Abstract  Multiple endocrine neoplasia type 2 (MEN2) is a autosomal dominat inherited tumour-syndrome caused by germline activating mutations of the RET proto-oncogene on chromosome 10. It is clinically characterized by the presence of medullary thyroid carcinoma (MTC), bilateral pheochromocytoma and primary hyperparathyroidism (MEN2A) within a single patient. Three distinct clinical forms have been described depending on the phenotype: the classical MEN 2A, MEN 2B, an association of MTC, pheochromocytoma and mucosal neuroma, (FMTC) familial MTC with a low incidence of other endocrinopathies. Each variant of MEN2 results from different RET gene mutation, with a good genotype phenotype correlation. Genetic testing detects nearly 100% of mutation carriers and is considered the standard of care for all first degree relatives of patients with newly diagnosed MTC. Recommendations on the timing of prophylactic thyroidectomy and extent of surgery are based on a classification into four risk levels utilizing the genotype-phenotype correlations. MEN 2 gives a unique model for early prevention and cure of cancer and for stratified roles of mutation-based diagnosis of carriers.

Keywords  Multiple endocrine neoplasia type 2 · Pheochromocytoma · Primary hyperparathyroidism · Ganglioneuromarosis · RET proto-oncogene · Tyrosine kinase inhibitors

Abbreviations
MEN  Multiple endocrine neoplasia
MTC  Medullary thyroid carcinoma
Ct  Calcitonin
Pheo  Pheochromocytoma
HPT  Primary hyperparathyroidism
FMTC  Familial medullary thyroid carcinoma
RET gene  Rearranged during transfection gene
CCH  C-cell hyperplasia

Introduction
Multiple endocrine neoplasia type 2 (MEN2) (OMIM 171400) is an autosomal dominant cancer syndrome that implies a 50% risk to offspring of a carrier to inherit the disorder. The estimated prevalence is 2.5 per 100,000 in the general population. Predisposition to MEN2 is caused by germline activating mutations of the RET proto-oncogene [1, 2]. MEN2 shows a high penetrance for medullary thyroid carcinoma (MTC), a rare calcitonin (Ct)-secreting tumour of the parafollicular or C-cells of the thyroid, which derive from neural crest. Most patients suffer from the sporadic (non-familial) form while 25–30% account for hereditary MTC. Hereditary MTC is usually bilateral and multicentric; multifocal C-cell hyperplasia is considered to be a precursor of MTC in patients with hereditary disease.

Classification and clinical manifestation of MEN 2
MEN type 2 syndrome occurs in three clinical distinct varieties with MTC as the common manifestation (Table 1). These three varieties of MEN2 are clinically
distinct with respect to incidence, genetics, age of onset, association with other diseases, aggressiveness of MTC, and prognosis. Both sexes are nearly equally affected in the familial variety [3, 4].

1. The MEN 2A syndrome (Sipple’s Syndrome), characterized by MTC in combination with pheochromocytoma (Pheo) and hyperplasia of the parathyroids (primary hyperparathyroidism, HPT); it is the most common form of all MEN 2 syndromes (55% of all cases).

2. The MEN 2B syndrome, consisting of MTC, Pheo, ganglioneuromatosis, and Marfanoid habitus; it is the most rare and aggressive form of MEN 2 (5–10% of all cases) [5].

3. Familial MTC (FMTC), with a low incidence other endocrinopathies; it is the mildest variant of MEN2 more often diagnosed in recent years (35–40% of all cases) [6].

<table>
<thead>
<tr>
<th>Subtype</th>
<th>% of total cases</th>
<th>MTC (%)</th>
<th>Pheo (%)</th>
<th>HPT (%)</th>
<th>Associated diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN 2A</td>
<td>56</td>
<td>100</td>
<td>50</td>
<td>25</td>
<td>Cutaneous lichen amyloidosis Hirschsprung’s disease</td>
</tr>
<tr>
<td>MEN 2B</td>
<td>9</td>
<td>100</td>
<td>50</td>
<td></td>
<td>Ganglioneuromatosis, Marfanoid Habitus</td>
</tr>
<tr>
<td>FMTC</td>
<td>35</td>
<td>95</td>
<td></td>
<td></td>
<td>Very rare</td>
</tr>
</tbody>
</table>

The respective frequency of MTC in MEN2A is over 90%, approximately 40–50% for Pheo, and 10–20% for multigland parathyroid hyperplasia with HPT. MTC is generally the first manifestation of MEN2A between the age of 20–30 years. At least two of the classical clinical features of MEN 2A are required in the patient or in the first-degree relatives of the patient to make a clinical diagnosis of MEN 2A.

Many patients with MEN 2B have an earlier onset in the first year of life and more aggressive MTC with a higher morbidity and mortality than in patients with MEN2A. Multivariate analysis suggests that the higher mortality rate of MEN 2B reflects a more advanced tumour stage at presentation rather than a more aggressive tumour behaviour once established [7]. HPT is not a feature of MEN2B. Patients with MEN2B also tend to have typical phenotypic features like mucosal neuromas and cutaneous neuromas visible physical stig mata such as raised bumps on the lips and tongue, intestinal ganglioneuromas, and in some instances, a Marfanoid habitus with skeletal deformations and joint laxity. The intestinal disturbances like chronic constipation or megacolon from birth are often initial disease manifestations that present for medical attention. Brauckhoff [8] reported that 86% of MEN2B patients demonstrated the inability to cry tears. They often do not have a family history of the disease due to de novo mutation.

FMTC is a variant of MEN2, in which there is a strong predisposition to MTC in the families with a low or no incidence of the other clinical manifestations of MEN2A. The diagnosis of FMTC can only be considered when four or more family members across a wide range of ages have isolated MTC. Nowadays, FMTC is viewed as a phenotypic variant of MEN 2A with decreased penetrance of pheochromocytoma and primary hyperparathyroidism. The penetrance and clinical course of MTC in FMTC is more benign than MEN2A and MEN2B with a late onset or no clinically manifest disease, and the prognosis is relative good. Therefore, a family history is often inadequate in establishing familial disease. FMTC has been diagnosed more frequently in recent years (35–40% of all cases).

The way of discovery of MTC in a patient has changed within the last decade by using specific strategies: Ct screening in patients with thyroid nodules and screening with molecular methods for mutations in the RET proto-oncogene in patients with apparently sporadic MTC and in family members at risk for MTC. About 1–7% of apparently sporadic cases have identifiable RET mutations, including about 2–9% with de novo germline mutations [4, 9]. By early identification of patients with MTC, the presentation changes from clinically evident tumours to preclinical disease resulting in a higher cure rate of affected patients with much better prognosis [10].

### Medullary thyroid carcinoma: pathology and biochemical marker

Hereditary MTC characteristically presents as a multifocal process with C-cell hyperplasia (CCH) as precursor lesion to MTC. Only familial primary CCH is a preneoplastic lesion. Secondary CCH, which has been associated with chronic lymphocytic thyroiditis, hypergastrinemia, near other follicular cell-derived thyroid tumours, and even aging, has a much lower, if any, potential for malignancy [11]. The time frame of the progression from CCH to microscopic carcinoma remains unclear but may take years. Metastasis may be found first in central and lateral cervical and mediastinal lymph nodes of the neck in 10% of patients with a micro-MTC operated on after discovery at familial screening, and in up to 90% of patients operated on for clinical MTC. Metastases outside the neck and
mediastinum may occur during the course of the disease in the lung, liver and bone.

The primary secretory product of MTC is calcitonin (Ct), which serves as a tumour marker for MTC. Measurement of monomeric Ct with two-site assays [12] is widely available, accurate, reproducible, and cost-effective. Slightly elevated Ct levels might be seen in CCH, renal failure, and autoimmune thyroiditis. Either basal or stimulated plasma Ct levels using pentagastrin or calcium are elevated in virtually all patients with MTC. Basal Ct concentrations usually correlate with tumour mass and are almost always high in patients with palpable tumours [13]. Similarly, elevated plasma Ct levels following surgery to remove the tumour are indicative of persistent or recurrent disease.

**RET-proto-oncogene: genetic abnormalities in MEN 2**

The MEN 2 gene was localized to centromeric chromosome 10 (10q11.2) by genetic linkage analysis in 1987 [14]. Point mutations of the RET proto-oncogene were first identified in 1993 in MEN 2A, MEN 2B and FMTC in seven closely located exons [1, 2] (Fig. 1). Analysis of RET in families with MEN 2A and FMTC revealed that only affected family members had germline missense mutations and they have been found in nearly 100% of these families. Up to now, mutation analysis in MEN 2 families has identified over 50 different missense mutations segregating with the disease [7].

The RET gene has 21 exons and encodes a receptor tyrosine kinase that appears to transduce growth and differentiation signals in several developing tissues including those derived from the neural crest. The tyrosinkinase is activated upon ligand-induced dimerization after binding of one of the four ligands known. Subsequently phosphorylation of the specific tyrosine residues and activation of multiple intracellular pathways with effects on development and differentiation occur.

Hereditary MTC is caused by autosomal dominant gain-of-function mutations in the RET proto-oncogene. It was demonstrated that mutation of the extracellular cysteine at codon 634 causes ligand-independent dimerization of receptor molecules, enhanced phosphorylation of intracellular substrates, and cell transformation. Mutation of the intracellular tyrosine kinase (codon 918) has no effect on receptor dimerization but causes constitutive activation of intracellular signalling pathways and also results in cellular transformation. A hereditary RET gene mutation results in expression of abnormally overactive RET protein in all tissues in which it is expressed; somatic RET mutations that occur later in life and are limited to C cells are present in 40–50% of sporadic MTCs [15, 16]. MTC is generally the first neoplastic manifestation because of its earlier and higher penetrance compared with pheochromocytoma or parathyroid hyperplasia.

**Genotype phenotype correlation**

In the majority of MEN2 families, associations between specific RET mutations (genotype) and aggressiveness of MTC and presence of other endocrine tumours (phenotype) are well documented (Table 2). The most common mutation of codon 634 is TGC-CGC (Cys-Arg), it has been associated with pheochromocytoma and parathyroid gland involvement with MEN 2A families [17–19]. Therefore, individuals with this mutation should be annually screened for these endocrinopathies. Pheo is associated with exon 634 and 918 mutations in approximately 50% of patients, with exon 10 mutations (codons 609, 611, 618, and 620) in up to 20% patients, and rarely with mutations in exons 5 and 11 of the RET proto-oncogene.

![Germline mutations of the RET proto-oncogene associated with multiple endocrine neoplasia type 2 and familial MTC, numbers indicate mutated codons of the RET gene](image-url)
13–15 (codons 791 and 804) [20, 21]. HPT in MEN 2A is most commonly associated with codon 634 mutations, with C634R in particular [22]. All cases of MEN 2A with Hirschsprung’s diseases are associated with mutations in exon 10 (codons 609, 611, 618, 620), and MEN 2A with cutaneous lichen amyloidosis is associated with mutations in codon 634 [23].

The actual analysis of the RET proto-oncogene in patients with hereditary MTC provided evidence for a change in the spectrum of detected mutations [24]: Meanwhile codon 634 mutations are still the most common missense change in patients with MEN 2A but the frequently decreased to 37%. On the other hand, so called “rare mutations” in exon 10 codon 609, exon 13 codons 768, 790, and 791, exon 14 codon 804, and exon 15 codon 891 increased to 39%. It is of considerable interest to note that identical germline mutations have been reported in families with MEN 2A and FMTC [25]. Therefore, FMTC associated with a RET gene exon 10 mutation constitutes a subtype of MEN 2A with a low frequency of pheochromocytoma, rather than a separate clinical entity. The same is true for mutations in exon 13 codon 768, 790 and 791, and in exon 14 (Val 804 Leu) [26], which thought to be specific for FMTC. However, some rare families with MTC and pheo were also identified [6].

In 95% of patients and families with MEN 2B a mutation in codon 918 in exon 16 coding for the intracellular TK2 domain was found [18]. In more than 50 percent of cases of MEN2B with codon 918 affected, mutations occur as new (de novo) germline mutations. In each family this mutation resulted in an ATG (methionine) to ACG (threonine) alternation. A germline mutation of RET codon 883 exon 15 in two cases of de novo MEN 2B was described [27].

### Risk levels

The association between disease phenotype and RET mutation genotype may have important implications for the clinical management of MEN 2 patients and their families. This information could be used to intensify screening for pheo or HPT in mutations associated with a higher risk of disease or to plan the prophylactic thyroidectomy depending on the aggressiveness of MTC associated with different mutations [4, 7]. The mutations were divided into four risk levels [7] (Table 3). Patients with level A mutations mostly FMTC (exon 13 codons 768, 790, and 791, exon 14 codon 804, and exon 15 codon 891) have the lowest risk for the development and aggressiveness of MTC. Patients with level B mutations, mostly MEN 2A (exons 10 codons 609, 611, 618, and 620) are at intermediate risk, and patients with level C mutations, the classical MEN2A (exon 11 codon 634), are at higher risk of...

### Table 2 Genotyp and age of onset of MTC

<table>
<thead>
<tr>
<th>RET codon</th>
<th>Earliest age of onset</th>
<th>ATA risk level</th>
<th>Age of proph. Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>918</td>
<td>2 months</td>
<td>D</td>
<td>ASAP</td>
</tr>
<tr>
<td>634</td>
<td>13 months</td>
<td>C</td>
<td>Before 5 years</td>
</tr>
<tr>
<td>609</td>
<td>5 years</td>
<td>B</td>
<td>Consider before 5 years</td>
</tr>
<tr>
<td>620</td>
<td>6 years</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>611</td>
<td>7 years</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>618</td>
<td>7 years</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>768</td>
<td>9 years</td>
<td>A</td>
<td>May delay &gt;5 years</td>
</tr>
<tr>
<td>790</td>
<td>10 years</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>804</td>
<td>12 years</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>891</td>
<td>13 years</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>791</td>
<td>15 years</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>533</td>
<td>21 years</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>631</td>
<td>22 years</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3 Codon based genotype phenotype correlation (adapted to the ATA classification [7])

<table>
<thead>
<tr>
<th>ATA risk level (2009)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codon</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>768, 790, 791, 804</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>618, 891</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>649</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>649, 891</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEN-2 subtype</td>
<td>FMTC</td>
<td>FMTC/MEN 2A</td>
<td>MEN 2A</td>
<td>MEN 2B</td>
</tr>
<tr>
<td>MTC aggressiveness</td>
<td>High</td>
<td>Higher</td>
<td>Higher</td>
<td>Highest</td>
</tr>
<tr>
<td>MTC age of onset</td>
<td>Adults</td>
<td>5 years</td>
<td>Before the age of 5 years</td>
<td>First year of life</td>
</tr>
<tr>
<td>Timing of prophylactic thyroidectomy</td>
<td>When calcitonin rises/age 5 or 10 years</td>
<td>5 years</td>
<td>Before the age of 5 years</td>
<td>First months of life</td>
</tr>
<tr>
<td>Screening for Pheo</td>
<td>Start at 20 years, periodically</td>
<td>Start at 20 years, annually</td>
<td>Start at 8 years, annually</td>
<td>Start at 8 years, annually</td>
</tr>
<tr>
<td>Screening for HPT</td>
<td>Start at 20 years, periodically</td>
<td>Start at 20 years, annually</td>
<td>Start at 8 years, annually</td>
<td>–</td>
</tr>
</tbody>
</table>
aggressive MTC. Patients with level D mutations the typical MEN2B (exon 15 codon 883, and exon 16 codon 918) are at the highest risk for early development and aggressive growth of MTC with the youngest age of onset and highest risk of metastases. This knowledge of the age and penetrance of MTC in the codon mutated gives informations for timing and surgical procedure to prevent metastatic MTC.

Recommendations for the timing of prophylactic thyroidectomy and the extent of surgery are based upon a model that utilizes these genotype-phenotype correlations to stratify mutations into four risk levels [7] (Table 2). Patients with level A mutations have the lowest risk for development and aggressiveness of MTC. Operation may be postponed beyond age 5 years until after an abnormal C cell stimulation test result is observed (i.e. an abnormal Ct response to calcium) and depending on the age that MTC developed in the family members. Patients with level B mutations (exon 11) are at intermediate risk should undergo total thyroidectomy before the age of five. Patients with level C mutations (exon 11, codon 634) should be operated before the age of 5 and patients with exon 16 codon 918 (MEN 2B) are at the highest risk for early development and aggressive growth of MTC. Thyroidectomy should be done as soon as possible during the first year of life, if done later surgery is often not curative.

### Diagnosis of MEN2

In index patients the clinical presentation and manifestation of MEN 2 associated MTC are similar to those of sporadic MTC. The typical age of clinical onset of MEN2 is the third decade of life, patients present with a thyroid mass or a cervical lymphadenopathy found incidentally during routine examination. MTC shows hypoechogenic regions, sometimes with calcifications, and a thyroid scan almost always shows no trapping of radioactive iodine or technetium. Cytologic examination of the cold, hypo-echogenic nodule, will lead to a strong suspicion of MTC. The diagnosis of MTC in index cases is often made postoperatively when pathohistological examination may show multifocal bilateral MTC accompanied by diffuse CCH. A plasma Ct measurement can clarify the diagnosis, since, preoperative Ct levels correlate significantly with tumour size [13] and in the presence of a palpable MTC, the plasma Ct concentration will usually be greater than 1000 pg/ml. CEA level will be elevated in most cases with clinical evident tumours. Therefore, measurement of plasma Ct in patients with thyroid nodules has been advocated a routine procedure by some European consensus groups [28]. Genetic testing for RET mutations in patients with suspicious MTC and elevated calcitonin levels may also be helpful, since, if a mutation is found, it will imply that the disease is hereditary and that the family should be screened. All patients with a personal medical history of primary CCH, MTC, or MEN 2 should be offered germline RET testing [7] (Table 4). Once a germline RET mutation has been identified in a family, genetic counselling and RET mutation analysis should be offered to all first-degree relatives. Mutations in the RET proto-oncogene can be used to confirm the clinical diagnosis and identify asymptomatic family members with the syndrome. Offspring of a RET mutation gene carrier have a 50% risk of inheriting the mutation. Those who have a negative test can be reassured and require no further biochemical screening. At present, genetic testing is performed before the age of 5 years in all first-degree relatives of an index case (in MEN 2B patients directly after birth). When it is decided to delay prophylactic thyroidectomy beyond the first 5 years of the children with MEN2A/ FMTC, basal and/or stimulated serum CT and cervical ultrasound should be performed annually starting by the age of 5 years.

Less common presentations of MTC include recognition during search initiated after an associated disease such as pheo or multiglandular hyperparathyroidism becomes apparent. The clinical manifestation of pheo associated with MEN2 is similar to that in sporadic cases with signs and symptoms such as headache, palpitations, nervousness, tachycardia and hypertension. Measurement of plasma and/or 24 h urinary excretion of catecholamines and metanephrines should be performed. Once the biochemical
diagnosis is made imaging studies like MRI and/or MIBG scanning are appropriate. The presence of Pheo must be ruled out prior to any surgical procedure, if untreated they can be lethal. Patients with MTC should be evaluated for possible Pheo. A coexisting Pheo should be removed before thyroidectomy. The possibility of bilateral disease must be carefully evaluated. The penetrance of pheo among different MEN 2 kindreds depends on specific RET germline mutations (see above) [21]. Pheo have usually become evident approximately 10 years later than manifestation of MTC. Therefore, they are usually identified during screening in patients with MEN2 often before clinical symptoms occur. Biochemical screening for pheo should be performed annually in MEN 2 patients depending on the genotype (see above) beginning by the age 8 years in carriers of RET mutations associated with MEN2B and in the other codons by the age of 20 years. Because of high risk to the fetus and the mother, women with a RET mutation associated with MEN 2 should be screened for pheo before pregnancy. Other hereditary syndromes associated with familial pheo are von Hippel-Lindau syndrome, paraganglioma syndromes and neurofibromatosis type 1 [29].

The primary hyperparathyroidism (HPT) is often clinical occult and do not differ from those seen in mild sporadic HPT. The diagnosis is established by finding high intact-parathyroid hormone concentrations in the presence of hypercalcemia. Pathological findings show chief cell hyperplasia involving multiple glands. Annual measurement of serum calcium concentration in gene carriers is probably adequate for screening purposes taking into account that clinical asymptomatic gene carrier of a RET mutation with Ct levels more than 150 pg/ml without cervical lymph node or distance metastases preoperatively total thyroidectomy and prophylactic central neck dissection is recommended. Patients with more than ten lymph nodes compartments involved, a T4 tumour, or invasion in the soft tissue could not be cured by aggressive surgery (bilateral neck dissection). Therefore, a more palliative approach with resection of the local disease and clearance of the central compartment for prevention of future complications such as invasion into the recurrent laryngeal nerve or aerodigestive tract with resulting loss of speech or swallowing.

Prophylactic thyroidectomy should be performed in a clinical asymptomatic gene carrier of a RET mutation with a normal thyroid and no suspicious lymph node on ultrasound examination and normal Ct levels. Recommendations on the timing of prophylactic thyroidectomy and extent of surgery are based on a classification into four risk levels utilizing the genotype–phenotype correlations (see above risk levels) [7].

Some authors suggest thyroidectomy at age 5 for risk group A, some at age 10, while others, including the current authors [30], suggest that surgery may be postponed until an abnormal C-cell stimulation test result is observed (i.e., an abnormal Ct response to pentagastrin or calcium stimulation). For asymptomatic patients with risk levels A to C who are older than 5 years with Ct levels more than 40 pg/ml and thyroid nodules more than 5 mm and/or or evidence for lymph node metastases a more extensive disease has to be suggested, which requires total thyroidectomy plus central lymph node dissection [7]. In order to avoid complications like recurrent laryngeal nerve injuries or hyperparathyroidisms this operation should be done by high-volume surgeons.

Surgery for Pheo in MEN 2 should precede surgery for MTC. Before adrenalectomy all patients should receive appropriate pharmacotherapy (alpha- with/or without beta-adrenergic antagonist). Approximately one-third of patients who undergo a unilateral adrenalectomy will eventually require a second operation for contralateral pheo, but this may not occur for many years, during which time the patient will not be steroid dependent. Adrenal cortical-sparing adrenalectomy is a promising technique for preventing adrenal insufficiency.

The parathyroid glands in MEN 2 patients are frequently found to be enlarged at thyroidectomy for MTC and should therefore be carefully evaluated. The goal in MEN2 patients with primary hyperparathyroidism is to excise the enlarged glands and to leave at least one normal parathyroid gland intact. If they are all enlarged, a subtotal parathyroidectomy or total parathyroidectomy with autotransplantation should be performed.

Postsurgical follow-up and management

All patients should receive adequate thyroxine replacement therapy after total thyroidectomy to restore euthyroidism [31]. All patients should undergo Ct and CEA determination at regular intervals after total thyroidectomy. Normal basal and pentagastrin-stimulated Ct levels suggest a tumour-free state. These patients can be followed-up at half.

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The natural history of MTC is variable and ranges from years of dormant residual disease after surgery to rapidly progressive disseminated disease and death related to either metastatic thyroid tumour or complications of pheo in MEN 2B. The 10-year survival rates for all MTC patients range from approximately 61–76% [36–38]. The main factors that influence survival are stage of disease at diagnosis, size of the tumour and lymph node involvement, the variety of the tumour (sporadic vs. familial), the age and sex of the patient, and calcitonin doubling time. Patients with MEN 2A have a better survival rate than do patients with sporadic disease. In a multivariate analysis adjusted for tumour stage, the significant difference in survival advantage between patients with sporadic and familial disease disappeared [36, 39, 40]. This underlines the importance of tumour stage and age at diagnosis for prognosis in MEN2. Early RET gene mutation analysis and prophylactic thyroidectomy in a presymptomatic state improve quality of life and prolonged life expectancy [10, 31, 41].

Preventing, counselling, health economics

Genetic testing in MEN2 adds much information in the management of the tumour syndrome. In clinically demonstrable MTC the specific RET mutation gives information on the risk of appearance of pheo and HPT, the aggressiveness of the MTC, and the prognosis. In screening family members the result of genetic testing allows for early treatment and thereby offers the chance of prophylactic thyroidectomy and cure of MTC. From a medical point of view MEN2 is a unique model using genetic information to cure a patient with a hereditary cancer syndrome. From the patients view there is a loss of privacy and autonomy and a feeling of stigmatization and discrimination. There appears to be a threshold for patients to inform their relatives about the hereditary disease. This has to be taken into account when counselling patients with MEN2. The confidentiality of genetic testing is an absolute with no exception therefore the duty to inform relatives at risk falls to the moral obligation of the patient. However, many guidelines do allow for disclosure of results to at-risk individuals without the patient’s consent when the information disclosed will prevent serious harm [7]. Our social attitude to rare hereditary diseases has to be reconsidered. We need precise laws preventing discrimination concerning full insurance coverage and employment. Patient interest groups may serve in providing information, support in emotional distress, and stand up for common political and social aspects.

Both preimplantation and prenatal testing are available in some/most countries to RET mutation carriers. These methods have the fascinating potential to remove the disease from the family. In balancing the potential advantages against the efforts and hazards of the methods most people would agree that MEN2 nowadays, if treated properly, has an acceptable morbidity and no excess mortality. In our

Fig. 2 Postoperative and long term follow up

yearly intervals with physical examination and Ct determination (Fig. 2). Patients with persistent elevation of plasma Ct after total thyroidectomy should be thoroughly evaluated to define the extent of local and distant disease (see above). If there is no evidence of distant metastases and if local disease is found in the neck, reoperation (completion) could be done using meticulous dissection and microsurgical techniques [32].

In patients remaining Ct-positive with evidence of non-curable and non-operable disease (diffuse distant metastases) or occult disease (no local recurrence is found and adequate operation has been done), close observation of changes in serum Ct und CEA concentration is required. Doubling time of the tumour markers should be calculated. Many patients may exhibit a remarkable stable course and no further treatment is recommended; a “wait and see” approach is advocated, as experience with non-surgical therapy in the management of slow growing metastatic MTC with doubling time of Ct of more than 2 years has been disappointing [33]. In those patients whose disease shows rapid and steady progress, e.g. doubling of tumour marker smaller than 6 month and progression of tumour burden evaluated by response evaluation criteria (RECIST), intervention with palliative surgical intervention, chemotherapy, radiotherapy, somatostatin, or nowadays with tyrosinkinase inhibitors can be considered as a palliative therapeutic modality [34]. Compounds that block RET kinase activity directly, or block subsequent downstream signalling molecules like tyrosinkinase inhibitors are under evaluation in clinical trials and preliminary evidence indicates that they may have important clinical benefit [35].

Prognostic factors

The natural history of MTC is variable and ranges from years of dormant residual disease after surgery to rapidly progressive disseminated disease and death related to either metastatic thyroid tumour or complications of pheo in MEN 2B. The 10-year survival rates for all MTC patients
experience most RET mutation carriers of childbearing age would not consider prenatal or preimplantation diagnostic testing when offered during counselling.

References

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