MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

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ABSTRACT

Multiple Endocrine Neoplasia (MEN) type 2 A and B are rare autosomal dominant inherited cancer syndromes characterized by tumors of the C cells of the thyroid, of the adrenal medulla, and parathyroid glands. MEN2 is caused by a genetic defect in the REarranged during Transfection (RET) proto-oncogene on chromosome 10 (10q11-2), leading to a ligand-independent activation of the transmembrane RET receptor tyrosine kinase and consequently its intra-cellular pathways. Different mutations lead to different levels of activation and MEN2 is therefore characterized by a strong genotype-phenotype correlation. Nearly all patients with MEN2A have either C-cell hyperplasia (CCH) or medullary thyroid cancer (MTC), 50% have pheochromocytoma (PHEO), and 20-30% hyperparathyroidism (pHPT) but incidence of these manifestations is depending on the underlying RET mutation. Patients with MEN2B have a 100% incidence of CCH or MTC, PHEO in 30-50%, mucosal neuromas, and rarely pHPT. Endocrine tumors in MEN2 are often multifocal and bilateral. Nowadays, the diagnosis of MEN2 is made by genetic testing. After diagnosis, annual screening for associated manifestations and prophylactic thyroidectomy for preventing metastasized MTC are advised. Optimal age for preventive surgery or when to start screening for each manifestation is based upon the underlying RET mutation. In patients with MTC present at diagnosis, adequate staging is needed before surgical resection, since surgery is the only curative treatment. The most important biomarker for MTC is calcitonin. Fractionated metanephrines are used for early diagnosing PHEO and calcium and PTH for hyperparathyroidism. For PHEO, a minimal invasive surgical resection is recommended. In pHPT the surgical approach should be tailored to the amount and location of the enlarged glands visualized with imaging. Recurrent MTC requires physical examination, neck ultrasound, and measurement of serum calcitonin and carcinoembryonic antigen (CEA)

levels every 6 months. For metastasized MTC, treatment can be successful with multikinase inhibitors (vandetanib, cabozantinib) and selective RET inhibitors (pralsetinib, selpercatinib).

INTRODUCTION

Multiple Endocrine Neoplasia (MEN) type 2 is a rare autosomal dominant inherited cancer syndrome characterized by benign and malignant tumors of multiple endocrine organs. MEN2 is caused by a genetic defect in the REarranged during Transfection (RET) proto-oncogene on chromosome 10, leading to a gain-of-function in the RET tyrosine kinase receptor (1–4). As a result, cell growth, proliferation, and differentiation is promoted, leading to multiple tumor formation in all tissues were RET predominantly is expressed (C-cells of the thyroid gland, adrenal medulla, and neurons) (5,6). Major clinical manifestations in MEN2 are medullary thyroid carcinoma (MTC), pheochromocytoma (PHEO) and, in case of MEN2A, primary hyperparathyroidism (pHPT).

MTC is a neuroendocrine tumor arising from the calcitonin secreting parafollicular C-cells of the thyroid gland. MTC in persons with MEN2 typically presents at a younger age than sporadic MTC (sMTC) and is more often associated with C-cell hyperplasia as well as multifocality or bilaterality. There is a genotype-phenotype correlation with the age of onset of MTC being associated with the underlying RET mutation.

PHEOs are catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla. The frequency of PHEO depends upon the underlying RET mutation. As with MTC, it manifests earlier in MEN2, compared to sporadic forms. PHEO usually present after MTC or concomitantly; however PHEO can be diagnosed before the (not clinically detected) MTC in 13-27% of individuals with MEN2A (7,8).

pHPT is suspected in patients with elevated serum calcium concentrations, in combination with a parathyroid hormone (PTH) concentration that is elevated or within the normal range but inappropriately given the patients hypercalcemia. In MEN2A, pHPT is typically mild and may range from a single parathyroid adenoma to marked parathyroid hyperplasia (9). pHPT usually presents many years after the diagnosis of MTC; the average age at onset is 38 years of age (10).

Nearly all patients with MEN2A have either C-cell hyperplasia (CCH) or MTC, approximately 50% have a PHEO and 20-30% have pHPT, but the incidence of these manifestations depends on the underlying RET mutation (11,12). Patients with MEN2B have a 100% incidence of CCH and MTC, frequently have PHEO (30-50%), and typically have physical characteristics including mucosal neuromas, intestinal ganglioneuromatosis (IGN), alacrima (the lack of tears), and hyperflexible joints. They rarely have pHPT. Both MEN2A and MEN2B have autosomal dominant transmission patterns and therefore children of affected individuals have a 50% chance of inheriting the genetic abnormality. However, MEN2B most frequently occurs as a de novo mutation. Offspring of MEN2B patients have not frequently been reported.

Early diagnosis of affected patients and families is critical to obtain the best outcomes. For MEN2A, genetic screening in individuals at risk enable early screening. For MEN2B awareness for and early recognition of presenting syndromes (IGN, alacrima, mucosal neurinomas) is of utmost importance. Management of MEN2 patients is challenging, and the decision making is often not straightforward, as impact of screening and early surgery have to be balanced with possible benefits, particularly in younger patients. Patients and families suspected of harboring or diagnosed with MEN2 should be evaluated by an experienced multidisciplinary team.

Classification

Close to 200 RET germline variants have been identified with a clear genotype-phenotype correlation

(13,14). Two distinct clinical syndromes are recognized within MEN2 syndrome: MEN2A (95%) and MEN2B (5%). MEN2A is categorized in four subtypes.

1. Classic MEN2A
2. MEN2A with cutaneous lichen amyloidosis (CLA)
3. MEN2A with Hirschsprung's disease (HD)
4. Familial medullary thyroid cancer (FMTC)

Incidence and prevalence rates vary with the population studied. Based on an analysis of Surveillance, Epidemiology, and End Results (SEER) data, MEN2A is most common, with an incidence of about 1 patient in 2 million, compared to MEN2B with an incidence of about 1 patient in 39 million (12). A nationwide study in Denmark described higher rates with MEN2A incidence of 28 per million live births per year and a point prevalence of 24 per million (15). MEN2B had an incidence in Denmark of 2.6 per million per year and a point prevalence of 1.06 per million. The patient distribution among the subtypes varies with the series and the population studied as well. A large series from China showed that of 65 families (214 patients) with MEN2, 30 (46%) families had classical MEN2A, 5 (8%) had MEN2A with CLA, 1 (2%) MEN2A with HD, 24 (37%) had FTMC, and 5 (8%) had MEN2B (16).

Previously, patients with FMTC were classified as a separate entity, because affected families appeared to have MTC alone, lacking other associated endocrine or neural-tissue involvement of MEN2. With extended follow-up, some members in many of these families developed PHEO or pHPT. Data such as these suggested FMTC patients might be more appropriately classified as a variant of MEN2A (12). Furthermore, distinguishing classical MEN2A from FMTC is difficult, making the clinical relevance of this phenotype limited.

In some families, MEN2A was associated with CLA (17). This might be limited to families with specific mutations in the RET gene, with C634 as most frequently described (table 1). Not all family members with the same mutation develop CLA and there is a variation in clinical appearance, although the scapular region of the upper back is typically affected in MEN2A (see clinical features). CLA can precede the other MEN2A manifestations (17).

The same goes for the association of MEN2A and HD. This association is especially challenging, since the type of mutation leading to the different phenotypes result in different effects in the RET gene (a gain of function in the MEN2A phenotype and a loss of function in the HD phenotype). Pathogenic RET variants are mainly associated with both these conditions when located at the 620 position. Mutations that impair RET signaling cause HD owing to failure of enteric neural crest-derived cells to migrate, proliferate and/or differentiate properly within the intestine. This seemingly paradoxical occurrence has led to speculation of a 'Janus mutation' in RET that causes overactivation or impairment of RET activity depending on the cellular context. In animal studies an alternative explanation was suggested that the coexistence of these two seemingly opposite phenotypes can be explained by excessive RET signaling alone and without invoking a Janus mutation. In this study it was also demonstrated that the cells comprising the ganglioneuroma-like masses induced by RET activation maintain their embryonic potential to generate an enteric nervous system, suggesting that these ganglioneuromas, and possibly other MEN-associated neoplasms, may be amenable to reprogramming along normal developmental trajectories (18).

GENETICS

The RET proto-oncogene (OMIM 164761) encodes one of the receptor tyrosine kinases, cell-surface molecules that transduce signals for cell growth and differentiation (6). The RET gene was defined as an oncogene by a classical transfection assay. RET can undergo oncogenic activation in vivo and in vitro by cytogenetic rearrangement (19). The RET protein

comprises an extracellular domain, a transmembrane segment that traverse the plasma membrane, and the intracellular domain that consist of the intracellular juxtamembrane segment and the tyrosine kinase domain (TKD). Activation of RET is complex and occurs throughout a binding of a ligand-coreceptor composition, leading to RET homodimerization, resulting in activation of several downstream pathways, including RAS/MAPK and PI3K/AKT pathways (20).

The oncogene contains 21 exons spanning more than 60kb of genomic DNA. It is expressed in tissues of neural crest origin, and appears to have an important function in cell migration and development. RET germline mutations in MEN2 typically result in constitutive activation. Different mutations lead to different levels of activation, which may have an effect on the clinical spectrum. In 95% of patients with MEN2A syndrome, germline RET mutations cluster in cysteine C609, C611, C618, C620 (in exon 10), or C630 and C634 (in exon 11), with mutation of C634 being the most frequent. These mutations, leading to affected cysteines in the *extra*cellular domain of the RET receptor due to replacement of other amino acids in the cysteines, cause dimerization of receptor molecules, enhanced phosphorylation and thus ligand-independent activation of intra-cellular pathways (14,21). Germline pathogenic variants in the intracellular tyrosine kinase domain of *RET are less frequent and encoded in exon 13-16.* MEN2B is almost exclusively associated with a mutation in RET exon 16, which causes a methionine to threonine (M918T) substitution within the activation segment of RET kinase. This substitution increases ATP-binding and auto phosphorylation activity, thereby mediating a dimerization-independent activation of RET kinase. In less than 10% of MEN2B patients, other mutations are found: the pathogenic A883F variant (exon 15) encoded in exon 15 of *RET* also leads to increased and independent activating of *RET*. Furthermore, very rare dual germline variants (E768D/L790F, V804M/Q781R, V804M/E805 K, V804M/Y806C) have been described to cause MEN2B (22,23).

Since the discovery of the RET receptor tyrosine kinase in 1985 (24), somatic alterations of this protein have also been found in sporadic tumors, like non-small cell lung cancer (1-2%), papillary thyroid carcinoma (10-20%) and sMTC (21,25). Somatic RET mutations have been found in up to 60% of patients with sMTC. The prevalence is higher in patients with large tumors, and up to 85% of patients with distant metastases have somatic RET mutations (21). The most common somatic mutation is M918T, which is present in up to 40% of patients with sMTC and is associated with disease aggressiveness. Other single amino acid changes might occur at residues C611, C618, C620, C630, C634, E768, A883 and S891; small RET deletions and/or insertions have also been detected.

Genotype-Phenotype Correlation

Genotype-phenotype correlations in MEN2 are well-established and have long been used to guide clinicians in making medical management recommendations. Currently, patients are classified based on their phenotype into three groups, according to the American Thyroid Association (ATA) guideline (table 1) (12):

- Highest risk: classic MEN2B - M918T carriers
- High Risk: patients with the RET codon C634 mutations and the RET codon A883F mutation
- Moderate risk includes patients with hereditary MTC (hMTC) and RET codon mutations other than M918T, C634, and A883F

These risk categories are based on the aggressiveness of MTC and used as a guidance for timing of prophylactic thyroid surgery (see therapy). Furthermore, there is evidence that certain mutations are more commonly associated with PHEO. Besides M918T and A883F, both leading to MEN2B, all C634 mutations and D631Y mutations have a high risk of PHEO (~50%). Some mutations, like RET variant R912P and E768D are not associated with PHEO. For

pHPT, C634 mutations have the highest risk as well. A clear overview of all manifestation per RET variant is illustrated in table 1. Despite a higher incidence of the various manifestations in some mutations, current data remain insufficient to determine the risk of PHEO or pHPT in a given patient or family, since there is also clear, yet unexplained intrafamilial variability. This suggests a role for genetic modifiers, such as polymorphisms/haplotypes. This leads to the suggestion that multi-step carcinogenesis may be applicable to patients with MEN2, with other non-RET genetic changes or modifiers responsible for the phenotypic differences. Limited evidence demonstrated that copy number variations (CNVs) play an important role in phenotypic expression, but other possible contributing factors have been evaluated as well (13,26). Since the observed intra- and interfamilial variability is still poorly understood, a possible divergent course of disease cannot be predicted in an individual patient. Thus, all patients need to be followed for the development of these tumors. Furthermore, ongoing evaluation of new data will be needed to update the risk categories and genotype-phenotype correlations periodically.

Table 1. Incidence and Occurrence of MEN2 Manifestations in Relation to Different Germline Mutation and the Advised Management According to ATA Guideline 2015 (12)

ATA risk category	RET Mutation	MTC timing surgery	Incidence of PHEO	Incidence of pHPT	Start PHEO/pHPT Screening	Occurrence CLA / HD
Highest	M918T	Within first year	50%	-	At age 11 (PHEO only)	- / -
High	C634 A883F	At 5 years or earlier if elevated calcitonin	50% 50%	20-30% -	At age 11	+ / - - / -
Moderate	All others - C609 F/G/R/S/Y - C611F/G/S/Y/ W - C618F/R/S - C620F/R/S - C630R/Y - D6311Y - E768D - G553C - K666E - L790F - R912P - S891A - V804L - V804M	When calcitonin becomes elevated or prophylactic before apparent disease	 10-30% 10-30% 10-30% 10-30% 10-30% 50% - 10% 10% 10% - 10% 10% 10%	 10% 10% 10% 10% 10% - - - - - - 10% 10% 10%	At age 16	 - / **+** - / **+** - / **+** - / **+** - / - - / - - / - - / - - / - - / - - / - - / - - / - **+** / -

Abbreviations: ATA, American thyroid association; *RET*, *RE*arranged during *T*ransfection; MTC, medullary thyroid carcinoma; PHEO; phaeochromocytoma; PHPT, primary hyperparathyroidism; CLA, cutaneous lichen amyloidosis; HD, Hirschsprung's disease; +, yes; -, no.

CLINICAL FEATURES

MEN2A and MEN2B share the same genetic defect and common manifestations but also have specific clinical features and course of disease, making them two separate clinical entities. The occurrence of multicentric tumor formation in the thyroid and adrenal glands is shared. However, MEN2B is characterized by a specific clinical phenotype with ganglioneuromas of the lips, tongue and conjunctiva, musculoskeletal abnormalities, narrow long face, and thickened lips, among other features (see below). Clinically relevant pHPT is absent in MEN2B. In general, patients with MEN2B will develop tumors at an earlier age and these tumors will show a more aggressive behavior (26). Biochemically, the tumors that arise in patients with MEN2 are similar to those with the sporadic forms and discrimination cannot be made based on biomarkers.

MEN2A

Virtually all patients with MEN2A will develop CCH or MTC, but there is much inter- and intra-familial variability in the other manifestations. Approximately 50% will develop a PHEO and 20-30% will develop pHPT, but the incidence depends on the underlying mutation (table1). No clear clinical phenotype is present to recognize MEN2A patients. Most index patients present with MTC as the first manifestation (27). Some patients will develop HD which then will reveal the diagnosis of MEN2 (table 1). CLA is dermatologic disease, typically located in the interscapular region of the back and is characterized by secondary skin changes (papular, pigmented) and intense pruritus (figure 1). It becomes apparent during late adolescence or young adulthood and can be the first presenting manifestation as well. For mutations associated with CLA, see table 1.

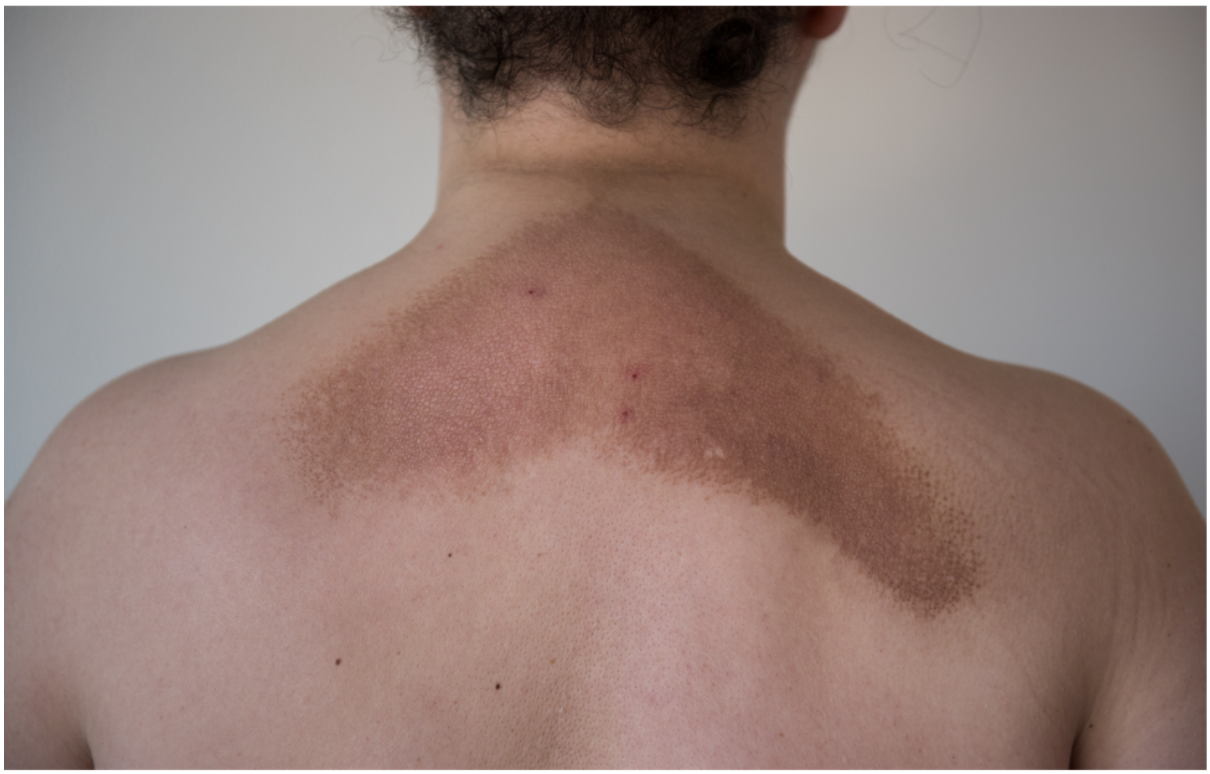

Figure 1. Cutaneous lichen amyloidosis.

MEN2B

All MEN2B patients will develop CCH or MTC, and 30-50% of them will have a PHEO (table 1). In the MEN2 literature, there is often reference to a characteristic Marfanoid physical appearance with hyperflexible joints but without the Marfanoid lens or aortic abnormalities. However, no studies have been published describing body proportions in MEN2B. A recent case series from the Netherlands described 8 MEN2B patients: all children and adults had normal body proportion(28). The typical marfanoid appearance in MEN2B is therefore questionable.

MEN-2B patients can have mucosal neuromas of the eyelids, lips, and tongue, and wide-spread ganglioneuromatosis of the gastrointestinal tract resulting in an abnormal gastrointestinal motility with complaints of diarrhea, constipation, colonic dilatation, or even megacolon at a young age (29).

As most MEN2B patients present with de novo mutations, the diagnosis is almost always delayed, even in the presence of clinical features (29,30). Recognition of nonendocrine symptoms like ocular symptoms (tearless crying) or the highly penetrant oral manifestations is important. Recent studies re-emphasize neonatal gastro-intestinal manifestations due to ganglioneuromatosis as the most important early feature for MEN2B diagnosis while body proportions and stature were non-specific in children with MEN2B (28,31). Those diagnosed based on nonendocrine symptoms instead of symptomatic MTC or PHEO were significantly younger (mean of 5.3 vs. 17.6 years), emphasizing the importance of early recognition.

Medullary Thyroid Carcinoma (MTC)

MTC is a tumor originating from the parafollicular cells (C-cells) of the thyroid. The production of calcitonin is a characteristic feature of this tumor. Most patients present with a solitary nodule or cervical

lymphadenopathy. Compared to sMTC, hMTC occur at a younger age and has typically multifocal and a bilateral pattern. It is often localized in the middle to upper regions of the thyroid lobe (32). In sMTC, up to 60% of cases appear to harbor a (driver) RET mutation, amongst other mutations, which has therapeutic implications (21). hMTC is preceded by CCH (33). The age-related penetrance of CCH and hMTC is mutation dependent. Most MEN2A patients (85%) are asymptomatic at MTC diagnosis, while 15% have presenting complaints (34). Especially in advanced disease diarrhea can be present. Peak incidence in index patients is in the third decade of life in MEN2A.

In MEN2B, MTC occurs very early, over 80% have MTC in their first year of life (30), underscoring the necessity of thyroidectomy before the age of 1. Unfortunately, the substantial diagnostic delay due to the high proportions of de novo mutations, median age of thyroidectomy in MEN2B patients is 14 years (30). The outcome of MTC in MEN2B is correlated to the way the diagnosis is made. If the diagnosis is made after recognition of nonendocrine symptoms, patients are significantly younger at diagnosis and therefore have often less lymph node metastases (43% vs 100%) or distant metastases (8% vs 79%) and were more often biochemically cured after treatment (58% vs 0%) (35). If the diagnosis is made before the age of 1 year, when there is only a preliminary stage of MTC, patients can be cured.

Pheochromocytoma (PHEO)

PHEOs are catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla. Prevalence of PHEO in MEN2A is 17-42% compared to 50% in MEN2B with median age at diagnosis 42 and 24 years respectively (13). Extra-adrenal PHEO is very rare in MEN2. Tumoral hypersecretion of epinephrine and norepinephrine causes episodic headache, sweating, and tachycardia with 50% of MEN2 patients being symptomatic. PHEO was the first presenting manifestation in 25% in MEN2A patients and 6% in MEN2B (8). PHEO is bilateral in most cases and rarely malignant (0-4%) (8,13). MEN2-related PHEO typically produce epinephrine or both epinephrine and norepinephrine, but not exclusively norepinephrine (36).

Primary Hyperparathyroidism (pHPT)

pHPT is caused by a parathyroid adenoma or hyperplasia with autonomous secretion of PTH, leading to elevated calcium levels. Disease is multiglandular in the majority of patients, but can occur metachronous, with long intervals with normocalcemia, simulating single gland disease (37). The prevalence in MEN2 is RET-mutation dependent, varying from 0-35% and pHPT is rarely the first manifestation with median age at diagnosis between 35-46 years of age (23,38). Since most MEN2 patients have mild pHPT, most patients are asymptomatic at diagnosis (56-88%). Symptoms of pHPT are often nonspecific, like constipation, fatigue, depression, anorexia, nausea, and polyuria. pHPT is rarely seen in MEN-2B patients.

Cutaneous Lichen Amyloidosis (CLA)

CLA is an uncommon disease characterized by pruritic lichenoid papules and
occurs rarely in MEN2A patients. In sporadic cases they occur in the pretibial bilateral regions, and in MEN2A patients the lesions typically occur in the (inter)scapular regions (fig 1) (39). Although MEN2A patients rarely develop CLA, if it occurs this will be at a mean age of 20 years and is often 11 years prior to the diagnosis of MEN2A in index patients. Therefore patients with an atypical location of CLA must be considered for RET testing (39).

Hirschsprung's Disease (HD)

Most patients with HD will present shortly after birth and those with exon 10 RET mutation must be screened for MEN2A (12). Older MEN-2A patients

with exon 10 RET mutations and colonic symptoms must be evaluated for HD.

DIAGNOSIS AND SCREENING

The diagnosis of MEN2 is established when a RET pathological variant is detected by molecular genetic testing. Genetic screening can identify gene carriers with high accuracy (98%) (40). Sanger or next generation sequencing are the recommended methods to detect RET mutations in exon 10 (codons 609, 611, 618, and 620), exon 11 (codons 630 and 634), and exons 8, 13, 14, 15, and 16 (12). For MEN2B, the M918T mutation (exon 16) and A883F mutation (exon 15) should be evaluated. If initial sequence analysis is negative, and the clinical suspicion of a genetic syndrome remains high based on family history, physical characteristics, young age at diagnosis, or pathologic findings in the thyroid such as extensive CCH or bilateral MTC, then whole gene sequencing should be considered (12). Patients who present with MTC, even with a negative family history need to be screened for RET mutations, as up to ~25% will be found to have a hereditary syndrome. At least 33% of all PHEO patients have a familial disorder, affected succinate dehydrogenase genes, Von Hippel Lindau (VHL) and MEN2 are the most frequently identified syndromes (41,42). The relative percentage of underlying germline mutation depends on the age of onset, family history, or clinical features like multifocal-, bilateral- or metastatic disease, but genetic screening need to be considered in all patients with PHEO. Those with other clinical characteristics, associated with MEN2, such as HD or CLA in the interscapular/scapular region should also be considered for testing (12). Those with physical characteristics suggestive of MEN2B such as mucosal neuromas and alacrima also need to be considered for genetic screening. Accurate evaluation of early onset severe constipation can lead to the detection of intestinal ganglioneuromatosis. These patients need to be screened as well for MEN2(31). A negative family history is not reliable in excluding patients from genetic testing, since about 40% of MEN2A gene carriers do not develop clinically apparent disease. De novo mutations are rare in MEN2A (up to 10%), in contrast to MEN2B, where de novo mutations are more frequent (45% of A883F carriers and 84% M918T carriers), emphasizing the limited value of a negative family history in MEN2B (13). First-degree relatives of patients with proven MEN2 should be offered genetic counseling. All patients of reproductive age carrying RET mutations, particularly those with mutations in codon 634 and 918, should be offered genetic counseling and be informed on the benefits and the potential risks of reproductive options, such as prenatal diagnosis and preimplantation diagnostic testing (12). Furthermore, the option of genetic testing in offspring should be discussed with future parents, where testing either directly after birth or at an older age could be discussed, based on the specific mutation in the family as well as individual preferences of the parents.

Patients at risk or with MTC, where genetic testing is not possible, should be under surveillance for MTC, PHEO and pHPT. There are very rare families who meet the clinical criteria for MEN2A (one or more first-degree relatives have characteristic clinical features for MEN2A), where no causative pathogenic variant in RET can be found. In these families, the periodically screening for MTC, PHEO and pHPT should be considered in the first degree relatives at risk (12).

Once a mutation is identified, the carrier should be screened for related manifestations, e.g., MTC, PHEO and pHPT. Prophylactic thyroidectomy is the mainstay of the treatment with the risk classification of the mutation defining the optimal age (see section on surgical treatment for MTC). Annual biochemical screening for all three manifestations is recommended, combined with neck ultrasound and physical examination, starting at an age based on the ATA risk category (12). Patients with M918T mutation should have a thyroidectomy within the first year of life. Patients with an ATA high risk often develop MTC in the first years of life as well, so annual screening from the age of 3 with physical examination, serum

calcitonin, and cervical ultrasound is recommended by the current ATA guideline (12). The phenotypes in the ATA moderate risk category varies significantly and the development of MTC is at a later age in most patients, but clinical MTC can occur before the age of 10 in this group as well. Therefore, annual screening for MTC is advised from the age of 5 (12). Family members, who have no pathological RET variant, do not need to undergo biochemical testing.

Medullary Thyroid Cancer

For MTC, biochemical testing is similar to patients with sporadic disease. Patients with clinical MTC have elevated serum calcitonin. Calcitonin is a neuropeptide derived from the parafollicular cells (C-cells) of the thyroid and calcitonin levels are directly related with C-cell (tumor) volume (43,44).

Patients with CCH or subclinical MTC usually do not have elevated basal serum levels of calcitonin. Physicians screening patients for CCH or subclinical MTC must be thoroughly familiar with the particular calcitonin assay being used, as normal ranges vary. Reference ranges for calcitonin differ among laboratories, and are also gender and age dependent (45,46). Calcitonin is higher in boys and in both sexes, a significant decrease in calcitonin levels is observed after the second year of life. Several studies defined age-, and gender specific calcitonin levels in a pediatric population, but since the normal range of calcitonin varies between the different assays and laboratories, basal calcitonin is of limited help in the initial management of very young children and infants (45,46). Since, there are no globally accepted calcitonin cutoff levels to predict MTC, each institution has to define its own reference ranges and clinicians should use the same laboratory and essay for serial measurements. Elevated calcitonin levels are an indication for thyroidectomy.

Provocative tests like pengastrin- or calcium stimulated calcitonin tests have no added value anymore since identification of mutation carriers is replaced by genetic testing and the newest immunochemiluminometric calcitonin assays are highly sensitive and specific for monomeric calcitonin. A recent study by Niederle, *et al.* illustrated no added value of calcium-stimulated calcitonin compared to basal calcitonin in the diagnosis of (sporadic) MTC or to differentiate between patients with CCH and micro-MTC in those with only mildly elevated calcitonin levels (47).

Pheochromocytoma

Screening for PHEO should be performed in all MEN2 patients prior to therapeutic thyroidectomy, as well as in female MEN2 patients who are considering pregnancy, to avoid a potential hypertensive crisis. Furthermore, annual screening for PHEO should be performed in all children in ATA highest and high risk categories from age 11 onwards, and in moderate risk children by age 16 (table 1) (12). PHEO is likely when elevated plasma concentrations of free metanephrines or elevated 24-hour urinary fractionated metanephrines and normetanephrines are detected. Practitioners should be aware of the pitfalls, conditions of sampling and possible influencing factors when analyzing the (nor)metanephrines to minimize the risk of false-positive results (42). MEN2-related PHEO produce epinephrine or both epinephrine and norepinephrine, but not exclusively norepinephrine (36).

When there is biochemical evidence for PHEO, imaging studies need to be initiated to locate the PHEO. Computed tomography (CT) or magnetic resonance imaging (MRI) of the adrenal glands is the first choice of imaging. CT has a high sensitivity (93-100%) in detecting intraadrenal tumors > 5 mm(36).

Primary Hyperparathyroidism

Screening for pHPT is similar to those with sporadic disease and includes measurement of (ionized) calcium or serum calcium with albumin and intact PTH. Additional evaluation and follow up of bone

density and kidney function in patients with pHPT is advised. ATA guidelines recommend that annual screening start at the same time as screening for PHEO: at age 11 for those in the high risk category and at age 16 for those in the moderate risk category (table 1) (12). Once pHPT is diagnosed, imaging studies are advised to visualize enlarged parathyroid glands. Neck ultrasound should be part of the diagnostic strategy. Combined radiology techniques increase localization accuracy, so the combination of neck ultrasound with parathyroid scintigraphy with Technetium (Tc) 99m sestamibi, ^{18}F-fluorocholine PET/CT, or 4-dimensional CT is recommended. The type of imaging to use must be based on knowledge of the clinician regional imaging capabilities and experience (48).

Given the intra- and interfamilial variability in PHEO and pHPT incidence, a static surveillance was advised by the ATA guideline. Some authors have suggested to tailor the frequency of biochemical screening for PHEO and pHPT, based on age and ATA risk category (49). However, large prospective studies are needed to validate their findings on age-related penetrance before a more tailored surveillance by age can be applied.

SURGICAL MANAGEMENT

PHEO may cause a dangerous hypertensive crisis during surgery (12,50). Therefore, PHEO should be excluded preoperatively in all patients. Very young patients who undergo prophylactic thyroidectomy may be excluded from this advice, since PHEO is not described in patients <8 years old (51). If present, the PHEO should be resected prior to surgery for either MTC or pHPT (12).

Adrenalectomy

Surgical resection is the cornerstone of treatment for PHEO (52). To prevent hypertensive crisis during surgery, caused by vasoconstriction due to catecholamine release, adult as well as pediatric patients should be prepared preoperatively during 1-2 weeks using α-adrenergic blockade (52–54). In case of tachycardia, additional treatment with β-adrenergic blockade should be started (52,54). A minimally invasive technique such as the laparoscopic or retroperitoneoscopic approach is recommended (12,52). The transabdominal and retroperitoneal approach take place in the lateral and prone position, respectively. There is increasing evidence in favor of the retroperitoneoscopic approach due to less blood loss, shorter operation time and length of stay, and less postoperative pain (55,56). Sixty-five percent of MEN2 associated PHEO are initially bilateral (54). The majority of patients with unilateral PHEO develop contralateral disease within 10 years (12,54). To prevent lifelong steroid dependency, adrenal cortical function should be preserved for as long as possible. Therefore, for patients with unilateral PHEO, unilateral resection is the treatment of choice, despite the high chance of developing a contralateral PHEO (12). Moreover, cortical function can be preserved by performing a subtotal adrenalectomy. This is appropriate for patients with bilateral, as well as unilateral PHEO (12,57). An international retrospective study showed excellent results in 563 MEN2 patients of who 114 (21%) underwent adrenal-sparing surgery. Steroid dependency was avoided in 57% of patients after adrenal-sparing surgery for bilateral PHEO. Recurrence of PHEO after adrenal-sparing surgery occurred in 3% of the 153 operated glands (57).

Parathyroidectomy

The amount of affected parathyroids in MEN2A patients varies from a single to all glands (5). Only the enlarged glands should be resected (12,48). Due to the short half-life (3 minutes) of PTH, intraoperative PTH monitoring can help determine whether parathyroidectomy has been successful. If PTH values remain elevated, it is necessary to look for other enlarged parathyroids (48). The surgical approach is tailored to the amount and location of the enlarged glands. In case of one affected parathyroid, minimally

invasive adenomectomy is the treatment of choice. In case of more enlarged glands a conventional exploration is performed. If all (four) glands are enlarged, a part of one parathyroid should be left in situ on a vascular pedicle or transplanted heterotopically to preserve parathyroid function (12,48). In some cases, pHPT is diagnosed at the same time as MTC. For these patients, thyroidectomy and parathyroidectomy can be performed during one surgery.

Preoperative imaging and marking of the location of the parathyroid adenoma is essential to perform minimally invasive adenomectomy. The incision is made right above the parathyroid, to reduce incision length and limit dissection. Conventional neck exploration is a more extensive procedure. After incision of the skin and passage of the platysma, the linea alba colli is dissected and the strap muscles are lateralized. Hereafter, mindful of the recurrent laryngeal nerve, the parathyroids can be identified and removed beyond the thyroid (58).

Thyroidectomy

Surgery is the only curative option for patients with MTC and remains the cornerstone of MTC treatment. Since virtually all MEN2 patients develop MTC, the question is not whether MEN2 patients should undergo thyroidectomy, but at what age? To prevent recurrence, it is essential that the thyroid is entirely removed, given the multifocal and bilateral growth in inherited MTC. If possible, thyroidectomy should be performed prophylactically, before developing (clinically relevant) MTC (12). Central neck dissection is not indicated in MEN2A patients with normal calcitonin and neck ultrasound undergoing prophylactic thyroidectomy. Genetic screening in family members of RET mutation carriers have led to the early diagnosis of MEN2 in a significant proportion of patients. Early prophylactic thyroidectomy in these patients is associated with excellent results and minimal operative morbidity: biochemical cure rates approximating 100% over 7-16 years of follow up (59,60). However, timing of thyroidectomy in known mutation carriers is challenging as risk of surgery in younger infants should be balanced with the probability of curing the patient. Surgery in (young) pediatric patients should be performed in specialized centers by experienced surgeons. Current decision making is mostly based on specific RET mutation (ATA risk category), age, and calcitonin levels (12,61).

Patients in the highest ATA risk category (table 1) should undergo total thyroidectomy within the first year of life. Timing of surgery in this group cannot be based on calcitonin levels since calcitonin levels are naturally high in the first months after birth. Risk of complications, especially the risk of hypoparathyroidism due to the inability to identify the parathyroids, is increased in children and infants (62). Therefore, if there are no suspicious lymph nodes and the parathyroids cannot be identified, central neck dissection might not be necessary.

The ATA high risk category consists of patients with RET codon C634 and A883F mutation. Children in this category should undergo screening for possible MTC from the age of three. These patients should undergo total thyroidectomy before the age of five, or earlier based on their calcitonin values (12). Considering the risk of complications, surgery before the age of three is not advised in this group (63). If lymph node metastases are suspected or calcitonin levels are >40 pg/ml, central neck dissection is needed.

Patients in the ATA moderate risk category generally develop a less aggressive type of MTC at an older age. These patients should be screened every 6-12 months from the age of five and should undergo thyroidectomy in childhood or early adulthood primarily based on calcitonin levels. Alternatively, thyroidectomy can be timed before calcitonin is elevated as yearly screening and calcitonin elevation might impose a psychological burden. Timing of thyroidectomy should be in consultation with child's parents and involved pediatricians and surgeons.

'Prophylactic' thyroidectomy is advised from the age of five in this moderate risk group (12).

The best calcitonin cut off point to prevent loco regional disease varies between studies. A large French multicenter study showed that no lymph node metastases were detected when calcitonin was <31 pg/mL while a Norwegian study found that all patients were cured when calcitonin was <40 pg/mL before total thyroidectomy (64,65). These studies on calcitonin levels illustrate that progression from CCH to MTC is imminent once calcitonin levels exceeds the upper limit of normal and the 'window of opportunity' to perform surgery without addition of extended node dissection is closing. Therefore, thyroidectomy should be performed once calcitonin levels exceed the upper limit of normal (12).

For patients with de novo mutations or unknown MEN2, MTC is often already present at first presentation. In adults with normal calcitonin values, the ATA guideline advises yearly screening and surgery when calcitonin becomes elevated (12). Two studies show that calcitonin values <20 and <60 pg/ml are associated with intrathyroidal MTC, and that calcitonin can be safely used to determine timing of surgery (61,66). Unfortunately, these patients usually present with higher calcitonin values and advanced disease. Ultrasound of the neck is performed prior to therapeutic surgery as it may give important information as to the extent of macroscopic thyroid and lymph node disease, not apparent on clinical exam. Patients with clinically apparent MTC on either clinical exam or neck ultrasound should undergo screening for metastatic disease, with attention to the most common sites such as the lungs, mediastinal lymph nodes, liver, and bones. Patients with markedly elevated serum calcitonin levels (>500 pg/ml) or extensive neck disease should also be screened for distant metastatic disease.

The standard treatment for MTC consists of total thyroidectomy and central neck dissection. There is no controversy regarding the need for central neck (level 6) lymph node dissection for MEN2 patients with clinically apparent MTC. Metastases to central neck lymph nodes are noted in up to 81% of patients with palpable tumors (67,68).

In case of cervical lymph node metastases in the lateral compartment of the neck, patients should undergo additional dissection of the lateral neck compartments (levels II–V) (12). Unfortunately, patients with cervical lymph node metastases can only be cured by total thyroidectomy and extensive lymph node dissection in 10% of cases (54,69,70). Lateral neck dissection in the absence of clinical or radiologic pathological lymph nodes (prophylactic lateral dissection) has no prognostic value (71). Patients with distant metastases cannot be treated with curative intent. In case of poor prognosis and locally advanced disease invading the surrounding structures, a less aggressive palliative resection should be considered for the purpose of local control and preservation of quality of life (12).

Standard procedure for thyroidectomy is the open approach. The patient's neck is positioned in hyperextension. After Kocher incision 1 cm above jugulum, the thyroid is visualized by dissection of the platysma, opening of the linea alba colli and lateralization of the strap muscles. The thyroid is dissected and mobilized starting at the superior or inferior pole, depending on the surgeon's preference. The thyroid vasculature should be ligated, clipped or sealed. Identification and preservation of the recurrent laryngeal nerve (located in the tracheoesophageal groove) and parathyroids (located posterior to the thyroid) is essential to prevent complications. After mobilization of one lobe, the same procedure is performed on the contralateral lobe. Thereafter, dissection of the central neck is performed (72,73).

RECURRENT OR METASTATIC DISEASE

Surveillance After Surgery

Patients who underwent surgery for one of the manifestations should be screened for disease recurrence. For PHEO and pHPT, screening is the same as initial screening, i.e. annual biochemical evaluation with plasma fractionated metanephrines and calcium (see diagnosis and screening), with the first evaluation 2-4 weeks after surgery, followed by imaging in case of biochemical evidence for disease (42).

After thyroidectomy, the risk of recurrence is based on the American Joint Committee on Cancer (AJCC) Tumor, Node, Metastases (TNM) classification, the total number of metastatic lymph nodes resected and pre- and postoperative calcitonin (12,64,65,69,74). Since calcitonin is a marker for tumor volume, pre- and post-operative calcitonin correlate with the extend of disease. A fairly standard post-operative follow up regimen to detect recurrent MTC includes physical examination, neck ultrasound, and measurement of serum calcitonin and carcinoembryonic antigen (CEA) levels every 6-12 months, depending on the initial postoperative findings (12). Post-operative calcitonin should be measured 3 months after surgery and undetectable following complete removal of thyroid tissue (75).

In patients with undetectable post-operative calcitonin, surveillance should be repeated after 6 months and then every 12 months if it remains undetectable. These patients are considered biochemically cured with 10-year disease specific survival rate of 100% (61).

In patients with detectable calcitonin <150 pg/ml, persistent disease is mostly confined to cervical lymph nodes. Calcitonin should be repeated every 6 months in these cases together with ultrasound of the neck to detect persistent disease (12,76). Fine-needle aspiration for cytology can be used to confirm recurrence or residual disease.

Post-operative calcitonin >150 pg/ml is an indication for evaluation of distant metastasis by imaging procedures (CT or MRI) with focus on the lungs, liver and axial skeleton. The clinical utility of PET/CT with various radiopharmaceutical tracers in MTC is limited (77). Currently, only ^{18}F-FDOPA PET/CT have an acceptable sensitivity for the detection of distant metastatic disease in MEN2 with a patient detection rate of 66% in patients suspected of recurrent MTC (77,78).

CEA is a non-specific marker which may be elevated in patients with MTC. It is not useful for early diagnosis, but has a role for monitoring disease progression and for detecting recurrence after thyroidectomy. CEA levels should be obtained concurrently with calcitonin measurements. In rare cases, serum CEA increases progressively while calcitonin remains stable or decreases. This suggests cellular dedifferentiation and a more aggressive course of disease, or secondary non-MEN2 related malignancy like colon carcinoma.

In case of biochemical or radiological evidence for residual disease, recurrence, or metastatic disease, the tumor growth rate can be estimated from sequential imaging studies using response evaluation criteria in solid tumors (RECIST) or by CEA and calcitonin serial measurements over time (12). Calcitonin and CEA doubling times are efficient biomarkers for assessing tumor progression. In one study, 94% of patients with doubling times within two years showed RECIST defined disease progression (79). Consequently, the doubling time of each biomarker has an important prognostic value, especially when values double within a year, survival rates are much lower compared to longer doubling times (80,81). Disease progression should be confirmed on imaging before initiating systemic treatment.

Treatment of Recurrent or Metastatic Disease in MTC

LOCAL RECURRENCE

The treatment of recurrent MTC in patients with genetic syndromes is similar to their sporadic counterparts and remains challenging. In patients with disease confined to the neck, an aggressive surgical approach may be considered since surgery is the only curative treatment in MTC. There is generally little role for external beam radiation therapy (EBRT) to the neck. The intent of EBRT is to achieve local control since there is no survival benefit demonstrated (82,83). The recent ATA guidelines suggest that EBRT may be helpful in selected circumstances where the risk of local recurrence is felt to be high (12). These circumstances are very limited since the benefits must outweigh toxicity and the potential for making subsequent neck re-exploration, if required, more difficult. Post-operative radiation therapy is reasonable in those patients in whom there is gross residual disease, particularly if there is a concern for potential airway compromise.

METASTATIC DISEASE

Patients with metastatic disease should be carefully evaluated and the course of disease must be determined to optimize and tailor treatment. The timing of treatment initiation and the choice of treatment depends on the rate of disease progression and symptoms versus the quality of life, treatment efficacy and toxicity.

In patients with an indolent course of disease or low tumor burden without symptoms, a watch-and-wait strategy can be followed. Imaging should be repeated every 6 months in these patients. If calcitonin doubling time is less than 6 months, imaging should be more frequent (84).

In patients presenting with local symptoms or complications such as airway- or spinal cord compression, neurological symptoms, or pathological bone fractures, local treatment modalities such as surgery, glucocorticoid therapy, and/or ERBT must be used before initiating systemic therapy. Treatment of symptomatic bone or brain metastases from MTC is similar to metastases due to other histologic types. Those with painful bone metastases may have a good symptomatic response to EBRT, and bisphosphonate therapy may also be helpful (12,85).

In patients with symptomatic or RECIST defined progressive disease and a significant tumor burden, systemic therapy should be considered. A significant tumor burden is defined as multiple lesions >1-2 centimeters in diameter (84).

The choice of first line systemic treatment is not clear, since the armamentarium of therapeutic options is still expanding, direct head-to-head comparison is missing, and availability and approval is varying between countries. There is no role for radioactive iodine (RAI). C-cells do not take up RAI and no benefit was observed in a multicenter study (86). Current options in metastatic MTC are chemotherapy, multikinase inhibitors (vandetanib, cabozantinib) and selective RET inhibitors (pralsetinib, selpercatinib).

Data on cytotoxic chemotherapy is heterogeneous and the study population is small in most papers. The response rate is around 20% in most studies and 5FU/dacarbazine regimen or doxorubicin, alone or in combination with cisplatin seems to be the best choice (84). Because of the poor response rates and adverse events, chemotherapy is no longer first line treatment.

Two multikinase inhibitors (MKI) have been approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of MTC patients: vandetanib and cabozantinib. Other multikinase inhibitors are under investigation (23). The kinases of RET and of vascular endothelial growth factor receptor-2 (VEGFR-2) are the main targets in MTC. Vandetanib and cabozantinib target both these kinases among others. Significant increases in progression free survival (PFS) were observed (vandetanib +11 months; cabozantinib +7 months), compared with placebo but toxicity was also significant (toxicity (>grade 2) for vandetanib and cabozantinib: 55% (24%) and 69% (33%))

respectively, leading to discontinuation of treatment or dose reduction in a significant proportion of study participants (87,88). Studies in hMTC showed better response rates. Vandetanib had an overall disease control rate of 73% in 30 patients with hMTC with an estimated PFS of >27 months (89). In 17 adolescents and children with MEN2B-associated MTC, 10 had partial response and 6 stable disease with vandetanib (90). PFS was prolonged with cabozantinib versus placebo (60 vs 20 weeks) in a subgroup of patients with RET mutations (91).

Selpercatinib and pralsetinib are selective RET kinase inhibitors with more specific RET-targeting. This have led to an improved side effect profile and higher response rates in phase I/II studies (92,93).

Selpercatinib (former LOXO-292) showed a 69% response rate and 82% 1-year PFS in 55 patients with progressive *RET*-mutant MTC who had previously received vandetanib or cabozantinib. Response rate in MKI treatment naïve patients (n=88) was 73% and 1-years PFS 92%. Hypertension (21%) and diarrhea (6%) were the most important grade 3 side effects and 2% discontinued medication because of adverse events (92).

Pralsetinib (former BLU-667) is being evaluated in the ARROW trial (ongoing). Response rate in previously MKI treated patients was 60% and 71% in TKI-naïve patients. Serious treatment related adverse events were reported in 15% and 4% discontinued medication.

Several other potential therapies are under investigation, including immunotherapy and peptide receptor radionuclide therapy (PRRT) (23). Despite the advances of MKI over conventional chemotherapy, the clinical utility is still limited. The absence of overall survival benefit and severe toxicity profiles leading to a reduction in quality of life are thresholds for treatment initiation. Drug resistance is another major issue in MKI treatment and still poorly understood. A selective RET kinase inhibitor seems to be a better treatment choice in patients harboring RET germline mutations, regarding the high objective response rates and better toxicity profiles in phase I/II studies. However, trials are still ongoing and large, phase 3 trials are needed before we can determine its true value in the clinical armamentarium.

Treatment of Metastatic Disease in PHEO

Malignant PHEO is rare in MEN2 (0-4%). Surgery is the only potential curative option in malignant PHEO. In recurrent or low volume metastatic disease, local inventions such as surgical resection, ablation, or ERBT must be discussed in an experienced multidisciplinary team. For the time being, systemic treatment is similar to sporadic malignant PHEO. With ongoing advances in MKI and selective RET inhibitors, tailored management for MEN2-related PHEO could be possible in the future. Current systemic options in metastatic disease are Iodine-131 metaiodobenzylguanidine (131I-MIBG), PRRT with radiolabeled somatostatin analogues (PRRT), MKI (i.e. sunitinib), or conventional chemotherapy with cyclophosphamide, vincristine, and dacarbazine (13,94).

PROGNOSIS

MTC is the major cause of death in MEN2. PHEO does not seem to have an association with shorter survival: median survival is 499 months in patients with PHEO vs. 444 months without (95). Prognosis of patients with sMTC and those with inherited disease is similar after adjustment of age and disease stage at diagnosis in multivariate analysis (34). Together with the presence of certain RET mutations, serum calcitonin, and number of lymph node metastases, these parameters are important factors influencing prognosis. The 10-year overall survival for patients with MTC was 64 % in population based study from Denmark (34)

Disease stage is one of the most important prognostic factors: 10-year disease specific survival for patients with MTC is 98%, 93%, 87%, and 53% for disease

stage I-IV, respectively (34). In children with MTC, higher disease stage also portends a worse prognosis (90).

Age as an independent prognostic factor is preserved in some studies but not all studies (23). A poorer prognosis in older patients may be related to a more advanced tumor stage at diagnosis. The 5-year and 15-year survival rates in children with MTC is 95% and 86%, respectively. Mean survival after diagnosis in children is 28 years (96).

10-year survival rate in MEN2A patients (97%) is better than in patients with MEN2B (76%) which might be influenced by an earlier onset of disease and delay in diagnosis of MTC in (de novo) MEN2B patients (97).

Furthermore, as mentioned above, a rapid CEA and/or calcitonin doubling time and high number of lymph node metastases at presentation are all harbingers of an aggressive disease course.

To conclude, the amount of data which has accumulated over the last decade has truly been staggering, and has resulted in significant changes in MEN2A and MEN2B patient management. Further refinements in risk stratification will undoubtedly occur as additional long-term data become available on genotype-phenotype, effects of prophylactic thyroid surgery, and effects of surveillance. Molecular based therapies now offer hope to those with advanced or metastatic MTC. The increasing molecular knowledge and selective RET inhibitors will hopefully lead to new treatment strategies or therapies useful not only for metastatic MTC, but as adjuvant treatment in high-risk patients, or perhaps even in prevention.

REFERENCES

1 Donis-keller H, Dou S, Chi D, Carlson KM, Toshima K, Lairmore TC, et al. Mutations in the RET proto-oncogene are associated with MEN 2a and FMTC. Hum Mol Genet. 1993 DOI: 10.1093/hmg/2.7.851

2 Mulligan LM, Kwok JBJ, Healey CS, Elsdon MJ, Eng C, Gardner E, et al. Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. Nature. 1993 DOI: 10.1038/363458a0

3 Carlson KM, Dou S, Chi D, Scavarda N, Toshima K, Jackson CE, et al. Single missense mutation in the tyrosine kinase catalytic domain of the RET protooncogene is associated with multiple endocrine neoplasia type 2B. Proc Natl Acad Sci U S A. 1994 DOI: 10.1073/pnas.91.4.1579

4 Hofstra RMW, Landsvater RM, Ceccherini I, Stulp RP, Stelwagen T, Luo Y, et al. A mutation in the RET proto-oncogene associated with multiple endocrine neoplasia type 2B and sporadic medullary thyroid carcinoma. Nature. 1994 DOI: 10.1038/367375a0

5 Takaya K, Yoshimasa T, Arai H, Tamura N, Miyamoto Y, Itoh H, et al. Expression of the RET proto-oncogene in normal human tissues, pheochromocytomas, and other tumors of neural crest origin. J Mol Med. 1996 DOI: 10.1007/s001090050065

6 Arighi E, Borrello MG, Sariola H. RET tyrosine kinase signaling in development and cancer. Cytokine Growth Factor Rev. 2005 DOI: 10.1016/j.cytogfr.2005.05.010

7 Inabnet WB, Caragliano P, Pertsemlidis D. Pheochromocytoma: Inherited associations, bilaterality, and cortex preservation. Surgery. 2000 DOI: 10.1067/msy.2000.110846

8 Modigliani E, Vasen HM, Raue K, Dralle H, Frilling A, Gheri RG, et al. Pheochromocytoma in multiple endocrine neoplasia type 2: European study. Journal of Internal Medicine. 1995. DOI: 10.1111/j.1365-2796.1995.tb01211.x

9 Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, et al. Consensus: Guidelines for diagnosis and therapy of MEN type 1 and type 2. Journal of Clinical Endocrinology and Metabolism. 2001. DOI: 10.1210/jcem.86.12.8070

10 Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid. 2009 DOI: 10.1089/thy.2008.0403

11 Raue F, Frank-Raue K, Grauer A. Multiple endocrine neoplasia type 2: Clinical features and screening. Endocrinol Metab Clin North Am. 1994 DOI: 10.1016/s0889-8529(18)30121-x

12 Wells SA, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American thyroid association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567–610.

13 Mathiesen JS, Effraimidis G, Rossing M, Rasmussen ÅK, Hoejberg L, Bastholt L, et al. Multiple endocrine neoplasia type 2: A reveiw. Semin Cancer Biol. 2021;(April). DOI: 10.1016/j.semcancer.2021.03.035
14 Eng C, Clayton D, Schuffenecker I, Lenoir G, Cote G, Gagel RF, et al. The relationship between specific ret proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2: International RET mutation consortium analysis. J Am Med Assoc. 1996 DOI: 10.1001/jama.276.19.1575
15 Mathiesen JS, Kroustrup JP, Vestergaard P, Stochholm K, Poulsen PL, Rasmussen ÅK, et al. Incidence and prevalence of multiple endocrine neoplasia 2a in denmark 1901–2014: A nationwide study. Clin Epidemiol. 2018;10:1479–87.
16 Qi XP, Zhao JQ, Fang XD, Lian BJ, Li F, Wang HH, et al. Spectrum of Germline RET variants identified by targeted sequencing and associated Multiple Endocrine Neoplasia type 2 susceptibility in China. BMC Cancer. 2021 DOI: 10.1186/s12885-021-08116-9
17 Qi XP, Peng JZ, Yang XW, Cao ZL, Yu XH, Fang XD, et al. The RET C611Y mutation causes MEN 2A and associated cutaneous lichen amyloidosis. Endocr Connect. 2018 DOI: 10.1530/EC-18-0220
18 Nagy N, Guyer RA, Hotta R, Zhang D, Newgreen DF, Halasy V, et al. RET overactivation leads to concurrent Hirschsprung disease and intestinal ganglioneuromas. Dev. 2020 DOI: 10.1242/dev.190900
19 Grieco M, Santoro M, Berlingieri MT, Melillo RM, Donghi R, Bongarzone I, et al. PTC is a novel rearranged form of the ret proto-oncogene and is frequently detected in vivo in human thyroid papillary carcinomas. Cell. 1990 DOI: 10.1016/0092-8674(90)90659-3
20 Goodman KM, Kjær S, Beuron F, Knowles PP, Nawrotek A, Burns EM, et al. RET recognition of GDNF-GFRα1 ligand by a composite binding site promotes membrane-proximal self-association. Cell Rep. 2014 DOI: 10.1016/j.celrep.2014.08.040
21 Romei C, Ciampi R, Elisei R. A comprehensive overview of the role of the RET proto-oncogene in thyroid carcinoma. Nat Rev Endocrinol. 2016 DOI: 10.1038/nrendo.2016.11
22 Cranston AN, Carniti C, Oakhill K, Radzio-Andzelm E, Stone EA, McCallion AS, et al. RET is constitutively activated by novel tandem mutations that alter the active site resulting in multiple endocrine neoplasia type 2B. Cancer Res. 2006 DOI: 10.1158/0008-5472.CAN-06-0884
23 Mathiesen JS, Effraimidis G, Rossing M, Rasmussen ÅK, Hoejberg L, Bastholt L, et al. Multiple endocrine neoplasia type 2: A reveiw. Semin Cancer Biol. 2021 DOI: 10.1016/j.semcancer.2021.03.035
24 Takahashi M, Ritz J, Cooper GM. Activation of a novel human transforming gene, ret, by DNA rearrangement. Cell. 1985 DOI: 10.1016/0092-8674(85)90115-1
25 Takeuchi K, Soda M, Togashi Y, Suzuki R, Sakata S, Hatano S, et al. RET, ROS1 and ALK fusions in lung cancer. Nat Med. 2012 DOI: 10.1038/nm.2658
26 Bergholm U, Bergström R, Ekbom A. Long term follow-up of patients with medullary carcinoma of the thyroid. Cancer. 1997 DOI: 10.1002/(SICI)1097-0142(19970101)79:1<132::AID-CNCR19>3.0.CO;2-5
27 Iihara M, Yamashita T, Okamoto T, Kanbe M, Yamazaki K, Egawa S, et al. A nationwide clinical survey of patients with multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma in Japan. Jpn J Clin Oncol. 1997 DOI: 10.1093/jjco/27.3.128
28 van den Broek MFM, van Santen HM, Valk GD, Verrijn Stuart AA. Children with multiple endocrine neoplasia type 2B: Not tall and marfanoid, but short with normal body proportions. Clin Endocrinol (Oxf). 2021 DOI: 10.1111/cen.14536
29 Wray CJ, Rich TA, Waguespack SG, Lee JE, Perrier ND, Evans DB. Failure to recognize multiple endocrine neoplasia 2B: More common than we think? Ann Surg Oncol. 2008 DOI: 10.1245/s10434-007-9665-4
30 Castinetti F, Waguespack SG, Machens A, Uchino S, Hasse-Lazar K, Sanso G, et al. Natural history, treatment, and long-term follow up of patients with multiple endocrine neoplasia type 2B: an international, multicentre, retrospective study. Lancet Diabetes Endocrinol. 2019 DOI: 10.1016/S2213-8587(18)30336-X
31 van den Broek MFM, Rijks EBG, Nikkels PGJ, Wolters VM, van Es RJJ, van Santen HM, et al. Timely diagnosis of multiple endocrine neoplasia 2B by identification of intestinal ganglioneuromatosis: a case series. Endocrine. 2021 DOI: 10.1007/s12020-021-02607-2
32 Block MA, Jackson CE, Greenawald KA, Yott JB, Tashjian AH. Clinical Characteristics Distinguishing Hereditary From Sporadic Medullary Thyroid Carcinoma: Treatment Implications. Arch Surg. 1980 DOI: 10.1001/archsurg.1980.01380020012004
33 Wolfe HJ, Melvin KEW, Cervi-Skinner SJ, AL Saadi AA, Juliar JF, Jackson CE, et al. C-Cell Hyperplasia Preceding Medullary Thyroid Carcinoma. N Engl J Med. 1973 DOI: 10.1056/nejm197308302890901
34 Mathiesen JS, Kroustrup JP, Vestergaard P, Stochholm K, Poulsen PL, Rasmussen ÅK, et al. Survival and Long-Term Biochemical Cure in Medullary Thyroid Carcinoma in Denmark 1997-2014: A Nationwide Study. Thyroid. 2019 DOI: 10.1089/thy.2018.0564
35 Brauckhoff M, Machens A, Lorenz K, Bjøro T, Varhaug JE, Dralle H. Surgical curability of medullary thyroid cancer in multiple endocrine neoplasia 2b: A changing perspective. Ann Surg. 2014 DOI: 10.1097/SLA.0b013e3182a6f43a
36 Pacak K, Eisenhofer G, Ilias I. Diagnosis of pheochromocytoma with special emphasis on MEN2 syndrome. Hormones. 2009 DOI: 10.14310/horm.2002.1227
37 Iacobone M, Carnaille B, Palazzo FF, Vriens M. Hereditary

hyperparathyroidism—a consensus report of the European Society of Endocrine Surgeons (ESES). Langenbeck's Arch Surg. 2015 DOI: 10.1007/s00423-015-1342-7

38 Larsen LV, Mirebeau-Prunier D, Imai T, Alvarez-Escola C, Hasse-Lazar K, Censi S, et al. Primary hyperparathyroidism as first manifestation in multiple endocrine neoplasia type 2A: An international multicenter study. Endocr Connect. 2020 DOI: 10.1530/EC-20-0163

39 Scapineli JO, Ceolin L, Puñales MK, Dora JM, Maia AL. MEN 2A-related cutaneous lichen amyloidosis: report of three kindred and systematic literature review of clinical, biochemical and molecular characteristics. Fam Cancer. 2016 DOI: 10.1007/s10689-016-9892-6

40 Taïeb D, Kebebew E, Castinetti F, Chen CC, Henry JF, Pacak K. Diagnosis and preoperative imaging of multiple endocrine neoplasia type 2: Current status and future directions. Clin Endocrinol (Oxf). 2014 DOI: 10.1111/cen.12513

41 Neumann HPH, Young WF, Eng C. Pheochromocytoma and Paraganglioma. N Engl J Med. 2019 DOI: 10.1056/nejmra1806651

42 Lenders JWM, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SKG, Murad MH, et al. Pheochromocytoma and paraganglioma: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014 DOI: 10.1210/jc.2014-1498

43 Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S, et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab. 2007 DOI: 10.1210/jc.2006-1590

44 Costante G, Durante C, Francis Z, Schlumberger M, Filetti S. Determination of calcitonin levels in C-cell disease: Clinical interest and potential pitfalls. Nat Clin Pract Endocrinol Metab. 2009 DOI: 10.1038/ncpendmet1023

45 Eckelt F, Vogel M, Geserick M, Kirsten T, Bae YJ, Baber R, et al. Calcitonin measurement in pediatrics: Reference ranges are gender-dependent, validation in medullary thyroid cancer and effects of thyroid diseases. Clin Chem Lab Med. 2019 DOI: 10.1515/cclm-2018-1186

46 Castagna MG, Fugazzola L, Maino F, Covelli D, Memmo S, Sestini F, et al. Reference range of serum calcitonin in pediatric population. J Clin Endocrinol Metab. 2015 DOI: 10.1210/jc.2014-4508

47 Niederle MB, Scheuba C, Riss P, Selberherr A, Koperek O, Niederle B. Early Diagnosis of Medullary Thyroid Cancer: Are Calcitonin Stimulation Tests Still Indicated in the Era of Highly Sensitive Calcitonin Immunoassays? Thyroid. 2020 DOI: 10.1089/thy.2019.0785

48 Wilhelm SM, Wang TS, Ruan DT, Lee JA, Asa SL, Duh QY, et al. The American association of endocrine surgeons guidelines for definitive management of primary hyperparathyroidism. JAMA Surg. 2016 DOI: 10.1001/jamasurg.2016.2310

49 Machens A, Lorenz K, Dralle H. Peak incidence of pheochromocytoma and primary hyperparathyroidism in multiple endocrine neoplasia 2: Need for age-adjusted biochemical screening. J Clin Endocrinol Metab. 2013 DOI: 10.1210/jc.2012-3192

50 Fassnacht M, Dekkers OM, Else T, Baudin E, Berruti A, De Krijger RR, et al. European society of endocrinology clinical practice guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the study of adrenal tumors. Eur J Endocrinol. 2018 DOI: 10.1530/EJE-18-0608

51 Amodru V, Taieb D, Guerin C, Romanet P, Paladino N, Brue T, et al. MEN2-related pheochromocytoma: current state of knowledge, specific characteristics in MEN2B, and perspectives. Endocrine. 2020 DOI: 10.1007/s12020-020-02332-2

52 Shah MH, Goldner WS, Benson AB, Bergsland E, Blaszkowsky LS, Brock P, et al. Neuroendocrine and Adrenal Tumors, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw. 2021 DOI: 10.6004/jnccn.2021.0032

53 Buitenwerf E, Osinga TE, Timmers HJLM, Lenders JWM, Feelders RA, Eekhoff EMW, et al. Efficacy of α-blockers on hemodynamic control during pheochromocytoma resection: A randomized controlled trial. J Clin Endocrinol Metab. 2020 DOI: 10.1210/clinem/dgz188

54 Wells SA, Pacini F, Robinson BG, Santoro M. Multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma: An update. J Clin Endocrinol Metab. 2013 DOI: 10.1210/jc.2013-1204

55 Dickson P V., Alex GC, Grubbs EG, Ayala-Ramirez M, Jimenez C, Evans DB, et al. Posterior retroperitoneoscopic adrenalectomy is a safe and effective alternative to transabdominal laparoscopic adrenalectomy for pheochromocytoma. Surgery. 2011 DOI: 10.1016/j.surg.2011.07.004

56 Vrielink OM, Wevers KP, Kist JW, Borel Rinkes IHM, Hemmer PHJ, Vriens MR, et al. Laparoscopic anterior versus endoscopic posterior approach for adrenalectomy: a shift to a new golden standard? Langenbeck's Arch Surg. 2017 DOI: 10.1007/s00423-016-1533-x

57 Castinetti F, Qi XP, Walz MK, Maia AL, Sansó G, Peczkowska M, et al. Outcomes of adrenal-sparing surgery or total adrenalectomy in phaeochromocytoma associated with multiple endocrine neoplasia type 2: An international retrospective population-based study. Lancet Oncol. 2014 DOI: 10.1016/S1470-2045(14)70154-8

58 Moalem J, Guerrero M, Kebebew E. Bilateral neck exploration in primary hyperparathyroidism-when is it selected and how is it performed? World J Surg. 2009 DOI: 10.1007/s00268-009-9941-5

59 Machens A, Elwerr M, Lorenz K, Weber F, Dralle H. Long-term outcome of prophylactic thyroidectomy in children

carrying RET germline mutations. Br J Surg. 2018 DOI: 10.1002/bjs.10746
60 Febrero B, Rodríguez JM, Ríos A, Segura P, Pérez-Sánchez B, Torregrosa N, et al. Prophylactic thyroidectomy in multiple endocrine neoplasia 2 (MEN2) patients with the C634Y mutation: A long-term follow-up in a large single-center cohort. Eur J Surg Oncol. 2019 DOI: 10.1016/j.ejso.2018.09.002
61 Elisei R, Romei C, Renzini G, Bottici V, Cosci B, Molinaro E, et al. The timing of total thyroidectomy in RET gene mutation carriers could be personalized and safely planned on the basis of serum calcitonin: 18 Years experience at one single center. J Clin Endocrinol Metab. 2012 DOI: 10.1210/jc.2011-2046
62 Machens A, Dralle H. Advances in risk-oriented surgery for multiple endocrine neoplasia type 2. Endocr Relat Cancer. 2018 DOI: 10.1530/ERC-17-0202
63 Kluijfhout WP, Van Beek DJ, Stuart AAV, Lodewijk L, Valk GD, Zee DCV Der, et al. Postoperative complications after prophylactic thyroidectomy for very young patients with multiple endocrine neoplasia type 2: Retrospective cohort analysis. Med (United States). 2015 DOI: 10.1097/MD.0000000000001108
64 Rohmer V, Vidal-Trecan G, Bourdelot A, Niccoli P, Murat A, Wemeau JL, et al. Prognostic factors of disease-free survival after thyroidectomy in 170 young patients with a RET germline mutation: A multicenter study of the Groupe Français d'Etude des Tumeurs Endocrines. J Clin Endocrinol Metab. 2011 DOI: 10.1210/jc.2010-1234
65 Opsahl EM, Brauckhoff M, Schlichting E, Helset K, Svartberg J, Brauckhoff K, et al. A Nationwide Study of Multiple Endocrine Neoplasia Type 2A in Norway: Predictive and Prognostic Factors for the Clinical Course of Medullary Thyroid Carcinoma. Thyroid. 2016. DOI: 10.1089/thy.2015.0673
66 Machens A, Dralle H. Biomarker-based risk stratification for previously untreated medullary thyroid cancer. J Clin Endocrinol Metab. 2010 DOI: 10.1210/jc.2009-2368
67 Moley JF, DeBenedetti MK. Patterns of nodal metastases in palpable medullary thyroid carcinoma: Recommendations for extent of node dissection. Annals of Surgery. 1999. DOI: 10.1097/00000658-199906000-00016
68 Weber T, Schilling T, Frank-Raue K, Colombo-Benkmann M, Hinz U, Ziegler R, et al. Impact of modified radical neck dissection on biochemical cure in medullary thyroid carcinomas. Surgery. 2001 DOI: 10.1067/msy.2001.118380a
69 Machens A, Schneyer U, Holzhausen HJ, Dralle H. Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level. J Clin Endocrinol Metab. 2005 DOI: 10.1210/jc.2004-1836
70 Machens A, Hofmann C, Hauptman S, Dralle H. Locoregional recurrence and death from medullary thyroid carcinoma in a contemporaneous series: 5-years results. Eur J Endocrinol. 2007 DOI: 10.1530/EJE-07-0095
71 Spanheimer PM, Ganly I, Chou JF, Capanu M, Nigam A, Ghossein RA, et al. Prophylactic Lateral Neck Dissection for Medullary Thyroid Carcinoma is not Associated with Improved Survival. Ann Surg Oncol. 2021 DOI: 10.1245/s10434-021-09683-8
72 Roman BR, Randolph GW, Kamani D. Conventional Thyroidectomy in the Treatment of Primary Thyroid Cancer. Endocrinol Metab Clin North Am. 2019 DOI: 10.1016/j.ecl.2018.11.003
73 Bliss RD, Gauger PG, Delbridge LW. Surgeon's approach to the thyroid gland: Surgical anatomy and the importance of technique. World J Surg. 2000 DOI: 10.1007/s002680010173
74 MacHens A, Dralle H. Prognostic impact of N staging in 715 medullary thyroid cancer patients: Proposal for a revised staging system. Ann Surg. 2013 DOI: 10.1097/SLA.0b013e318268301d
75 Engelbach M, Görges R, Forst T, Pfützner A, Dawood R, Heerdt S, et al. Improved diagnostic methods in the follow-up of medullary thyroid carcinoma by highly specific calcitonin measurements. J Clin Endocrinol Metab. 2000 DOI: 10.1210/jc.85.5.1890
76 Pellegriti G, Leboulleux S, Baudin E, Bellon N, Scollo C, Travagli JP, et al. Long-term outcome of medullary thyroid carcinoma in patients with normal postoperative medical imaging. Br J Cancer. 2003 DOI: 10.1038/sj.bjc.6600930
77 Giovanella L, Treglia G, Iakovou I, Mihailovic J, Verburg FA, Luster M. EANM practice guideline for PET/CT imaging in medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging. 2020 DOI: 10.1007/s00259-019-04458-6
78 July M, Santhanam P, Giovanella L, Treglia G. Role of positron emission tomography imaging in Multiple Endocrine Neoplasia syndromes. Clin Physiol Funct Imaging. 2018 DOI: 10.1111/cpf.12391
79 Giraudet AL, Al Ghulzan A, Aupérin A, Leboulleux S, Chehboun A, Troalen F, et al. Progression of medullary thyroid carcinoma: Assessment with calcitonin and carcinoembryonic antigen doubling times. Eur J Endocrinol. 2008 DOI: 10.1530/EJE-07-0667
80 Meijer JAA, Le Cessie S, Van Den Hout WB, Kievit J, Schoones JW, Romijn JA, et al. Calcitonin and carcinoembryonic antigen doubling times as prognostic factors in medullary thyroid carcinoma: A structured meta-analysis. Clin Endocrinol (Oxf). 2010 DOI: 10.1111/j.1365-2265.2009.03666.x
81 Barbet J, Campion L, Kraeber-Bodéré F, Chatal JF. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. J Clin Endocrinol Metab. 2005 DOI: 10.1210/jc.2005-0044
82 Martinez SR, Beal SH, Chen A, Chen SL, Schneider PD. Adjuvant external beam radiation for medullary thyroid carcinoma. J Surg Oncol. 2010 DOI: 10.1002/jso.21557

83 Jin M, Megwalu UC, Noel JE. External Beam Radiotherapy for Medullary Thyroid Cancer Following Total or Near-Total Thyroidectomy. Otolaryngol - Head Neck Surg (United States). 2021 DOI: 10.1177/0194599820947696

84 Hadoux J, Schlumberger M. Chemotherapy and tyrosine-kinase inhibitors for medullary thyroid cancer. Best Pract Res Clin Endocrinol Metab. 2017 DOI: 10.1016/j.beem.2017.04.009

85 Vitale G, Fonderico F, Martignetti A, Caraglia M, Ciccarelli A, Nuzzo V, et al. Pamidronate improves the quality of life and induces clinical remission of bone metastases in patients with thyroid cancer. Br J Cancer. 2001 DOI: 10.1054/bjoc.2001.1832

86 Meijer JAA, Bakker LEH, Valk GD, De Herder WW, De Wilt JHW, Netea-Maier RT, et al. Radioactive iodine in the treatment of medullary thyroid carcinoma: A controlled multicenter study. Eur J Endocrinol. 2013 DOI: 10.1530/EJE-12-0943

87 Wells SA, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: A randomized, double-blind phase III trial. J Clin Oncol. 2012 DOI: 10.1200/JCO.2011.35.5040

88 Elisei R, Schlumberger MJ, Müller SP, Schöffski P, Brose MS, Shah MH, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol. 2013 DOI: 10.1200/JCO.2012.48.4659

89 Ceolin L, Da Silveira Duval MA, Benini AF, Ferreira CV, Maia AL. Medullary thyroid carcinoma beyond surgery: Advances, challenges, and perspectives. Endocr Relat Cancer. 2019 DOI: 10.1530/ERC-18-0574

90 Kraft IL, Akshintala S, Zhu Y, Lei H, Derse-Anthony C, Dombi E, et al. Outcomes of children and adolescents with advanced hereditary medullary thyroid carcinoma treated with vandetanib. Clin Cancer Res. 2018 DOI: 10.1158/1078-0432.CCR-17-2101

91 Sherman SI, Clary DO, Elisei R, Schlumberger MJ, Cohen EEW, Schöffski P, et al. Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib in patients with progressive, metastatic medullary thyroid cancer. Cancer. 2016 DOI: 10.1002/cncr.30252

92 Wirth LJ, Sherman E, Robinson B, Solomon B, Kang H, Lorch J, et al. Efficacy of Selpercatinib in RET -Altered Thyroid Cancers . N Engl J Med. 2020 DOI: 10.1056/nejmoa2005651

93 Subbiah V, Hu MI, Wirth LJ, Schuler M, Mansfield AS, Curigliano G, et al. Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study. Lancet Diabetes Endocrinol. 2021 DOI: 10.1016/S2213-8587(21)00120-0

94 Young WF. Metastatic pheochromocytoma: In search of a cure. Endocrinol (United States). 2020 DOI: 10.1210/endocr/bqz019

95 Thosani S, Ayala-Ramirez M, Palmer L, Hu MI, Rich T, Gagel RF, et al. The characterization of pheochromocytoma and its impact on overall survival in multiple endocrine neoplasia type 2. J Clin Endocrinol Metab. 2013 DOI: 10.1210/jc.2013-1653

96 Hogan AR, Zhuge Y, Perez EA, Koniaris LG, Lew JI, Sola JE. Pediatric Thyroid Carcinoma: Incidence and Outcomes in 1753 Patients. J Surg Res. 2009 DOI: 10.1016/j.jss.2009.03.098

97 Modigliani E, Cohen R, Campos JM, Conte-Devolx B, Maes B, Boneu A, et al. Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: results in 899 patients. The GETC Study Group. Groupe d'étude des tumeurs à calcitonine. Clin Endocrinol (Oxf). 1998

98 Shepet K, Alhefdhi A, Lai N, Mazeh H, Sippel R, Chen H. Hereditary medullary thyroid cancer: Age-appropriate thyroidectomy improves disease-free survival. Ann Surg Oncol. 2013 DOI: 10.1245/s10434-012-2757-9

99 Sandoval JA, Fernandez-Pineda I, Malkan AD. Risk-reduction surgery in pediatric surgical oncology: A perspective. J Pediatr Surg. 2016 DOI: 10.1016/j.jpedsurg.2016.01.004