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Present status of prophylactic thyroidectomy in pediatric multiple endocrine neoplasia 2: a nationwide survey in Japan 1997–2017

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Abstract

Background: In Japan, prophylactic thyroidectomy involves out-of-pocket expense. The American Thyroid Association (ATA) recommends prophylactic thyroidectomy for medullary thyroid carcinoma (MTC) during early childhood in patients with multiple endocrine neoplasia type 2 (MEN2). The ATA reports a high frequency of postoperative complications in childhood, which also influenced the delay of prophylactic thyroidectomy in Japan.

Methods: This retrospective study of multiple medical centers in Japan included individuals aged <20 years diagnosed with germline *RET* mutations between 1997 and 2017. The onset and onset possibility were defined based on confirmed lesions or calcitonin levels. The definition of risk and prophylactic thyroidectomy were based on the ATA 2015 revised guideline.

Results: Twenty-one patients with MEN2 were enrolled (highest risk, $n=5$; high risk, $n=5$; and moderate risk, $n=11$). The cumulative incidence of the onset/onset possibility reached 50% at 5 and 8 years and 100% at 9 years

and 17 years in high- and moderate-risk patients, respectively. Of 7 patients with MEN2A, 71% underwent prophylactic thyroidectomy. Only one 5-year-old patient (C634Y) had increased serum calcitonin level after prophylactic thyroidectomy in the MEN2A group. The only permanent complication, which did not occur in patients who underwent total thyroidectomy alone, was hypoparathyroidism (33% of patients). This permanent complication occurred with clinically developed MTC. No permanent postoperative complications occurred in patients aged 5–6 years.

Conclusions: Prophylactic thyroidectomy reduces recurrence and postoperative complications in pediatric patients with MEN2. Early thyroidectomy based on only calcitonin level could possibly reduce thyroidectomy delay.

Keywords: central node dissection; medullary thyroid carcinoma; multiple endocrine neoplasia type 2; postoperative complications; prophylactic thyroidectomy; recurrence.

Introduction

Medullary thyroid carcinoma (MTC) arises from C cells and occurs in almost all patients with multiple endocrine neoplasia type 2 (MEN2) caused by germline mutations in the

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RET gene. Because lymph node metastasis starting during the early stage of tumorigenesis is common, patients with MTC are at increased risk of postoperative recurrence [1]. Moreover, in hereditary MTC, the rate of progression from C cell hyperplasia (CCH) to MTC increases with age [2].

For hereditary MTC, prophylactic total thyroidectomy in early childhood is recommended by a consensus statement by Brandi et al. and the guidelines established by the American Thyroid Association (ATA), according to the estimated recurrence risk [3–5], and is an important treatment option for recurrence-free survival in all carriers of *RET* gene mutations [3–5]. Based on genotype-phenotype correlations, ATA classified the risks of hereditary MTC as highest (*RET* M918T mutation, phenotype MEN2B), high (codon 634 mutations, phenotype MEN2A and *RET* A883F mutation, phenotype MEN2B), and moderate (*RET* codon mutations other than M918T, C634, and A883F, phenotype MEN2A) in the 2015 revised guidelines for the diagnosis and management of patients with MTC [5].

However, the ATA also reports that thyroid surgery frequently causes postoperative complications in children, particularly in infants [5, 6]; the most common postoperative complications are hypoparathyroidism [7–9] and recurrent laryngeal nerve (RLN) palsy.

Due to concerns about balancing the need for prophylactic resection and overtreatment/postoperative complications, thyroid surgery is often performed at age >10 years in Japan [10, 11]. Moreover, in Japan, *RET* gene testing during screening of patients with MTC is covered by insurance, but *RET* screening test before onset in the proband's family and prophylactic thyroidectomy are out-of-pocket expenses. Surgery at a higher age than the ATA-recommended age may be the cause of the 39% recurrence at age 10–20 years among Japanese pediatric hereditary MTC patients [10, 11].

It remains unclear whether the low rate of complications from thyroid surgery in early childhood reported in large facilities is also true when a smaller number of pediatric patients with thyroid cancer are treated. Thyroid cancer rarely occurs in children, with an incidence of 0.54 per 100,000 person-years. Furthermore, MTC accounts for only 5% of all pediatric thyroid cancer patients [12]. Therefore, few studies concerning postoperative complications of prophylactic thyroidectomy in children with MEN2 have been reported from large facilities [7–9].

The introduction of a sensitive diagnostic assay using calcitonin as a tumor marker for MTC has increased the accuracy of predicting malignancy [13]. Electrochemiluminescence immunoassay (ECLIA) is currently considered the most sensitive diagnostic test for MTC [14] and has been used to measure calcitonin in all medical facilities in Japan since April 2015. Herein, we aimed to identify the

pathological onset or timing of increased calcitonin levels among Japanese children, the frequency of prophylactic thyroidectomy, prognosis, complications and rate of recurrence in patients with hereditary MTC. Toward this goal, the Japanese Society for Pediatric Endocrinology (JSPE) conducted a nationwide survey of young patients with *RET* gene mutations or MEN2.

Subjects and methods

Inclusion and exclusion criteria

Participants included patients aged <20 years diagnosed with MEN2 or an *RET* gene mutation between January 1997 and January 2017. Patients were excluded if they [1] did not consent to participate in this study, [2] did not undergo a genetic test, or [3] had neither an operative record nor a record of calcitonin levels. The study was conducted in accordance with the tenets of the Declaration of Helsinki. The research protocol was approved by the Ethics Committee of the Hamamatsu University School of Medicine (#E16–230) and the ethics committees of the facilities of the co-authors. Written informed consent was obtained from all participants or their parents or guardians. Four patients who were lost to follow-up were considered as “opted out”.

Research design and setting

The study design was a survey of medical records. We reviewed clinical records and mailed a questionnaire (including questions on the subjects' sex, age at diagnosis and at thyroidectomy, duration of follow-up, genetic testing, phenotype, calcitonin values over time, dates of calcitonin measurements, surgical interventions, node dissection area, pathological diagnoses, postoperative complications, type of surgeon and facility [own vs. other], and outcomes) to 190 councilors of the JSPE, pediatricians and pediatric surgeons who submitted data on MEN2 to the Research Group for “Comprehensive Study and Seamless Guidelines” on rare and intractable gastrointestinal diseases of childhood supported by the Japanese Ministry of Health, Labor and Welfare.

Calcitonin testing

In Japan, radioimmunoassay (RIA [using the LSIM® Calcitonin test system, LSI Medience, Tokyo, Japan]) was used to evaluate calcitonin levels until March 2015. In the RIA, the reference values for basal and stimulated levels for calcitonin are <86 pg/mL [15] and <300 pg/mL, respectively [16]. The ECLIA (using the ECLusys® Calcitonin test system, Roche Diagnostics, Mannheim, Germany) has been used since April 2015. In this test, the reference values of basal calcitonin are <3.91 pg/mL in women and <5.15 pg/mL in men [15], and those of the stimulated level are <67.6 pg/mL in women and <83.7 pg/mL in men [17, 18]. The lower limit of detection is 0.5 pg/mL. Calcitonin stimulation testing is performed as follows: calcium 25 mg/kg is intravenously injected, after which blood is collected at 0 (pre), 2, 5, and 10 min [19]. Only Roche's Japanese agency handled the calcitonin

ECLIA reagent and all institutes included in this study measured calcitonin via the ECLIA after April 2015.

Definition of prophylactic thyroidectomy

In this study, prophylactic thyroidectomy was defined as removal of the thyroid before MTC development or while MTC was clinically unapparent and confined to the gland. This definition was based on the following ATA specifications: resection performed within a year of birth in the highest-risk patients, resection performed at the age of 5 years or younger depending on calcitonin levels in high-risk patients, and resection performed when calcitonin levels were elevated or the patient's parents preferred a resection and did not desire long-term active surveillance in moderate-risk patients [5].

Definitions of disease onset or first increased serum calcitonin levels and recurrence, persistent disease or residual thyroid tissue

Disease onset was defined as the time when MTC or CCH was pathologically diagnosed. First increased serum calcitonin levels were defined as the time when the calcitonin levels in the stimulation test exceeded 300 pg/mL for patients followed-up through calcitonin measurements via RIA, or when the basal value first exceeded the adult reference value for patients followed via ECLIA. Because the basal calcitonin level is physiologically high in patients aged <3 years [20, 21], first increased serum calcitonin level in these patients was defined as the time when both basal and stimulated values simultaneously exceeded the adult baseline level.

The evaluation term of patients following thyroidectomy was based on the ATA revised guidelines [5]. Biochemical recurrence or

persistence was defined as a calcitonin level ≥ 0.5 pg/mL via ECLIA more than 6 months after total thyroidectomy. When calcitonin level was measured after total thyroidectomy, additional evaluation for residual tissue and thyroglobulin measurement was performed. Clinical recurrence or persistence was defined as tumors diagnosed via imaging after treatment or pathologically-diagnosed MTC after second surgery.

Statistical analysis

Kaplan-Meier analysis was used to evaluate the association between disease onset and age. Competing risks resulting from prophylactic thyroidectomy were assumed using the Weibull parameters by adjustment with exclusion. For the analysis of postoperative complications, we used descriptive statistics and prepared a cross table of the age at surgery and the level of neck lymphadenectomy. JMP version 8.00 (SAS Institute, Cary, NC) was used for all analyses. Statistical significance was set at $p < 0.05$.

Results

Of the 26 patients registered by the Thyroid Committee of the JSPE, 21 patients with MEN2 were enrolled (highest risk, $n = 5$; high risk, $n = 5$; and moderate risk, $n = 11$) (Figure 1). Patient characteristics are shown in Table 1. All 16 patients with MEN2A, i.e. those with a high or moderate risk, had a family history of MEN2 and had undergone genetic testing at a young age (median, 3 years; range, 0–8 years). All patients with MEN2B,

Figure 1: Inclusion and exclusion criteria.

Table 1: Demographic and clinical characteristics of the patients

Patient no.	Sex	RET mutation	Age at genetic screening (I), pathological onset or first calcitonin increase timing (II), thyroidectomy (III)			Calcitonin level at first increase or at thyroidectomy ECLIA RIA*		TNM stage or pathological findings/Node dissection	Postoperative calcitonin level ECLIA RIA*		Duration of follow-up (from onset)
			I	II	III	Basal	Peak		Basal	Peak	
			Years			pg/mL			pg/mL		Years
1 [§]	M	C634Y	0	5	5	71*	428*	CCH /Not performed	1.33	NT	2
2	F	C634G	0	8	9	11.3	333	T1aN0M0 /Central	<0.5	NT	1.1
3	F	C634S	8	9	10	72*	670*	T1aN0M0 /Central	<0.5	NT	3.3
4	F	C634R	1	5		18.6	148				(0.5)
5	F	C634Y	0	2		17.9	187				(1.8)
6	F	C620	4	17	17	28*	110*	TxNxM0 /Not performed	<0.5	NT	7.8
7	M	C620R	5		10	41*	43*	NED /Not performed	<0.5	NT	3.1
8	F	C620	6	6	6	29*	NT	T1N0M0 /Central	<0.5	NT	2.4
9	F	C620	0		5	34*	NT	NED /Central	<0.5	NT	7.8
10	M	C618S	5	8		6.8	NT				(1.8)
11	F	C620Y	2	8		7.4	NT				(1.0)
12	F	C618R	0	2		4.9	120				(0.8)
13¶	F	C618R	7	LOF		46*	NT				
14¶	F	C618R	5	LOF		63*	NT				
15¶	M	C618R	6	LOF		33*	NT				
16¶	M	C618R	0	LOF		NT	NT				
17 ^{//}	F	M918T	12	UNK	12	12,000*	NT	TxN1M0 /D2b	UNK		2.6
18*	M	M918T	11	UNK	11	78*	720*	T1aN1M0 /Central	52*	300*	2.5
19	M	M918T	12	UNK	12	380*	>1,600*	T1bN0M0 /Central, lateral	46*	45*	0.2
20 [§]	M	M918T	13	UNK	13	>1,600*	NT	T2N1M0 /D2b	332	NT	5.6
21*	F	M918T	10	UNK	10	8,870*	NT	T2N0M0 /Central	3.160	NT	11.9

¶Same family.

*Calcitonin measurement via the radioimmunoassay.

§Biochemical recurrence.

‡Clinical recurrence.

//No clinical recurrence.

Notes: “Basal” denotes plasma calcitonin levels before calcium stimulation; “peak” denotes plasma calcitonin levels after stimulation. Normal calcitonin levels in the radioimmunoassay (RIA) are ≤85 pg/mL (basal) and 300 pg/mL (peak). Normal calcitonin levels in the electrochemiluminescence immune assay (ECLIA) are ≤3.91 pg/mL (basal) and 67.6 pg/mL (peak) in girls and ≤5.15 pg/mL (basal) and 83.7 pg/mL (peak) in boys. Patient 17 was followed up for calcitonin at another facility that performed the thyroidectomy; she was followed-up regarding pheochromocytoma at our facility.

Abbreviations: CCH, C cell hyperplasia; ECLIA, electrochemiluminescence immune assay; LOF, loss of follow-up; NED, no evidence of disease; NT, not tested; RIA, radioimmunoassay; UNK, unknown.

i.e. those with the highest risk, had a *de novo* mutation and had been diagnosed at an older age, after the MTC clinically occurred. Of the five patients with MEN2B, four

(80%) underwent a detailed examination for refractory diarrhea or constipation before being diagnosed with MTC (data not shown).

Figure 2: Cumulative incidence of first serum calcitonin increased timing, C cell hyperplasia (CCH) or medullary thyroid carcinoma (MTC) in patients with multiple endocrine neoplasia type 2A (MEN2A) (n=16).

The solid line indicates high-risk patients (n=5), whereas the dotted line indicates moderate-risk patients (n=11). Each curve represents adjustments for competing risks for high- and moderate-risk patients. The onset in patients with pathological MTC or CCH and the adjusted onset in pathologically normal patients undergoing surgery are shown as follows: ●: MTC, ○: CCH, and □: normal. Δ Patients with increased calcitonin levels who did not undergo surgery. ¶ The need for prophylactic thyroidectomy was determined according to the American Thyroid Association (ATA) definition: high risk, before or at 5 years of age based on serum calcitonin levels; moderate risk, serum calcitonin level increase or children of parents who refused long-term treatment. * Increased serum calcitonin levels after total thyroidectomy was defined as an increase in baseline calcitonin levels of >0.5 pg/mL after total thyroidectomy, as measured via the electrochemiluminescence immunoassay (ECLIA). The baseline level of this patient was 1.33 pg/mL.

Pre-symptomatic thyroidectomy was performed in seven of 16 patients with MEN2A (44%); five patients were awaiting surgery after disease onset possibility (median, 1.0 [range, 0.5–1.8] year), and four patients in the same family were lost to follow-up. Five of the seven patients (71%) with MEN2A who underwent surgery received prophylactic thyroidectomy as defined by the ATA. No thyroid lesion was detected preoperatively in any patient with MEN2A.

The dates of pathological disease onset or first increased calcitonin timing, surgical pathological diagnosis, prognosis, and rate of recurrence or residual disease or residual thyroid tissues in patients with MEN2A are shown in Figure 2.

ATA high-risk patients

Calcitonin measurements via ECLIA showed that the mean disease onset possibility was at 5 years of age in ATA high-risk patients. The cumulative incidence of pathological onset or first calcitonin elevation timing reached 50% at the age of 5 years and 100% at the age of

9 years (Figure 2). Patient no. 1 underwent prophylactic total thyroidectomy at the age of 5 years and 6 months; surgical pathology showed CCH. Only this patient experienced increased serum calcitonin postoperatively; thus, complete total thyroidectomy was performed by an experienced endocrine surgeon and pediatric surgeons. At the operation time his height was 105.4 cm and body weight 18.05 kg. His preoperative thyroglobulin level was 42.0–106.4 ng/mL. After total thyroidectomy, the thyroglobulin level was 0.55–2.41 ng/mL (his institutional normal thyroglobulin level was 0.0–32.7 ng/mL).

Patient no. 2 was the only patient whose preoperative calcitonin level was measured via ECLIA. An MTC tumor with a maximum diameter of 2 mm was found; it was cured biochemically following surgery. This case was reported in detail by Abe et al. [22].

ATA moderate-risk patients

All patients in this category who underwent surgery had prophylactic resection before without increased

Table 2: Incidence of any complications after thyroidectomy according to age.

Type of complication	Total (%)	Children with any postoperative complications		
		Age (years)		
		3–6	7–12	13–18
Transient RLN palsy	2 of 12 (17)	0 of 3 (0)	1 of 7 (14) [¶]	1 of 2 (50) [§]
Transient hypoparathyroidism	2 of 12 (17)	1 of 3 (33) [§]	1 of 7 (14) [¶]	0 of 2 (0)
Permanent hypoparathyroidism	4 of 12 (33)	0 of 3 (0)	3 of 7 (43) ^{¶,*}	1 of 2 (50)*
Any complication	8 of 12 (67)	1 of 3 (33)	5 of 7 (71)	2 of 2 (100)

[¶]With central dissection.

*With central and lateral dissection.

[§]Thyroidectomy.

Abbreviations: RLN, recurrent laryngeal nerve.

calcitonin levels determined via RIA. The cumulative incidence of pathological onset or first calcitonin elevated timing reached 50% at the age of 8 years (11 years upon adjustment for competing risks) and 100% at the age of 17 years (Figure 2). Because the high calcitonin levels in patient 12 further increased from 4.9 pg/mL to 10.8 pg/mL (basal value) and from 120 pg/mL to 338 pg/mL (stimulated value) at the age of 3 years 4 months, we considered the high calcitonin levels at the age of 2 years to be the first elevated calcitonin timing.

Surgical and postoperative complications

Postoperative complications are shown in Tables 2 and 3. Transient RLN palsy occurred in a moderate-risk patient aged 17 years (patient no. 6) and a high-risk patient aged 10 years (patient no. 3). Two high-risk patients (aged 5 and 9 years; no. 1 and 2, respectively) experienced transient hypoparathyroidism (Table 2). Hypoparathyroidism was the only permanent complication (n=4; patients no. 17, 19, 20, and 21); it occurred only in the highest-risk patients who required lymphadenectomy (Table 3). No permanent complications were observed in patients who did not undergo cervical lymphadenectomy or were aged

5–6 years. The incidence of permanent complications increased with age and as the area of the neck lymphadenectomy widened. As shown in Figure 3, patients were referred to many different surgeons by the physician in charge. The surgery department showed no correlation with postoperative complications.

Discussion

We confirmed the several tendencies in Japanese pediatric MEN2: those of therapy policy variations in each facility and higher age at thyroidectomy than that recommended by the ATA. There were no permanent complications due to prophylactic thyroidectomy, but there were many transient surgical complications. Moreover, there was a high proportion of surgical complications among advanced MEN2B cases with lymphadenectomy. In order to solve these problems, it is necessary to discuss whether prophylactic thyroidectomy at low age will reduce surgical complications and improve the probability of recurrence. It is also necessary to consider whether there is merit in cost.

First, regarding operative complications, few studies have reported on postoperative complications of

Table 3: Permanent complications after surgery by extent of surgery according to age.

Extent of surgery	Total (%)	Children with permanent postoperative hypoparathyroidism		
		Age, years		
		3–6	7–12	13–18
Thyroidectomy	0 of 3 (0)	0 of 1 (0)	0 of 1 (0)	0 of 1 (0)
With central dissection	1 of 6 (17)	0 of 2 (0)	1 of 4 (25)	
With central and lateral dissection	3 of 3 (100)		2 of 2 (100)	1 of 1 (100)
Any surgery	4 of 12 (33)	0 of 3 (0)	3 of 7 (43)	1 of 2 (50)

Figure 3: Types of referrals from physicians in charge to surgeons and postoperative complications.

Own: Surgery was performed at the same institution (the physician in charge referred the patient to a surgeon within the same facility for surgery). Other: Patient was referred to a surgeon at another facility.

prophylactic thyroidectomy in children (Table 4) [7, 9, 23, 24], revealing a higher risk of postoperative complications when neck lymphadenectomy was performed at a young age. In those studies, and ours, permanent RLN palsy occurred in only a 1-year-old boy [7] out of 347 patients (0.3%). Permanent hypothyroidism occurred in 27/347 patients (7.8%). There was no surgery-related death. Generally, the parathyroid glands of children younger than 5 years are translucent and small; postoperative complications, including hypoparathyroidism, are more common with pediatric thyroid surgery when compared to those in adults [6]. However, adult Japanese MEN2 patients who underwent thyroidectomy with 94.9% neck lymphadenectomy also had a high operative complication rate: permanent RLN palsy 11/330 (3.3%), permanent hypothyroidism 74/327 (22.6%) [11]; 80% of MEN2B patients of higher age in our study had permanent hypoparathyroidism. These suggest that clinically apparent disease requiring aggressive surgery with neck lymphadenectomy is associated with a high rate of permanent complications.

The ATA guidelines recommend that patients should be referred to experienced surgeons to decrease the rate of postoperative complications [5, 6]. It is noteworthy that facilities with a high number of pediatric thyroid surgeries exhibited no permanent surgical complications [9]. The present study analyzed data from multiple facilities at which thyroid surgeries were not frequently performed in children. The incidence of transient RLN palsy was 1.8% in high-volume facilities; in contrast, it was 28.6% (2/7 patients with MEN2A) in our study [9]. Another nationwide report described a high proportion of permanent hypoparathyroidism in 15/79 patients (19.0%) [24].

Second, regarding recurrence, we believe that operations for children in high-volume facilities also reduce recurrence. In reports where the definition of prophylactic thyroidectomy was closest to that of the ATA and where age was considered in high-volume facilities, the rate of recurrence or residual disease was 0.7–5% [7, 9]. On the other hand, a nationwide survey that included cases with delayed surgery had 62% recurrence or residual disease proportion [24]. Of course, it was obvious that the definitions were different in that report. The data regarding prophylactic thyroidectomy among pediatric patients with MEN2 are shown in Table 4 [7, 9, 23, 24]. Patients with suspected recurrence or residual disease all had biochemical recurrence or were at the residual disease stage, except for one MEN2B patient with advanced MTC [24]. Notably, in hereditary MTC, recurrence was observed in both high- and moderate-risk patients aged >8 years, even if MTC was not in the advanced stage [23].

Our study included a patient with a high-risk C634Y mutation who had elevated serum calcitonin levels after undergoing total thyroidectomy at 5 years of age with CCH in pathology. Detectable thyroglobulin level may indicate remnant thyroid tissue in this patient. However, because micrometastases can occur during an early stage in MTC, recurrence or residual disease cannot also be denied. The recurrence proportion in hereditary MTC is 4% among cases with tumor size <2 mm and node negative at surgery [1]. Hereditary MTC has an estimated annual growth of 0.4–0.5 mm [25]. Accordingly, at least after the elevation of calcitonin, surgery should not be postponed. MTC-related death at 12 years has been reported in moderate-risk patients [26]. The ATA states that delaying surgery after

Table 4: Total thyroidectomy in pediatric MEN2 within no clinical apparent thyroidal disease.

Reference, Country	Study design	No	Age at TT, years Median (range)	ATA Risk category (%) HST H MOD	Operative complication				Histology normal CCH MTC	Recurrence or residual structural disease (%)	
					Operative management					Youngest age (risk)	Duration of follow-up (median, months (range))
					Age, year (%)						
					≤ 6	> 6	TT alone	TT + LND			
Skinner et al. N Engl J Med, 2005 USA	Retrospective cohort, single center, 1993–2005	50	9 (3–19)	0/50 (0)	ND	ND	ND	ND	4/50 (8)	6/50 (12)	
				19/50 (38)	3/16 (19)	0/34 (0)	0/1 (0)	3/49 (6)	13/50 (26)	8 years (H)	
				31/50 (62)	ND	ND	ND	ND	33/50 (66)	81 (60–121)	
				ND	ND	ND	ND	ND			
Kluijfhout et al. Medicine, 2015 Netherlands	Retrospective cohort, single center, 1993–2014	44	5 (0–17)	4/44 (9)	9/24 (38)	3/20 (15)	ND/42	ND/2	1/44 (2)	2/44 (5)	
				37/44 (84)	4/24 (17)	5/20 (25)		21/44 (48)	ND		
				3/44 (7)	0/24 (0)	1/20 (5)		22/44 (50)	126 (4–252)		
					1/24 (4)	0/20 (0)					
Machens et al. Br J Surg, 2018 Germany	Retrospective cohort, single center, 1994–2017	167	6 (0.5–18)	6/167 (4)	12/99 (12)	19/68 (28)	19/109 (17)	12/58 (21)	Normal, CCH;	1/149 (0.7)	
				73/167 (44)	0/99 (0)	0/68 (0)	0/109 (0)	0/58 (0)	117/167 (70)	7 months (HST)	
				88/167 (53)	2/99 (2)	2/68 (3)	0/109 (0)	3/58 (5)	50/167 (30)	72 (1–255)	
					0/99 (0)	0/68 (0)	0/109 (0)	0/58 (0)			
Prete et al. Br J Surg, 2018 UK	Retrospective, nationwide medical record review, 1995–2013	79	6.2 (0.8–15.6)	4/79 (5)	ND	2/54 (4)	2/54 (4)	1/25 (4)	10/79 (13)	24 to 44 /71 (34 to 62) [¶]	
				40/79 (51)	age at surgery was not associated.	6/54 (11)	9/25 (36)	39/79 (49)	ND		
				35/79 (44)		1/54 (2)	2/25 (8)	30/79 (38)	104.5 (18.2–240.6)		
						0/54 (0)	0/25 (0)				
Current study Japan	Retrospective, nationwide medical record review, 1997–2017	7	9 (5–17)	0/7 (0)	1/3 (33)	1/4 (25)	1/3 (33)	1/4 (25)	2/7 (29)	1/7 (14)	
				3/7 (43)	0/3 (0)	0/4 (0)	0/3 (0)	0/4 (0)	1/7 (14)	5 years (H)	
				4/7 (57)	0/3 (0)	2/4 (50)	1/3 (33)	1/4 (25)	4/7 (57)	37 (13–94)	
					0/3 (0)	0/4 (0)	0/3 (0)	0/4 (0)			

Note: ¶, 24/71 means postoperative basal calcitonin was detectable, within normal range. 44/71 means all postoperative calcitonin detectable patients including above normal range.

Abbreviations: ATA, American Thyroid Association; RLN, recurrent laryngeal nerve; HST, ATA-highest risk; H, ATA-high risk; MOD, ATA-moderate risk; TT, total thyroidectomy; CCH, C cell hyperplasia; MTC, medullary thyroid carcinoma; LND, lymph node dissection; ND, not described or not able to calculate.

disease onset increases the risk of recurrence. However, in patients aged ≤ 3 years, calcitonin levels are physiologically high; thus, an early determination of disease onset is challenging [20]. Moreover, unexpected postoperative complications can occur [7]. Thyroid hormones substantially affect an individual's growth and development [27], particularly in children; thus, cautious judgment is necessary. Because metastatic MTC is extremely rare in patients with MEN2A aged ≤ 3 years, the ATA does not recommend surveillance in this patient population.

Lastly, we should solve the cost problem for children. In Japan, most medical expenses are covered by the universal healthcare insurance system. However, prophylactic surgery is not covered. This may be one reason why most children aged < 10 years do not undergo prophylactic resection [10]. This may have influenced the mean age at MTC-related death in patients with MEN2, i.e. 53 years [28], causing economic loss.

There is an obvious cost benefit for preventive removal. About 30 MEN2 patients were born yearly in Japan. If the gene mutation is already known, the cost of 1 exon is \$350 (1\$ = 110 JPY), and the total cost for 30 persons with autosomal dominant siblings without genetic mutation is about \$10,820. This is not high considering unnecessary surveillance. In addition, the fee for levothyroxine 100 μg per day per year comes to \$36 per person. When hypoparathyroidism occurs, the cost of 0.5 μg per day of alfacalcidol per year comes to \$198 per person. The monthly per capita expenditure for one person using vandetanib in the event of a recurrence is \$12,236.40 [29].

In countries similar to Japan that have cost problems with prophylactic thyroidectomy, early calcitonin level-based thyroidectomy not based on age is needed to reduce surgical delay and postoperative complications and improve prognosis in pediatric MEN2. This is because early thyroidectomy may improve the timing of surgery with a large heterogeneity in the age of onset and aggressiveness of MTC. A previous study reported that prognosis after disease onset is similar in high- and moderate-risk patients [30], even in MEN2B [31]. The penetration rate of MTC among individuals aged 50 years is 83% in high-risk patients [32], whereas it varies among those with a familial history of identical genetic mutations [22, 33].

Our study showed that, in patients with MEN2A, using ECLIA-based calcitonin measurements to speculate the onset allowed for earlier recognition of the disease when compared to the results of other studies. In our study, the cumulative incidence of CCH or MTC or first increased serum calcitonin reached 50% at the age of 5 years and 100% at the age of 9 years and reached 50% at the age of 8 years and 100% in moderate-risk patients

aged ≥ 17 years. A study in high-risk MEN2A patients who underwent surgery reported that CCH and MTC occurred at the ages of 6.9 years and 10.1 years on average, respectively [2]. For moderate-risk, another report showed that the cumulative incidence of MTC reached 50% in moderate-risk patients aged 13–18 years [9]. Reasons potentially explaining these differences are as follows. First, our study could not distinguish CCH or MTC in patients who did not undergo surgery. Second, there were differences in patient risks that were included. In our study, moderate-risk included only extracellular *RET* mutations that were classified as level B in the previous ATA guideline [4]. However, there may not be a strong selection bias. For example, in the German series, the prevalence of risk was determined as level B, that is higher risk in moderate-risk 144/567 (25.4%) or level A 163/567 (28.7%) [34], whereas in the Japan series, risk was level B 144/505 (28.5%) and level A 45/505 (8.9%) [11]. Lastly, as this study included patients without surgery, there is a possibility of false positives.

A study of medullary thyroid microcarcinoma in adults reported that lymph node metastases in the neck were observed in patients with calcitonin levels of 10–40 pg/mL , measured via the solid two-site immunoradiometric calcitonin assay [13]. Meanwhile, no recurrence was observed among children whose preoperative calcitonin level was < 30 pg/mL , as measured via immunoradiometric assays during long-term follow-up [35]. In our study, disease onset possibility was recognized starting at very low calcitonin levels (< 10 pg/mL). Thus, even in cases in which total thyroidectomy was performed at a higher age, the indication for surgery, i.e. the prevention of recurrence was still within that stipulated by the ATA.

The present study has many limitations, including its retrospective design and the small number of included cases due to the rarity of the disease. Moreover, the data were only collected from pediatricians and pediatric surgeons; thus, selection bias was unavoidable. The degree of progression in patients who did not undergo surgery was unclear, and the number of cases in which preoperative calcitonin levels were measured via the ECLIA was small. The calcium stimulation test is the only test used in Japan that is nonspecific compared to the pentagastrin stimulation test. Our study also included patients whose detailed clinical histories and prognoses were unavailable, due to changing hospitals or for other reasons, and the follow-up period was short; thus, the long-term prognosis related to recurrence could not be analyzed.

In conclusion, prophylactic thyroidectomy may be advantageous in patients with MEN2 as it can achieve a balance between a reduction of postoperative

complications and the risk of recurrence. However, considering the large heterogeneity in hereditary MTC, measuring calcitonin levels via the ECLIA can provide a clinical basis for early thyroidectomy in collaboration with various medical specialties and in consideration of the country's medical system.

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