how the parathyroid glands should be managed in these patients. Total parathyroidectomy with parathyroid autotransplantation and parathyroid preservation procedures have both been advocated. A strong argument can be made in this disease that it may not be possible to perform an adequate nodal clearance unless at least the inferior parathyroid glands are removed. The parathyroid glands may also be devascularized during the course of the central lymph node dissection. Thus, Moley and colleagues advocate total parathyroidectomy with autotransplantation as a part of total thyroidectomy and central nodal clearance in MTC. Alternatively, an attempt may be made to preserve in situ the superior parathyroid glands (usually located just superior and posterior to the junction of the recurrent laryngeal nerve and inferior thyroid artery). As suggested earlier, the inferior parathyroids are usually inseparable from the central compartment lymph nodes and the thymic horn that extends from the lower pole of the thyroid gland. Thus, the inferior parathyroids should be identified when possible, confirmed histologically to avoid autografting a lymph node metastasis, and then autografted into either the sternocleidomastoid muscle in the neck (and marked with a clip to facilitate identification if hyperparathyroidism was to develop) or into the non-dominant forearm.

There are, of course, other management issues of importance to consider in the overall surgical management of patients with MTC including

1. Work-up preoperatively for pheochromocytoma
2. The surgical management of coexisting endocrinopathies in patients with multiple endocrine neoplasia (MEN) IIA AND MEN IIB
3. The timing and extent of surgery in patients carrying the RET proto-oncogene mutation.

PREOPERATIVE PHEOCHROMOCYTOMA WORK-UP

All patients with a diagnosis of MTC should be investigated for the possibility of a concurrent pheochromocytoma, which may occur in patients with MEN 2A and MEN 2B. A history of hypertension should be sought, associated with the triad of symptoms consisting of headache, palpitations, and diaphoresis. Other symptoms may include anxiety and tremor. Some patients may report panic attacks, and may have been previously diagnosed with an anxiety disorder.

The diagnosis of pheochromocytoma in patients with a history suggestive of this disorder is then based on biochemical tests and the demonstration of elevated catecholamines or catecholamine breakdown products. The diagnostic standard in these patients is a 24-hour collection of urine for determination of catecholamines, vanillylmandelic acid, and metanephrine levels. Plasma catecholamine and metanephrine levels may also be used. Abdominal imaging with three-dimensional CT, and in some circumstances metaiodobenzylguanidine, identifies the anatomic location of the pheochromocytoma.

SURGICAL MANAGEMENT OF COEXISTING ENDOCRINOPATHIES IN PATIENTS WITH MULTIPLE ENDOCRINE NEOPLASIA IIA AND MULTIPLE ENDOCRINE NEOPLASIA IIB

All patients with MTC should have a detailed history taken to determine a family history of any thyroid, parathyroid, or adrenal disorders. As noted earlier, in patients with
hereditary MTC there is essentially complete penetrance of MTC; all patients who inherit the mutant allele will develop MTC. Other endocrinopathies in the MEN 2 syndromes demonstrate incomplete penetrance patterns. Specifically, in MEN 2A, approximately 40% of patients inheriting the mutant allele will develop pheochromocytomas and 30% of patients will have hyperparathyroidism. In MEN 2B, approximately 50% of patients will develop pheochromocytomas, and complete penetrance of neural gangliomas (lips, tongue, digestive tract) is observed. Hyperparathyroidism does not occur in MEN 2B. These patients also have a distinct clinical phenotype with a marfanoid habitus, skeletal abnormalities, and the potential for development of megacolon.

All patients with a preoperative diagnosis of MTC should be screened for pheochromocytoma with a 24-hour urine collection for metanephrine, vanillylmandelic acid, and free catecholamines. Hyperparathyroidism is assessed by the measurement of serum calcium levels and intact parathyroid hormone levels. Blood should also be drawn for RET oncogene analysis.

The parathyroid lesion in MEN 2A, like that in MEN 1, is a generalized but asymmetric hyperplasia that often may not result in hypercalcemia. For MEN 2A patients with hypercalcemia, either subtotal parathyroidectomy or total parathyroidectomy with thymectomy and parathyroid autotransplantation may be performed.

Patients from MEN 2 families should undergo yearly screening for pheochromocytoma beginning at 5 to 10 years of age. In contrast to the aggressive behavior of MTC, if not treated early, pheochromocytoma in MEN 2 is rarely malignant. The adrenal glands in patients with MEN 2 should ideally be removed when a pheochromocytoma develops, before the onset of symptoms of excess catecholamines. Evidence suggests that unilateral adrenalectomy be performed as the initial procedure in patients who have MEN 2 with a unilateral adrenal abnormality on CT scan. Approximately one third of patients who undergo a unilateral adrenalectomy will ultimately require a subsequent operation for a contralateral tumor. However, this may not occur for many years and patients are not left Addisonian and steroid dependent in the interim. In patients that requires bilateral adrenalectomy, cortical sparing techniques may prevent the need for exogenous steroid replacement.

TIMING AND EXTENT OF SURGERY IN PATIENTS CARRYING THE RET PROTO-ONCOGENE MUTATION

The recent American Thyroid Association treatment guidelines also address this critical issue and reaffirm the importance of germline DNA testing for RET mutations in all patients with MTC whether or not they have a positive family history. This is a Grade “A” recommendation and based on the classic “Brandi paper” as reported as a part of the Gubbio International Consensus. This paper is highly recommended reading for clinicians involved in the care of patients with MTC. The Gubbio International Consensus clarified the genotype: phenotype correlations observed in patients with specific RET oncogene mutations and recommended appropriate timing for thyroidectomy in these patients and their families (Fig. 2).

**Gubbio International Consensus**

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<th>Level 3 (Highest Risk)</th>
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<tr>
<td>1. Children with MEN 2B and RET codon 883, 918, 922 mutations</td>
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<tr>
<td>2. Total thyroidectomy in first 6 months of life with central compartment nodal dissection</td>
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Level 2 (Higher Risk)
1. Children with RET codon 611, 618, 620, 634 mutations
2. Total thyroidectomy before 5 years of age
3. Central compartment nodal dissection (no consensus).

Level 1 (High Risk)
1. Children with RET codon 609, 768, 790, 791, 804, 891 mutations

Fig. 2. The RET proto-oncogene and genotype-phenotype correlation in MTC. (From Kouvaraki MA, Shapiro SE, Perrier ND, et al. RET proto-oncogene: a review and update of genotype-phenotype correlations in hereditary medullary thyroid cancer and associated endocrine tumours. Thyroid 2005;15:531–44; with permission.)
2. Total thyroidectomy recommended
3. No consensus at what age.

PROGNOSTIC FACTORS

Stage of disease at diagnosis most accurately predicts length of patients’ survival. Long-term survival (>10 years) is common (60% to 90%) in patients without metastatic disease or unresectable local-regional disease. Patients with metastatic disease, however, have 5-year survival rates of approximately 50%. Thus, prognosis for patients with medullary thyroid cancer falls between those patients with well-differentiated thyroid tumors and anaplastic thyroid cancer. Adverse prognostic factors also include patient age greater than 50 years and MEN 2B. Seventy percent of patients with MEN 2B have metastasis at the time of diagnosis and less than 5% survive 5 years.

The degree of primary tumor invasiveness has also been determined to be an important prognostic variable. In these series, primary tumor invasiveness was the only parameter that correlated with a failure to reduce postoperative calcitonin levels to the normal range in patients who were reoperated for recurrent or persistent MTC.

INDICATIONS FOR REOPERATIVE SURGERY

Following primary surgical treatment for MTC, up to 50% of patients have persistently elevated serum calcitonin levels. Initial evaluation of these patients should follow two important principles:

1. Determine the extent and adequacy of the primary surgery that has been performed.
2. Consider and systematically evaluate sites of potential disease recurrence: cervical and mediastinal lymph nodes, thyroid bed, liver, lung and bone.

Reoperative lymphadenectomy should be performed as a part of a standardized diagnostic and treatment algorithm. In a recent series Fleming and colleagues reported the MD Anderson Cancer Center results and surgical strategy for medullary thyroid cancer. In this series, 40 subjects underwent surgery for MTC and were divided into three groups based on whether they had undergone previous thyroidectomy and on the results of standardized staging studies. Group 1 subjects had not had previous surgery and consisted of 11 individuals. Group 2 subjects (13) had undergone thyroidectomy before referral and had elevated calcitonin levels but no radiologic evidence of loco-regional or distant metastatic disease. Finally, group 3 consisted of 16 subjects who underwent thyroidectomy before referral but now had an elevated calcitonin with radiologic evidence of local-regional recurrence. Twenty-nine percent of subjects in groups 1 and 2 achieved normal calcitonin levels postoperatively, whereas only 6% of subjects (one subject) in group 3 achieved normal calcitonin levels with a much higher incidence of postoperative hypoparathyroidism. The authors thus advocate that compartment oriented lymphadenectomy be performed early in the course of MTC.

EXTENT OF REOPERATIVE SURGERY

In patients who have evidence of elevated serum calcitonin levels after previous thyroidectomy, meticulously performed reoperative surgery may result in biochemical cure in 20% to 30% of patients and may improve survival. After the adequacy of the initial surgery is assessed, the subsequent operation is planned. Compartmental cervical nodal dissection is now indicated if it had not been performed previously
and is guided by neck and mediastinal imaging. The central compartment of the neck including the thyroid bed is re-explored with a unilateral or bilateral lateral neck dissection. Mediastinal lymphadenectomy is generally performed only when imaging studies suggest recurrent tumor in the Level VII nodes.

The goal of lymphadenectomy for asymptomatic calcitonin elevations is the removal of microscopic metastatic nodal disease to prevent dissemination. However, a number of case series have shown that only a minority of patients actually achieve a biochemical cure following reoperative regional lymphadenectomy. In a recent series from Moley and colleagues, an improved ability to normalize postoperative serum calcitonin levels was found compared with an earlier series. Calcitonin levels were normalized in 17 out of 45 subjects at reoperative surgery. The authors note that improved subject selection was an important factor in these improved results including the use of staging laparoscopy.

ROLE OF DIAGNOSTIC LAPAROSCOPY

Laparoscopy has been advocated for the diagnosis of subclinical hepatic metastases before reoperative surgery. Because of the hypervascular nature of MTC hepatic metastases, these tumors are poorly visualized on CT, and are generally not seen on MRI until they approach 1 cm in size. Tung and colleagues reported that in a series of 44 subjects, metastatic MTC lesions were detected in 10 of these subjects and 9 of these 10 subjects had negative preoperative CT or MRI. These lesions may have a miliary appearance with multiple, small, white raised lesion on the liver surface (1–5 mm in diameter) or a small subcapsular lesion may be detected appearing as a small mass on the surface of the liver. Unfortunately, laparoscopy will detect only these surface metastases; laparoscopic hepatic sonography may be useful in detection of hepatic parenchymal lesions.

In summary, significant advances in the understanding of the biology and clinical outcomes of MTC have been made over the last decade, resulting most recently in the publication of treatment guidelines by the American Thyroid Association. This scholarly work is strongly recommended to the reader to gain further understanding and in-depth insight in the management of patients with medullary thyroid cancer.

REFERENCES


