Therapy for Medullary Thyroid Cancer 19

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19.1 Introduction

In 1959, Hazard described a thyroid carcinoma characterized by a nonfollicular histological pattern, the presence of amyloid in the stroma, and a high incidence of lymph node metastases as a clinicopathological entity [20]. This histological subtype of thyroid carcinoma has already been described by Horn in 1951 [22], and the description of thyroid tumors with amyloid deposition was made at the beginning of the twentieth century [23]. But it was Hazard who clearly identified it as an individual entity to be distinguished from other types of thyroid carcinoma. Hazard also proposed the term "medullary thyroid carcinoma" (MTC).

The incidence of MTC is not well known. The only population-based studies were made shortly after MTC had been identified as an entity [4, 21]. The low incidence of 3.6–3.8% of MTC in those studies is, hence, at least in part most likely due to misdiagnosis of MTC as anaplastic carcinoma. In contrast, recent studies which emphasized the necessity of measuring calcitonin levels in patients with thyroid nodules reported the incidence of MTC as high as 16–40% [36, 39, 42]. In general, MTC is believed to comprise about 5–10% of all thyroid malignancies.

In contrast to differentiated thyroid carcinoma, MTC derives from the parafollicular C-cells (see Chap. 2). Hence, it does not take up radioiodine and is, therefore, not susceptible to radioiodine treatment. Surgery is still the treatment of choice for the primary tumor and local metastases.

19.2 Sporadic Versus Familial Medullary Thyroid Carcinoma

The majority (75%) of MTCs are sporadic [38]. These tumors are often unifocal but almost always larger than 1 cm in diameter at the time of diagnosis. At this time, about 50–80% of patients have lymph node metastases [19].

About a quarter of patients with MTCs do have a familial form. More than 95% of these patients harbor a germline mutation in the proto-oncogene *RET*, which is almost always a missense mutation (see Chap. 17) [13]. The remaining patients, less than 5%, have a family history or accompanying diseases suggestive of MEN 2 but no germline *RET* mutation. Clinically, three familial

forms of MTC are distinguished: familial MTC only (FMTC), MTC as part of multiple endocrine neoplasia type 2A (MEN 2A–MTC, pheochromocytoma, hyperparathyroidism), and MTC as part of MEN 2B (MTC, pheochromocytoma, marfanoid habitus, intestinal ganglioneuromatosis, mucosal neuromas, corneal nerve fibers). In a given family, the "index patient" is that person who was first identified as having MTC or, less likely, one of the accompanying diseases as part of MEN 2, i.e., the diagnosis MTC is made and subsequent analysis revealed a mutation in the proto-oncogene *RET*. These individuals often present with multifocal tumors of which the largest one is almost always larger than 1 cm in diameter. Like patients with sporadic MTC, they often present with lymph node metastases. "Screening patients" are those members of a given family who are identified as harboring the same germline mutation as the index patient. It is estimated that *RET* mutation carriers have a risk of 70% of developing clinically significant MTC by the age of 70 years [37]. Every single thyroid C-cell harbors the potency to become malignant. This is the rationale for advocating removal of the total thyroid gland in every patient with FMTC/MEN 2-specific *RET* mutation. Patients can be screened at a very young age. The genetically determined development of C-cell neoplasia might therefore still be at the beginning, when solely C-cell hyperplasia (increased number of C cells) or even a normal thyroid gland is found histologically. The risk of lymph node metastases is only given once C-cell carcinoma (i.e., MTC) has developed.

Family members of FMTC/MEN 2 families are often referred to as "gene carriers." This term is incorrect, since we all "carry" the gene and therefore pose a threat. The correct term would be "FMTC/MEN 2-specific *RET* mutation carriers." Since this term is very long and awkward, the term "*RET* mutation carriers" or just "mutation carriers" might be used instead.

19.3 Therapy

Among solid tumors, MTC is almost unique regarding its production of a quite specific tumor marker. This tumor marker, calcitonin, is not only helpful in making the diagnosis (see Chap. 17), but also in assessing the therapeutic success. It has been shown that pre- and early postoperative calcitonin levels in a given individual correlate very well with the remaining tumor burden [43]. In some instances [e.g., extrathyroidal tumor extension (pT4 tumor), lymph node metastases in all four locoregional lymph compartments, presence of distant metastases], "biochemical cure" (i.e., calcitonin levels within normal basal limits and after stimulation with either pentagastrin or calcium or both) cannot be expected despite extensive surgery [17]. The indication to operate on these patients is, however, still almost always given, since MTC is generally a slowly progressing tumor and tumor-related complications (e.g., airway obstruction) must be avoided.

19.3.1 Surgical Treatment

Surgery is the treatment of choice for MTC, no matter whether MTC is sporadic or familiar, primary or recurrent, restricted to the thyroid gland or extending beyond it. To facilitate the identification, preparation, and preservation of important structures (e.g., parathyroid glands, recurrent laryngeal nerve), the use of magnifying glasses, bipolar coagulation forceps, and neuromonitoring is recommended [9, 34].

19.3.1.1 Thyroid gland

MTC is often multifocal (sporadic MTC 10–20%, familial MTC 80–90%) [41] and not susceptible to radioiodine ablation. Hence, most investigators recommend total thyroidectomy in any patient with MTC. However, a unifocal approach in sporadic cases has been proposed by some authors [30].

19.3.1.2 Lymph node metastases

Multivariate analysis of long-term follow-up data showed that lymph node metastases are of prognostic value in MTC [2, 7]. Based on anatomical structures, four locoregional lymph node compartments have been defined [11]:

- Cervicocentral compartment (C1). This compartment is limited laterally by the carotid sheaths, cranially by the hyoid bone, and caudally by the brachiocephalic vein, and includes the cervical paratracheoesophageal lymph nodes.
- Cervicolateral compartments (C2, right; C3, left). These compartments extend laterally from the carotid sheath to the trapezoid muscle, and caudally from the subclavian vein up to the hypoglossal nerve.
- Mediastinal compartment (C4). The mediastinal compartment lies retrosternally and includes the lymph nodes between the brachiocephalic vein and the tracheal bifurcation in the upper anterior and posterior mediastinum.

This classification has been proved useful both for defining the extent of lymphadenectomy (compartment-oriented lymphadenectomy) [8, 14] and for comparing patterns of metastasis [17, 19]. Once, the decision to operate on a compartment is made, the whole compartment, i.e., lymph nodes and the surrounding adipose and connective tissue should be removed en-bloc. The technique has been termed "systematic compartment-oriented lymphadenectomy" or "compartment-oriented microdissection" [9]. The reason for advocating this technique is that pre- and/or intraoperative detection of lymph nodes can be impossible, since they tend to be small.

Routine lymphadenectomy of the cervicocentral compartment (C1) as part of total thyroidectomy is recommended and widely accepted for the following reasons:

1. Lymph node metastases derived from MTC have a prognostic influence [2, 7].
2. About 50–80% of patients with sporadic MTC have lymph node metastases at the time of diagnosis, most often in the cervicocentral compartment [19]. Lymph node metastases are also found in almost 9% of patients with familial MTC who underwent screening procedures [25]. Among children and adolescents with FMTC/MEN 2A (younger than 20 years), lymph node metastases are still found in 4–6% [10, 35].
3. No adequate nonsurgical treatment modalities exist yet.

It is also widely accepted to dissect compartments which obviously contain lymph node metastases. No strategy has gained common acceptance in the absence of obvious lymph node involvement. The following algorithms have been proposed.

19.3.1.2.1 Inclusion of the cervicolateral compartments (C2 and/or C3)

1. Bilateral cervicolateral (C2 and C3) lymphadenectomy in any patient with clinical evidence of disease [29]
2. General inclusion of the ipsilateral cervicolateral (with regard to the site of the primary tumor) compartment (C2 or C3)
3. Inclusion of the cervicolateral compartments (C2 and/or C3) only in the presence of cervicocentral lymph node metastases
4. Inclusion of the ipsilateral cervicolateral compartment (C2 or C3) if the primary tumor is >2 cm in diameter [31]

19.3.1.2.2 Inclusion of the mediastinal compartment (C4)

1. More than three lymph node metastases in the cervicocentral compartment (C1) [18]
2. Lymph node metastases in one of the cervicolateral compartments (C2 and/or C3) [18]
3. Lymph node metastases in the cervicomediastinal transition.

Based on the results reported [3, 8, 12, 17, 19, 31, 32], the following approach is currently recommended:

1. Total thyroidectomy and lymphadenectomy of the three cervical (cervicocentral, cervicolateral right and left) compartments is performed in any patient with primary MTC. The only exception to perform a less extended operation is given in a young *RET* mutation carrier; see below)
2. Since involvement of the mediastinal compartment rarely (<10%) enables "biochemical cure" and since dissection of this compartment via a transsternal approach inherits a higher morbidity rate, dissection is nowadays recommended if mediastinal metastases are proven by imaging techniques.

19.3.1.3 Distant metastases

Surgical treatment of distant metastases derived from MTC is rarely, if ever, curative. Hence, the indications to operate are prevention of local complications and alleviation of symptoms. For example, removal of asymptomatic retrosternal lymph node metastases via a transsternal approach is most likely unjustified if multiple, progressing distant metastases are present also.

19.3.1.4 Reoperation

Persistent or recurrent disease is quite frequent in MTC [17, 33, 41]. The first sign of persistent or recurrent disease is an elevated calcitonin level. Calcitonin is a sensitive tumor marker of MTC. It serves as a useful tool both at primary diagnosis and during follow-up (see Chap. 17). Indeed, calcitonin levels may already be elevated when imaging techniques fail to show evidence of tumor. The surgeon might therefore be confronted with the following situations:

1. Calcitonin levels are within normal range (basal and after injection of provocative reagents), but the primary operation was "incomplete" (less than total thyroidectomy and cervicocentral lymphadenectomy): If the patient turns out to have MTC as part of FMTC/MEN 2, the indication to reoperate is clearly given, since every single C cell carries the potency to become malignant. In sporadic cases, the indication to perform reoperation is less clear. In the case of a small primary tumor (<2 cm), no reoperation but thorough follow-up is recommended. If compliance cannot be reassured or if primary tumors are large (>2 cm), reoperation should be performed.
2. Elevated calcitonin levels without proved tumor persistence or recurrence: This is another challenging situation. Elevated calcitonin levels and in particular rising calcitonin levels after injection of provocative reagents almost always indicate persistent or recurrent tumor. If previous operation consisted of less than total thyroidectomy and/or cervicocentral (C1) lymphadenectomy, it is almost certain that tumor remnants can be found in compartment C1. Further effort should be undertaken to exclude or confirm the presence of distant metastases, since their presence may alter the extent of reoperation.
3. Elevated calcitonin levels and proved local tumor persistence or recurrence: The indication to reoperate in these patients is almost always given.
4. Caution must be exercised if imaging techniques are suggestive of tumor but calcitonin levels are within normal levels. Two explanations are possible. Scarring tissue might be mistaken as tumor or the tumor is dedifferentiated and has lost its ability to synthesize and/or secrete calcitonin. Fine-needle aspiration cytology with immunohistochemistry staining (e.g., calcitonin, CEA, chromogranin) should be performed.

In any case, if reoperation is indicated it should at least consist of completion thyroidectomy and cervicocentral lymphadenectomy if not performed previ-

ously. We recommend performing a bilateral cervicolateral lymphadenectomy in addition. Otherwise, the same considerations to limit or extend the extent of lymph node dissection beyond the cervicocentral compartment that apply at primary therapy also apply at reoperation.

19.3.2 Special Therapeutic Considerations in Familial MTC

The identification of *RET* as the disease causing gene of familial MTC in 1993 has changed the diagnostic strategy. Since then, patients at risk for MTC can be identified at an asymptomatic stage (see Chap. 17). However, due to the nature of this subject, our knowledge is limited and recommendations regarding therapeutic strategies are so far based on relatively small numbers of patients and short follow-up periods.

19.3.2.1 Thyroid gland

The identification of *RET* mutation carriers is nowadays often made before clinical disease is present. In these cases, the removal of the thyroid gland is often referred to as "prophylactic thyroidectomy." In many instances, however, histopathological analysis of these thyroid glands already revealed the presence of MTC [10]. Some investigators find that the term "prophylactic thyroidectomy" is misleading in these cases. Instead, they propose to use the term "early thyroidectomy." No matter what one considers to be the correct term, most surgeons recommend performance of a prophylactic/early thyroidectomy at the age of 4–6 years [5, 10, 44], when the risk of MTC and, in particular, of metastases is low. Others recommend performing thyroidectomy when calcitonin levels turn pathological. This strategy, however, inherits some pitfalls. On the one hand, calcitonin can be pathological when only C cell hyperplasia is present [10] and surgery at a young age inherits an increased risk of complications. On the other hand, calcitonin levels can still be normal despite the presence of MTC [10, 44] (false-negative). Therefore, calcitonin level does not seem to be a good indicator of when to operate. Recently, several studies have shown that a genotype-phenotype correlation exists [27, 45], i.e., some mutations (e.g., E768D, Y791F) inherit a lower risk of transformation from C cell hyperplasia to MTC than other mutations (e.g., C634R). In these instances, surgery may be postponed unless calcitonin level turns pathological.

19.3.2.2 Lymph node metastases

Similar to patients with sporadic MTC, a cervicocentral lymphadenectomy is generally recommended in addition to total thyroidectomy. Since familial MTC

is often multifocal and bilateral, a bilateral cervicolateral (compartment C2 and C3) is highly recommended to avoid unnecessary reoperations.

Despite apparent differences between sporadic and hereditary MTC, therapeutic recommendations do obviously not differ a lot. It remains to be shown whether cervicocentral lymphadenectomy, which carries an increased morbidity, can be avoided in some cases. For instance, lymph node involvement seems to be extremely rare if stimulated calcitonin is within normal limits or if patients are younger than 10 years. Also, patients harboring some *RET* mutations (e.g., E768D, Y791F) seem to develop lymph node metastases at a later age. Therefore, in these patients, routine inclusion of the cervicocentral compartment might not be necessary. However, further analysis of larger series will be necessary to provide general recommendations.

19.3.3 Nonsurgical Treatment Modalities

Nonsurgical treatment modalities should only be used if surgery is not feasible.

19.3.3.1 Octreotide

Octreotide is a synthetic somatostatin analog. It has been shown to be useful in the diagnosis of MTC, since 40–60% of primary MTCs are found to be somatostatin receptor-positive by immunohistochemical means (see Chap. 17). Octreotide, however, has not fulfilled the expectations regarding treatment of MTC beyond the thyroid gland [15]. At least, in patients with symptoms related to excessive calcitonin secretion (e.g., diarrhea), octreotide may be of help [28].

19.3.3.2 Radioactive iodine

Radioiodine is a tremendously helpful tool in the diagnosis and treatment of follicular thyroid cancer (see Chap. 6). Since MTC does not derive from the follicular thyroid cells, it does not accumulate radioiodine. Some progress has been made using radioiodine labeled anti-CEA monoclonal antibodies (anti-CEA MAbs). They have not only been proved to be useful in detecting but also showed to be suitable to treat metastatic disease [24]. In combination with chemotherapeutic agents, anti-CEA MAbs showed synergistic therapeutic efficacy [1] which has been confirmed more recently [40]. Clinical studies have still not been reported.

19.3.3.3 External radiation

External radiation should be avoided for as long as possible. There is no need for prophylactic radiation, and the distressing long-term side effects of cough and dryness should not be underestimated. Also, assessment of local tumor recurrence both clinically and by imaging techniques as well as reoperation can be difficult due to scarring of the neck. If surgery cannot be performed, however, radiation may be helpful in treating symptomatic and/or rapidly progressing local and distant disease.

19.3.3.4 Chemotherapy

MTC has been shown to be almost unresponsive to chemotherapy. Partial responses and long-term disease control could only be achieved in rare instances. In general, combination chemotherapy seems to be superior to monotherapy. Various combinations (e.g., doxorubicin and cisplatin; 5-fluorouracil and streptozocin; cyclophosphamide and vincristine; and dacarbazine) have been investigated. Combined radiochemotherapy has been shown to improve treatment outcome in a nude mouse model but clinical experience is lacking [1]. In patients with multiple symptomatic liver metastases, chemoembolization has been shown to be of help [26].

In summary, the available nonsurgical treatment modalities for MTC are limited and of low efficacy. Chemotherapy per se will most likely not be the answer. Curative agents will have to target the molecular. Recently, it has been shown that MDM 2, an oncoprotein that physically interacts with the *p53* tumor suppressor gene product, promotes apoptosis in p53-deficient human MTC cells [6]. It remains to be shown whether this knowledge will be of help in developing new therapeutic tools.

19.3.3.5 Psychological support

From the clinical point of view, it seems to be justified to screen patients with MTC and relatives of mutations carriers for germline *RET* mutations. The psychological impact, however, is often neglected. It is therefore not surprising that a study from France about the psychological impact of genetic testing in familial MTC revealed a high level of frustration and latent discontent [16]. The discontent was related either to the management of genetic information given by the clinicians and its psychological consequences or simply to the knowledge of the genetic risk of cancer. Surgeons, endocrinologists, oncologists, radiologists, geneticists, and genetic counselors have to keep in mind that we are not just treating a disease but also an individual. Much more effort should, hence, be put into the interaction between clinicians and the potentially affected individual.

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