

Review of Multiple Endocrine Neoplasia Type 2A in Children: Therapeutic Results of Early Thyroidectomy and Prognostic Value of Codon Analysis

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ABSTRACT. *Objectives.* The aim of this study was first to investigate whether early total thyroidectomy (ETT; 1–5 years of age) can prevent medullary thyroid carcinoma with persistent or recurrent disease (PRD) in pediatric patients with multiple endocrine neoplasia type 2A (MEN-2A) and second, to evaluate the strength of codon analysis in children with MEN-2A as prognostic parameter.

Methods. Case reports and review of the literature for pediatric patients with MEN-2A were conducted. Inclusion criteria were age (0–20 years) and histologic degree of C-cell disease (normal = N, C-cell hyperplasia = CCH, medullary thyroid carcinoma = MTC, metastatic MTC = MMTC). To evaluate therapeutic results of ETT (1–5 years) versus late total thyroidectomy (LTT; 6–20 years), age-dependent histologic stages of C-cell disease and postoperative occurrence of PRD were compared. Prognostic value of specific codons, age-dependent histologic distribution, and long-term outcome were analyzed.

Results. In a total of 260 cases, 42 (16%) underwent ETT, and 218 (84%) underwent LTT. Histologic analysis showed significant difference between ETT versus LTT (57% vs 76%) regarding malignant stage of C-cell disease (of combined rate of MTC and MMTC). Long-term outcome was documented in 74 patients (28%). During a median follow-up period of 2 years (range: 0–15 years), 21 of 65 of the LTT group versus 0 of 9 of the ETT group suffered PRD. Information about codon analysis was available in 150 patients (58%). Mutated codons were c634 (63%), c618 (19%), c620 (9%), and c804 (6%). Codon-related histologic analysis resulted in prognostic differences: 81% of patients with c634-mutation had MTC or MMTC in contrast to c804 (44%), c618 (34%), and c620 (7%). Fifteen of 17 MMTC and 7 of 9 PRD occurred in patients with c634-mutation.

Conclusions. 1) ETT until 5 years of age in MEN-2A gene carriers results in significant reduction of MTC and MMTC in favor of CCH and improved disease-free long-term outcome. 2) Codon analysis is an important prognostic factor. Timing of TT could be individualized based on codon-specific prognosis. Until more detailed knowledge is available, consequent genetic and biochemical screening is mandatory for appropriate individual timing of ETT before age of 5 years. *Pediatrics* 2003;111:e132–e139. URL: <http://www.pediatrics.org/cgi/content/full/111/2/e132>; multiple endocrine neoplasia type 2A, familial medullary thyroid carcinoma, RET proto-oncogene, thyroidectomy, prognosis, children.

ABBREVIATIONS. MEN-2A, multiple endocrine neoplasia type 2A; MEN-2B, multiple endocrine neoplasia type 2B; RET, rearranged during transfection; TT, total thyroidectomy; ETT, early total thyroidectomy; LTT, late total thyroidectomy; PRD, persistent and recurrent disease; N, Normal; CCH, C-cell hyperplasia; MTC, medullary thyroid carcinoma; MMTC, metastatic medullary thyroid carcinoma.

Multiple endocrine neoplasia type 2A (MEN-2A) is a hereditary tumor syndrome with the triad of medullary thyroid carcinoma, pheochromocytoma, and primary hyperparathyroidism,^{1,2} while MEN type 2B (MEN-2B) is characterized by medullary thyroid carcinoma, pheochromocytoma, mucosal ganglioneuroma, and a marfanoid habitus.³ MEN-2A is transmitted in an autosomal dominant manner with virtually 100% penetrance.⁴ Usually, the first tumor occurring during life is medullary thyroid carcinoma (MTC),⁵ a neoplasm of parafollicular C-cell origin. Malignant transformation of C-cells is multifocal in both thyroid lobes and characterized by different histologic stages: Diffuse C-cell hyperplasia (carcinoma in situ), uni- and multifocal MTC with or without local (lymph nodes), or distant metastasis (liver, bone).⁶ The malignant transformation of the C-cells begins very early in life: in MEN-2B patients, MTC can occur in infancy, whereas MTC is less aggressive in MEN 2A.^{7–10} Nevertheless, in children of MEN-2A families thyroidectomized at 1 to 6 years of age, histologic analyses revealed all stages of C-cell disease, even metastatic MTC.^{7–12} The only potentially curative treatment for medullary thyroid carcinoma is surgical removal of all thyroid tissue,^{13–15} a goal that is not regularly achieved in patients with clinically manifest MTC.¹⁶

The molecular bases of MEN-2A and MEN-2B are missense mutations in the RET protooncogene, a transmembrane tyrosine kinase receptor located on chromosome 10q11.2. In MEN 2A, the most frequent germ line mutations involve the extracellular domain of rearranged during transfection (RET) at codons 609, 611, 618, 620, 630, and 634.^{17,18} Rarely, mutations occur in the tyrosine kinase domain of RET at codons 768, 790, 791, 804, and 891.^{19,20}

The detection of germ line mutations in the RET

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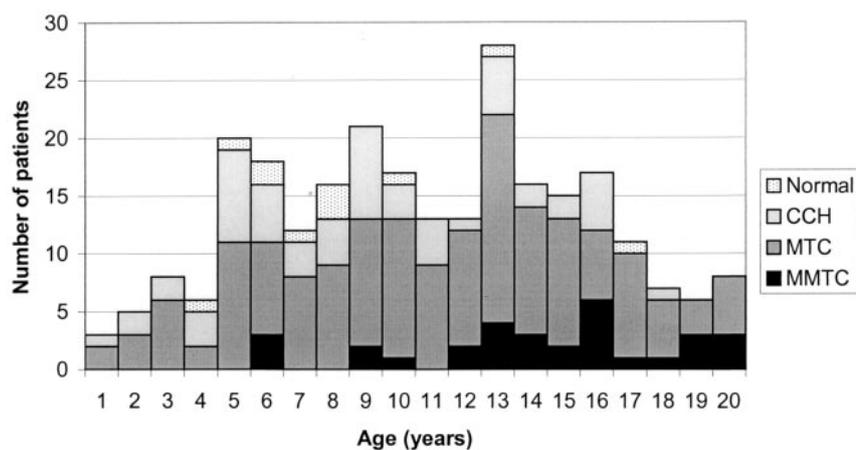


Fig 1. Age-dependent distribution of C-cell disease in all patients ($n = 260$).

TABLE 1. Age-Dependent Distribution of C-Cell Pathology

	Total N = 260	N	CCH	MTC	MMTC	MTC + MMTC
ETT	16% (42)	5% (2)	38% (16)	57% (24)	0% (0)	57% (24)
LTT	84% (218)	4% (9)	20% (44)	61% (134)	14% (31)	76% (165)
		$P = .795$	$P = .019^*$	$P = .75$	$P = .019^*$	$P = .023$

protooncogene has important diagnostic and therapeutic impacts: First, genetic screening of patients at risk allows one to identify disease gene carriers with very high specificity and sensitivity.^{21,22} Second, total thyroidectomy (TT) can be performed based on mutation carrier status in a prophylactic attempt, ideally in a premalignant stage of disease.²³ Currently, TT is recommended at 5 years of age in disease gene carriers.^{11,24,25} Based on the experience with very young children with MTC at the time of surgery, several authors even propose TT at the age of 2 years^{10,25,26} or between 3 and 5 years²⁸ to obtain optimal cure rates.

The first aim of this study was to compare therapeutic results of early TT (ETT: 1–5 years) versus late TT (LTT: 6–20 years) in the pediatric age group in a retrospective manner. Independent predictors of survival for MTC are patient age and TNM stage of C-cell pathology at presentation.¹⁵ Based on a review of the current literature, the effect of ETT on reduction of advanced histologic stages was analyzed, including 4 of our own MEN-2A patients. Furthermore, postoperative morbidity (persistent or recurrent disease after TT = PRD) was assessed as variable for long-term outcome comparing ETT versus LTT patients.

The second aim of this study was to evaluate the prognostic value of codon analysis. There is evidence from *in vitro* experiments that transforming capacities of RET-mutations are codon-dependent,²⁹ and a significant correlation exists between genotype and oncological features in adult MEN-2A patients.³⁰ Current recommendations do not take codon analysis into account for treatment planning. Codon-specific prognosis would allow individualized risk stratification for each patient: timing of TT could be adapted to codon-specific aggressiveness of C-cell disease.

METHODS

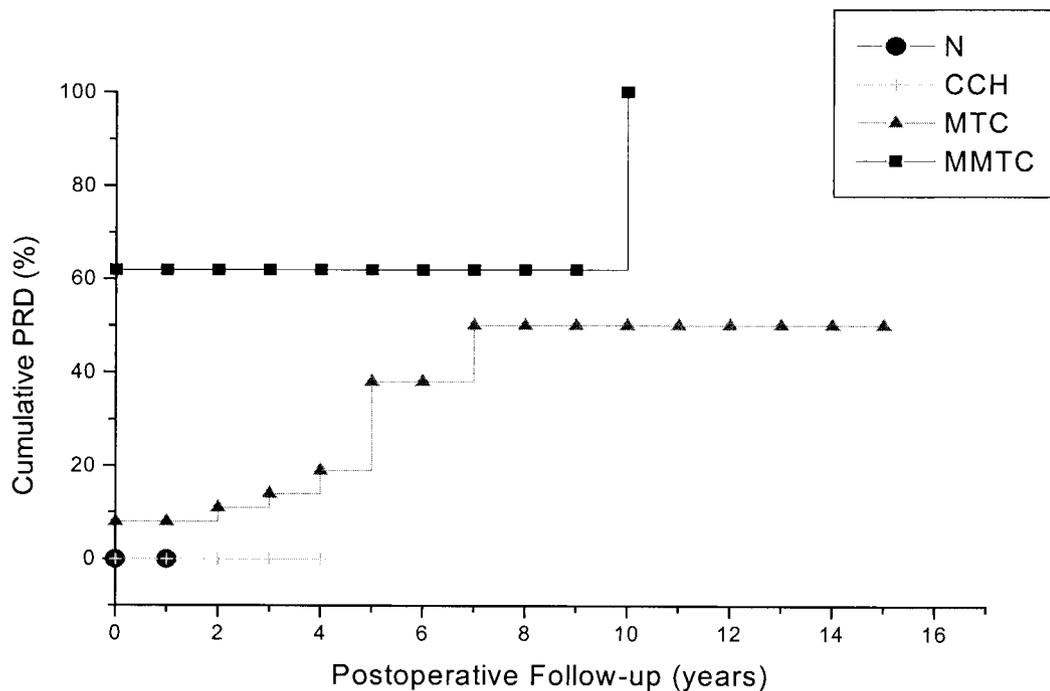
Patients

Case reports of 4 children of 2 different MEN-2A families treated in our clinics and systematic review of the literature (language: English and German) by a Medline search. Key words were “MEN-2A,” “FMTC,” “medullary thyroid carcinoma,” and “child.” Inclusion criteria for the analysis were 1) individual thyroidectomized patients, 2) age ≤ 20 years at total thyroidectomy, and 3) exact information about histologic degree of C-cell disease. Using these search criteria, we identified 256 pediatric patients reported in 47 publications. When available, information about codon analysis and follow-up after thyroidectomy was included. All the patients covered by our retrospective review are independent. If the same patient identifiable by the inclusion criteria was reported in 2 papers by the same author, he was only included once.

C-Cell Disease

The different histologic degrees of C-cell disease were defined as normal (N), C-cell hyperplasia (CCH), medullary thyroid carcinoma independent of tumor diameter (MTC), and metastatic medullary thyroid carcinoma proved by local or distant spread to lymph nodes, liver and bone (MMTC). Total thyroidectomy: TT performed between 1–5 years was defined as early TT (ETT), while TT between 6 to 20 years was defined as late TT (LTT). Outcome: For outcome analyzes, only patients with individually documented follow-up period and outcome were included. Cured patients were defined as those with long-term follow-up with normal calcitonin levels. Recurrent disease is defined as initial normalization of postoperative calcitonin levels but recurrence of pathologic levels during documented follow-up, whereas persistent disease stands for patients without postoperative normalization of calcitonin tests. Two patients with persistent disease attributable to proven thyroid rest (proof of thyroid rest in 1 patient by ultrasound, in 1 patient by ultrasound and surgery) after TT were not considered for outcome analysis.

To evaluate the therapeutic outcome of ETT, the percentage of MTC and MMTC and the rate of persistent or recurrent disease was compared with LTT. To evaluate prognostic strength of codon analysis, codon-dependent age-related histologic results and long-term outcome were compared. Statistical analysis: To analyze statistical significance between ordinal values the χ^2 test was used. The level of statistical significance was set at 0.05. For multiple comparisons the significance level was corrected by Bonferroni



N	0	0													
	3	3													
CCH	0	0	0	0	0										
	9	9	4	1	1										
MTC	4	0	1	1	1	3	0	1	0	0	0	0	0	0	0
	48	44	37	24	20	13	9	5	4	4	2	1	1	1	1
MMTC	9	0	0	0	0	0	0	0	0	0	1				
	14	5	3	3	2	2	1	1	1	1	1				

Fig 2. PRD for different stages of C-cell disease ($n = 74$). Numerators are the number of events during, and denominators the number of patients at the beginning of each time interval (combined rates of PRD in N+CCH versus MTC + MMTC; $P = .075$, log rank test).

procedure. The Kaplan-Meier methodology was used to analyze follow-up data and to construct time curves of patients with recurrent disease. To compare disease-free survival in ETT versus LTT, N+CCH versus MTC+MMTC, and in c634+c804 versus c618+c620, log rank test was used. Cox regression was calculated to describe impact of various prognostic factors on outcome.

RESULTS

We identified 256 pediatric MEN-2A patients in 47 studies^{7-12,21,23-28,30-63} published between 1982 and April 2002 and included 4 of our own patients. The median age of patients at TT is 11 years.¹⁻²⁰ Median age at TT varied with histology: N histology, 8 years (4-17 years); CCH, 8 years (1-18 years); MTC, 12 years (1-20 years); and MMTC, 15 years (6-20 years). Median age at ETT was 4 years versus 12 years at LTT.

Stage of C-Cell Disease at Thyroidectomy

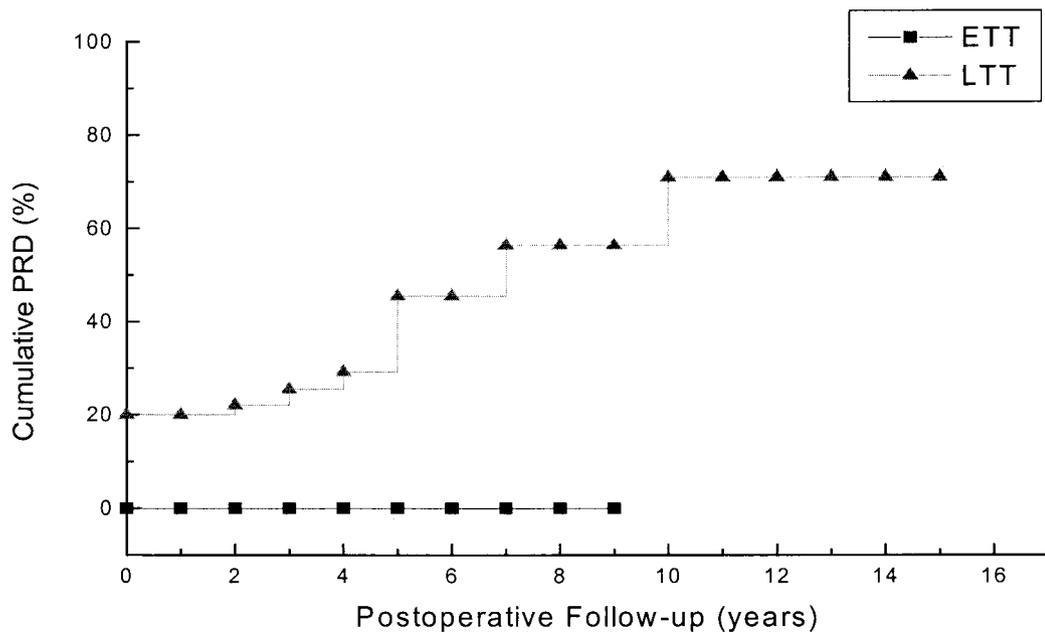
The distribution of different histologic degrees of C-cell disease in 260 patients is as follows: N, 4%; CCH, 23%; MTC, 61%; and MMTC, 12%. The results of age-dependent histologic analysis in all patients are shown in Fig 1. Forty-two (16%) of 260 patients underwent ETT, and 218 patients (84%) underwent LTT. The combined rate of MTC + MMTC is signifi-

cantly lower in the ETT group compared with the LTT group ($P = .023$; Table 1). ETT results in a significant reduction of MMTC from 14% to 0% ($P = .019$) and in a significant increase of CCH from 20% to 38% ($P = .019$).

Outcome After Thyroidectomy

Information about individual long-term outcome was only available in 74 (28%) patients: In 121 cases no information was available, 29 had a single postoperative normalized calcitonin value without long-term follow-up, and in 36 patients with long-term follow-up, the follow-up period was only stated as mean for a whole group of patients. One patient with widely metastatic MTC diagnosed at 6 years of age died of the disease at the age of 12 years. Median age in MTC patients with persistent (16 years) or recurrent disease (14 years) is higher than in cured MTC patients (9 years).

Outcome after TT was calculated by the Kaplan-Meier methodology for different histologic stages of C-cell disease and for ETT versus LTT (Fig 2 and 3). PRD rate is higher in patients with MTC or MMTC (21/62) versus N or CCH (0/12) patients; however, the difference is not statistically significant ($P = .075$,



ETT	0	0	0	0	0	0	0	0	0	0					
	9	9	5	4	3	2	2	1	1	1					
LTT	13	0	1	1	1	3	0	1	0	0	1	0	0	0	0
	65	52	39	24	20	13	8	5	4	4	3	1	1	1	1

Fig 3. PRD after ETT and LTT ($n = 74$). Numerators are the number of events during, and denominators the number of patients at the beginning of each time interval ($P = .068$, log rank test).

log rank test). The difference in rate of PRD in ETT (0/9) versus LTT (21/65) patients reaches not entirely significance level ($P = .068$, log rank test), but a strong trend is obvious.

Codon- and Age-Dependent Stage of C-Cell Disease After Thyroidectomy

Codon analysis was documented in 150 of 260 patients, the distribution was as follows: c634: 94 (63%), c618: 29 (19%), c620: 14 (9%), and c804: 9 (6%). The mutations c609, c611, and c790 are rare in pediatric patients (c609: one patient;⁵⁴ c611: 2 patients;^{39,51} c790: 1 patient³⁰). Codon-dependent rates of MTC and MMTC versus N and CCH (Table 2) are significantly higher in c634 (81%) versus c618 (34%) and c620 (7%) ($P < .001$). For multiple comparisons, the significance level was adjusted by Bonferroni procedure and was set at 0.008. Differences between c620 versus c618 ($P = .12$) and c804 versus c620, c618, and c634 do not reach statistical significance ($P = .11$, $P = .88$, and $P = .035$, respectively) in these small groups. Age dependence of codon-specific histologic findings is shown in Fig 4. The youngest patient with MTC was 1 year old in the c634 group versus 7, 15, and 15 years in the c618, c804, and c620 group, respectively. MMTC occurred as early as 6 years of age in patients with c634 and c804, although no pediatric patient with c618 and c620 suffered MMTC.

Codon-Dependent Persistent or Recurrent Disease After Thyroidectomy

Informations about long-term outcome were only available in 40 of 150 patients with codon analysis. The PRD rate in the c634+c804 group (9/30) versus c618+c620 group (0/9) is not statistically significant ($P = .30$, log rank test). Codon specific rates of PRD are shown in Fig 5.

Tumor Diameter

Tumor diameter was documented in 18/32 MMTC and 82/158 MTC cases. MMTC occurred in 10 microcarcinomas (tumor diameter <10 mm) and in 8 macrocarcinomas (tumor diameter ≥ 10 mm). In MTC patients 72 (88%) tumors were microcarcinomas. Eight of 13 patients with PRD had microcarcinoma.

Incidence of Pheochromocytoma and Primary Hyperparathyroidism at Diagnosis of MEN-2A

Biochemical screening for pheochromocytoma and primary hyperparathyroidism with urinary catecholamines and serum calcium was documented in 161 (62%) patients. Pheochromocytoma occurred in 3 patients (1.9%) at diagnosis of C-cell disease (all patients with codon 634, age 13–20 years), and primary hyperparathyroidism was detected in 9 patients corresponding to 5.6% (all patients with codon 634, age 10–20 years).

TABLE 2. Codon Distribution and Codon-Dependent Distribution of C-Cell Pathology

Codons	Total <i>n</i> = 150	N	CCH	MTC	MMTC
c609	1	0	0	1	0
c611	2	0	1	1	0
c618	29 (19%)	5	14	10	0
c620	14 (9%)	3	10	1	0
c634	94 (63%)	0	18	61	15]*
c790	1	0	0	1	0
c804	9 (6%)	3	2	2	1 + 1†

One hundred fifty of 260 patients with codon information. Different age-independent rates of MTC + MMTC: c634 versus c620 and c618, * $P < .001$; c634 versus c804, $P = .035$; c620 versus c618, $P = .12$; c620 versus c804, $P = .11$; c618 versus c804, $P = .88$.

† One patient with combination of 804 germ line mutation and 918 somatic mutation.⁶³

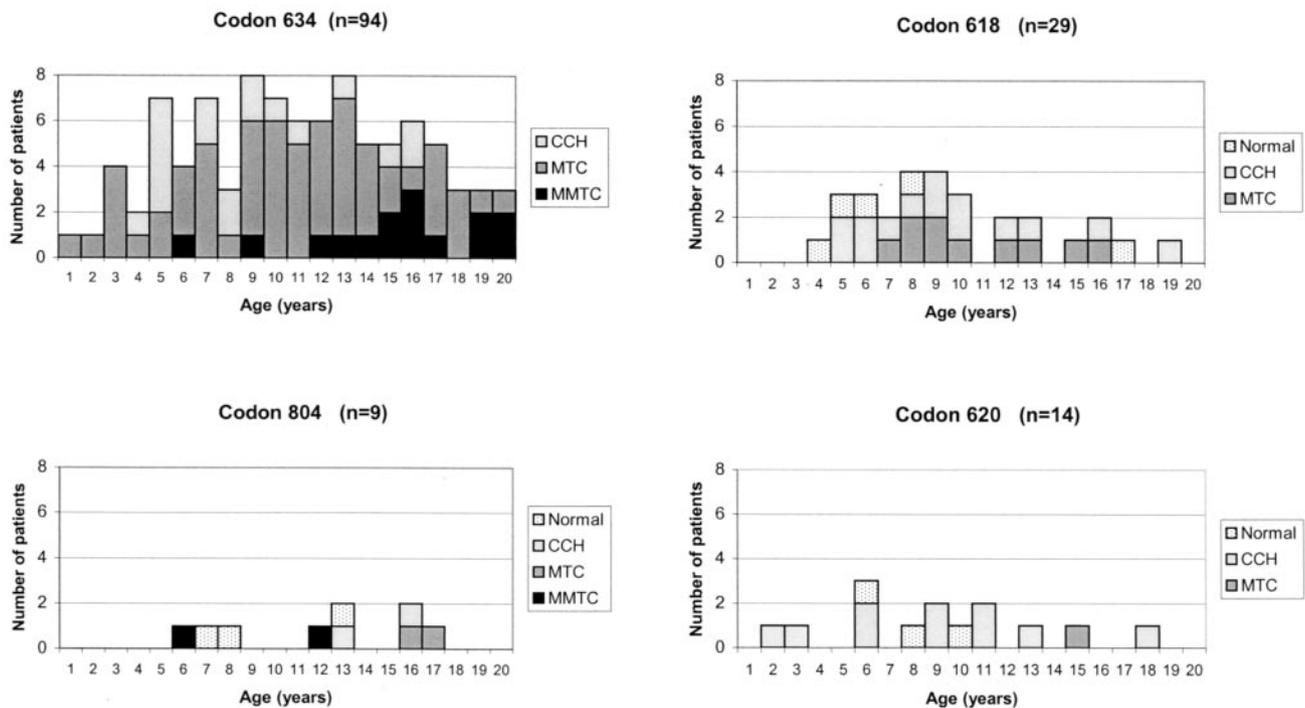


Fig 4. Codon- and age-dependent distribution of C-cell disease. (The 12-year-old c804 patient with MMTC had a combination of c804 germ line mutation and c918 somatic mutation.⁶³)

Multivariate Analysis of Patient and Tumor Features

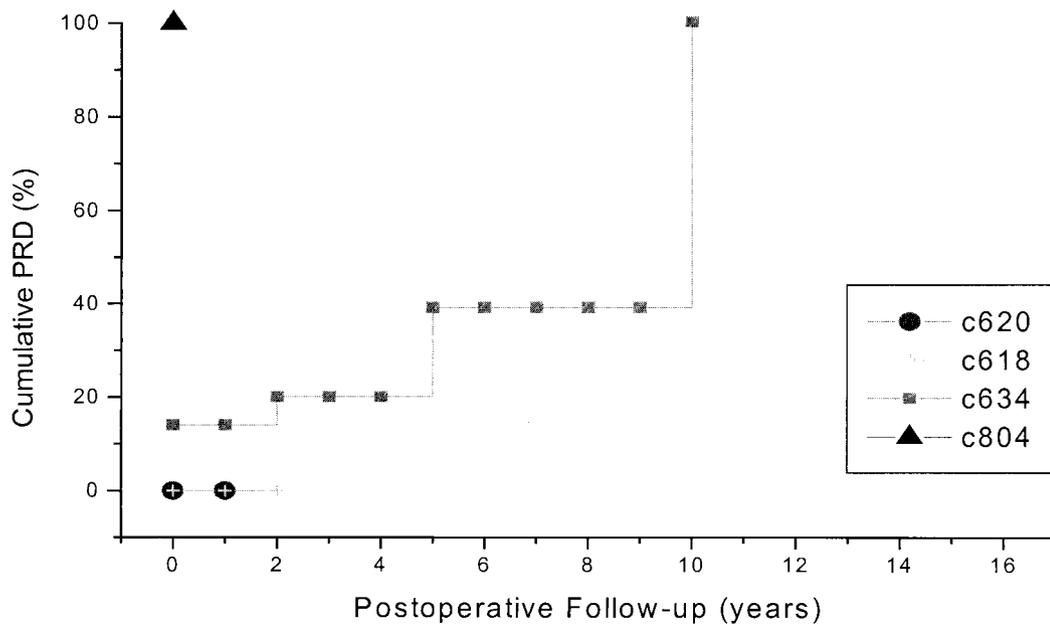
Cox regression model was used to analyze the impact age at TT, histologic stage of C-cell disease, size of tumor, and specific mutation on outcome in 74 patients with documented individual follow-up time. Although clear tendencies were present, none of the differences met statistical significance.

DISCUSSION

MEN-2A is inherited in an autosomal dominant manner with nearly 100% penetrance for MTC. The gene responsible for the disease, the RET protooncogene, was identified in 1993,^{17,18} and a variety of mutations causing MEN-2A have been described. Genetic testing before development of the disease phenotype can make diagnosis of MEN-2A and DNA analysis replaced the biochemical testing of basal and stimulated calcitonin levels as first line screening test in family members of index patients. TT before tumor development is the only potentially curative treatment for thyroid disease and should be performed during childhood.^{13,14}

Experiences of thyroidectomy in adolescents and children led to constant adjustment of timing of TT during the last 2 decades.^{9,11,21,26} Currently, most authors recommend TT at 5 years of age, while several groups propose surgery even at 2 and 3 to 5 years of age.^{10,26-28}

To evaluate the evidence of these recommendations, we performed a meta-analysis of all published cases being aware that retrospective analysis has limitations and may not truly describe the clinical course of all MEN-2A patients. The following factors influence the results: First, the inclusion criteria (individual age and histology) are not given for all patients of several large cohorts.^{12,24,26,28} Second, information about long-term outcome is only available in 74 (28%) of 260 patients. Third, our analysis of disease-free survival with the Kaplan-Meier methodology is influenced by the fact, that median follow-up period (ETT and LTT median: 2 years) is shorter than median time after which recurrence of MTC occurs (5 years in our review, 10 years in the literature²⁴), indicating that probably not all recurrences are de-



c804	$\frac{2}{2}$											
c634	$\frac{4}{28}$	$\frac{0}{24}$	$\frac{1}{16}$	$\frac{0}{5}$	$\frac{0}{5}$	$\frac{1}{4}$	$\frac{0}{2}$	$\frac{0}{2}$	$\frac{0}{2}$	$\frac{0}{2}$	$\frac{1}{1}$	
c618	$\frac{0}{4}$	$\frac{0}{4}$	$\frac{0}{1}$									
c620	$\frac{0}{5}$	$\frac{0}{5}$										

Fig 5. PRD for different codons ($n = 39$). Numerators are the number of events during, and denominators the number of patients at the beginning of each time interval (combined rates of PRD in c618+c620 versus c634+c804 $P = .30$, log rank test).

tected. Fourth, impact of different surgical techniques on outcome may be important but cannot be analyzed adequately in this review.

Our retrospective analysis shows nevertheless important results. ETT leads, compared with LTT, to a significant reduction of combined rate of MTC+MMTC ($P = .023$) in favor of N+CCH, representing a shift to premalignant stages of C-cell disease. Thus, we provide evidence that ETT interrupts progressive malignant transformation of C-cells at an earlier stage than LTT.

Because long-term mortality in MEN-2A patients 10 to 15 years after surgery shows no difference compared with the normal population,⁶⁴ we assessed long-term morbidity defined as PRD after ETT and LTT. In a subgroup of 74 patients with individual information about outcome and follow-up period, log rank test results in a near significant reduction of PRD rate in the ETT group versus the LTT group ($P = .068$), indicating improved long-term prognosis. A large cohort with complete data on all factors as outcome, age at TT, stage of C-cell disease, tumor diameter, and codon analysis would be necessary to perform multivariate analysis.

DNA analysis is the most sensitive and specific method to screen for genetically affected pa-

tients,^{21,22} whereas calcitonin testing allows detection of clinically inapparent malignant transformation of C-cells in mutation carriers.¹⁶ In our opinion, both consequent genetic and yearly preoperative biochemical screening starting in the first year of life is mandatory to monitor individual biology of the C-cell disease in MEN-2A patients and to plan ETT between 2 to 5 years of age. If biochemical screening demonstrates an abnormality, ETT should be performed immediately at any age.

Prognostic value of DNA analysis was first documented in vitro by Ito et al²⁹ demonstrating a variable codon specific transforming capacity of c609, c611, c618, c620, c630, and c634 mutations in C-cells with highest values for the c634 mutation. These results were confirmed by the clinical observation that MTC occurs earliest in patients with c634 mutation, whereas patients with c611 and c804 mutations display slow progression to MTC.^{30,46,53,63} Because multivariate analysis in a subset of 74 patients failed to show impact of specific mutations on outcome, we compared distribution of N, CCH, MTC, and MMTC for different codons at TT (Table 2). We found that c634 patients have significantly higher combined rates of MTC + MMTC compared with c618 and c620 ($P < .001$). Our results provide evidence of codon-

specific differences in tumor biology being relevant in the pediatric age group already.

These results may have important clinical implications in the future: the knowledge of specific malignant potential and long-term prognosis of each codon will possibly allow to individualize timing of TT based on DNA-results. In accordance with data in adult patients,^{30,46} our meta-analysis shows highest malignant potential of c634 mutations with occurrence of MTC already as early as 1 year of age. For the c804 mutation, we found highly variable expression of the MTC phenotype (Fig 4), and management of these patients is controversial.^{52,65} In c618 patients, 6 of 11 children developed MTC before age of 10. Therefore, children affected with mutations in these 3 codons should undergo ETT after careful screening at latest with 5 years. In contrast, the c620 mutations bear low risk for postoperative morbidity and delayed TT in analogy to recommendations for c611 mutations might be appropriate.^{53,66}

However, more clinical data on all relevant codons and the possible influence of different point mutations in the same codon are needed to define definitive codon-specific guidelines in the future. Until then, ETT in combination with preoperative calcitonin screening is a save approach and can assure maximal cure rate in all kindred of MEN-2A families.

CONCLUSION

ETT in the first 5 years of life in MEN-2A gene carriers reduces significantly the proportion of MTC+MMTC and improves significantly long-term outcome of these patients. Consequent genetic and biochemical screening starting in the first year of life is mandatory to detect aggressive C-cell disease before the time of planned TT. Furthermore, codon-specific biology has great impact on therapeutic results in the pediatric age group. Detailed knowledge of codon-specific prognosis could implicate risk-adjusted timing of TT for the individual patient.

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