

Surgical strategy for the treatment of sporadic medullary thyroid carcinoma: our experience

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SUMMARY: Surgical strategy for the treatment of sporadic medullary thyroid carcinoma: our experience.

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Background. Medullary thyroid carcinoma (MTC) is a rare disease which accounts for approximately 5-9% of all thyroid cancers and originates from the calcitonin-secreting parafollicular C cells. MTC can be divided into two subgroups: sporadic (75%) or inherited (25%). The majority of patients with invasive MTC have metastasis to regional lymph nodes at the time of diagnosis, as evidenced by the frequent finding of persistently elevated calcitonin levels after thyroidectomy and the high rates of recurrence in the cervical lymph nodes reported in retrospective studies.

Objectives. The purpose of the study is to review our single institution's experience with MTC since 1998 and to evaluate surgical strategy, patterns of lymph node metastases and calcitonin response to compartment-oriented lymphadenectomy in patients with primary or recurrent sporadic medullary thyroid carcinoma.

Methods. A retrospective review of 26 patients treated for MTC at the "Antonio Cardarelli" Hospital referral center, in Naples, between

1998 and 2012. There were 18 female and 8 male patients, median age at presentation was 55 years, and median follow-up for survivors was 5 years. Total thyroidectomy was performed in all 26 patients; central compartment (CC) node dissection (level VI) in 12 (46%) patients; central plus lateral compartment (LC) node dissection (levels II, III, and IV) in 7 (27%) patients. 4 patients (15%) underwent reoperation for loco-regional recurrent/persistent MTC.

Results. After a median post-surgical follow-up of 5 years (range 1-10 years), 63 % of patients were living disease-free, 15% were living with disease and/or persistently elevated calcitonin levels after surgery, 11% were deceased due to MTC and 11 % were lost to follow-up.

Conclusions. We agree with most authors advocating for a total thyroidectomy and prophylactic central neck dissection in the setting of clinically detected MTC. Lateral neck dissection may be best reserved for patients with positive preoperative imaging. Nevertheless MTC has a high rate of lymph node metastases that are sub optimally detected preoperatively in the central compartment by neck ultrasound or intra-operatively by the surgeon, and reoperation is associated with a higher rate of surgical complications. In our limited experience, patients with thyroid confined nodular pathology, without nodal disease and unknown preoperative diagnosis of MTC, underwent only total thyroidectomy with a good prognosis.

KEY WORDS: Medullary thyroid carcinoma - Total thyroidectomy - Neck dissection.

Introduction

Medullary Thyroid Carcinoma (MTC) was first described by Jaquet in the German literature as "malignant goiter with amyloid" (1). In 1959, Hazard et al. provided a definitive histological description, while Williams further suggested that MTC originated

from the calcitonin-secreting parafollicular C cells of the thyroid gland, which derive from the neural crest (2-5). MTC accounts for approximately 5-9% of all thyroid cancers (6). MTC presents worldwide as part of an autosomal dominant inherited disorder in about 20-25% of cases and as a sporadic tumor in the remainder (7,8). Inherited MTC syndromes (multiple endocrine neoplasia type 2, MEN 2) affect approximately 1 in 30,000 individuals and consist of MEN 2A (Sipple's syndrome), familial MTC (FMTC), and MEN 2B (9-12). Affected individuals initially develop primary C-cell hyperplasia (CCH) that progresses to early invasive medullary microcarcinoma, and eventually develop grossly invasive macroscopic MTC (13). The RET gene was first identified in 1985 (14). In 1987, the genetic defect causing MEN 2A was lo-

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cated on chromosome 10 (15). In 1993 and 1994 it was demonstrated that MEN 2A and FMTC, and MEN 2B, respectively, were caused by germline RET mutations (9,16-18). Thus, a RET gene mutation occurring in the germline that results in expression of abnormally overactive Ret protein in all tissues in which it is expressed causes these specific inherited syndromes. Somatic RET mutations that occur later in life and are limited to C cells are present in 40–50% of sporadic MTCs (19-21). The 10-year disease-specific survival of MTC is about 75%. Important prognostic factors that predict adverse outcome include advanced age at diagnosis, extent of primary tumor, nodal disease, and distant metastases (22,23).

Diagnosis is currently made with the routine use of serum calcitonin (CT) measurements to screen patients with nodular thyroid disease. Surgery is the only curative treatment of MTC and since cervical lymph nodes metastases are frequent and can occur at an early stage, a standardized lymph node dissection should be associated to total thyroidectomy. When tumor remnants persist after surgery, there are very few therapeutic alternatives, and these are generally of limited curative value (23-30).

We reviewed the records of 29 patients who underwent surgery between October 1998 and September 2012 in order to evaluate surgical strategy, patterns of lymph node metastases, and calcitonin response to compartment-oriented lymphadenectomy in patients with primary or recurrent sporadic medullary thyroid carcinoma.

Patients and methods

After referral to our Endocrine and General Surgery Unit, all patients underwent standard pretreatment staging studies that included physical examination, cervical ultrasonography or computed tomography (CT), CT of the chest, CT or magnetic resonance imaging (MRI) of the liver, and a bone scan. Cervical ultrasonography was the preferred technique for assessing the extent of cervical disease and/or cervical recurrences. Preoperative serum calcitonin levels were assessed by radioimmunoassay. Patients with normal or undetectable calcitonin values were assayed at 30, 60, 120, and 240 seconds after stimulation with 0.5 g/kg of pentagastrin.

In patients with known or highly suspected MTC without advanced local invasion or cervical node or distant metastases, we performed total thyroidectomy and prophylactic central compartment lymphadenectomy. Instead, in patients with suspected local metastatic disease to regional lymph nodes in the central and lateral neck compartments, better with US-visible lymph

node metastases in the lateral neck compartments, in the setting of no or limited distant metastases, we performed a total thyroidectomy, central (level VI), and lateral neck (levels IIA, III, IV, V) dissection. Patients referred after thyroidectomy with or without some form of neck dissection, or in cases of recurrent MTC, underwent re-excision of the central neck compartment and eventually, also bilateral modified radical neck dissection if it had not already performed and in the presence of visible disease preoperatively on ultrasonography or during surgical exploration.

One to two months after surgery, the calcitonin and CEA levels of all patients were assessed; those with normal or undetectable calcitonin levels were evaluated using pentagastrin stimulation. Postoperative basal and stimulated calcitonin levels were used to define partial response (decrease in calcitonin by >50% after surgery), complete response (normal basal calcitonin level after surgery), and sustained complete response (normal basal and stimulated calcitonin level after surgery) on all follow-up outpatient visits. Patients with an elevated calcitonin level and no abnormal physical findings underwent ultrasound examination of the cervical and supraclavicular regions, chest x-ray or CT, and US or MRI of the liver at 6-month intervals. Suspected cervical recurrences identified on radiologic images were subjected to fine-needle aspiration biopsy; reoperation was performed to confirm cervical recurrences.

Local-regional external beam radiotherapy (EBRT) was recommended to patients with microscopic residual disease or histologic evidence of extranodal soft tissue extension of tumor and to patients who had recurrences after a cervical operation performed at our surgical Unit. Systemic chemotherapy was reserved to patients with rapidly progressive measurable metastatic disease.

Results

In our Endocrine and General Surgery Unit, from October 1998 to September 2012, 3218 patients underwent thyroidectomy; among these, 484 thyroidectomies (15%) done for cancer, including 26 MTC (5,37%). There were 18 female (69%) and 8 male patients (31%), median age at presentation was 55 years (range 31-80 years) and median follow-up for survivors was 5 years. Total thyroidectomy was performed in all 26 patients; central compartment (CC) node dissection (level VI) in 12 (46%) patients; central plus lateral compartment (LC) node dissection (levels II, III, and IV) in 7 (27%) patients, in 6 unilateral (23%) and in 1 (4%) bilateral. 4 patients (15%) underwent reoperation for loco-regional recurrent/persistent MTC: 1 patient underwent re-excision of the

central neck compartment; 2 patients a bilateral radical neck dissection, with the resection of right internal jugular vein in one case; the last patient underwent a bilateral mediastinal lymphadenectomy through posterolateral thoracotomy. Histopathological examination of specimens showed 21 intracapsular MTC and 5 MTC with loco-regional invasion; in 9 cases were detected lymph node metastases.

After a median post-surgical follow-up of 5 years (range 1-10 years), 63 % of (16) patients were living disease-free, 15 % (4) were living with disease and/or persistently elevated calcitonin levels after surgery, 11 % (3) were deceased due to MTC and 11% (3) were lost to follow-up.

Discussion

Medullary thyroid carcinoma is unique among solid tumors because of its ability to secrete calcitonin, a highly sensitive and specific serum marker of persistent or recurrent disease even at a microscopic level (29). Previous investigators have focused on the use of cervical lymphadenectomy to achieve a clinical and biochemical systemic cure as assessed by serum levels of calcitonin (29). This approach was based on the theory that indolent diseases such as MTC may metastasize to regional lymph nodes in the absence of established distant organ (liver, lung, or bone) metastasis (31). Critics of extended surgical procedures for MTC favor a biologic view, suggesting that lymph nodes are a marker of systemic disease and therefore that wider surgical resections would not affect critical host-tumor relationships, which determine the development of distant metastasis, and that lymphadenectomy would result in little change in the overall survival duration (32). However, serum calcitonin is easily measured and accurately reflects the presence or absence of disease. It was therefore unavoidable that the end point for surgical therapy would be the presence or absence of microscopic disease as assessed by serum levels of calcitonin (29). The relatively long survival duration experienced by most patients with MTC, regardless of the extent of surgical treatment, combined with the visible nature of surgical complications, including voice change and permanent hypoparathyroidism, has caused most surgeons to take a conservative approach to the surgical management and follow-up of patients with MTC (33). According to our experience we agree with most authors advocating for a total thyroidectomy and prophylactic central neck dissection in the setting of clinically detected MTC (22). Particularly, in MTC patients without advanced local invasion and no evidence of cervical lymph node metastases or distant metastases by preoperative imaging, we

advocates for total thyroidectomy and eventually, also according to surgical exploration with palpation, prophylactic central compartment (level VI) neck dissection; in MTC patients with suspected limited local metastatic disease to regional lymph nodes only in the central compartment, detected preoperatively by US, and in the setting of no distant (extracervical) metastases, we perform a total thyroidectomy and level VI compartmental dissection; in MTC patients with suspected limited local metastatic disease to regional lymph nodes in the central and lateral neck compartments, detected preoperatively by US, and in the setting of no distant metastases, we perform a total thyroidectomy, central (level VI) and lateral neck (levels IIA, III, IV, V) dissection. In synthesis, lateral neck dissection may be best reserved for patients with positive preoperative imaging.

Finally, in most MTC patients with advanced local disease or extensive distant metastases, the surgical goal is thyroidectomy, level VI compartmental dissection and therapeutic (clinical or image-positive) lateral neck dissection. However, in the presence of extensive distant metastases or advanced local features, the goals of surgical therapy are typically more palliative with attention to minimizing complications, such as hypoparathyroidism, and maintaining normal speech and swallowing. These patients should additionally be considered for clinical trials, and other palliative therapies including surgery, external beam radiation therapy (EBRT) and hepatic embolization (22). Preoperative imaging for presumed MTC when an FNA or Ct level is diagnostic or suspicious for MTC is indicated because local neck or distant metastatic disease may change the operative approach. The sensitivity of intra-operative palpation to detect lymph node metastases by experienced surgeons is only 64% (34). Lymph node metastases are present in >75% of patients with palpable MTC (34,35). In the setting of an experienced ultrasonographer, neck US is the most sensitive test to detect local metastases in the cervical compartments and upper aspect of the superior mediastinum (35-39). However, it is common that a higher number of malignant lymph nodes are removed surgically during compartmental lymph node dissections than were visualized preoperatively with US, which demonstrates the reduced sensitivity of all diagnostic maneuvers to localize the smallest lymph node metastases (22,39). Furthermore, calcitonin-negative MTC is a rare occurrence but possible (40). In our limited experience, 7 patients (27%) with MTC confined pathology, without nodal disease and unknown diagnosis, underwent only total thyroidectomy with a good prognosis. Of these, in 4 cases (15%) preoperative elevation of serum calcitonin levels was not significant.

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