Medullary Thyroid Carcinoma: Why Is Specialization Mandatory?

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Keywords

Medullary thyroid carcinoma · Calcitonin · Thyroidectomy · Lymph node metastases · Endocrine surgery

Summary

Medullary thyroid carcinoma (MTC) represents a distinct form of thyroid cancer with a potentially aggressive behavior, early lymph node metastases, and sporadic as well as hereditary forms. Only surgery with total thyroidectomy and lymph node dissection is able to achieve biochemical cure. Due to the uncommon nature of MTC, a specialization in endocrine surgery for diagnosis as well as therapy of MTC seem to be mandatory for a successful treatment. Knowledge of genotype-phenotype correlations for hereditary forms or routine calcitonin screening for sporadic forms is important to analyze preoperative findings and plan surgical procedures. Postoperative follow-up depends on biochemical cure or monitoring for patients with elevated calcitonin levels.

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Introduction

According to the data of the Robert Koch Institute, which is responsible for German cancer statistics, the estimated incidence of thyroid cancer is 6,700 cases/year in 2018. The incidence of medullary thyroid carcinoma (MTC) in Germany can only be related to other European countries such as Denmark with 0.2 cases per 100,000 inhabitants per year [1]. In the USA, medullary thyroid carcinoma accounts approximately for 1–2% of thyroid cancers [2].

Data from this manuscript have in part been presented at the symposium 'Frontiers in Surgical Evolution' on September 21, 2018 in honor of Prof. Dr. Ernst Klar, Rostock, Germany.

In 1959, Hazard et al. [3] histologically described MTC for the first time. Williams [4] discovered in 1966 that MTC derived from the parafollicular C cells, and only 2 years later, Tashjian and Melvin [5] showed that these cells produce calcitonin. During the next decades, many physicians and endocrine surgeons observed an increasing number of familial forms of MTC, but it took quite a long time until molecular techniques were able to identify mutations of the *RET* proto-oncogene responsible for hereditary MTC. In 1993 [6, 7], germline mutations of the *RET* proto-oncogene, located on chromosome 10q11.2, were found to be responsible for the hereditary forms of MTC (FMTC) and multiple endocrine neoplasia (MEN2A and MEN2B) syndromes. These findings enabled not only a completely new insight in the pathogenesis of MTC but the results of molecular genetics also justified to perform prophylactic thyroidectomies in patients at risk for MEN2A [8]. In 2015, the revised American Thyroid Association (ATA) guidelines for the management of medullary thyroid carcinoma described the most common 17 mutations of the *RET* proto-oncogene and their risk for developing MTC as well as pheochromocytoma and hyperparathyroidism [2].

Diagnosis and Surgical Therapy of Medullary Thyroid Carcinoma

While the rate of surgery performed for hereditary MTC was as high as 66% during the 1990s [9], it has now been decreasing constantly to about 20% during the last years (table 1). Today, physicians see mainly sporadic forms of MTC, with tumors often presenting as quite unremarkable thyroid nodules in ultrasound. A multicenter analysis of the results of 641 MTC lesions which underwent fine needle aspiration cytology showed relatively heterogeneous results ranging from 12.5 to 88.2% [10].

Moley and colleagues found out that more than 70–75% of the patients presenting with palpable MTC have lymph node involvement and that 10% already have distant metastases [11, 12]. Therefore, surgical procedures for MTC do not only require a meticulous

Table 1. Time trends of sporadic and hereditary medullary thyroid carcinoma (MTC) between 1994–2000 and 2009–2018

	1994–2000	03/2009–09/2018
Patients, n	36	27
Sporadic/hereditary MTC, %	44 / 66	92 / 8
Preoperative calcitonin levels, pg/ml	44–22,280	15–16,000
T categories: pT1 / pT2 / pT3/ pT4, %	17 / 72 / 0 / 11	56 / 26 / 11 / 7
Lymph node metastases, %	75	37
Biochemical cure, %	44	72
5-year survival rate, %	96	96
Recurrence-free survival, %	71	82

technique for total thyroidectomy but also a routine or systematic lymph node dissection of the central and lateral cervical compartment of the neck to provide the goal of biochemical cure (= postoperative normalization of calcitonin) [9, 13, 14].

In the majority of studies, prognosis of MTC is related to the patient's age at diagnosis, male gender, extrathyroidal invasion, lymph node metastases, and distant metastases, mostly detected in the lung, the liver, and the bones. Currently, biochemical cure rates of 62–76% are reported in experienced centers [15–17].

Why Is Specialization Mandatory?

With an increasing number of sporadic MTC appearing often as inconspicuous thyroid nodules, preoperative calcitonin screening provides an important tool to discriminate between benign and malignant findings. During the last years, biochemical cure rates of patients with sporadic MTC improved constantly in the era of calcitonin screening [17]. Therefore, the German Association of Endocrine Surgeons recommends routine calcitonin screening before every thyroid operation to exclude or detect MTC [18, 19]. The interpretation of calcitonin levels, however, can be challenging because of a variety of falsely high levels caused by medication such as proton pump inhibitors or lithium, alcohol abuse, renal insufficiency, or children under 3 years of age. To assess possible problems of the interpretation of calcitonin testing, a differentiated knowledge of these side effects and the various calcitonin assays seems mandatory. In female patients with calcitonin levels ≥ 35 pg/ml and male patients with calcitonin levels ≥ 46 pg/ml, the risk for MTC is considered to be markedly elevated [20]. Other studies defined 60–65 pg/ml as cut-off values of calcitonin to detect MTC [21, 22]. Earlier detection of MTC leads to better biochemical cure rates, as shown by Machens and Dralle in 2015 [17].

If calcitonin is elevated in two different blood samples obtained at different visits, further diagnostic should be performed with laboratory tests for catecholamines and adrenal ultrasound or computed tomography (CT) scan to exclude pheochromocytoma to prevent hypertensive crisis during thyroidectomy. A family history should be obtained. Patients with sporadic MTC should be offered a genetic counseling and DNA analysis for *RET* germline muta-

tions. Patients with MEN2B syndrome often have a typical phenotype which can only be noticed by an experienced physician and should be tested for the *RET* codon M918T mutation.

Operative procedures for MTC require a specialization in endocrine surgery to enforce an oncologic approach for this potentially aggressive cancer in order to achieve the best biochemical cure rates for the patients. In addition, special training is necessary to preserve intraoperatively important structures such as the recurrent laryngeal nerves, the vagal nerves, the spinal accessory nerve, the brachial and cervical plexus, as well as the thoracic duct or the parathyroid glands. Continuous intraoperative nerve monitoring seems to better preserve the recurrent laryngeal nerves, especially from traction to the nerve. The goal of MTC surgery is to be as aggressive as necessary but to preserve all of the important structures and the patient's quality of life.

Total thyroidectomy and compartment-oriented central and ipsilateral lateral lymph node dissection are the recommended procedures for patients with calcitonin levels > 20 pg/ml and < 200 pg/ml. If calcitonin levels are ≥ 200 pg/ml, the contralateral lateral compartment should be dissected too. Compartment-oriented neck dissection does not only enable better biochemical cure rates but also prevents local recurrence in the neck.

If MTC is diagnosed incidentally by histopathological examination, the results of completion thyroidectomy and lymph node dissection are less favorable than for primary surgery [9, 17].

Postoperative biochemical chemical cure rates do not only depend on calcitonin levels or the experience of the surgeon. They are also influenced by important other aspects of MTC such as a more aggressive clinical course due to a somatic *RET* codon M918T mutation in sporadic MTC [23] or the histopathologic finding of desmoplasia in the tumor tissue, which seems to be the most reliable indicator of metastatic potential of MTC [24]. Both examinations require highly specialized pathologists to describe these conditions.

According to the ATA management guidelines for MTC [2], serum levels of calcitonin and carcinoembryonic antigen (CEA) should be measured 3 months postoperatively, and if undetectable or within the normal range, these should be measured every 6 months for 1 year, and then yearly thereafter. In patients with detectable serum levels of calcitonin and CEA, a follow-up should be provided at least every 6 months. Barbet et al. [25] described the prognostic impact of calcitonin doubling times for follow-up in MTC. If calcitonin doubling times were less than 6 months, 5-year survival rates were 25% compared to 92% in those with calcitonin doubling times between 6 and 24 months.

In case of postoperatively elevated calcitonin levels, detection of persistent or recurrent MTC should start with ultrasound, followed by neck and chest CT, contrast-enhanced magnetic resonance imaging of the liver and F-Dopa-PET(positron emission tomography)/CT [26], which seems to have a higher sensitivity compared with FDG(fluorodeoxyglucose)-PET/CT [27]. PET/CT imaging is not only expensive but it should also be analyzed only by experienced nuclear medicine physicians with knowledge of the patient's calcitonin levels.

Patients with persistent or recurrent MTC localized to the neck can be subjected to repeated neck surgery [2]. A meta-analysis of 984 patients with reoperations for MTC found an overall calcitonin normalization in 16.2% [28]. Stratified by operative procedure, selective lymph node removal led to biochemical cure rates of 10.5% compared to 18.6% after compartment-oriented lymph node dissection.

For patients with non-resectable distant metastases and progressive disease, tyrosine kinase inhibitors should be considered as systemic therapy, being provided by specialized endocrinologists or oncologists.

MTC is a rare tumor which differs from other forms of thyroid carcinoma due to its potentially aggressive growth, early lymph node metastases, and sporadic as well as hereditary forms. Since surgery is the best therapy, a special training in endocrine surgery is strongly recommended to achieve biochemical cure in these patients.

To educate and train future leaders in endocrine surgery, clinical fellowship programs including clinical workups, operative treatment, and postoperative care are communicated by the American Association of Endocrine Surgeons (AAES). In Europe, fellowship programs are currently being offered by hospitals in Sweden and the UK. A European Board of Surgery Qualification (EBSQ) in endocrine surgery can be obtained by passing an oral examination. Since 2003, 142 candidates have successfully passed the EBSQ exam in endocrine or neck endocrine surgery, 27 of them coming from Germany. In Germany, there are no specialized training programs for endocrine surgeons until now, and the number of positions as chiefs in endocrine surgery, in specialized hospitals, or in an academic setting is low.

Disclosure Statement

There is no conflict of interest to declare.

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