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An Introduction to Managing Medullary Thyroid Cancer

Jan Willem de Groot[1], Thera P. Links[2], Robert M.W. Hofstra[3], John T.M. Plukker[4]

[1]Department of Internal Medicine, Isala Klinieken Zwolle, the Netherlands; [2]Departments of Endocrinology, [3]Genetics and [4]Surgical Oncology, University Medical Center Groningen, University of Groningen, the Netherlands

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Corresponding author: J.W.B. de Groot, M.D. Ph.D., Department of Internal Medicine, Isala Klinieken Zwolle, PO Box 10400, 8000 GK Zwolle, the Netherlands, tel.: 0031-38-4247427, fax: 0031-38-4247676, e-mail: j.w.b.de.groot@isala.nl

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Abstract

MTC is a rare neuroendocrine thyroid tumour accounting for 3% to 10% of all thyroid malignancies. It can occur in a sporadic and a hereditary clinical setting. Hereditary MTC may either occur alone (familial MTC, FMTC) or as part of multiple endocrine neoplasia (MEN) type 2A, or MEN 2B. These disorders are due to germline mutations in the *RET* (REarranged during Transfection) gene. In carriers of MEN 2B-associated RET mutations, prophylactic thyroidectomy is indicated before the first year of life. In the case of MEN 2A-associated germline RET mutations with a high-risk profile, total thyroidectomy is warranted before the age of 2 years and certainly before the age of 4 years. At that age the risk of invasive MTC and metastases is acceptably low. Depending on the type of RET mutation, thyroidectomy can take place at an older age in patients with a lower risk profile. In case of elevated basal or stimulated serum calcitonin, preventive surgery including total thyroidectomy and central compartment dissection should be performed regardless of age. When MTC presents as a palpable tumour, total thyroidectomy should be combined with extensive lymph node dissection of levels II-V on both sides and level VI to prevent locoregional recurrences.

Introduction

In 1959, Hazard et al. described a case of thyroid carcinoma with a solid, non-follicular structure with amyloid in the stroma [1]. This tumour was called solid or medullary thyroid carcinoma. Since then, medullary thyroid cancer (MTC) has been regarded as a separate clinical and pathological entity that should be distinguished from differentiated thyroid carcinomas.

MTC is a tumour originating in the parafollicular C-cells. The parafollicular C-cells are dispersed inside the follicles of the thyroid gland between the basal layer and the follicular cells and produce a hormone called calcitonin. C-cells derive from the neural crest and are not related to the follicular cells. They account for about 1% of thyroid cells and are most numerous at the junction of the upper third and the lower two-thirds of the thyroid lobes.

MTC is a very rare neuroendocrine thyroid tumour accounting for 3% to 10% of all thyroid malignancies [2-4]. It can occur in a sporadic and a hereditary clinical setting. Hereditary MTC may either occur alone (familial MTC, FMTC) or as part of multiple endocrine neoplasia (MEN) type 2A, or MEN 2B. These disorders are due to germline mutations in the *RET* (REarranged during Transfection) gene [5-7].

Histopathology

Macroscopically, MTC is typically located in the upper two-thirds of the thyroid lobes. Usually it is solid in consistency and whitish or red in colour. Histologically, MTC consists of nests of predominantly round cells with abundant, finely granular amphophilic cytoplasm and ovoid to round nuclei. Occasional red cytoplasmic granules are seen, and the supporting stroma frequently stains for amyloid (these are in fact calcitonin deposits [8]). In practically all MTCs, immunohistochemical staining for calcitonin and carcino-embryonic antigen (CEA) is positive (Figure 1).

Hereditary MTC is generally bilateral and multifocal, whereas in sporadic MTC the tumour is most frequently unilateral. In addition, in practically all patients with hereditary MTC, C-cell hyperplasia (CCH) is present (Figure 1) [9]. Wolfe et al. were in 1973 the first to describe CCH as the presence of a multifocal increase and clustering of noninvasive calcitonin-containing cells in the absence of grossly visible tumour in two related patients with abnormally high serum levels of stimulated calcitonin [10]. Hereditary MTC develops stepwise via CCH (Figure 2). In addition, CCH accompanies (and probably precedes) a number of sporadic MTC but CCH is frequently absent in these cases [11]. Moreover, physiologic CCH is associated with inflammatory and metabolic thyroid disorders as well as with hypercalcaemia and in the general population it is present in 20% to 30% of normal (non-cancerous) thyroids [12].

Metastases to regional lymph nodes happen early in the course of disease and have frequently already occurred at the time of diagnosis. The central

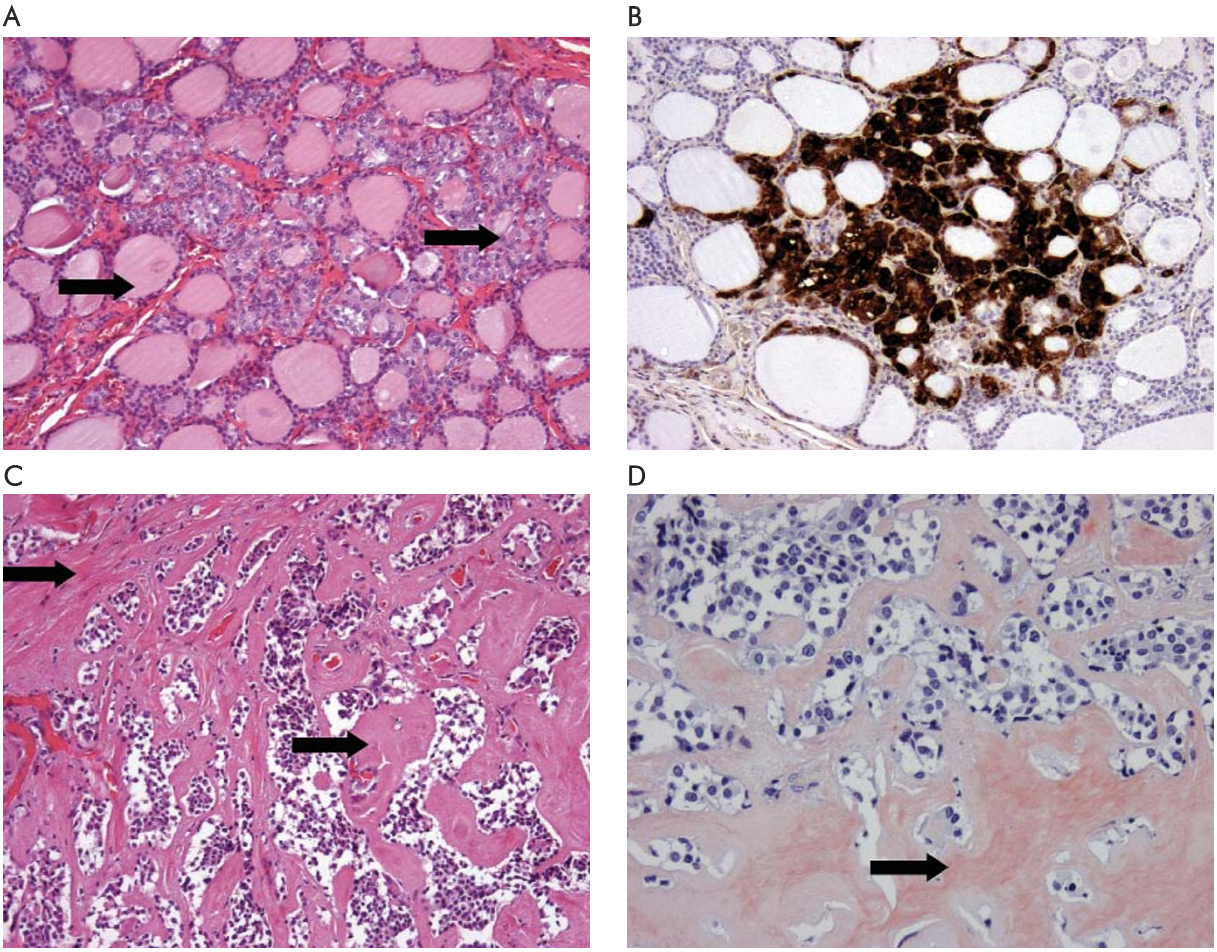

Fig. 1. [A] Microscopic view of normal thyroid tissue with hyperplastic C-cells (arrows) dispersed between the follicles. C-cell hyperplasia (CCH) was defined as clusters of intrafollicular atypical C-cells (more than 50 per "low-power field" at 100x magnification) that lead to partial or complete obliteration of the follicular space. [B] C-cells are positive for immunohistochemical staining for calcitonin (dark areas). [C] Microscopic view of medullary thyroid cancer (MTC). Malignant C-cells have broken through the basement membrane and invaded the interstitium, which has led to stromal fibrosis (arrows). MTC lesions are composed of solid nests of epithelial cells with poorly defined cell borders. [D] Occasionally there is deposition of intensely eosinophilic material, amyloid, which can be stained with Congo-red (arrow). Amyloid is derived from calcitonin

(paratracheal) lymph nodes are most often involved followed by the ipsilateral, contralateral (jugular) and mediastinal lymph nodes [13]. Distant metastases develop variably in the course of MTC, usually to the liver, lungs, and bone [3, 14].

Secretion products

MTC synthesizes and secretes a wide range of substances, the most abundant being calcitonin [15]. Calcitonin is a small 32 amino acid polypeptide hormone and the main biochemical marker used for detection and postoperative management of patients with MTC [16, 17]. Elevated serum calcitonin levels are found in patients with MTC, CCH or, rarely, in patients without any C-cell abnormalities. Patients with renal insufficiency, Hashimoto's thyroiditis and (metastatic) carcinoids can also have elevated serum calcitonin levels. In neonates, serum calcitonin levels are high but these levels decline to normal by one year of age [4, 18]. Generally, basal serum calcitonin roughly correlates with tumour burden, although there are exceptions, especially in patients with extensively metastasized MTC. Furthermore, in small tumours and CCH serum calcitonin levels may be normal. Calcitonin can then be stimulated by pentagastrin, calcium or omeprazole but pentagastrin is the provocative agent of choice [18-20].

Another tumour marker for MTC is CEA, which is mainly produced by neoplastic C-cells but also found in normal C-cells. Measurement of serum CEA levels is useful in the follow-up of MTC since rapidly increasing CEA levels can indicate dedifferentiation of the tumour [21, 22].

MTCs not only secrete calcitonin and CEA. Other secretion products include serotonin (causing carcinoid syndrome), prostaglandins, corticotropin releasing factor, adrenocorticotropic hormone (causing Cushing's syndrome), histaminase, and somatostatin (which may cause paraneoplastic clinical syndromes). Furthermore, MTC is known to produce several gastrointestinal hormones and neuroendocrine peptides, including calcitonin gene related peptide, chromogranin A, vasoactive intestinal peptide, and ghrelin [15].

There is increasing evidence for a subgroup of MTCs that do not secrete calcitonin, CEA or both, making tumour follow-up difficult [23-25]. Although calcitonin (and CEA) is not a perfect tumour marker, none of the other secretion products is comparable to calcitonin in terms of sensitivity and specificity.

Clinical presentation

Most patients with sporadic MTC present in the fourth or fifth decade of life with a painless thyroid nodule often accompanied by cervical lymphadenopathy (Figure 3). Sometimes patients have pain in the neck, dysphagia, respiratory difficulties, hoarseness or symptoms of ectopic hormone production such as diarrhoea, flushes or Cushing's syndrome [15]. Patients with hereditary MTC may also present with a neck mass. Additionally, patients with MEN 2 or FMTC may have symptoms characteristic of pheochromocytoma.

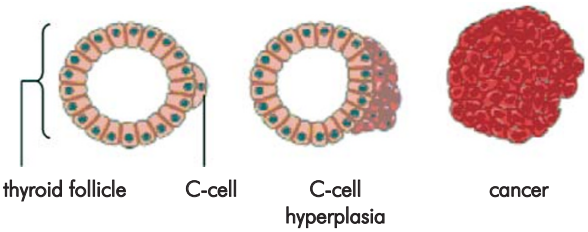

Fig. 2. Development of medullary thyroid cancer (MTC) from a normal C-cell via C-cell hyperplasia (CCH) to MTC

Fine-needle aspiration cytology (FNAC) can reveal the diagnosis prior to surgery, especially when immunohistochemical staining for calcitonin is performed, but FNAC may be inconclusive or only diagnose malignancy. Measurement of serum calcitonin may then be a complementary approach to make the final diagnosis [26]. However, if basal calcitonin is elevated, a pentagastrin stimulation test should always follow to confirm that the source of elevated calcitonin concentrations is indeed MTC.

Sporadic and hereditary medullary thyroid cancer

As mentioned earlier, MTC may be sporadic or hereditary. Sporadic MTC is the most common form of MTC, accounting for approximately 75% of all cases at initial presentation. The remaining 25% comprise hereditary MTC including MEN 2A (most common), MEN 2B, and FMTC (the least common) (Table 1).

In 1962 Sipple was the first to describe the association of MTC with pheochromocytoma and hyperparathyroidism [27]. In 1966 Williams and Pollock described the association between oral mucosal and eyelid neuromas, MTC, pheochromocytoma, and ganglioneuromatosis of the gastro-intestinal tract in a father and a daughter [28].

Two years later, in 1968, Steiner et al. introduced the term "multiple endocrine neoplasia" to describe different combinations of endocrine tumours. They designated the combination MTC, pheochromocytoma and parathyroid adenoma as MEN 2 [29]. Sizemore

Table 1. Clinical expression of the variants of hereditary MTC associated syndromes

	FMTC	MEN 2A	MEN 2B
medullary thyroid cancer	100%	100%	100%
C-cell hyperplasia	100%	100%	100%
Pheochromocytoma	0%	10% to 60%	50%
Hyperparathyroidism	0%	10% to 25%	0%
Marfanoid habitus	0%	0%	100%
Intestinal ganglioneuromatosis	0%	0%	60% to 90%
Mucosal neuromas	0%	0%	70% to 100%
thick corneal nerves	0%	Rare	60% to 90%

FMTC, familial medullary thyroid cancer; MEN 2A/2B, multiple endocrine neoplasia type 2A/2B

et al. concluded in 1973 that the MEN 2 category included two distinct groups of patients with MTC and pheochromocytoma: patients with hyperparathyroidism and a normal physical appearance and patients without parathyroid disease but with marfanoid habitus, mucosal neuromas, and alimentary abnormalities. They suggested the title "MEN type 2B" for the group without parathyroid disease [30]. Subsequently, in 1975, Chong et al. proposed that the combination of MTC, pheochromocytoma, and parathyroid disease in patients with a normal appearance be referred to as MEN type 2A [31].

Genetic background

In 1993, characteristic germline mutations of the *RET* gene on chromosome 10 were shown to be responsible for the inherited forms of MTC [5-7]. *RET* contains 21 exons and encodes the transmembrane tyrosine kinase receptor *RET* (Figure 4). In patients with a family history of MEN 2 or FMTC, it is now possible to determine the risk of MTC by genetic screening. As it is a dominantly inherited disease, about 50% of family members do not carry a germline *RET* mutation. Family members with a *RET* mutation have a 100% risk

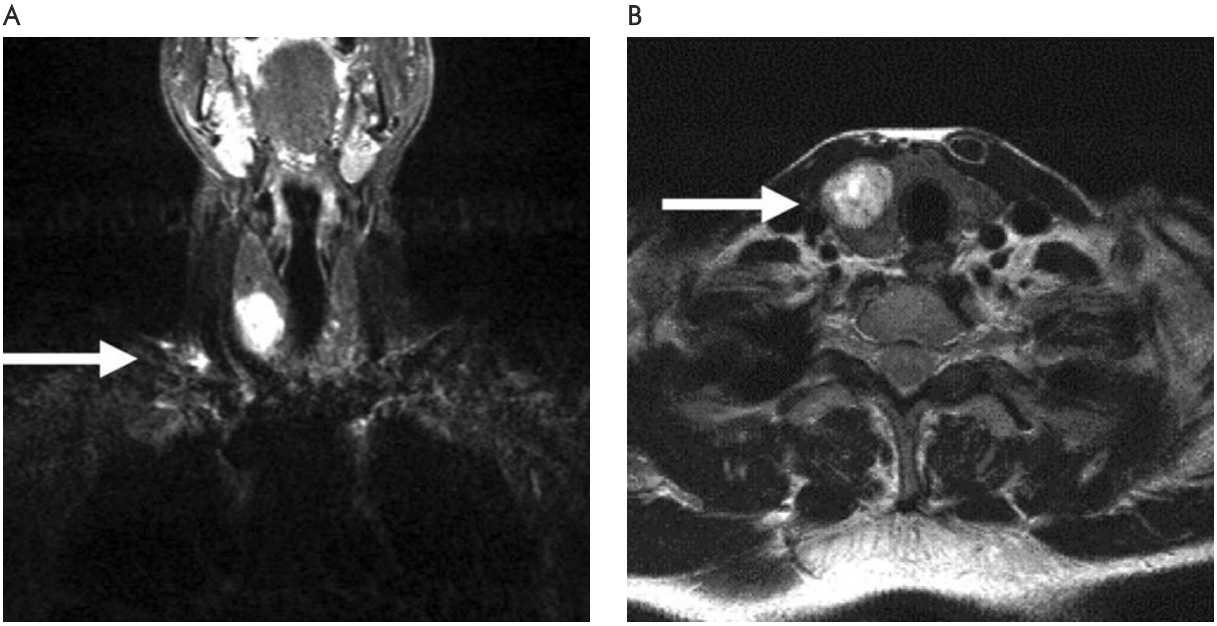

Fig. 3. Magnetic Resonance Imaging (MRI) of the neck of a 51-year-old woman with a germline V804L *RET* mutation demonstrating a thyroid nodule (arrow on the right) and cervical lymphadenopathy (arrow on the left)

of developing MTC, whereas family members that do not carry a *RET* mutation have a risk that is similar to the general population. In patients with apparently sporadic MTC germline *RET* mutations are found in 4% to 10% of cases [4]. In up to 30% of patients with sporadic MTC, somatic mutations (occurring only in the tumour) in *RET* are present [32].

Before 1993, screening for hereditary MTC consisted primarily of family history followed by testing for elevated basal and pentagastrin stimulated serum calcitonin levels to identify asymptomatic gene carriers. This method requires frequent screening and the main disadvantage is that it is impossible to distinguish between asymptomatic gene carriers and family members that will never develop MTC. Furthermore, there is a risk of false-positive test results leading to unnecessary thyroidectomy and it is not possible to distinguish between CCH and invasive cancer [33, 34].

After 1993, DNA testing was used to classify MTC as being of the inherited type and to identify relatives of patients with a mutated *RET* gene prior to the development of clinical and biochemical signs of the disease. Using DNA analysis, a reliable estimation of the risk of MTC can be given since all patients with a germline *RET* mutation will eventually develop MTC. Identification of the type of *RET* mutation has led to the implementation of early prophylactic thyroidectomy [35].

Treatment

Management of MTC is primarily surgical. MTC does not respond to standard chemotherapeutic regimens and external beam radiotherapy has a limited effect in selected groups of patients. Moreover, treatment with radioactive iodine is of no significant value since C-cells do not take up iodine [15, 32].

Due to the high likelihood of a familial component and the risks of other tumours associated with MEN 2, all patients with MTC should be genetically screened for *RET* mutations. Furthermore, a systematic work-up for pheochromocytoma including 24-hour urine collection for catecholamines and metabolites should be performed. Pheochromocytomas need to be treated before undertaking surgery for MTC in order to avoid a potentially lethal intraoperative hypertensive crisis. Patients with possible MEN 2A should also have serum calcium and possible parathormone levels evaluated to rule out hyperparathyroidism.

In recent years great progress has been made regarding genotype-phenotype correlations in MEN 2 and FMTC. Based on the biological behaviour of MTC observed in patients with a germline *RET* mutation, a codon-specific estimation of the risk for MTC can be made (Table 2). Figure 5 shows an overview of the known germline mutations of *RET*. In MEN 2A the most frequent mutations are found in exons 10 and 11 on codons 609, 611, 618, 620, 630 and 634. Mutations in exons 13, 14, and 15 on codons 768, 790, 791, 804 and 891 and mutations in codon 666 on exon 11 are very rare. In FMTC mutations are found in the same codons as in MEN 2A except for FMTC-specific mutations in codons 533 (exon 8), 600, 603, 606, 649, 778, 781, 852 and 912 but they are more evenly

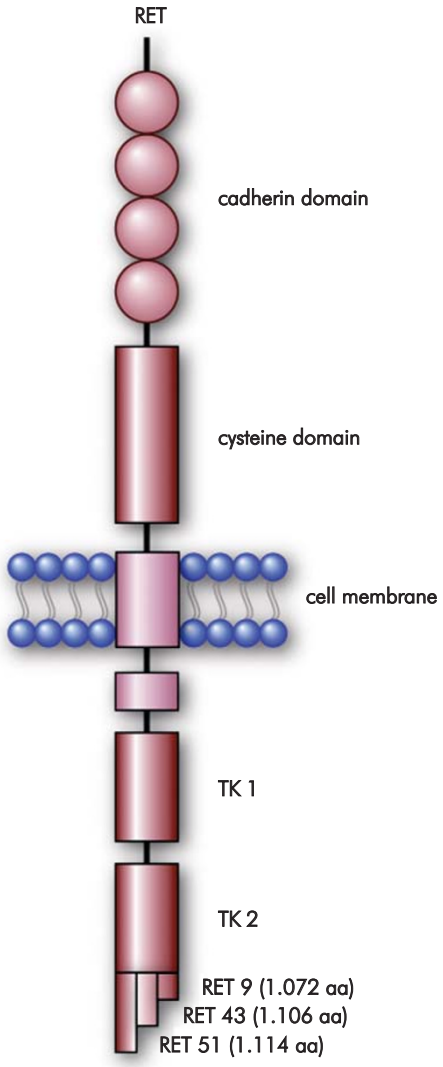

Fig. 4. *Copyright 2006, The Endocrine Society*. Schematic representation of the RET tyrosine kinase. The extracellular region comprises four cadherin domains and a cysteine rich domain. A single transmembrane region spans the cell membrane, and the two tyrosine kinase domains (TK1 and TK2) are located in the intracellular region. There are three isoforms of RET (RET9, RET43, RET 51) which are indicated. aa, Amino acids. [Adapted from De Groot et al. [35]]

Table 2. Management of MEN 2 and FMTC patients according to *RET* genotype[a]

risk category	risk level	*RET* codon	youngest age at first diagnosis of MTC	youngest age at first diagnosis of PCC	youngest age at first diagnosis of HPT	Recommended age for surgery		recommended age to start screening for PCC	recommended age to start screening for HPT
						thyroidectomy	central lymph node dissection		
highest	3	883	not described	not described	–	<1 years	<1 years	10 years	–
highest	3	918	9 months	12 years	–	<1 years	<1 years	10 years	–
high	2	609	5 years	22 years	unspecified	<5 years	≥20 years[b]	20 years	20 years
high	2	611	7 years	30 years	unspecified	<5 years	≥20 years[b]	20 years	20 years
high	2	618	7 years	29 years	41 years	<5 years	≥20 years[b]	20 years	20 years
high	2	620	6 years	22 years	unspecified	<5 years	≥20 years[b]	20 years	20 years
high	2	630	12 months	–	32 years	<2 years	≥10 years[b]	5 years	20 years
high	2	634	13 months	5 years	10 years	<2 years	≥10 years[b]	5 years	<10 years
high	2	912	14 years	–	–	<5 years	≥10 years[b]	20 years	20 years
least high	1	533	21 years	–	–	5-10 years	≥20 years[b]	20 years	20 years
least high	1	649	44 years	–	–	5-10 years	≥20 years[b]	20 years	20 years
least high	1	666	35 years	35 years	–	5-10 years	≥20 years[b]	20 years	20 years
least high	1	768	22 years	59 years	–	5-10 years	≥20 years[b]	20 years	20 years
least high	1	790	10 years	28 years	–	5-10 years	≥20 years[b]	20 years	20 years
least high	1	791	21 years	38 years	38 years	5-10 years	≥20 years[b]	20 years	20 years
least high	1	804	6 years	28 years	10 years	5-10 years	≥20 years[b]	20 years	<10 years
least high	1	891	13 years	52 years	–	5-10 years	≥20 years[b]	20 years	20 years

[a]the recommendations are made based on results from recent literature [35]. This table was adapted from De Groot et al. [35]. *Copyright 2006, The Endocrine Society*.
[b]no consensus has been reached for the extent of surgery for MTC in patients carrying these germline mutations in the *RET* gene. Recommendations are based on recent literature. If basal or pentagastrin-stimulated calcitonin levels are abnormal in *RET* mutation carriers, thyroidectomy and central lymph node dissection should be performed immediately.
For mutations at codons 600, 603, 606, 778, 781, and 852 insufficient data are available for recommendations, but most likely they belong to risk level 1.
MEN 2, multiple endocrine neoplasia type 2; FMTC, familial medullary thyroid cancer; *RET*, rearranged during transfection; MTC, medullary thyroid cancer; PCC, pheochromocytoma; HPT, hyperparathyroidism.

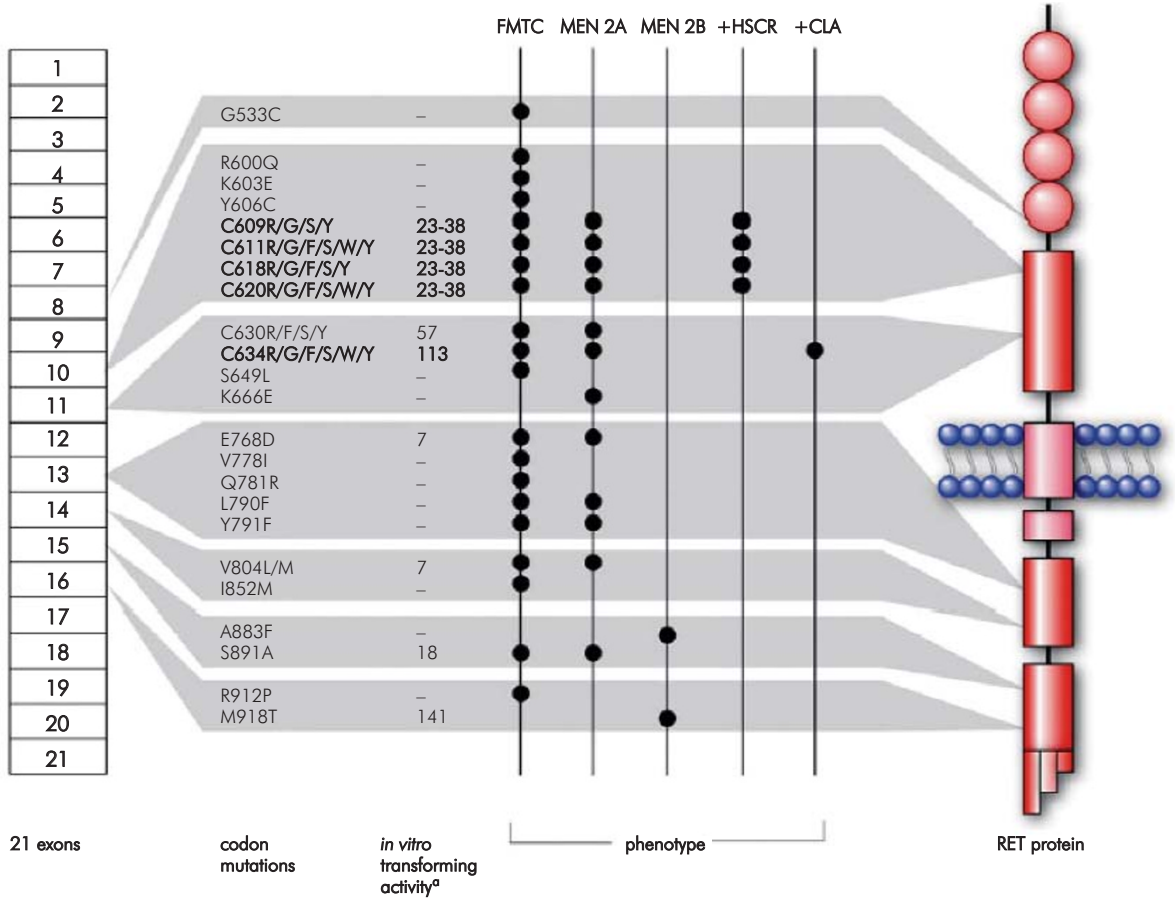

Fig. 5. *Copyright 2006, The Endocrine Society*. Overview of the known germline missense mutations in the *RET* gene and their associated human diseases. The structure of the RET mRNA and the *RET* protein are depicted schematically. The mutations responsible for the diverse inherited cancer syndromes and the location of the mutations relative to the exons and the functional domains are shown. The most common mutations that are found in about 95% of MEN 2A and FMTC cases are depicted in bold, and MEN 2B mutations are depicted in italics. CLA, Cutaneous lichen amyloidosis. [Adapted from De Groot et al. [35]]

divided among the different exons. In MEN 2B mutations are almost always found in exon 16 (codons 883, 918) [35]. In the Netherlands exons 10, 11, 13, 14, 15 and 16 are routinely screened for germline mutations when a form of hereditary MTC is suspected. In case of a strong suspicion of inherited MTC and the absence of mutations in exons 10, 11, 13, 14, 15 and 16, screening of exon 8 may be considered.

In the University Medical Center of Groningen, 21 children with MEN 2A underwent prophylactic thyroidectomy. The clinical characteristics are summarized in Table 3. MTC was already present at the age of three years, and in the literature MEN 2A-associated MTC is described at the age of one year [36]. Therefore, early surgical intervention in patients with an *RET* mutation is warranted.

Carriers of a germline *RET* mutation sooner or later will develop MTC and surgery is the only curatively intended treatment of this form of cancer. The turning point of progression from CCH into invasive MTC is as yet unknown. When surgery takes place at a young age (at the age of three or four years) the risk of invasive MTC is low and the extent of surgery can be minimal (only a total thyroidectomy) with low risk of hypoparathyroidism or paralysis of the recurrent laryngeal nerve.

In our patients, 20 of 21 patients had C-cell disease and in five of seven patients (71%) younger than five years old (the youngest being three years old) MTC was already present. Based on the youngest age at which MTC was already present a total thyroidectomy seems warranted before the age of two in carriers of *RET* mutations in codons 630 and 634 (Table 2). However, it should be noted that all patients with such a mutation who have been operated on around the age of 4 years were biochemically cured [35].

The prognosis of MTC attenuates with the presence of lymph node metastases [36]. Therefore it is crucial that prophylactic thyroidectomy is performed before the

Table 3. Occurrence of MTC related to patient characteristics and type of *RET* gene mutation in children who underwent prophylactic thyroidectomy for multiple endocrine neoplasia type 2A

Patient/ family	Year of surgery	Sex	Age (year)	Type of *RET* mutation	Calcitonin (ng/L) Basal/Stimulated[a]	Lymph node dissection (initially)	Histology
1/A	1976	M	17	M918T[b]	–	central and unilateral (level II-V)	multifocal MTC; positive lymph nodes
2/B	1998	F	18	C634G	2000/31600	central	multifocal MTC; positive lymph nodes
3/C	1999	M	14	C634R	151/1200	central	multifocal MTC; positive lymph nodes
4/D	1977	F	18	C634R	–	central	multifocal MTC
5/D	1978	M	17	C634R	489/–	central	multifocal MTC
6/E	1995	F	5	C634R	61/198	central exploration	multifocal MTC
7/C	1999	F	12	C634R	12/125	central exploration	multifocal MTC
8/F	2000	F	5	C634Y	34/–	central exploration	multifocal MTC
9/B	2004	F	3	C634G	72/188	central	multifocal MTC
10/G	2005	F	11	C634R	13/–	central	multifocal MTC
11/F	1995	F	11	C634Y	24/122	central exploration	unifocal MTC
12/H	1999	M	4	C634R	5/384	–	unifocal MTC
13/I	2000	F	6	C620R	15/–	central	unifocal MTC
14/J	1995	F	4	C634W/R635G	18/447	central	unifoclal MTC
15/J	1990	F	14	C634W/R635G	632/–	–	CCH
16/K	1990	F	7	C634R	63/–	central exploration	CCH
17/K	1990	M	10	C634R	92/–	central	CCH
18/F	1995	M	11	C634Y	79/177	central exploration	CCH
19/F	2004	F	1	C634Y	48/–	central	CCH
20/L	2005	M	16	V804L	13/32	central	CCH
21/I	1997	F	5	C620R	13/–	–	no C-cell disease

[a]before 2001 the reference value was <50 ng/L, after 2001 the reference value was <12 ng/L;
[b]patient with multiple endocrine neoplasia type 2B;
RET – rearranged during transfection; F – female; CCH – C-cel hyperplasia; M – male; MTC – medullary thyroid carcinoma

development of MTC and possible node metastases. In adults with MTC, lymph node metastases are already present in about 50% of cases, even in tumours smaller than 1 cm. However, in children without symptoms in whom a *RET* mutation is detected via genetic screening lymph node metastases infrequently occur [36, 37].

There is still no 'gold standard' concerning the extent of lymph node dissection that should be performed in addition to total thyroidectomy [38]. Furthermore, it is controversial from what age to perform a lymph node dissection. The results of this study confirm the data of others in which lymph node metastases in patients with MEN 2A and FMTC are almost always found after the age of 10 years. Patients with an *RET* mutation in codon 630 or 634 hardly ever have metastases before the age of 10 years and patients with mutations in codons 609, 611, 618, 620, 768, 790, 791, 804 and 891 rarely have metastases before the age of 20 years [36, 37]. Until the age of 10 years, a total thyroidectomy should be sufficient in patients with MEN 2A or FMTC. However, several patients younger than 10 years old have been described with lymph node metastases. The risk of invasive MTC and possible nodal metastases is present in the case of elevated serum calcitonin levels as recently illustrated by Van Santen and colleagues [39]. For that reason, a central compartment dissection in addition to

total thyroidectomy to remove possible occult lymph node metastases is indicated when basal or stimulated serum calcitonin levels are elevated (Table 2) [35, 36].

Careful preservation of recurrent nerves and parathyroid glands may be difficult in very young children. The risk of injuring recurrent nerves at risk after thyroid surgery in the literature varies between 0% and 4% and symptomatic hypoparathyroidism with calcium supplementation occurs in 0% to 21% [40-56]. The incidence of complications strongly depends on the experience of the surgeon [44, 50, 57]. Hence, thyroid surgery in children should be performed in a referral centre with large experience in this form of surgery. Total thyroidectomy and central compartment dissection is then relatively safe. Even with meticulous dissection however, the blood supply to the parathyroid glands may be impaired. In these circumstances autotransplantation after microscopic verification may reduce the incidence of hypoparathyroidism [40, 41, 47].

The risk of bilateral lymph node metastases is high in patients who present with a palpable thyroid nodule or nodal metastases (the majority of patients with sporadic MTC). In these cases, elective bilateral selective neck dissection of level II to V is recommended in addition to total thyroidectomy and central compartment dissection [36]. In children with MEN 2B the risk of node metastases is very high and total thyroidectomy with central compartment dissection is justified in the first year of life [36, 37, 48].

Prognosis and follow-up

The prognosis of patients with MTC varies considerably: some patients survive several decades with persistent MTC, whereas others die within months of initial presentation [3, 14]. Five and 10-year overall survival rates in patients with MTC without the presence of distant metastases at initial diagnosis range from 70% to 90% and 60% to 80%, respectively [14, 58-60]. When matched for age and extent of disease, no differences in survival were seen in patients with either hereditary or sporadic MTC but MEN 2B-associated MTC has been reported to be more aggressive than MTC associated with MEN 2A or FMTC [3, 59]. In multivariate analysis, only the patients' stage of disease at diagnosis is a significantly independent indicator of survival [60].

Patients with normal basal and stimulated serum calcitonin levels are likely to be cured. However, in approximately 5% of these patients, serum calcitonin levels can rise again during follow-up [4]. Currently, the only treatment option in patients with detectable serum calcitonin levels after initial treatment is re-operation. Yet re-operation can only be with curative intent in the absence of distant metastases when residual or recurrent MTC is confined to the neck. In patients with postoperative hypercalcitoninemia, the source of calcitonin production is hard to identify with conventional medical imaging and distant metastases cannot be reliably ruled out [61]. When distant metastases are present, therapeutic options are limited.

Conclusion

MTC can occur in a sporadic form and as part of the hereditary cancer syndromes MEN 2A/B or FMTC. In carriers of MEN 2B-associated RET mutations, prophylactic thyroidectomy is indicated before the first year of life. In case of MEN 2A-associated germline RET mutations with a high-risk profile, total thyroidectomy is warranted before the age of 2 years and certainly before the age of 4 years. At that age the risk of invasive MTC and metastases is acceptably low. Depending on the type of *RET* mutation, thyroidectomy can be performed at an older age in patients with a lower risk profile. In case of elevated basal or stimulated serum calcitonin preventive surgery including total thyroidectomy and central compartment dissection should in any case be performed at any age. When MTC presents as a palpable tumour, total thyroidectomy should be combined with extensive lymph node dissection of levels II-V on both sides and level VI to prevent locoregional recurrences. This kind of surgery can be performed relatively safely by well-experienced surgeons.

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