Natural history, treatment, and long-term follow up of patients with multiple endocrine neoplasia type 2B: an international, multicentre, retrospective study

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MULTIPLE ENDOCRINE NEOPLASIA TYPE 2B REVISITED: AN INTERNATIONAL MULTICENTRIC RETROSPECTIVE STUDY ON 345 PATIENTS

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ABSTRACT (248 words)

Background: Multiple endocrine neoplasia type 2B (MEN 2B) is a rare syndrome caused mainly by p.M918T germline *RET* mutation, and characterized by medullary thyroid carcinoma (MTC), phaeochromocytoma and extra-endocrine features. Data are scarce on the natural history of MEN2B.

Methods: This was a retrospective multicentric international study on patients carrying the p.M918T RET variant.

Findings: 345 patients were included. Thyroidectomy was performed before the age of 1 in 20 patients, which led to long term remission in 83·3% of these cases. In the other operated 318 patients, biochemical and structural remission was obtained in 14·8% of cases, while 71 patients (20·6%) were dead at a median age of 25 years (range, 0·5-59). Bilateral phaeochromocytoma was present in half of the patients by age 28. Adrenal-sparing surgery was performed in 31 patients: 3 of them had long-term recurrence, while normal adrenal function was obtained in 61·5% of them. All the patients had at least one extra-endocrine feature: the association of marfanoid body habitus, mucosal neuromas and gastro-intestinal signs was observed in 106/190 patients (55·8%).

Interpretation: Thyroidectomy no later than 1 year of age is associated with a high chance of cure. The reality is that the majority of children will be diagnosed beyond this recommended age. Adrenal-sparing surgery is feasible in MEN2B and affords a good chance for normal adrenal function. To improve the prognosis of such patients, it is imperative that every healthcare provider be aware of the extra-endocrine signs and the natural history of this rare syndrome.

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INTRODUCTION

Multiple endocrine neoplasia type 2B (MEN 2B) is a rare genetic syndrome (prevalence, 0·9-1·6 per million) caused by germline mutations of the proto-oncogene *RET*[1,2]. MEN 2B is most commonly caused by the p.M918T *RET* mutation (> 95% cases) followed by the p.A883F *RET* mutation (< 5% cases)[3,4]; very rarely, MEN 2B results from tandem *RET* mutations[5].

Precise data on the phenotypic characteristics and natural history of patients carrying the most common p.M918T mutation remain scarce. MEN2B can include medullary thyroid carcinoma (MTC), pheochromocytoma and extra-endocrine features. MEN 2B prognosis is hampered by its main clinical manifestation, MTC. MEN 2B-associated MTC is universally present, often clinically aggressive, and of early onset[6]. It is preceded by a C-cell hyperplasia and can evolve relatively quickly to lymph node invasion as well as systemic disease through vascular invasion[6,7]. The largest study to date based on 75 patients concluded that the prognosis has improved over the last 20 years due to earlier management of MTC[8]. Three previous studies, based on 18-44 patients, gave insight into the natural history of the disease and became the basis for the guidelines on the management of MEN 2B[9–12]. These studies showed that the prognosis of MTC in MEN 2B depends on the stage at diagnosis and that only early diagnosis and intervention provided a chance for cure. Brauckhoff *et al.* emphasized the need for awareness of the extra-endocrine signs, given the fact that MTC would be only palpable on clinical exam far later than the age recommended for thyroidectomy[11,13], and the majority of MEN 2B cases arise due to *de novo RET* mutations[10]. Therefore, all healthcare providers treating children should be aware of the various extra-endocrine clinical signs[4,14,15] that should raise concern for MEN 2B in the differential diagnosis, which would help patients benefit from early thyroidectomy in order to avoid metastatic disease [12]. The second principle manifestation of MEN 2B is phaeochromocytoma, but only few data are available. The two largest series reported 26 and 15 patients with MEN 2B and phaeochromocytoma[8,16]. The penetrance of phaeochromocytoma is lower than that of MTC[16].

Given the sparsity of published data, and taking advantage of a large international tertiary referral centre network, we sought to provide more insight into the natural history of MEN 2B. Our main aim was to improve understanding of the phenotype and natural history of MEN2B, based on current guidelines, which in turn would lead to improved awareness of this complex syndrome and the extra-endocrine signs to allow for optimal detection and vital and functional prognosis of these predominantly young patients.

METHODS

Research participants and study design

This international MEN 2B study was initiated in 2016: experts from 48 centres all over the world founded a consortium to include their retrospective data in a registry to analyze in detail the diagnosis, management and outcomes of MEN 2B patients. Three additional expert centres refused to be part of the study, while 20 patients were excluded because of incomplete data.

Patients included in the database had to be diagnosed as carriers of a germline pathogenic p.M918T *RET* mutation. Additionally, first-degree relatives with histologically proven MTC and patients presenting with the association of MTC, phaeochromocytoma and extra-endocrine signs suggestive of MEN 2B (at a time when genetic testing was not available) were included. Data from patients followed from 1970 to 2016 were retrieved from May 2016 to May 2018. Some of these patients had been previously reported with incomplete data; for them, updated and exhaustive data were re-extracted for their updated medical records [2,9,17–19] (additional table 1). Patients who were carriers of a germline pathogenic RET p.A883F mutation were not included due to a recent report on the natural history of such patients[20].

We included retrospective routinely collected data about MTC, phaeochromocytoma, non-endocrine features, and school or professional outcome (for this latter item, exclusively for patients older than 10 years). Our primary objective was to analyze the disease free survival and MTC-specific survival in MEN 2B patients based on whether they had been treated with early (≤ 12 months) thyroidectomy, as recommended by international guidelines [12]. Our secondary objectives were specifically to better characterize the natural history of MTC and phaeochromocytoma and to determine the penetrance of extra-endocrine features. For MTC, final disease status was defined as follows: structural and biochemical remission was defined by normal calcitonin and carcinoembryonic antigen (CEA) levels and no residual disease on imaging; biochemical persistence was defined by increased calcitonin and/or CEA with no residual disease on imaging; biochemical and structural persistence was defined by increased calcitonin and/or CEA with pathological cervical lymph nodes or systemic metastases on imaging. Follow-up imaging modalities were defined by each investigator. For phaeochromocytoma, the size of the tumour was defined by the pathological analysis when available, or initial imaging in the other cases. Phaeochromocytoma was determined to be malignant by the presence of metastases to lymph nodes or other tissues (e.g., the lungs, bones, or liver). Data on extra-adrenal tumours (paraganglioma) were also collected. Finally, data were also gathered about the extra-endocrine features of MEN 2B, as well as any other diseases the patients might have presented during their follow-up. The presence or absence of a specific extra-endocrine feature was noted only when it was specifically reported in the data file of the patients.

This work conforms to the Declaration of Helsinki, Good Clinical Practice guidelines, and was approved by the appropriate local Institutional Review Boards or ethics committee. All patients gave signed informed consent for genetic DNA analysis. For the retrospective analysis of existing data sets from routine patient care, the majority of the Centers did not require additional specific institutional review board. Some centers had ethics committee approval or institutional review board authorizing the use of anonymized data without additional patient consent (Poland, China, Canada, The Netherlands, Belgium, France, Denmark, Japan, Czech republic, China, Hungary). Some centers had an additional consent signed from the patients (Argentina, Chile, UK, Spain). NIH patients included in this study were enrolled in a National Cancer Institute, Pediatric Oncology Branch MTC natural history study (NCT01660984).

The corresponding author had full access to all of the data and the final responsibility to submit for publication. There is no funding source.

Statistical analysis

We summarized continuous variables as mean +/-SD and/or median (range). We performed statistical comparisons of quantitative data with Student's *t* test or ANOVA. For statistical

comparisons of dichotomous data, we used the $\chi 2$ test with Yates correction. We determined overall survival and compared patients with thyroidectomy before or after 1 year of age with log-rank analysis. We calculated age-dependent penetrance estimates of phaeochromocytoma with the Kaplan-Meier method. All statistical tests were two sided, and p values of less than 0.05 were deemed to indicate statistical significance. All analyses were done with Prism 6 for MacOs X.

RESULTS

Natural history of patients with MEN 2B

A total of 345 patients (161 males, 184 females) were included. Among them, 276 (83·7% of 330 with available data) were *de novo* cases. At last follow-up (median age, 25 years; range, 0·5-66), 71 (20·6%) patients were deceased. Median age at death was 25 years (range, 0·5-59). Overall survival is shown in figure 1.

- **C-cell hyperplasia and MTC**

338 (98%) patients had a thyroidectomy. Seven patients (2%) were never operated upon: 6 patients because of metastatic and progressive disease at the time of diagnosis (median age, 27 years old; range, 21-32), and 1 because of fatal complications of intestinal ganglioneuromatosis at age 6 months. At a median age at thyroidectomy of 14 years (range, 0·25-47 years), MTC was found in 327/338 patients (86·7%): it was limited to the thyroid in only 53/312 patients (16·9%) for whom lymph node dissection was performed. A total of 48/338 patients (13·2%) died due to metastatic MTC (liver [n=28], lungs [n=26], bones [n=17], brain [n=8]) at a median age of 25 years (range 6-59) (table 1).

- **Phaeochromocytoma**

Clinical data regarding phaeochromocytoma were available for 313 patients. A diagnosis of at least 1 phaeochromocytoma was made in 153 patients (48·9%) at a median age of 24 years (range, 13-52) (table 2). 146 patients (95.4%) had been operated at last follow-up. Bilateral synchronous phaeochromocytoma was the initial diagnosis in 79 patients (51·6%): the median size of the larger phaeochromocytoma was 30 mm in diameter (range, 6-175 mm) while the contralateral one was 19 mm (range, 3-75). Among the 74 remaining patients (48·4%) with a first diagnosis of unilateral phaeochromocytoma, 32 patients developed a metachronous contralateral phaeochromocytoma at a median of 4 years (range 2-16) after the 1st phaeochromocytoma diagnosis. Penetrance of unilateral phaeochromocytoma was 50% by age 25, while penetrance of bilateral phaeochromocytoma was 50% by age 28 (Figure 3).

Four patients (2·6%) had metastatic phaeochromocytoma at last follow-up, as evidenced by metanephrins hypersecretion, at a median age of 41 (range, 35-45): 2 had bilateral synchronous phaeochromocytoma at 27 and 40 years old, and 2 had metachronous phaeochromocytoma at an age of 19 and 23 for the first, and 25 and 29 for the second.

- **Extra-endocrine features of MEN 2B (table 3)**

The prevalence of non-endocrine manifestations is reported in table 3. All the patients with available data (n=287) had at least one extra-endocrine manifestation. The association of marfanoid body habitus, ganglioneuromatosis and gastro-intestinal signs was reported in 106/190 patients (55·8%) for whom the presence/absence of these manifestations was clearly noted in the medical records. Surgical intervention for non-endocrine manifestations was necessary in 28 patients (19 gastro-intestinal surgeries including 10 cases for symptomatic megacolon and 9 with achalasia requiring esophageal dilatation, 5 hip surgeries, and 4 bladder, prostate or ureteral surgeries). Additional non-endocrine features, likely not linked to MEN 2B, included seizures in 4 cases (without brain metastases), micrognathia in 4 cases and congenital cataract in 2 cases.

School and socio-professional data from patients aged more than 10 were available for 129 patients (median age, 31 ; min, 10 ; max, 66): 32 patients (24·8%) were unable to work or attend school due to disability at last follow-up.

Specific management of MEN 2B

- **Early (≤ 12 months old) versus late thyroidectomy**

MTC-specific survival curves did not show any significant difference between patients treated with early or delayed thyroidectomy (figure 2, p=0·2; HR, 0·35; 95% OF CI, 0·07-1·74). In contrast, there

was a significant difference in remission status between patients operated before and after the age of 1 (p<0.0001) (table 1).
As shown in additional table 2, 20 patients had thyroidectomy no later than 12 months of age (median, 9 months; range 3-12). During follow-up, 2 patients were deceased (neither from MTC): one at the age of 6 months because of complications of intestinal ganglioneuromatosis and the other at the age of 3 with no cause of death specified. At last follow-up, at a median of 5.2 years after thyroidectomy (range, 0·25-32), 15/18 alive patients (83·3%) operated on ≤ 12 months were in biochemical and structural remission, while 3 (16·7%) had persistent biochemical and structural disease.
In the group of 318 patients who had thyroidectomy after 12 months of age, 64 patients (20·1%) were deceased, including 48 due to MTC, at a median age of 25 years (range, 8-59). At last follow-up, at a median of 13 years after thyroidectomy (min, 1·7; max, 25), 47 patients (14·8%) were in biochemical and structural remission, while 207 (85.2%) had persistent disease, including 103 (32·4%) who progressed to systemic metastases requiring chemotherapy (n=8), oral targeted therapy (n=34), or liver-directed radiofrequency ablation (n=2). TNM status at diagnosis is shown in additional table 3.

- **Adrenal sparing vs total adrenalectomy**

31 patients (21·2%) had at least 1 adrenal-sparing surgery. In all operated patients, 14/146 patients (9·6%) developed recurrence at a median age of 33·5 years (range 24-54), including 3 who had undergone adrenal sparing surgery and 11 who had adrenalectomy (p=0·56). For these 3 patients, recurrence had been diagnosed at 5, 6 and 6 years, respectively, after the organ-sparing surgery. Among the 26 patients with bilateral adrenal surgery and at least 1 adrenal sparing surgery, normal adrenocortical function was observed in 16 patients (61·5%) (p<0.0001 vs 0% in the adrenalectomy group) (table 2).

DISCUSSION

This large international retrospective study provides a detailed description of the natural history and outcome of p.M918T *RET* MEN 2B. It emphasizes the need the need for early thyroidectomy to improve the vital outcome, and the possibility of adrenal sparing surgery to improve the functional outcome of patients with p.M918T *RET* MEN2B. It also emphasizes the need for an optimal extra-endocrine management of these patients, as a fourth of them will be unable to work or attend school due to MEN 2B endocrine and extra-endocrine related disability, a point that had never been raised previously on studies mainly focusing on the outcome of MTC. These results should thus modify patient care and help establish future guidelines.

The importance of early diagnosis is shown by the MTC outcome of operated patients. While 14.8% of patients were cured when thyroidectomy was performed after the age of 1 year, 83% were cured when thyroidectomy was performed before or at the age of 1 ($p<0.0001$, table 1). This clearly emphasizes the need for performing early thyroidectomy, *ie.* before the age of 1. While there had been suggestions to postpone thyroidectomy to age 4[10], the current study calls for caution as 9 of our 16 patients (56·3%) operated between 1 and 4 had persistent disease at last follow-up (data not shown). Although our study did not collect data on surgical complications, the high rate of cure of MTC with early thyroidectomy may outweigh the associated risks, such as laryngeal nerve injury or hypoparathyroidism, even though these can significantly impact an infant's life. In order to minimize risks, surgeries in MEN 2B patients should only be conducted by experienced, high-volume thyroid cancer surgeons. However, the possibility of early thyroidectomy is hampered by the difficulty in making an early diagnosis [11,13]. Indeed, the diagnosis of MEN 2B remains a challenge due to the high rate of *de novo* mutations and the lack of endocrine symptoms at an early age. In a series of 44 patients, Brauckhoff *et al.* had reported that the chance of remission was higher in young patients who had been diagnosed based on recognition of non-endocrine features of MEN2B, *ie.* by a non-endocrinologist[10]. While marfanoid body habitus and mucosal neuromas typically appear after the age of 1, manifestations such as constipation, pseudo-obstruction or feeding difficulties are early signs that should lead to further evaluation for MEN 2B. Gastrointestinal signs were present in 2/3 of our patients and Brauckhoff reported the failure to produce tears (alacrima) as an additional early sign of MEN 2B[11]. Proper education of paediatricians, eye doctors, dentists, gastroenterologists, orthopedic surgeons, and general practitioners is thus crucial, as they represent the front line for early diagnosis. Interestingly, we also found a surprisingly large number of patients (n=47, ie. 14·8%) operated after the age of 1 who were in biochemical and structural remission at last follow-up. These results also emphasize the heterogeneity and phenotypic variability of MEN 2B, as all but one of these 47 patients required only a single delayed surgery to achieve remission.

In the present series, the penetrance of phaeochromocytoma was high: 50% of all patients developed a phaeochromocytoma and half of these were bilateral by age 28. As a comparison, we had previously reported that 20% of patients with *RET* 634 codon mutation and 5% with *RET* exon 10 mutations had bilateral phaeochromocytoma by the same age[18]. Makri *et al.* recently reported in a series of 8 patients with MEN 2B-associated phaeochromocytoma a 10 year old patient with an asymptomatic phaeochromocytoma [19]. This is in line with international guidelines, which recommend a first biological screening at age 11 in p.M918T MEN2B. Overall, considering synchronous or metachronous appearance, phaeochromocytoma was bilateral in most of our cases (72%). This observation emphasizes the need to consider adrenal-sparing surgery in these patients, who will otherwise be at risk for lifelong adrenal insufficiency. With 61% normal adrenocortical function, the results seem comparable with the one reported for MEN2A[18]. The rate of malignant phaeochromocytoma was similar to reported numbers for other *RET* mutations[18], and only 2 patients died of phaeochromocytoma or consequences of catecholamine hypersecretion.

Our study has inherent limitations due to its retrospective nature. However, MEN 2B is a very rare syndrome and the only way to improve its understanding was to retrospectively analyze the data from a large number of centers: this implies incomplete data (especially for the earlier signs that allowed diagnosis, the age at which these signs were first seen by the physician or the presence or absence of extra-endocrine features in patients diagnosed at adult age; some precise pathological characteristics such as TNM status for phaeochromocytoma or extent of lymph node resection), subjective data extraction, and heterogeneous follow-up. We only collected the data of 20 patients with thyroidectomy before the age of 1: this low number, associated with a short follow-up, probably explains why we did not show any significant difference between patients operated before and after 1 year old. This should not modify the aggressive early management of such patients, as shown in table 1.

In summary, the different clinical courses and outcomes of MTC and phaeochromocytoma, in addition to the varying penetrance of extra-endocrine features, make MEN2B a complex syndrome characterized by wide phenotypic variability despite being a defined single gene disorder. Our data i) underscore the importance of pursuing thyroidectomy before 12 months of age, which requires an early non-endocrine diagnosis ii) highlight the value of performing adrenal sparing surgery in patients with phaeochromocytoma when technically feasible and iii) emphasize the need for a multidisciplinary approach lifelong to the treatment of both the endocrine and non-endocrine manifestations (that should be systematically reported in medical files, whether present or not) in these young patients who disproportionately become disabled. One of our future aims will be to show whether the natural history of MEN2B patients will be modified by novel drugs or techniques. Our study thus currently improves understanding regarding the long-term outcomes of MEN 2B, but is only a first step in the global understanding of this rare syndrome.

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LEGEND TO TABLES AND FIGURES

Table 1: MTC in MEN2B. Structural and biochemical remission was defined by normal calcitonin and carcinoembryonic antigen (CEA) levels and no residual disease on imaging; biochemical persistence was defined by increased calcitonin and/or CEA with no residual disease on imaging; cervical structural persistence was defined by increased calcitonin and/or CEA with pathological cervical lymph nodes on imaging; systemic structural persistence was defined by increased calcitonin and/or CEA and systemic metastases.
Table 2: Data on MEN 2B pheochromocytoma. *, for a total of 69 patients with bilateral adrenalectomy; **, for a total of 26 patients with bilateral adrenal surgery and at least 1 adrenal sparing surgery.
Table 3: Extra-endocrine features of MEN 2B. Note that the penetrance was based on the presence/absence of each feature specifically noted in the medical files of each patient. When no mention of the feature was noted, the information was considered as not available.

Figure 1: MEN 2B-Overall survival based on age at last follow-up (Kaplan Meier estimates).
Figure 2: MTC specific survival in early (≤ 12 months) vs late thyroidectomy (> 12 months old) (Kaplan Meier estimates)
Figure 3: Unilateral and bilateral phaeochromocytoma penetrance (Kaplan-Meier estimates with subjects at risk)

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Research in context panel

Evidence before this study

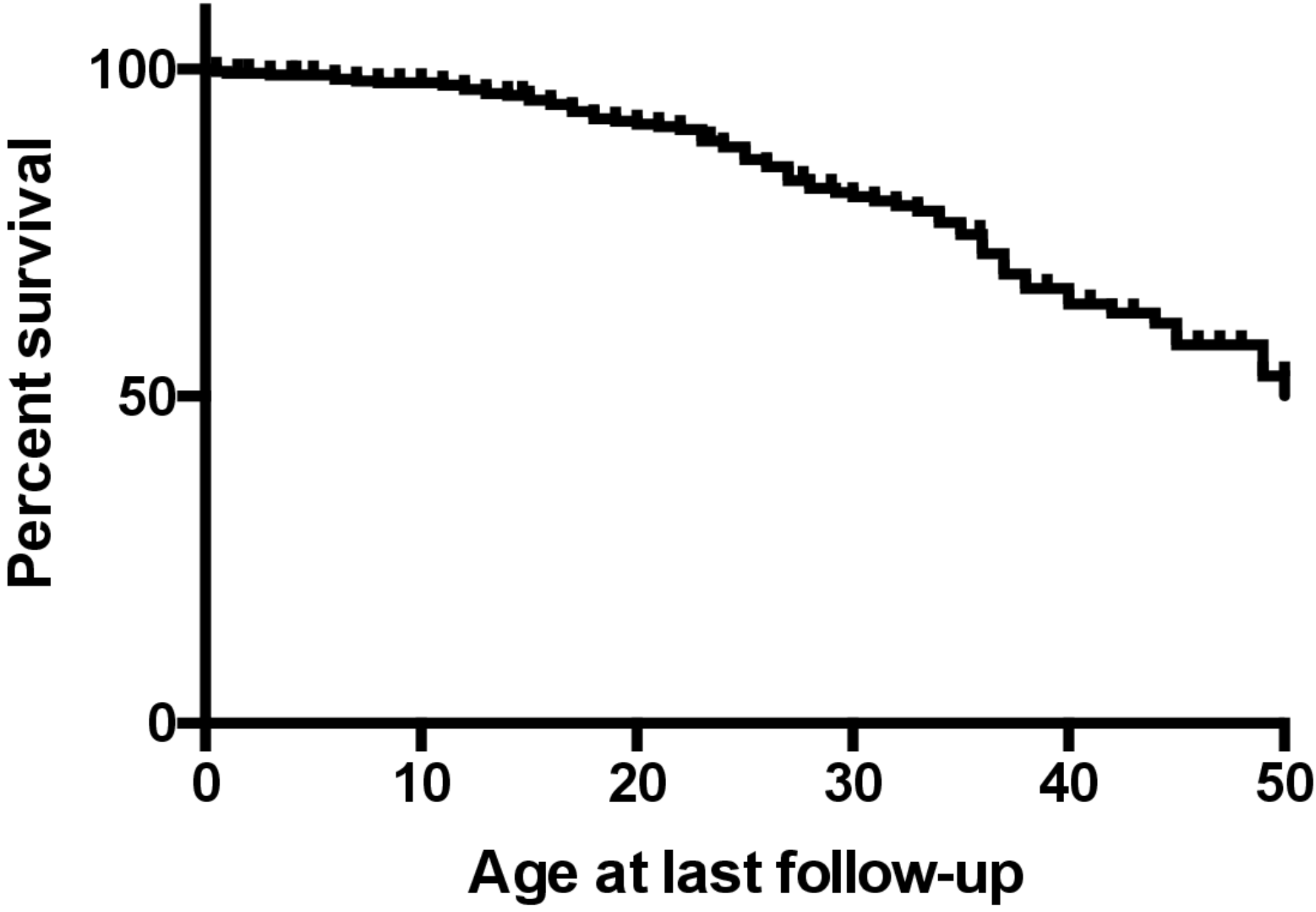
As recently reviewed by Castinetti *et al.* in *Endocrine-Related Cancer*, multiple endocrine neoplasia type 2B (MEN2B) is a very rare genetic syndrome that arises from an activating mutation (primarily the p.M918T variant) in the Rearranged during Transfection (*RET*) proto-oncogene. Given the rarity of MEN2B, published data remain scarce and are primarily limited to a few referral centers. Medullary thyroid cancer (MTC) is the predominant finding in MEN2B, developing within the first year of life and leading to early death due to metastatic MTC in most cases. It is currently recommended that thyroidectomy be performed before the age of one year to prevent the early metastatic spread of MTC, yet this recommendation is not very evidence-based and is, in fact, rarely done because most MENB cases arise *de novo* and the diagnosis is not made until far after the onset of metastatic and incurable MTC. The second major component of MEN2B is pheochromocytoma, for which the first-line treatment is adrenalectomy. Historically, this has been total adrenalectomy although recent surgical advances have led to the broader use of adrenal-sparing procedures, which have not been studied in MEN2B specifically. Finally, MEN2B is also associated with extra-endocrine features, such as alacrima and symptoms of gastrointestinal dysmotility, that can present during infancy, thus allowing the astute clinician who recognizes this association to make the correct diagnosis early enough to prevent the onset of metastatic MTC through early thyroidectomy.

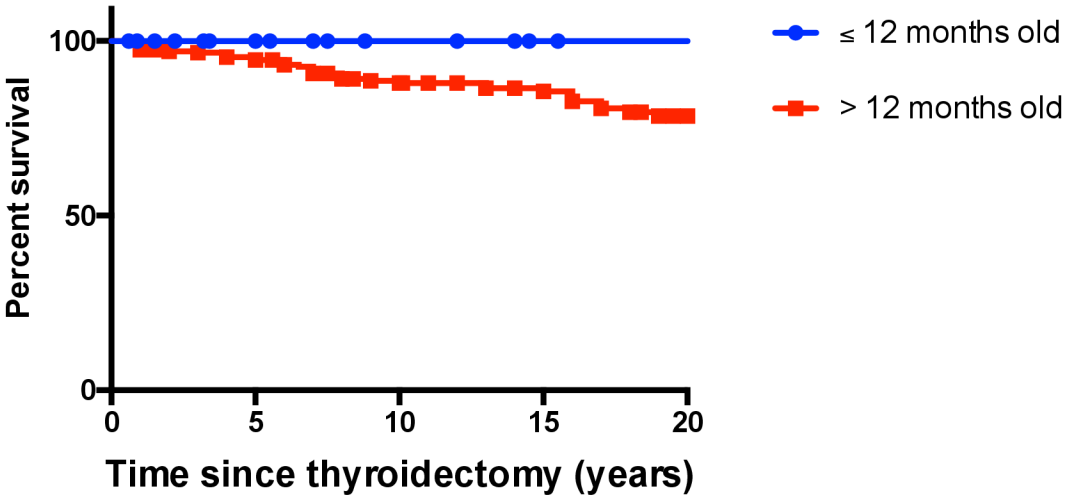
Added value of this study

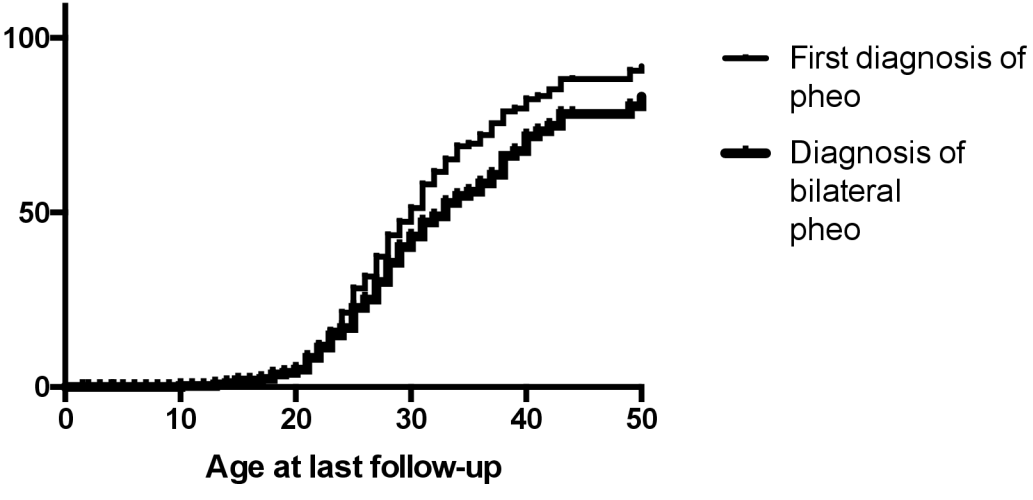
In the current study, 345 patients from 48 centers across the world are included in the largest study on MEN2B ever published. We report for the first time an exhaustive description of the phenotype and natural history of MEN2B. This study emphasizes the benefits of early thyroidectomy before the age of one year, as it led to a long-term cure in 83% of operated patients. Surprisingly, at a median age of 25 years, 14.8% of the patients operated later than one year were still cured while 20% of our patients had died, emphasizing the phenotypic heterogeneity of the syndrome. All of the patients had at least one extra-endocrine feature, and more than half of them had the classic association of marfanoid body habitus, gastrointestinal signs and mucosal neuromas, clinical signs that should warn health providers on a potential diagnosis of MEN2B. Half of the patients had bilateral pheochromocytomas by age 28 years and, for the first time, the benefits of adrenal-sparing surgery are shown, which resulted in normal adrenocortical function in 61.5% of patients and was associated with a low risk of recurrence. Finally, we report for the first time the social consequences of MEN2B, as a fourth of our patients were disabled due to the clinical manifestations of MEN2B.

Implications of all the available evidence

MEN2B is an orphan disease associated with a significantly altered quality of life and poor survival primarily due to metastatic MTC. Means to improve the prognosis of patients with MEN2B include making the diagnosis earlier and better understanding the natural history and management of disease manifestations. The evidence has clearly shown that the clinical presentation of MEN2B begins at birth, and improved education of all health providers about the extra-endocrine signs should lead to earlier diagnosis and improved outcomes through earlier thyroidectomy. Improving the functional prognosis can also be achieved through appropriate management of pheochromocytoma via adrenal-sparing surgery, which should lead to less adrenal insufficiency and the need to take lifelong adrenal replacement therapy. Future studies should focus on the factors explaining the phenotypic variations in terms of disease aggressiveness.


100
50
0
Percent survival
0
10
20
30
40
50
Age at last follow-up


100
50
0
Percent survival
0
5
10
15
20
Time since thyroidectomy (years)
≤ 12 months old
> 12 months old


100
50
0
0
10
20
30
40
50
Age at last follow-up
First diagnosis of pheo
Diagnosis of bilateral pheo

	All operated patients n=338	No later than 1 year old n=20	Later than 1 year old n=318	p
Median age at thyroidectomy (median; range)	14 years (0·25-47)	9 months (3-12)	14 years (1·1-47)	<0.0001
Median calcitonin fold upper limit normal (range)	180·3 (1-57000)	6·2 (1-44)	182 (1·1-57000)	<0.0001
Pathology				<0.0001
- **Normal**	2	2	0	
- **C cell hyperplasia without MTC**	9	3	6	
- **Medullary thyroid cancer**	327	15	312	
Median MTC size, mm (range)	21 (1-100)	3·7 (1-13)	23 (1-100)	<0.0001
MTC size < 10 mm	51	14	37	
Systematic lymph node dissection	241 (77·2% of 312 available)	14 (73% of 19 available)	227 (77·4% of 293 available)	0.24
Normal calcitonin after surgery	25·6% (57 of 223 available)	83·3% (15 of 18 available)	20·9% (43 of 206 available)	<0.0001
Median age at last follow-up (range)	25 years (1-66)	6 years (1-33)	26 years (1·1-66)	<0.0001
Final outcome				<0.0001
- **Remission**	62 (18·3%)	15 (75%)	47 (14·8%)	
- **Biochemical persistence**	58 (17·1%)	0	58 (18·2%)	
- **Biochemical and cervical persistence**	47 (13·9%)	2 (10%)	45 (14·1%)	
- **Biochemical and systemic persistence**	105 (31·1%)	1 (5%)	104 (32·7%	
- **Dead**	66 (19·5%)	2 (10%)	64 (20·1%)	
o **Due to MTC**	43	0	43	
o **Due to pheochromocytoma**	2	0	2	
o **Due to gastro-intestinal complications of MEN2B**	2	1	1	
o **Due to unknown reasons**	19	1	18	

Table 1: MEN2B-related medullary thyroid carcinoma with thyroid surgery

Patients with pheochromocytoma	153 (48·9%)
Median age at first diagnosis of pheochromocytoma, years (range)	24 (13-52)
Symptomatic at first diagnosis	71 (of 127 available) (55·9%)
Diagnosis - Before MTC - At the same time as MTC - After MTC	 8 (5·8%) (delay of 3 years, range 1-23) 35 (26·5%) 94 (67·7%) (delay of 8 years, range 1-42)
Unilateral pheochromocytoma at last follow-up	42 (27·4%)
Bilateral pheochromocytoma at last follow-up	111 (72·5%)
Synchronous bilateral pheochromocytoma	79 (51·6%)
Asynchronous bilateral pheochromocytoma	32 (20·9%)
Patients with adrenal surgery - Unilateral adrenal surgery - Bilateral adrenal surgery	146 (95·4%) 51 95
Patients with adrenalectomy - Recurrence - Adrenal insufficiency	115 (78.8%) 11 (9.6%) 69 *(100%)
Patients with at least 1 adrenal sparing surgery - Right adrenal - Left adrenal - Both sides - Recurrence - Adrenal insufficiency	31 (21.2%) 13 11 7 3 (9.6%) 10** (28.5%)
Metastatic pheochromocytoma	4 (2·6%)
Median age at last follow-up, years (range)	25 (1-66)
Death due to pheochromocytoma	2 (0·6%)

Table 2: Data on MEN 2B pheochromocytoma. *, for a total of 69 patients with bilateral adrenalectomy; **, for a total of 26 patients with bilateral adrenal surgery and at least 1 adrenal sparing surgery.

Extra-endocrine features	Number	Percent
Ganglioneuromatosis	258/266	97%
- Tongue	165/266	62%
- Lips	142/266	53·4%
- Eyelid/conjunctival	51/266	19·2%
Marfanoid habitus	193/266	72·5%
Pseudo-Hirschsprung/Severe constipation	168/257	65·4%
Achalasia/Gastroparesis	9/257	3·5%
Pes cavum	63/166	38%
Pectus excavatus	45/172	26·2%
Motor/muscle weakness (hypotonia, muscle weakness)	51/190	26·8%
Scoliosis	18/190	9·5%
Corneal hypertrophy	82/182	45%
Alacrymia	66/167	39·5%
Kidney anomalies (kidney atrophy, kidney cysts, hydronephrosis, ureteral atonia)	25/189	13·2%

Table 3: Extra-endocrine features of MEN 2B. Note that the penetrance was based on the presence/absence of each feature specifically noted in the medical files of each patient. When no mention of the feature was noted, the information was considered as not available.