European Journal of Surgical Oncology 45 (2019) 625–630

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Prophylactic thyroidectomy in multiple endocrine neoplasia 2 (MEN2) patients with the C634Y mutation: A long-term follow-up in a large single-center cohort

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ARTICLE INFO

Article history:
Received 9 March 2018
Received in revised form
12 July 2018
Accepted 4 September 2018
Available online 17 October 2018

Keywords:
Prophylactic
Thyroidectomy
MEN2
Medullary thyroid carcinoma

ABSTRACT

Background: Medullary thyroid carcinoma (MTC) is the main cause of death in multiple endocrine neoplasia 2A (MEN2A) patients. It is therefore important to treat this disease at an early stage. The mutation in codon 634 is considered to be associated with an aggressive clinical course, whereas the C634Y mutation may result in a more indolent course. Prophylactic thyroidectomy is performed before thyroid disease occurs. However, controversy surrounds this disease regarding levels of calcitonin (Ct) and age. In this context, few studies have investigated this mutation over a long period.
Objective: To analyze a large cohort of patients with the C634Y mutation who received prophylactic thyroidectomy.
Materials and methods: In a group of 110 MEN2 patients, we analyzed those with the C634Y mutation who had received prophylactic thyroidectomy (absence of clinical and radiological thyroid disease) treated in a tertiary referral hospital between 1983 and 2016. MTC is related to age and Ct. Statistical analysis was performed using the χ^2 test, partial correlations, and logistic regression.
Results: Fifty patients with a mean age of 12 ± 9 years were analyzed; 56% of these had MTC (100% stage I). There was no case of hypoparathyroidism or permanent recurrent damage. MTC was associated mainly with age (OR 1.38). One 5-year-old patient presented with MTC. Mean follow-up time was 16 ± 6 years, and no cases of recurrence were observed.
Conclusions: Performing prophylactic thyroidectomy in patients with the C634Y mutation allows us to cure the disease without causing long-term complications. Our results support the notion that age <5 years should be a criterion for carrying out prophylactic thyroidectomy in these patients.

Introduction

Medullary thyroid carcinoma (MTC) is caused by a germinal mutation in the *RET* proto-oncogene which forms part of multiple endocrine neoplasia syndrome 2 (MEN2) [1]. MTC is the main cause of death in patients with this syndrome [1,2], and so it is very important to treat it at an early stage. Over the course of this disease there is progression from normal thyroid tissue, passing through a preneoplastic period of C-cell hyperplasia (CCH), until hereditary MTC takes place [3]. It should be noted that there is a high incidence of lymph-node involvement in the phase during which MTC becomes established [4,5]. In fact, more than 50% of the patients with lymph-node involvement had recurrence of the disease and died as a consequence of their MTC [6]. It is therefore important to perform an early thyroidectomy to prevent the development of carcinoma and its complications. Furthermore, surgical treatment is the only curative treatment available [4].

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https://doi.org/10.1016/j.ejso.2018.09.002
0748-7983/

Prophylactic thyroidectomy is the term used to describe thyroidectomy in patients diagnosed with MEN2A who are asymptomatic at the time of diagnosis, with no thyroid disease according to clinical and radiological criteria [1]. The discovery in 1993 of the *RET* oncogene changed the way in which this disease was treated, as it became possible to carry out thyroidectomy in patients with this mutation before MTC could develop [1,2,7–9]. In this context we should pay particular attention to the controversy in recent years regarding prophylactic thyroidectomy in terms of levels of calcitonin (Ct) and the patient's age [10–15]. Currently, the American Thyroid Association (ATA) recommends carrying out thyroidectomy in MEN2 patients aged ≤5 years with the most common mutation (codon 634); the ATA also recommends central neck dissection (CND) when basal calcitonin (bCt) levels go above 40 pg/mL [1,16]. In the case of adults, CND is also recommended depending on the levels of bCt [16]. Previously, CND had been indicated in a general way in patients with above-normal levels of Ct and/or an age >10 years [2,17].

Most series show the results of the mutation in codon 634, with the amino acid Cys→Arg (C634R) mutation being predominant [18–20]. This mutation in codon 634 is considered aggressive, but the Cys→Tyr (C634Y) mutation, which is less common, could present a more indolent clinical course [21]. Long-term follow-up has not been carried out in most series of prophylactic thyroidectomies [10,11,22,23].

The objective of this study was to analyze the long-term results of a large cohort of MEN2 patients with the C634Y mutation who had undergone prophylactic thyroidectomy in a tertiary referral hospital, and to analyze the results in terms of age and Ct levels.

Materials and methods

Study population

In a group of 110 MEN2 patients we analyzed carriers of the C634Y mutation who had undergone a prophylactic thyroidectomy. All patients were treated between the years 1983 and 2016 at the Virgen de la Arrixaca University Hospital (Murcia, Spain).

Inclusion criteria

Patients who fulfilled the following prophylactic thyroidectomy criteria were included: (1) those who were asymptomatic at the time of diagnosis, with the absence of thyroid disease according to clinical and radiological criteria [1,10,11]; (2) those who had a normal result in the neck examination and did not have any signs of thyroid nodules or lymphadenopathy; and (3) patients with a neck ultrasound showing a normal thyroid gland or one with nodules <5 mm and the absence of suspicious nodes. In addition, we analyzed the subgroup of patients who were treated with prophylactic thyroidectomy, taking into account the criterion of age according to the recommendations valid at that time (age ≤5 years) [1,16].

Exclusion criteria

Patients who presented with clinical and/or radiological disease preoperatively were excluded, along with those who had a follow-up time of less than a year.

Variables analyzed

Variables analyzed included age at the time of thyroidectomy, gender, and other components of MEN2A syndrome (the presence of pheochromocytoma and/or hyperparathyroidism).

Blood levels of bCt and stimulated calcitonin (sCt) were taken (in some cases). For measuring sCt: after the measurement of bCt, pentagastrin was administered intravenously (0.5 mg/kg body weight; Pentavlon, ICI Pharma) in 20 s, or a 10% calcium gluconate solution was administered intravenously (2 mg/kg body weight) in 1 min; Ct blood samples were obtained at 2.5, 5 and 10 min. Until 2003, Ct was measured using radioimmunoassay (RIA; Incstar Corporation, Stillwater, MN, USA). In our laboratory the following normal values were established: bCt <100 pg/mL and sCt <250 pg/mL. From 2003 onwards the measurement of Ct has been carried out using chemiluminescence (immunoluminometric assay), with normal values set at <10 pg/mL for bCt and <100 pg/mL for sCt.

A total thyroidectomy was performed either with or without CND. The use of CND was adopted when patients had above-normal Ct levels and/or were aged >10 years [2,17]. Following the ATA recommendations in 2009, bCt levels had to be > 40 pg/mL for CND to be applied [1,16]. The same team of surgeons performed the thyroidectomy over the period of the study.

Histologically, the surgical samples were analyzed by two pathologists who were experienced in thyroid disease. The presence of MTC—characterized by the destruction of the follicular basement membrane and the diminished intensity of immunostaining or the presence of CCH—was determined by the presence of >50 C cells per low-amplification field (x100) in at least three optical fields. If MTC was present, the size of the dominant node was determined together with its multifocality. The presence or absence of lymphadenopathy was also determined in the cases with CND.

TNM tumor staging was based on the classification proposed by the American Joint Committee on Cancer (AJCC) [24]. In cases in which more than one tumor coexisted, the size of the largest tumor was the one taken into account.

Postsurgical complications (hypoparathyroidism and/or permanent recurrent lesion) were determined.

In all the patients, periodic examinations of Ct levels were taken after the surgery. Follow-up examinations were carried out at 1 month after surgery and every 6 months thereafter. At a later stage, this was changed to an annual follow-up. The cure and recurrence rate were assessed in the patients who presented with MTC, and the disease was considered to be cured when the patient had Ct levels within a normal range in the most recent consultation. Mortality was also determined in these patients.

An analysis was carried out concerning the relationship between the development of MTC and both age and Ct levels.

Statistical methods

SPSS statistics software was used (version 21.0; SPSS Inc. Chicago, Illinois, USA). A descriptive analysis was carried out. In order to test the independence of the two qualitative variables, asymptotic χ^2 analysis was used, and Fisher's exact test was applied when the expected frequencies were <5 in more than 20% of the boxes in the tables. In order to test the equality of means of the quantitative variables in two groups, normality was previously confirmed using the Kolmogorov–Smirnov test, and when there was rejection, Mann–Whitney's *U* test was used.

Table 1
Epidemiological, clinical, histological and follow-up characteristics of patients with prophylactic thyroidectomy according to clinical and radiological criteria in patients with C634Y mutation.

Nº	Age	Gender	Mutation	Ctb*	Ctp*	Surgery	Histology	T	MF	B	TNM	Follow-up	Ctbf
1	4	M	Tyr	10 (N)		TT	CCH				Pre	4	4,2
2	4	M	Tyr	9,5 (N)		TT	CCH				I	5	6,3
3	4	M	Tyr	8,7 (N)		TT	CCH				Pre	6	7,4
4	4	F	Tyr	12,4 (N)	243 (N)	TT	CCH				Pre	15	4,1
5	4	F	Tyr	7,3 (N)	90 (N)	TT	CCH				Pre	12	7,9
6	5	M	Tyr	8 (N)	95 (N)	TT	MTC	0,3	x	x	I	16	3
7	5	F	Tyr	74 (N)	111 (N)	TT	CCH				Pre	15	8,6
8	5	M	Tyr	7,7 (N)		TT	CCH				Pre	2	9,0
9	5	F	Tyr	129 (E)	225 (E)	TT+CND	CCH				Pre	12	8,6
10	6	F	Tyr	7,6 (N)		TT	Normal				Pre	5	5,4
11	6	F	Tyr	9 (N)		TT	MTC F L	0,2			I	3	5
12	6	M	Tyr	10 (N)	152 (N)	TT	CCH				Pre	15	9
13	7	M	Tyr	10 (N)	52 (N)	TT	CCH				Pre	15	7,8
14	7	M	Tyr	60 (N)	150 (N)	TT	MTC	0,2	x	x	I	16	4
15	6	F	Tyr	82 (N)	121 (N)	TT	CCH				Pre	16	7,6
16	6	M	Tyr	12 (N)	13 (N)	TT	CCH				Pre	16	7,5
17	6	M	Tyr	10 (N)	67 (N)	TT	MTC F L	0,4			I	16	6,2
18	6	F	Tyr	75 (N)	163 (N)	TT	MTC	1	x	x	I	16	4,6
19	9	M	Tyr	12,6 (N)	17 (N)	TT	CCH				Pre	10	7,7
20	9	M	Tyr	19 (N)	120 (N)	TT	MTC F R	0,3			I	21	9,2
21	12	F	Tyr	22 (N)	64 (N)	TT+CND	MTC	1	x	x	I	18	9,8
22	12	M	Tyr	28 (N)	67 (N)	TT+CND	MTC F L	0,2			I	19	17
23	11	F	Tyr	41 (N)	137 (N)	TT+CND	MTC	0,3	x	x	I	19	5
24	12	M	Tyr	26 (N)	44 (N)	TT+CND	MTC	1	x	x	I	19	8,9
25	17	F	Tyr	51 (N)	93 (N)	TT+CND	MTC	0,6	x	x	I	19	4,8
26	12	F	Tyr	33 (N)	180 (N)	TT+CND	MTC	0,6	x	x	I	14	7,2
27	8	F	Tyr	84 (N)	134 (N)	TT	MTC	0,5		x	I	17	3,5
28	9	F	Tyr	49 (N)	227 (N)	TT	MTC	0,2	x	x	I	18	7,3
29	9	M	Tyr	27 (N)	80 (N)	TT	MTC F L	0,3			I	18	9,1
30	10	M	Tyr	39 (N)	99 (N)	TT	CCH				Pre	18	8
31	8	F	Tyr	23 (N)	184 (N)	TT	MTC F R	0,2			I	19	6,2
32	9	F	Tyr	9,3 (N)	14 (N)	TT	CCH				Pre	18	3,1
33	14	M	Tyr	30 (N)	213 (N)	TT+CND	MTC	0,4	x	x	I	19	6,7
34	11	M	Tyr	15 (N)	134 (N)	TT+CND	CCH				Pre	18	9,2
35	10	F	Tyr	19 (N)	38 (N)	TT	CCH				Pre	20	8,9
36	14	M	Tyr	31 (N)	59 (N)	TT+CND	CCH				Pre	21	5
37	12	M	Tyr	55 (N)	65 (N)	TT+CND	CCH				Pre	21	41
38	28	M	Tyr	82 (N)	496 (E)	TT+CND	MTC	0,7	x	x	I	18	7,2
39	25	F	Tyr	12 (N)	264 (E)	TT+CND	MTC L	0,7	x		I	18	9,5
40	18	F	Tyr	47 (N)	285 (E)	TT+CND	MTC	0,6	x	x	I	20	9
41	42	F	Tyr	242 (E)	320 (E)	TT+CND	MTC	0,9	x	x	I	20	6,8
42	30	M	Tyr	25 (N)	280 (E)	TT+CND	MTC	0,2	x	x	I	22	9,8
43	40	M	Tyr	88 (N)	384 (E)	TT+CND	MTC	1	x	x	I	22	9,4
44	17	F	Tyr	115 (E)	707 (E)	TT+CND	MTC	0,3	x	x	I	24	8,4
45	19	M	Tyr	10 (N)	440 (E)	TT+CND	MTC	0,3	x	x	I	24	7,9
46	10	F	Tyr	96 (N)	509 (E)	TT+CND	MTC	0,5	x	x	I	17	4,5
47	22	F	Tyr	29 (E)	338 (N)	TT	MTC F R	0,5			I	2	9,2
48	14	F	Tyr	40 (N)	355 (E)	TT+CND	MTC	0,3	x	x	I	21	6,2
49	6	M	Tyr	39 (E)	117 (N)	TT+CND	CCH				Pre	12	9,6
50	7	F	Tyr	60 (N)	273 (E)	TT+CND	CCH				Pre	15	9,2

Nº: number of patient. F: female. M: male. Tyr: tirosine. Ctb: levels of basal calcitonin. Ctp: levels of stimulated calcitonin. *Until the year 2003, Ct had been measured using radioimmunoassay (RIA). The following normal values were established: bCt <100 pg/mL, and pCt, <250 pg/mL. Since the year 2003 (inclusive) the measurement of Ct has been carried out using chemoluminescence (immunoluminometric assay), with normal values set at bCt <10 pg/mL, and pCt, <100 pg/mL. N: Ct normal value, E: Ct value elevated.
TT: total thyroidectomy. CND: central neck disection. CCH: C-cell hiperplasia. MTC: medullary thyroid carcinoma. F: focal. R: right. L: left. T: tumor size. MF: multifocal. B: bilateral. (TNM classification) Pre: pre-tumoral. I: stage 1. Follow-up (years). Ctbf: last level of basal calcitonin in the follow-up.

The statistically significant variables ($p < 0.05$) in the bivariate analysis were taken to calculate the partial correlations, and a logistic regression model was adjusted to obtain the odds ratio.

Results

Patients with the C634Y mutation who underwent a prophylactic thyroidectomy according to clinical and radiological criteria

From the year 1983 until 2015 a total of 50 patients were recorded with criteria for prophylactic thyroidectomy (Table 1). At the time of the thyroidectomy, the patient's mean age was 12 ± 9 years, with a range of 4–42 years. Half of them ($n = 25$) were males. With regard to other components of MEN2A, 13 patients (26%) were treated for pheochromocytoma and one patient (2%) was treated for hyperparathyroidism.

With regard to the blood test, five patients (10%) had above-normal levels of bCt. Three of these patients (operated on before the year 2003) had the following values: 129, 242 and 115 pg/mL (0–100 pg/mL). The other two (treated after 2003) had Ct levels of 39 and 29 pg/mL (0–10).

Regarding the surgical treatment used, 27 patients (54%) were

Table 2
Development of MTC according to age, gender and Ct levels.

	CCH (n = 22)	MTC (n = 28)	p
Age at the time of the thyroidectomy:	7 ± 3 years	15± 10 years	**<0.001**
Ct levels	19 (53%)	17 (47%)	**0.045**
Within normal levels (n = 36)	3 (21%)	11 (79%)	
Above normal levels (n = 14)			

MTC: medullary thyroid carcinoma. CCH: C cell hyperplasia. Ct: calcitonin.
p < 0.05: statistically significant.

Table 3
Partial correlations between the variables: age and Ct levels.

Controlled by		Correlation	p
Ct levels	Age-MTC	0.407	**0.004**
Age	Ct levels-MTC	0.027	0.856

MTC: medullary thyroid carcinoma. Ct: calcitonin.
p < 0.05: statistically significant.

given a total thyroidectomy, and 23 (46%) received an associated CND. In these cases no pathological lymphadenopathy was found, and all the patients who had MTC were at stage 1.

In the histological analysis, 22 patients (44%) had only CCH, and 28 (56%) had already developed MTC. Of the latter group, 20 patients had a multifocal MTC (71%). Mean tumor size was 4 ± 3 mm (100% with a size of <10 mm).

As for postoperative complications, there were no cases of hypoparathyroidism or permanent recurrent damage in any of the 50 patients treated.

Relationship between MTC and age at the time of thyroidectomy and Ct levels

The development of MTC was significantly associated with age (7 ± 3 versus 15 ± 10 years, respectively; p < 0.001) and with Ct levels; an above-normal Ct level was associated with a greater development of MTC (79% versus 47% at normal levels of Ct; p = 0.045) (Table 2). However, on analyzing the partial correlations, it was seen that age persisted as a significant variable (controlling the variable of Ct; p = 0.004) (Table 3).

When we carried out a logistic regression analysis to estimate the risk of developing MTC, it was seen that for every extra year of age, the risk of developing MTC was multiplied by 1.388 (Table 4).

Follow-up

The mean follow-up time of the patients was 16 ± 6 years, with a range of 1–24 years. During the follow-up no case of recurrence was found, and currently all patients have been cured with a survival rate of 100%.

Prophylactic thyroidectomy also taking into account the criterion of age (≤5 years)

This corresponded to the nine initial patients in Table 1. One of these, a 5-year-old child, presented with MTC. Another of these patients presented with above-normal bCt levels (129 pg/mL, 0–100), but did not present with MTC in the histological analysis.

Discussion

The importance of prophylactic thyroidectomy in MEN2 syndrome rests on its ability to prevent the development of the disease [25,26]. Once MTC has developed, it has been seen how tumor sizes of >1 cm affect the disease-free rate [27] and can lead to a higher recurrence rate in patients at more advanced stages with nodal metastasis [26].

This study included a large cohort of 50 patients with the C634Y mutation who underwent prophylactic thyroidectomy; the mean follow-up time was 16 years with a maximum follow-up of 23 years. The mutation in codon 634 is the most prevalent in most series [18,19,28–31], but the C634R mutation is the dominant one [18–20]. The sample of patients in our series is the largest found in the literature, involving 50 subjects with the C634Y mutation who had received a prophylactic thyroidectomy.

Mutations in MEN2 syndrome are divided into the following risk groups: (1) highest risk: M918T (MEN2B); (2) high risk: C634F/G/R/S/W/Y and A883F; and (3) moderate risk: G533C, C609F/G/R/S/Y, C611F/G/S/Y/W, C618F/R/S, C620F/R/S, C630R/Y, D631Y, K666E, E768D, L790F, V804L, V804M, S891A, and R912P [16]. It has been demonstrated that the 634 mutation is considered 'high-risk' [16], being related to the progression from CCH to CMT in proportion to increase in age [20,28,32,33]. In light of this, it is currently recommended that prophylactic thyroidectomy be carried out in these patients before the age of 5 [2,16,34].

Previous studies have already described a more aggressive MTC in the C634R mutation [21]. Nevertheless, the present study shows that more than half of the patients with this mutation had already developed MTC which was multicentric in 71% of cases.

In the analysis of the factors affecting the development of MTC, age persists as an independent factor in the multivariate analysis. Age is a factor related to progression from CCH to CMT [3,20,35,36], as well as to the presence of metastasis [29] and disease persistence or recurrence [28]. In our experience, it has been shown that the age of patients who have already developed MTC differs significantly from that in patients with CCH. Importantly, we have found that the probability of developing MTC reaches 23% at the age of 5, as can be deduced from Table 4. In fact, one of our 5-year-old patients had already developed MTC. These findings would support the recommendations of the ATA to carry out thyroidectomy in

Table 4
Logistic regression analysis.

VARIABLES	Regression coefficient (β)	Standard Error	Odds Ratio (Confidence intervals)	p
Age:	0.328	0.109	**1.388** (1.049–1.525)	**0.003**
Ct levels:	−0.187	1.026	0.829 (0.928–19.589)	0.855
Constant	−2.821	0.969	0.060	0.004

Ct: calcitonin.
P < 0.05: statistically significant.

patients with the Tyr mutation before the age of 5 [16].

In the case of adults, on the other hand, the criterion for prophylactic thyroidectomy that the ATA puts forward seems questionable, being recommended according to Ct levels [16]. Elisei et al. also tend to prefer to carry out thyroidectomy when levels of bCt increase, regardless of age [37]. However, it should be noted that all the patients with this mutation were eventually operated on, and, given the relationship between age and MTC in this series, it would seem to be necessary to carry out a total thyroidectomy in all patients with this mutation. Having said that, it is true that Ct levels are also related to the development of MTC [38]. Recent studies have revealed the importance of Ct levels in the evolution of the disease, regardless of the mutation and age [37,39]. Machens et al. have reported that when bCt rises, there is the possibility of the patient having MTC with nodal metastasis [26,40].

The data in this study reflect how Ct affects the appearance of MTC. However, it has also been seen that if we control the variable of age, Ct is no longer a significant factor. Only five patients had above-normal levels of bCt, and they were in a range that was slightly high, something that could have affected the results.

Another aspect is the recommendation of an associated prophylactic CND. The performance of CND can involve complications such as hypoparathyroidism or recurrent lesion [32]. Some authors perform CND systematically [17,21]. In the series presented by Dralle et al. none of the patients aged <14 years had lymphadenopathy [17]. Therefore, they only considered the recommendation of CND in cases >10 years. This was similarly established in the first consensus guide on prophylactic thyroidectomy in 2001 [2], in which it was indicated that CND should not be performed in younger patients if they have normal Ct levels. This is the criterion that our group followed in a general way until the recommendations of 2009 [1]. However, positive lymphadenopathy did not occur in any of the 23 cases in which CND was carried out, so that these data do not support the recommendations of 2001 to carry out CND in older patients, especially if it is taken into account that 63% of the patients had an age $\geq$10 years.

The long follow-up time of these patients allows us to evaluate the results in terms of their long-term prognosis. The majority of previous studies show follow-up times of <10 years [10,22,23], and this makes it difficult to assess the results.

To conclude, performing prophylactic thyroidectomy in MEN2A patients with the C634Y mutation allows us to cure the disease without causing any long-term complications. Moreover, our results support the notion that an age of <5 years should be considered as a criterion for prophylactic thyroidectomy in these patients.

Conflict of interest

There is not conflict of interest.

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