The genetic basis of hereditary medullary thyroid cancer: clinical implications for the surgeon, with a particular emphasis on the role of prophylactic thyroidectomy

George H Sakorafas, Helmut Friess and George Peros

Abstract

Medullary thyroid cancer (MTC) may occur either sporadically or on a hereditary basis. Hereditary MTC may be observed with either multiple endocrine neoplasia syndromes (MEN 2A and MEN 2B) or as familial MTC (FMTC). Despite the rarity of these syndromes, early diagnosis is especially important, since MTC is a lethal disease if not promptly and appropriately treated. Recently, the development of genetic testing and direct DNA analysis allows the identification of asymptomatic patients. Surgical prophylaxis should be considered in these cases, ideally to prevent the development of MTC. During the recent decade, the concept of ‘codon-directed’ timing of prophylactic surgery emerged as a reasonable strategy in the management of these patients. Currently, genetic analysis offers the possibility to define genotype–phenotype correlations and to adjust the time of prophylactic surgery. Hereditary MTC is a model of genetically determined cancer in which both diagnostic and therapeutic strategies rely on the identification of specific mutations.

Introduction

Medullary thyroid cancer (MTC) is a relatively rare type of thyroid cancer, constituting 4–8% of all thyroid malignancies (Pozon 1993, Phay et al. 2000, Clayman & El-Baradie 2003). MTC was first described by Hazard et al. (1959). It arises from the parafollicular C-cells, thereby differing from the classic follicular cell origin of tumors of the thyroid, and may occur either sporadically or, less commonly, on a hereditary basis (Phay et al. 2000, Clayman & El-Baradie 2003). The familial occurrence of MTC was first reported in 1961, when MTC was diagnosed in a pair of young siblings (in their early 20s) and whose mother had previously died following surgery for thyroid carcinoma (Friedell et al. 1961). Since that time, it has been observed that the familial MTC is inherited as an autosomal dominant trait in about 20–30% of patients (Komminoth et al. 1995, Phay et al. 2000, Brandi et al. 2001, Clayman & El-Baradie 2003, Shaha et al. 2006).

Sipple (1961) reported the association of thyroid cancer with pheochromocytoma. Williams (1963), at the Hammersmith Hospital, was the first to point out that the pattern of thyroid cancer in this disease was always medullary. The genetic component of the disease was first described by Schmimke & Hartmann (1965) who demonstrated the mode of inheritance through an autosomal dominant trait. In 1968, Steiner et al. (1968) coined the term multiple endocrine neoplasia type 2 (MEN 2) and included hyperparathyroidism as part of the constellation of clinical problems. In 1977, Norman noted that, apart from the dominant pattern of familial disease, there may be a recessive inheritance in isolated families (Normann 1977).

MTC is the most common cause of death in patients with MEN 2 (Modigliani et al. 1998, Skinner et al. 2005). Once established, it spreads early on and poses many difficulties in clinical management, since it is both...
chemo- and radioresistant. Early surgery is the only therapeutic method that can achieve cure of the patient. In the past, the diagnosis in the familial setting of MTC was generally not made until the disease was symptomatic or clinically evident. Thus, the MTC was not discovered until the third or fourth decade of life in affected patients and was usually at an advanced and incurable stage (Skinner 2003). Recent advances in molecular biology allowed an in-depth understanding of the mechanisms of carcinogenesis and the detection of specific genetic alterations associated with MTC. These advances have led to major changes in the diagnostic and therapeutic algorithm in these increasingly common malignancies (You et al. 2007). The concept of prophylactic surgery (thyroidectomy) has proven effective in preventing or curing hereditary MTC in young patients. The aim of this paper is to present currently available data regarding the molecular basis of hereditary MTC and to emphasize the role of prophylactic surgery in these patients.

Pathology, epidemiology, clinical, and genetic aspects of the hereditary MTC

MTC is a rare calcitonin-producing tumor of the parafollicular or C-cells of the thyroid gland (Kakudo et al. 1985). Multifocal C-cell hyperplasia (CCH) is a precursor lesion to hereditary MTC. The progression from CCH to microscopic MTC is undoubtedly variable and may take several years (Papotti et al. 1993). Metastasis may be in the central and lateral, cervical, and mediastinal lymph nodes or more distantly in the lung, liver, or bone.

Hereditary MTC occurs with either multiple endocrine neoplasia type 2A (in 60% of cases), MEN type 2B (5%), or familial medullary thyroid carcinoma (FMTC, 35%; Brandi et al. 2001). To avoid delayed diagnosis and adverse clinical outcomes, the clinician should always consider the possibility of hereditary MTC; therefore, care must be taken in labeling a patient as a ‘sporadic’ MTC and then failing to screen the rest of the family carefully. The astute physician should keep in his/her mind the possibility of an underlying MEN 2 syndrome in these cases, and therefore he/she should screen for pheochromocytoma and hypercalcemia preoperatively and during follow-up.

MEN2 syndromes

Multiple endocrine neoplasia type 2 (MEN 2) is an autosomal dominant inherited disorder consisting of two main different syndrome variants, the MEN 2A and MEN 2B syndromes. These two MEN 2 variants have the greatest syndromic consistency (Brandi et al. 2001). Other clinical variants have also been described (Table 1; Verdy et al. 1982, Famdon et al. 1986, Donovan et al. 1989, Nunziata et al. 1989). As a result of the high penetrance of the MEN 2 phenotype, tumors may present at an earlier age, even under the age of 5 years (Machens et al. 2001). Especially, medullary thyroid cancer (MTC) may have a more aggressive biological behavior (Schilling et al. 2001). In MEN 2B families, MTC can be observed even within the first year of life in germline mutation carriers (Sanso et al. 2005), while metastases have been reported at 3 years of age (Kaufman et al. 1982).

MEN2A

MEN 2A accounts for the vast majority (up to 90%) of MEN 2A cases and is characterized by MTC (in nearly 100% of patients), pheochromocytoma (in about 50% of cases), and primary hyperparathyroidism (in about 30% of patients; Vasen et al. 1987, Howe et al. 1993, Lee & Norton 2000, Skinner 2003, Danko & Skinner 2006). The MTC is the first neoplasm to develop, and, as noted

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<td>Familial medullary thyroid cancer</td>
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From Brandi et al. (2001).
above, it represents the most common cause of cancer-related deaths in MEN patients (Danko & Skinner 2006).

**MEN 2B**

MEN 2B is very rare and presents as MTC and bilateral pheochromocytomas, but without any parathyroid gland abnormalities (Howe et al. 1993, Ponder & Smith 1996, Skinner 2003). MEN 2B is also associated with distinct physical manifestations and an easily recognizable phenotype (marfanoid habitus, multiple mucosal neuromas of the lips and tongue, intestinal ganglioneuromatosis, and pigment spots on the face (Carney et al. 1976, O’Riordain et al. 1995, Lee & Norton 2000, Skinner 2003). The MTC associated with MEN 2B is extremely aggressive than in the other familial syndromes, often developing metastases in early childhood (Samaan et al. 1991, Skinner et al. 1996). As a result, most patients die before the age of 30 years. Diarrhea from humoral factors produced by MTC combined with gastrointestinal dysmotility from intestinal ganglioneuromatosis can significantly alter quality of life (Brandi et al. 2001).

**FMTC**

In FMTC, there are no manifestations of the disease outside of the thyroid gland and MTC is the only neoplasm present (Famdon et al. 1986, Skinner 2003). It is an autosomal dominant inherited disease, in general less aggressive, with a late onset of the disease clinically between 30 and 50 years of age (Niccoli-Sire et al. 2003).

**Genetic alterations in hereditary MTC**

In 1988, linkage analysis was applied to kindreds affected with MEN 2A and a mutation was found on chromosome 10q11.2. In 1993 and 1994, germline mutations in the RET (rearranged during transfection) proto-oncogene, located at 10q11.2, were identified in patients with MEN 2A, MEN 2B or FMTC (Donis-Keller et al. 1993, Mulligan et al. 1993, Carlson et al. 1994, Eng et al. 1994, Hofstra et al. 1994). The encoded RET protein, a receptor tyrosine kinase expressed in neural crest-derived cells (i.e., thyroid parafollicular cells, parathyroid cells, adrenal medulla chromaffin cells, and enteric autonomic plexuses), mediates downstream pathways of cell survival and mitogenesis (Frilling et al. 2003, Shaha et al. 2006). Specific germ line mutations in the gene lead to constitutive activation of the receptor and cause the dominant inherited cancer MEN 2 syndrome and FMTC (Skinner 2003, Gertner & Kebebew 2004; Table 2). Because RET is a proto-oncogene, a single activating mutation of one allele is sufficient to cause neoplastic transformation. A mutation in the RET proto-oncogene is present in a variable proportion (usually around 25%) of cases with MTC (Leboulleux et al. 2004). MTC became the first identified inherited human neoplasm to be associated with the dominant activation of a proto-oncogene. Recent advances in our understanding of molecular carcinogenesis of MTC have significant clinical implications and, nowadays, genetic screening is considered of key importance in the management of these patients (Moore et al. 2007). Identification of a germline mutation in a patient with MTC enables classification of the tumor as being of the inherited type, regardless of the absence of family history or associated endocrinopathies (Bugalho et al. 2007). Currently, DNA-based strategies allow a correct identification of asymptomatic carriers, while avoiding the unpleasant stimulation tests.

In 98% of MEN 2A patients and in 80–90% of FMTC patients, the germinal RET mutation occurs in one of five cysteine codons of the extracellular domain of the RET protein: 609, 611, 618, 629 (exon 10), and 634 (exon 11; Eng et al. 1996). In the remaining cases, cysteine codon mutations may occur in codon 610, 620, or 630.

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Modified, from Ref. Clayman & El-Baradie (2003). Timing of prophylactic thyroidectomy: (*) before the age of 5 years. (**) within the first year of life. (***) no clear consensus exists (some suggest surgery before the age of 5 and others before the age of 10 years). PS. The frequencies of the various phenotypes depend on the length of follow-up. For example, some FMTC patients may convert to MEN 2A phenotypes over time as they develop pheochromocytomas or hyperparathyroidism over time. Therefore, screening for pheochromocytoma and hypercalcemia both preoperatively as well as during follow-up should strongly be considered.
(Komminoth et al. 1995, Bugalho et al. 2007). These ‘gain of function’ mutations result in receptor dimerization and constitutive activation, ultimately giving rise to MEN 2A and FMTC (Chappuis-Flament et al. 1998, Gimm et al. 2004, You et al. 2007). Codon 634 (exon 11) is the most commonly affected (mutated in 80% of MEN 2A cases; Machens et al. 2003a,b).

In addition to these genetic changes, other rarer non-cysteine mutations located within the intracellular catalytic domain of RET have been described. These mutations can give rise to FMTC (codons 768, 790, 791, 804, 806, and 891) and to MEN 2B (codons 833 and 918) (Bolino et al. 1995, Eng et al. 1995a,b, Hofstra et al. 1997, Berndt et al. 1998, You et al. 2007). More than 95% of patients with MEN 2B have a mutation at codon 918, causing receptor autophosphorylation and activation (Hansford & Mulligan 2000). Altered signaling is responsible for the more aggressive MTC and the visible phenotypic features associated with MEN 2B (Santoro et al. 1995, Hansford & Mulligan 2000). Rarely, more than one mutation in RET can be associated with MTC.

Of particular clinical importance is that these mutations are associated with specific component tumors and phenotypes (Eng 1999). In other words, a significant genotype–phenotype interaction exists with some mutations being significantly less aggressive than others (Yip et al. 2003, Gertner & Kebebew 2004, Kouvaraki et al. 2005). No RET genetic variations appear to carry the same risk, however, and the quantification of specific risk of RET – related genetic variations appear to be codon specific. Machens et al. (2005) have proposed the stratification of the risk (high versus intermediate versus low risk) based on the specific encountered mutations ((codons 634 and 918) versus (codons 790, 620 and 611) versus (codons 768 and 804) respectively; see below, Management). Codon 634 and 918 mutations have the highest transforming activity and correlate strongly with the onset of MEN 2. As a consequence, there is a significant correlation between codon 634 mutation and early development of MTC, pheochromocytoma, and hyperparathyroidism (Calender et al. 1997, Ponder 1999, Szinnai et al. 2003). Codon 634 mutations have been associated with the development of MTC as early as at the age of 15 months (Modigliani et al. 1998) and with the development of cervical lymph node metastases at the age of 5 years and 11 months (Gill et al. 1996). Other cysteine codon mutations (i.e., codons 609, 618, and 620) have a lower risk (intermediate risk group). They are associated with a 3x–5x risk of MTC, but only half the risk of a 634 mutation (Ito et al. 1997). Mutations in non-cysteine domains of the RET (see above) afford a weaker activation, resulting in a attenuated form with low penetrance, late-onset MTC (classically between 30 and 50 years of age) and the FMTC phenotype only and infrequently result in disease-associated mortality (Bolino et al. 1995, Pasini et al. 1997, Rossel et al. 1997, Berndt 1998, Feldman et al. 2000, Lombardo et al. 2002, Niccoli-Sire et al. 2003, Lebouleux et al. 2004, Menacho et al. 2005, Vestergaard et al. 2007). This has led to the supposition that these patients have a mild ‘C-cell disease phenotype’ (Berndt et al. 1998, Fattoruso et al. 1998). A possible explanation of these differences seen between the codons is that the mechanism of RET activation may differ between specific codons within the gene. For example, mutations at residues 618 and 620 (and 609 to a much lesser extent) result in a much lower expression of the cell-surface form of RET than the 634 mutation (Ito et al. 1997, Pasini et al. 1997, Chappuis-Flament et al. 1998).

This knowledge generated the concept of ‘codon-directed’ timing of surgery (see ‘Management’ below); according to this surgical philosophy, the timing of prophylactic surgery is dictated by the specific genotype (i.e., surgery being performed before the earliest reported age of MTC diagnosis for that specific codon). However, the clinician should keep in his/her mind that – although generally the risk is codon specific – the age of onset of MTC is not always constant and that there are always exceptions to the rule. For example, in some cases, these mutations have been associated with a more aggressive biological behavior (development of locally invasive disease and distant metastases) (Fattoruso et al. 1998, Feldman et al. 2000, Niccoli-Sire et al. 2001, 2003). It may be possible that, in association with these genetic changes, there may be some additional influence by other modifying factors (Cebrian et al. 2005). Therefore, the risk associated with some (especially non-cysteine) mutations may be uncertain.

**Diagnostic approach**

Although MEN 2 syndromes are rare, early diagnosis is especially important. Up until the last decade, these syndromes were recognized mainly through family history. Nowadays, with the development of genetic testing and direct DNA analysis, molecular techniques are increasingly used to identify asymptomatic patients. As a result of these recent advances, MEN 2 syndromes are increasingly and more commonly diagnosed in the pediatric population, presenting challenging clinical scenarios. Surgical prophylaxis has a central role in the management of these patients.
Measurement of basal and stimulated calcitonin levels

Calcitonin is the primary secretory product of malignant C-cells of MTC; it can be measured by using a sensitive immunometric calcitonin assay (Barbot et al. 1994). Calcitonin is important as an excellent tumor marker (Gagel et al. 1988, Pacini et al. 1994). Calcitonin levels (both basal as well as stimulated by pentagastrin, calcium, or both; Heshmati et al. 1994). Calcitonin levels (both basal as well as stimulated by pentagastrin, calcium, or both; Heshmati et al. 1994, Niccoli et al. 1997, Cohen et al. 2000) are nearly always elevated with MTC.

Basal calcitonin levels

MTC can be diagnosed before being clinically evident (presymptomatic diagnosis) based on increased basal calcitonin levels (Melvin et al. 1971). In the study by Niccoli-Sire et al. (2003), when a basal calcitonin level was elevated, all but one patient had MTC and nodal metastases were found in 37.1% of the patients. These investigators reported a continuous progression in the staged disease with regard to basal calcitonin levels above 30 pg/ml. Nodal involvement was nearly constant when calcitonin was more than 100 pg/ml and was associated with macroscopic MTC in one half of the cases (Niccoli-Sire et al. 2003). It therefore appears that progression from CCH parallels increasing basal calcitonin levels and more advanced staged disease (Niccoli-Sire et al. 1999, 2001, Cohen et al. 2000); in other words, there is a positive correlation between tumoral mass and calcitonin levels. However, despite that basal calcitonin levels are higher in MTC than in CCH, this difference cannot be used for an accurate differential diagnosis between these two entities (Franck-Raue et al. 1996, Guyetant et al. 1997, Feldman et al. 2000, Gimm et al. 2002, Niccoli-Sire et al. 2003).

Stimulated calcitonin levels

The sensitivity of biochemical diagnosis of MTC and MEN 2 syndromes was further increased by the use of secretagogues (i.e., pentagastrin or calcium) to stimulate tumor secretion of calcitonin (Niccoli-Sire et al. 2003). In this test, pentagastrin is infused intravenously (0.5 µg/kg, for 3 min) to stimulate secretion of calcitonin, and blood samples are collected before and 3, 5, and 10 min after the initiation of the pentagastrin injection. It should, however, be noted that pentagastrin peptide for parenteral (i.v.) testing is currently in very restricted availability. Alternatively, calcium gluconate can be used as a secretagogue (2 mg/kg infused over 1 min) (Skinner 2003). Calcitonin response is considered normal (i.e., negative pentagastrin test results) when less than 10 pg/ml (Barbot et al. 1994). However, this upper limit obviously is assay dependent. Pentagastrin test allows the detection of MTC at an early stage – even with normal basal calcitonin levels, when MTC is isolated to the thyroid gland, thereby increasing the chances of cure by surgery (Wells et al. 1982). Pentagastrin test can accurately detect C-cell disease. For example, it has been shown that when preoperative peak calcitonin level was pathologic, MTC was present in over 92% of cases (Heizmann et al. 2006). However, up to 20% of patients had normal pentagastrin-stimulated calcitonin levels, although CCH or MTC was documented on histologic examination (Dralle et al. 1998, Niccoli-Sire et al. 1999). Most authors agree that differential diagnosis between CCH and MTC is not possible based on stimulated calcitonin levels (Niccoli-Sire 2003, Heizmann et al. 2006).

A major limitation of biochemical diagnosis of MTC is that the diagnosis is made after the development of the disease (even if diagnosed before the appearance of any clinical signs or symptoms of MTC); at this stage, a truly prophylactic surgery is not possible. Moreover, measurement of calcitonin levels (basal and stimulated (which is unpleasant to the patient)) needs to be done yearly and indefinitely (Ponder et al. 1988).

Today the role of basal and stimulated calcitonin levels is of limited value in accurately predicting the stage of neoplastic development of the C-cells or the long-term patient outcome (Iler et al. 1999). These tests should not be used to define the timing of thyroid surgery in children with RET syndromes (see below, management; Iler et al. 1999). Today, they have been replaced by genetic analysis that allows the identification of mutations in the RET proto-oncogene (see below).

Genetic testing

Screening of DNA for the detection of RET mutations is effective and widely available (Skinner et al. 2005). When performed rigorously, it reveals a RET mutation in over 95% of MEN 2 index cases (Brandi et al. 2001). The RET test has a higher rate of true positives and lower rates of false negatives and false positives than the calcitonin tests. It allows early diagnosis of MEN 2 syndromes, before the development of any neoplastic changes within the thyroid, thereby facilitating surgical decision making regarding prophylactic thyroidectomy (Skinner 2003). Genetic testing is useful for confirming
hereditary MTC and for identifying asymptomatic gene carriers in known kindreds with MTC who probably will develop thyroid cancer (Lips et al. 1994, Wells et al. 1994). This strategy has obvious clinical implications. Early genetic screening in children of parents with MEN 2 or FMTC has led to prophylactic total thyroidectomy. Interestingly, genetic analysis offers the possibility to define genotype–phenotype correlations and to adjust the time of prophylactic surgery (Machens et al. 2005). Hereditary MTC is thus a model of genetically determined cancer in which both diagnostic and therapeutic strategies rely on the identification of specific mutations (see below).

Management

In older MEN 2A series, with treatment initiated after the identification of a thyroid nodule, MTC progressed and showed a 15–20% cancer mortality (Kakudo et al. 1985). Early thyroidectomy reduced mortality from hereditary MTC to less than 5% (Brandi et al. 2001). Before the recognition of MEN 2 sudden death from pheochromocytoma was frequent in these families, perhaps as frequent as death from progression of MTC (Steiner et al. 1968). However, it is probable that improved management of pheochromocytoma has decreased the rate of premature mortality in MEN 2 even more than has the improved management of MTC (Brandi et al. 2001).

The specifically mutated codon of RET correlates with the MEN 2 variant, including the aggressiveness of MTC. Thus, the mutated RET codon and the features within the family should receive careful attention in planning thyroid management. The MTC risk can be stratified, according to the known RET mutation (Brandi et al. 2001).

In patients with RET positivity a clear progression from CCH to MTC has been documented (Machens et al. 2003a,b, Ashworth 2005). This observation raised the question about the role of preventive measures in RET mutation carriers. Obviously, the first step in the management of these patients is the recognition of these genetic changes; RET genetic screening is therefore indicated. Interestingly, the American Society of Clinical Oncology (ASCO) and recently-the National Comprehensive Cancer Network proposed that patients with apparently sporadic MTC should undergo RET mutational analysis to rule out germline mutations, which would prompt the testing of offspring for similar mutations (Statement of the ASCO 1996, NCCN Oncology Practice Guidelines 2005). Early identification of mutation carriers can significantly change the decision making in these patients. As above noted, in MEN 2A, the risk of developing MTC is 90–100%, and therefore the only curative treatment is total thyroidectomy, ideally before the development of MTC, or at least when the MTC is still confined within the thyroid and before the spread of the disease beyond the gland (Wells et al. 1994, Gimm et al. 2001, Danko & Skinner 2006, Heizmann et al. 2006, You et al. 2007). To appreciate the value of prophylactic thyroidectomy, the clinician should keep in his/her mind that, although infrequently, even microscopic MTC may be aggressive and can metastasize in about 5% of patients (Guyetant et al. 1999). Some large series have confirmed this hypothesis, as all individuals who underwent thyroidectomy had MTC or its assumed precursor lesion CCH (Lips et al. 1994, Dralle et al. 1998, Niccoli-Sire et al. 1999). This therapeutic strategy is especially important since advanced disease is incurable by conventional chemotherapy or radiotherapy, which further emphasizes the importance of early detection and prompt intervention (Niccoli-Sire et al. 1999, Machens et al. 2003a,b, Skinner et al. 2005, You et al. 2007). Thyroidectomy performed on the basis of positive genetic screening and before the development of MTC is truly prophylactic, while thyroidectomy performed after the development of MTC is essentially therapeutic. RET mutation carriers should also be screened for pheochromocytoma (Heizmann et al. 2006). Historically, the MEN 2 syndromes represent the first disease for which prophylactic removal of an organ target is recommended before the development of malignancy, solely on the basis of a genetic test (Skinner 2003). It has been, in fact, the near-perfect model for developing such approaches in that, unlike all other familial cancers, there exists an accurate diagnostic genetic test, there is minimal morbidity from the surgical intervention of total thyroidectomy, organ function is able to be fully replaced with thyroxine, and a test of subsequent disease status (calcitonin) is available (Gosnell et al. 2006).

The likelihood of a RET germline mutation in a patient with apparently sporadic MTC is 1–7% (Eng et al. 1995a,b). A RET germline mutation is more likely if apparently sporadic MTC has an early age of onset, if there is multiplicity within the thyroid, or if it is observed in association with a pheochromocytoma (Brandi et al. 2001).

Obviously, surgical morbidity should be minimal and within acceptable limits. The reported incidences of permanent hypocalcemia and recurrent laryngeal nerve dysfunction have ranged from 1 to 7% and 1% respectively (Dralle et al. 1998, Niccoli-Sire et al. 2005).
1999, Brandi et al. 2001, Ukkat et al. 2001, Rodriguez et al. 2002). While in situ preservation of parathyroid tissue is often possible, long-term success has been demonstrated with parathyroid autotransplantation in either the brachioradialis or the sternocleidomastoid muscle (Olson et al. 1996). Certainly, the risk of complications following thyroidectomy is decreased when the procedure is performed by surgeons with considerable experience in the procedure (Sosa et al. 1998). Anesthesia and airway management in children may be viewed as a barrier, but the risk is decreased when a pediatric anesthesiologist is available.

Timing of prophylactic thyroidectomy

Contrasting with the remarkable achievements in genetic diagnosis, no major progress has been registered concerning treatment, particularly for distant metastases. As above noted, children carrying activating RET mutations firstly develop thyroid CCH, which progressively transforms into MTC, in virtually all gene carriers and often before the age of 5 years (Machens et al. 2002, Piolat et al. 2006). MTC then rapidly spreads to cervical lymph nodes and ultimately leads to distant metastasis, the main cause of death of these patients. Operation removing the target organ (thyroidectomy), ideally before the development of MTC, remains the only effective preventive/therapeutic approach (Evans et al. 1999, Gimmi et al. 2001), thus explaining the importance of early diagnosis of germline carriers as well as of early prophylactic thyroidectomy (Niccoli-Sire et al. 1999, Machens et al. 2003a,b, Skinner et al. 2005). Often, prophylactic thyroidectomy in RET mutation carriers should be performed before age of 5 years or in the first decade of life (Brandi et al. 2001, Moore et al. 2007).

The limitations of measurements of calcitonin levels (basal/stimulated) are well-known (see above; Ilter et al. 1999). Surgery on the basis of abnormal calcitonin tests fails to be truly prophylactic, since a positive pentagastrin test result indicates the presence of C-cell disease or even MTC (Machens et al. 2001, Niccoli-Sire 2003). Genetic testing has a higher rate of true positives and lower rates of false negatives and false positives than the calcitonin tests, and it facilitates earlier thyroidectomy (Brandi et al. 2001) and currently prophylactic thyroidectomy should be carried out regardless of serum calcitonin levels (Gosnell et al. 2006). At the MEN97 Workshop consensus was reached that the decision to perform thyroidectomy in MEN 2 should be based predominately on the result of RET mutation testing rather than on calcitonin testing (Lips 1998). Nowadays, it is well known that the onset of neoplastic development and the aggressiveness of MTC are closely related to the location of the mutated codon within the RET gene. Thus, genotype analysis allows the classification of carriers of the RET mutation into risk categories and a more tailored approach to management of these patients (Shapiro et al. 2003). Thus, thyroidectomy can be performed before the development of MTC, thereby preventing this potentially lethal disease by removing the still ‘normal’ but at-risk thyroid parenchyma. The finding of normal pathology in RET mutation carriers has been reported elsewhere and supports the concept that early recognition and treatment can in fact lead to surgical cure before the development of CCH or MTC (Kebebew et al. 1999). Recommendations for the optimal timing of prophylactic surgery depend on this risk stratification (Brandi 2001).

The International RET Mutation Consortium correlated codon genotypes with clinical aggressiveness of hereditary MTC and provided guidelines for the timing of prophylactic thyroidectomy (Eng et al. 1996, Brandi 2001). Patients with MEN 2B or RET mutations in codons 883, 918, or 922 are at the highest risk (level 3) and should undergo thyroidectomy within the first year of life. Others have suggested prophylactic thyroidectomy even earlier (within the first 6 months or preferentially within the first month) in these cases (You et al. 2007). To support their recommendations, these investigators emphasized that the finding of microscopic MTC within the first year of life in this setting is common, and that even metastasis during the first year of life has been described (Stjernholm et al. 1980, Kaufman et al. 1982, Samaan et al. 1991, Smith et al. 1999).

Patients with MEN 2A or FMTC who have mutations in codons 611, 618, 620, and 634 are at high risk (level 2) and thyroidectomy should be performed before the age of 5 years (Wells et al. 1994, Brandi 2001, Machens et al. 2001, Danko & Skinner 2006, You et al. 2007). However, early thyroidectomy with a codon 634 mutation has helped to identify microscopic MTC in a child as young as 2 years of age (Modigliani et al. 1998).

Children with RET codon 609, 768, 790, 791, 804, and 891 mutations or with FMTC are classified as level 1 (the lowest risk among the three RET codon mutation stratification categories; Brandi et al. 2001). The biological behavior of MTC in patients with these mutations is variable, but in general MTC grows more slowly and develops at a later age than with the high risk mutations. However, lymph node metastases and death caused by MTC have been observed for mutation in each of these except codons 790 and 791. Currently, there is no clear consensus regarding
the optimal timing of thyroidectomy in this group of patients. Some recommend surgery before age of 5 years (as in the high risk (level 2) group of patients) and others suggest surgery before age of 10 years, and still others believe that intervention is only required when stimulated calcitonin levels are abnormal (Brandi et al. 2001, Colombo-Benkmann et al. 2002, Fitze et al. 2002, Vestergaard et al. 2007). In this group of patients, if delay of thyroidectomy is decided, a clear plan of evaluation should be followed (You et al. 2007).

It appears that this surgical philosophy is effective in preventing the development of MTC and improves the long-term results of treatment (Skinner et al. 2005). Indeed, Szinnai et al. (2003) found a difference between patients who underwent ‘early’ thyroidectomy (by age 1–5 years) and those with ‘late’ thyroidectomy (by age 6–20 years). Whereas all children with early total thyroidectomy seemed to be cured (median follow-up, 3 years; maximum, 9 years), the patients aged between 6 and 20 years at operation showed a considerable proportion of persistent or recurrent disease (55%) after 10 years. Skinner et al. (2005) reported the long-term outcome of prophylactic thyroidectomy in 50 children (mean age 10 years) with allelic mutations characteristic of MEN 2A. These patients had prophylactic thyroidectomy, central lymphadenectomy, and routine parathyroid autotransplantation. CCH, microscopic MTC, or macroscopic MTC was found in 94% of the patients and nodal metastases were present in 6%. After a minimum follow-up of 5 years, 88% of the 50 patients remained disease-free, as defined by undetectable calcitonin levels following provocative testing. Other institutional series with smaller numbers of patients (Lallier et al. 1998, van Heurn et al. 1999, Sanso et al. 2005), less complete or shorted follow-up (Lips et al. 1994, Pacini et al. 1995, Dralle et al. 1998, Niccoli-Sire et al. 1999, Ukkat et al. 2001, Rodriguez et al. 2002) have reported variably defined ‘cure rates’ of 76–100%. As expected, the prognosis of hereditary MTC in more advanced stages is not favorable. When hereditary MTC is detected clinically (as palpable tumors), survival is significantly diminished (5- and 10-year survival rates, 78 and 64% respectively (Bergholm et al. 1990).

Not surprisingly, a significant delay between the date of genetic diagnosis and the date of thyroidectomy has been reported (Pirot et al. 2006). Mostly, this delay was related to the time parents needed to accept and allow for a total thyroidectomy in their asymptomatic and apparently ‘healthy’ child. Cultural factors may also affect the acceptance of early prophylactic surgery in asymptomatic children.

The role of cervical lymph node dissection

It is evident that if total thyroidectomy is truly prophylactic (i.e., it is performed before the development of MTC), then the at-risk thyroid parenchyma is removed and the risk of MTC is totally (at least theoretically) eliminated. In this case, prophylactic cervical lymph node dissection is not indicated. The problem is that none can be sure preoperatively that no MTC will be found after a presumably prophylactic thyroidectomy in mutation carriers. Therefore, the role of cervical lymph node dissection during prophylactic thyroidectomy remains controversial. Lymph node metastases are common in MTC and, albeit rarely, can be observed even in the presence of microscopic MTC (Dralle et al. 1998). MTC size cannot be used to predict the presence of cervical lymph node metastases. Lymph node metastases in patients with hereditary MTC of less than 1 cm may reach an incidence of 20% (Bigner et al. 1981, Dralle et al. 1995). Recurrent disease is observed in a large proportion of patients (33%) if a central neck dissection is omitted at the time of total thyroidectomy for established MTC (Decker 1992). These data emphasize the significance of the unresolved problem about the role of cervical lymph node dissection in the management of patients at risk for the development of hereditary MTC. The radicality during initial surgery is of utmost importance, because of its influence on the outcome of patients with hereditary MTC (Ellenhorn et al. 1993, Kallinowski et al. 1993, Dralle et al. 1995, Tamagnini et al. 2005).

The role of cervical lymph node dissection during prophylactic thyroidectomy remains controversial. In the past, patients who underwent prophylactic thyroidectomy did not undergo concomitant standard lymphadenectomy (Dralle et al. 1995). Currently, it is generally accepted that in MEN 2B patients undergoing prophylactic thyroidectomy, central lymph node dissection is indicated and, if nodal metastases are found, a more extensive node dissection should be considered (Brandi et al. 2001). In contrast, despite that nodal metastases from MTC have been reported in a child at age of 5 years (Gill et al. 1996), there is no consensus regarding the need for prophylactic dissection of central lymph nodes in MEN 2A and FMTC, with most authors supporting prophylactic thyroidectomy alone (i.e., without concomitant cervical lymph node dissection), since in these patients the likelihood of metastatic lymph node disease is very low (Lallier et al. 1998, Brandi et al. 2001, Frilling et al. 2003, Machens et al. 2003a,b, Skinner 2003, Danko & Skinner 2006, Gosnell et al. 2006, Butter et al. 2007).
In the presence of elevated basal or stimulated calcitonin levels (which indicates the presence of C-cell disease, either CCH or MTC), central lymph node dissection at the time of total thyroidectomy should be considered (Brandi et al. 2001, Niccoli-Sire et al. 2003, Heizmann et al. 2006). Obviously, a more aggressive neck dissection should be performed if there is evidence of involved lymph nodes in the lateral neck. Cervical lymph node dissection should also be performed in older (above 10 years) patients with MEN 2A and FMTC undergoing, for a variety of reasons, delayed thyroidectomy or when MTC is diagnosed during a presumably prophylactic thyroidectomy (Heizmann et al. 2006).

From a technical point of view, it should be noted that central lymph node dissection during the primary operative procedure should be preferred because the risk of permanent complications increases if lymphadenectomy is carried out as a reoperation (Colombo-Benkmann et al. 1998). However, primary central lymph node dissection is associated with a higher rate of permanent hypoparathyroïdism and recurrent laryngeal nerve damage compared with total thyroidectomy alone (Piolat et al. 2006). To remove potentially existing locoregional metastases from MTC, it is recommended that the lymph nodes be removed in the central neck from the hyoid bone to the clavicles, and between the carotid sheaths (Skinner 2003). This is usually the first nodal basin to collect metastatic MTC.

Complications, follow-up and recurrence of the disease

Currently, prophylactic surgery can be performed safely and with minimal postoperative morbidity (Iler et al. 1999). Expertise is required from the part of both the surgeon and the anesthesiologist to maintain complications rates within acceptable limits. In experienced hands, the risks associated with a delayed thyroidectomy outweigh the morbidity of early surgery (Iler et al. 1999).

Postoperatively, follow-up is indicated to allow early detection of a possible recurrence. As expected, recurrence is more common in node-positive patients (Skinner et al. 2005). Calcitonin is an excellent tumor marker not only for diagnostic but also for follow-up purposes (Shaha et al. 2006). Generally, elevated calcitonin levels after surgery are generally the first sign of persistent or recurrent disease (Brandi et al. 2001, Shaha et al. 2006). Stimulated calcitonin levels have also been used to detect recurrent disease (Skinner 2003). Unfortunately, due to the lack of published data, it remains unknown how frequently these tests should be performed. Furthermore, it is unknown how many years should pass without the development of MTC before the child can be declared ‘cured’ by his thyroidectomy.

If the basal or stimulated plasma calcitonin levels are high after primary thyroid surgery, the presence and extent of local and/or distant (metastatic) disease should be documented (Dottorini et al. 1996, Scopsi et al. 1996, Modigliani et al. 1998). Unfortunately, as a result of the exquisite sensitivity of calcitonin levels in detecting MTC, localization of recurrent metastatic disease may be very challenging (Danko & Skinner 2006). Most radiographic modalities have very low sensitivities for the detection of early recurrent or metastatic MTC. Following adequate diagnosis of recurrence, a decision regarding optimal management should be made (Dottorini et al. 1996, Scopsi et al. 1996, Bergholm et al. 1997). If there is no evidence of distant metastases and if local disease is found suspected in the neck and/or upper mediastinum, then reoperation is advocated. Exploration of the mediastinum is controversial because of the greater morbidity and the few examples of cures. If distant metastases are found, surgery is not indicated.

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