

# Prophylactic thyroidectomy in ethnic Chinese patients with multiple endocrine neoplasia type 2A syndrome after the introduction of genetic testing

CME

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**Objective** To evaluate the impact of genetic testing in the management of familial multiple endocrine neoplasia 2A patients.

**Design** Retrospective study.

**Setting** University teaching hospital, Hong Kong.

**Patients** Twenty-two patients from eight multiple endocrine neoplasia 2A families underwent prophylactic total thyroidectomy based on a positive RET mutation genetic testing. All mutations were located at codon 634 of exon 11. Nineteen patients had preoperative basal serum calcitonin measured, and the 12 with normal levels had pentagastrin stimulation tests. Preoperative thyroid ultrasound examination was performed for 17 patients.

**Results** There were 13 females and 9 males with a median age of 25.1 (range, 6.1-71.9) years. Histopathology revealed medullary thyroid carcinoma in 17 (77%), C-cell hyperplasia in four (18%), and normal pathology in one (5%) of the patients. Five patients with either C-cell hyperplasia or normal pathology were among the youngest (age range, 6-9 years). The youngest patient with medullary thyroid carcinoma was nearly 9 years old. The median size of medullary thyroid carcinomas was 8.3 (range, 0.1-18) mm, but there were no lymph node metastases. Of 15 patients with normal basal calcitonin levels, 10 had medullary thyroid carcinoma, though two tested negative with the pentagastrin-stimulated calcitonin assay. Five of six patients with normal preoperative ultrasonographic examinations had medullary thyroid carcinoma. Three (14%) of the patients were prescribed long-term calcium and vitamin D supplementation. After a median follow-up of 49 (range, 13-128) months, no patient had recurrence of medullary thyroid carcinoma.

**Conclusions** Genetic testing has replaced conventional biochemical and radiological modalities to identifying multiple endocrine neoplasia 2A carriers, in order to offer them prophylactic thyroidectomy. Chinese multiple endocrine neoplasia 2A patients with codon 634 mutation seem to have less aggressive forms of medullary thyroid carcinoma, for whom prophylactic thyroidectomy can be considered at the age of 8 years.

## Key words

Genetic screening; Multiple endocrine neoplasia type 2a; Proto-oncogene proteins c-ret; Thyroid neoplasms; Thyroidectomy

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## Introduction

Multiple endocrine neoplasia type 2A (MEN2A) is an autosomal dominant disorder associated with the occurrence of medullary thyroid carcinoma (MTC), pheochromocytoma and parathyroid hyperplasia. The penetrance is almost 100% for MTC while approximately 50% and 30% of patients will develop subsequent pheochromocytomas and hyperparathyroidism, respectively.<sup>1-4</sup>

Medullary thyroid carcinoma remains a major cause of death in MEN2A patients.<sup>5</sup> Before the introduction of genetic screening for the RET proto-oncogene, the diagnosis was usually delayed and led to frequent presence of nodal and distant metastases on presentation. Cancer-related mortality occurred in up to 15 to 20% of these patients.<sup>6,7</sup> Moreover, biochemical surveillance based on stimulated calcitonin for early diagnosis was associated with false-negative and false-positive results. In addition, the test was unpleasant and troublesome and needed to be repeated regularly for all at-risk patients. With the

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availability of accurate genetic testing, prophylactic thyroidectomy can now be offered to all asymptomatic RET proto-oncogene carriers.<sup>5,8-10</sup> Furthermore, with a better understanding of the genotype-phenotype correlation, for 'high-risk' carriers with codon 611, 618, 620, or 634 mutations, it is now recommended that the operation should be offered as early as the age of 5 years.<sup>8,11</sup> This advice was based on the fact that invasive MTC rarely developed earlier, but the recommendation provoked controversy because of the increased potential for surgical complications, parental concerns, and problems related to long-term drug compliance.<sup>12,13</sup>

Clinicopathological features of ethnic Chinese patients with MEN2A syndrome have been reported, but the impact of genetic testing and the recommendation for the optimal timing of prophylactic thyroidectomy have not been addressed.<sup>14,15</sup>

The present study aimed at reviewing our experience of prophylactic thyroidectomy in asymptomatic MEN2A carriers after the introduction of genetic testing for the RET proto-oncogene, and to make recommendations on the optimal age for prophylactic thyroidectomy for our Chinese MEN2A patients.

## Methods

### Subjects

Since 2005, a territory-wide registry for patients with hereditary endocrinopathy has been established at our institution. Patients from families with suspected or documented MEN2 syndrome were managed by a multidisciplinary team, including endocrine surgeons, endocrinologists, radiologists, endocrine pathologists, and clinical oncologists. All the patients were followed up in the special clinic at our institution and genetic testing was performed in our research laboratory. To date, our registry has identified a total of eight MEN2A families. Molecular testing for the RET germline mutation was performed in 79 at-risk or affected individuals from these families, after they had received genetic counselling; and 40 were confirmed to have a germline mutation in the RET proto-oncogene. Thyroidectomy was performed on a prophylactic basis for 22 genetic carriers who were completely asymptomatic and had no clinical evidence of MTC. They included 13 women and nine men. At the time of surgery, their median age was 25.1 years (range, 6.1-71.9) years.

### Genetic testing

All patients and/or their legal guardians gave written consent, in accordance with the requirements of our institutional ethics committee. Blood samples were

## 遺傳檢測後為多發性內分泌腫瘤2A型的華籍患者進行預防性甲狀腺切除術

**目的** 檢討遺傳檢測對多發性內分泌腫瘤2A型患者的影響。

**設計** 回顧研究。

**安排** 香港一所大學教學醫院。

**患者** 本研究對象為接受RET原致癌基因檢查而呈陽性反應的22位多發性內分泌腫瘤2A型患者，他們來自八個家庭，並已接受預防性全甲狀腺切除術。所有患者的基因突變位置都在exon 11的codon 634上。19位術前接受血降鈣素濃度測試中，12位有正常濃度的患者進行五肽胃泌素激發測試。另為17位患者進行術前甲狀腺超聲波檢查。

**結果** 13位女性及9位男性患者的年齡中位數為25.1（介乎6.1至71.9）歲。組織病理學顯示17人（77%）有甲狀腺髓質癌，其餘4人（18%）有C細胞增生，另1人（5%）屬正常；這5位是22位病人中最年青的（介乎6至9歲）。甲狀腺髓質癌患者中，年紀最小為9歲；髓質癌的大小中位數為8.3 mm（介乎0.1至18 mm），沒有出現淋巴結轉移。15位有正常血降鈣素濃度的患者中，10位有甲狀腺髓質癌，縱然2位的五肽胃泌素激發測試結果呈陰性。6位甲狀腺超聲波檢查屬正常的病人中，5位有甲狀腺髓質癌。3位（14%）病人要長期服食鈣及維他命D補充劑。中位數為49個月（介乎13至128個月）的隨訪期內，沒有病人出現甲狀腺髓質復發。

**結論** 為了讓多發性內分泌腫瘤2A型的患者進行預防性甲狀腺切除術，遺傳檢測已取代傳統的生化及放射性檢查方法。基因突變位置為codon 634的華籍患者，似乎其多發性內分泌腫瘤都屬非惡性的，這種情況下，可考慮在當患者8歲時施行預防性甲狀腺切除術。

obtained from at-risk family members by peripheral veni-puncture. Genomic DNA was prepared from peripheral blood leukocytes by standard procedures, and RET mutations were screened for by restriction enzyme digestion and/or direct sequencing, as described previously.<sup>14</sup>

### Preoperative evaluation and surgery

Before surgery, all confirmed RET mutation carriers were advised to undergo a complete physical examination, and measurement of basal and stimulated plasma calcitonin, as well as serum-adjusted calcium and parathyroid hormone levels. At least two samples of 24-hour urinary fractionated catecholamines were assayed for patients older than 16 years to rule out a concomitant pheochromocytoma. Before the operation, ultrasonography (USG) of the thyroid gland was also recommended for all confirmed RET carriers. For those with biochemical or imaging evidence of MTC, in addition to 'prophylactic' total

TABLE. The clinical, biochemical, and molecular features of the 22 asymptomatic multiple endocrine neoplasia type 2A patients who underwent prophylactic thyroidectomy\*

Patient No.	Age at operation (years)	RET mutation	Basal calcitonin (pmol/L) <sup>†</sup>	Peak calcitonin (pmol/L)	Positive SCT response	USG nodule	Histology	Lymph node metastasis	Calcium supplement	Follow-up period (months)
1	6.1	C634W	1.8	1.7	No	Yes	CCH	No	No	14
2	6.3	C634Y	1.6	1.8	No	Yes	CCH	0/2	Yes	13
3	7.1	C634Y	0.0	0.36	No	Yes	CCH	0/4	Yes	13
4	8.6	C634W	0.38	0.38	No	Yes	Normal	No	No	13
5	8.9	C634Y	1.1	1.5	No	No	CCH	0/2	No	13
6	8.6	C634R	3.1	35.0	Yes	No	MTC 0.1 mm	No	No	49
7	10.7	C634Y	4.1	4.6	No	-	MTC 3.4 mm	No	Yes	13
8	12.3	C634Y	1.2	2.9	No	No	MTC 1.8 mm	0/3	No	15
9	11.9	C634Y	-	-	-	Yes	MTC 5 mm	No	No	50
10	18.4	C634R	8.4	-	-	-	MTC 12 mm	0/1	No	88
11	20.1	C634Y	0.44	6.5	Yes	No	MTC 15 mm	No	No	50
12	25.4	C634Y	1.6	-	-	No	MTC in-situ	0/5	No	14
13	28.0	C634G	0.5	44.0	Yes	No	MTC 0.1 mm	No	Yes	53
14	32.1	C634G	6.5	109.0	Yes	Yes	MTC 5 mm	0/3	Yes	101
15	33.1	C634G	1.1	53.0	Yes	Yes	MTC 3 mm	0/2	Yes	52
16	34.0	C634Y	122.0	3900.0	Yes	-	MTC 15 mm	No	No	48
17	34.8	C634Y	-	-	-	-	MTC 15 mm	No	No	128
18	41.0	C634R	4.0	72.0	Yes	Yes	MTC 4 mm	No	Yes	118
19	41.9	C634W	-	-	-	Yes	MTC 8 mm	0/17	No	45
20	41.4	C634Y	4.0	-	-	-	MTC 18 mm	No	Yes	56
21	50.7	C634Y	693.0	930.0	No	Yes	MTC 10 mm	0/3	No	57
22	71.9	C634R	4.9	-	-	Yes	MTC 8 mm	0/1	No	83

\* SCT denotes stimulated calcitonin test, USG ultrasonography, CCH C-cell hyperplasia, and MTC medullary thyroid carcinoma

<sup>†</sup> Normal level: <6.0 pmol/L

thyroidectomy, a unilateral central compartment (level VI) neck dissection was also performed.

levels of more than 12 months after the operation.

**Follow-up**

All patients received lifelong thyroxine replacement after surgical treatment and were followed up regularly in our special clinic. Follow-up visits were arranged at 3-monthly interval in the first 2 years, 6 monthly for the subsequent 3 years, and annually thereafter. Clinical examinations, basal plasma calcitonin, serum calcium and thyroid function tests were performed during follow-up visits. A stimulated calcitonin assay was selectively repeated for those with abnormal findings before surgical treatment. Cervical USG was performed annually to look for potential local/regional recurrence. Patients with undetectable calcitonin levels and normal USG findings were regarded as disease-free. Postoperative hypoparathyroidism was regarded as permanent if calcium and/or vitamin D analogues were required to maintain normocalcaemia in the presence of subnormal or undetectable parathyroid hormone

**Results**

The Table shows the clinical, biochemical, and molecular features of the 22 RET proto-oncogene carriers who underwent prophylactic thyroidectomy based on positive genetic testing. All the RET mutations were located at codon 634. The specific identified RET mutations were as follows: C634Y (12 patients; 55%), C634R (4 patients; 18%), C634W (3 patients; 14%), and C634G (3 patients; 14%). Three (14%) patients were identified to have had pheochromocytomas, and adrenalectomy was performed 3.8 years, 7 months, and 3 months before their prophylactic total thyroidectomy. One of these three patients had a malignant pheochromocytoma extending to the right atrium and was previously reported.<sup>16</sup> Two patients underwent concomitant parathyroidectomy at the time of prophylactic thyroidectomy because of hypercalcaemia and parathyroid hyperplasia. One had a subtotal parathyroidectomy, while the other had a total parathyroidectomy and forearm

reimplantation.

### Laboratory and ultrasonographic findings

Nineteen patients had preoperative plasma basal calcitonin measured, of whom 15 had normal levels. All four patients with an elevated basal calcitonin level had MTC, while 10 (67%) of 15 with normal basal calcitonin levels also had MTC. Five (33%) of the 15 patients with normal calcitonin levels had a positive calcium-pentagastrin test and an invasive MTC, whilst among the remaining seven with normal basal calcitonin level and negative calcium-pentagastrin test results, three had MTC on histological examination. Ultrasonography of the thyroid gland was performed in 17 patients. Five (83%) of six patients with a normal USG examination subsequently turned out to have MTC, as did seven of the 11 with one or more thyroid nodules detected preoperatively.

### Thyroid gland pathology

Histological examination of the resected thyroid gland showed normal pathology in one (5%), C-cell hyperplasia in four (18%), and MTC in 17 (77%) patients. Twelve (55%) patients had concomitant C-cell hyperplasia associated with the invasive carcinoma. C-cell hyperplasia or a normal thyroid gland without invasive MTC was encountered in the five youngest patients, with a median age of 7.1 (range, 6.1-8.9) years. The youngest patient with MTC identified was 8.6 years old. The mean MTC tumour size on histological section was 8.3 mm (range, 0.1-18 mm). Central lymph node dissection was performed in 11 (50%) of the 22 patients but none was found to have metastasis.

### Surgical outcome and follow-up data

Postoperative laryngoscopic examination did not reveal any vocal cord paralysis. Eight patients developed postoperative hypocalcaemia for which both oral calcium and vitamin D supplementation was given, in three (14%) of whom the supplements became permanent. During a median follow-up of 49 (range, 13-128) months, pheochromocytoma was diagnosed in five of the patients through urinary screening of fractionated catecholamines, and after localisation with imaging they underwent adrenalectomy. In addition to the three patients who presented with pheochromocytoma as their initial manifestation, five others developed pheochromocytoma later during the course of their disease. At the time of analysis, two (9%) additional patients had mild hyperparathyroidism and were being managed expectantly. At 1-year follow-up, one paediatric patient had fluctuating thyroid function test results, despite good thyroxine compliance

with replacement. After a median follow-up of 49 months, no patient had any clinical, biochemical, or ultrasonographic evidence of MTC recurrence.

### Discussion

Invasive MTC invariably develops in all patients with MEN2A. Since these tumours tend to metastasise early and are both chemo- as well as radio-resistant, early prophylactic surgery remains the only curative option.<sup>17</sup> Graze et al<sup>18</sup> showed that selection of affected kindred for prophylactic thyroidectomy through identification by calcitonin testing alone resulted in discovery of primary tumours of smaller size (0.2 cm vs 0.8 cm), fewer bilateral tumours (13% vs 100%), and fewer patients with lymph node metastases (0% vs 58%). With recent introduction of RET proto-oncogene testing for the accurate identification of gene carriers, prophylactic thyroidectomy can be offered to asymptomatic affected individuals at the stage of pre-malignant C-cell hyperplasia before the histological occurrence of invasive MTC.<sup>5,8-10</sup>

Our study confirmed that neither traditional biochemical tests with pentagastrin-stimulated calcitonin assay nor radiological imaging with USG could reliably predict the occurrence of invasive MTC. Two thirds (10/15) of the patients with normal preoperative basal calcitonin levels had MTC on final histology. Although the accuracy of the calcitonin assay improved with pentagastrin stimulation, three (20%) of the 15 patients with normal results harboured MTC in their thyroidectomy specimens. Preoperative USG imaging to identify invasive MTC was also inaccurate. Five (83%) of six patients with normal USG had MTC histologically. Even when combined with the pentagastrin-stimulated calcitonin assay, the false-negative rate remained at 50%, of which the finding was consistent with results reported from previous studies.<sup>19-21</sup>

Although the role of RET proto-oncogene genetic testing to facilitate the identification of gene carriers for prophylactic surgery is not in dispute, the most appropriate timing for the operation remains controversial. Ideally it should be before the development of invasive MTC (at the stage of pre-malignant C-cell hyperplasia) and lymph node metastasis. Too early or overly aggressive surgical treatment, however, could be associated with an increased surgical morbidity and the issue of long-term drug compliance.<sup>17,22</sup> A recent territory-wide multi-centre study reported by Bergenfelz et al<sup>23</sup> highlighted these issues. They reported a 3.9% rate of vocal cord paresis, and 4.4% rate of hypocalcaemia for which the patients were receiving calcium and/or vitamin D supplements at 6 months. Also in a recent review of 41 MEN2A patients aged less than 25 years who underwent thyroidectomy, 29% had permanent hypoparathyroidism.<sup>13</sup> In our

study, although none of the subjects suffered from postoperative vocal cord paresis, three (14%) of 22 had permanent hypocalcaemia, two of whom were among the youngest patients (<8 years). Further improvement in outcomes in terms of decreased incidence of hypocalcaemia in this growing age-group would be of benefit for patients undergoing prophylactic thyroidectomy. In terms of long-term drug administration and compliance, two of the nine patients below the age of 18 years had fluctuating thyroid function test results on follow-up, mostly with persistently elevated thyroid-stimulating hormone levels. In this age-group, the changing requirement of thyroxine during growth and development, as well as long-term compliance with thyroxine replacement, also needs further evaluation.

The application of 'codon-directed' guidelines for management of MEN2A patients apparently originated from the West. The objective of the present study was to identify any potential differences with respect to this genetic disease in our population. Based on the international consensus statement in 2001,<sup>11</sup> all our 22 patients (with codon 634 mutation) belonged to the 'high-risk' group, for which surgery was recommended before the age of 5 years in order to avoid the occurrence of invasive MTC. In our series, the earliest age for positive identification of MTC development in our MEN2A patients was 8 years, while four other younger patients were confirmed to have either normal histology or C-cell hyperplasia. Based on our experience, and taking into consideration the problems emanating from surgery in very young patients as well as the need to take long-term thyroxine, it might be worth considering prophylactic thyroidectomy at the age of 8 rather than 5 years. In

addition, despite the 'prophylactic' operation being performed in patients up to 71 years old and a tumour size of 1.8 cm (owing to genetic study at a delayed stage), none of our patients were identified to have lymph node metastases and all have remained free of disease till their latest follow-up. Our findings should be interpreted cautiously however, as the number of patients studied was relatively small, whilst in other populations undergoing prophylactic thyroidectomy, invasive MTC has been reported in patients as young as 17 months.<sup>24,25</sup> In summary, although our ethnic Chinese MEN2A patients with codon 634 mutation appeared to be suffering from a less aggressive form of MTC, a prospective study involving a larger number of ethnic Chinese patients is required.

## Conclusions

Genetic RET proto-oncogene testing has replaced traditional biochemical tests and imaging to facilitate decisions about prophylactic thyroidectomy in MEN2A families. To prevent the development of invasive MTC, our experience in the management of local MEN2A patients suggests resorting to prophylactic thyroidectomy for these children possibly at the age of 8 years or younger. The risk of permanent hypoparathyroidism and the issue of early long-term thyroid function and replacement therapy remain a concern in this group of young children.

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## References

- Vasen HF, Nieuwenhuijzen Kruseman AC, Berkel H, et al. Multiple endocrine neoplasia syndrome type 2: the value of screening and central registration. A study of 15 kindreds in The Netherlands. *Am J Med* 1987;83:847-52.
- Howe JR, Norton JA, Wells SA Jr. Prevalence of pheochromocytoma and hyperparathyroidism in multiple endocrine neoplasia type 2A: results of long-term follow-up. *Surgery* 1993;114:1070-7.
- Skinner MA. Management of hereditary thyroid cancer in children. *Surg Oncol* 2003;12:101-4.
- Danko ME, Skinner MA. Surgical intervention in children with multiple endocrine neoplasia type 2. *Curr Opin Pediatr* 2006;18:312-5.
- Skinner MA, Moley JA, Diley WG, Owzar K, Debenedetti MK, Wells SA Jr. Prophylactic thyroidectomy in multiple endocrine neoplasia type 2A. *N Engl J Med* 2005;353:1105-13.
- Kakudo K, Carney JA, Sizemore GW. Medullary carcinoma of thyroid. Biologic behavior of the sporadic and familial neoplasm. *Cancer* 1985;55:2818-21.
- Moley JF, DeBenedetti MK. Patterns of nodal metastases in palpable medullary thyroid carcinoma: recommendations for extent of node dissection. *Ann Surg* 1999;229:880-8.
- Eng C, Clayton D, Schuffenecker I, et al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. International RET mutation consortium analysis. *JAMA* 1996;276:1575-9.
- Machens A, Ukkat J, Brauckhoff M, Gimm O, Dralle H. Advances in the management of hereditary medullary thyroid cancer. *J Intern Med* 2005;257:50-9.
- Niccoli-Sire P, Murat A, Rohmer V, et al. Familial medullary thyroid carcinoma with noncysteine RET mutations: phenotype-genotype relationship in a large series of patients. *J Clin Endocrinol Metab* 2001;86:3746-53.
- Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 2001;86:5658-71.
- Piolat C, Dyon JF, Sturm N, et al. Very early prophylactic thyroid surgery for infants with a mutation of the RET proto-oncogene at codon 634: evaluation of the implementation of international guidelines for MEN type 2 in a single centre.

- Clin Endocrinol (Oxf) 2006;65:118-24.
13. Puñales MK, da Rocha AP, Meotti C, Gross JL, Maia AL. Clinical and oncological features of children and young adults with multiple endocrine neoplasia type 2A. *Thyroid* 2008;18:1261-8.
  14. Lo CY, Wat NM, Lam KY, Tiu SC, Chan J, Lam KS. Multiple endocrine neoplasia type 2A in Chinese families. *Clin Endocrinol (Oxf)* 2003;58:528.
  15. Zhou Y, Zhao Y, Cui B, et al. RET proto-oncogene mutations are restricted to codons 634 and 918 in mainland Chinese families with MEN2A and MEN2B. *Clin Endocrinol (Oxf)* 2007;67:570-6.
  16. Ku CF, Lo CY, Chan WF, Chiu SW, Fan ST, Lam KS. Resection of pheochromocytoma extending into the right atrium in a patient with multiple endocrine neoplasia type 2A. *Hong Kong Med J* 2005;11:59-62.
  17. Sakorafas GH, Friess H, Peros G. The genetic basis of hereditary medullary thyroid cancer: clinical implications for the surgeon, with a particular emphasis on the role of prophylactic thyroidectomy. *Endocr Relat Cancer* 2008;15:871-84.
  18. Graze K, Spiler IJ, Tashjian AH Jr, et al. Natural history of familial medullary thyroid carcinoma: effects of a program for early diagnosis. *N Engl J Med* 1978;299:980-5.
  19. Learoyd DL, Marsh DJ, Richardson AL, Twigg SM, Delbridge L, Robinson BG. Genetic testing for familial cancer. Consequences of RET proto-oncogene mutation analysis in multiple endocrine neoplasia, type 2. *Arch Surg* 1997;132:1022-5.
  20. Wells SA Jr, Chi DD, Toshima K, et al. Predictive DNA testing and prophylactic thyroidectomy in patients at risk for multiple endocrine neoplasia type 2A. *Ann Surg* 1994;220:237-50.
  21. Lips CJ, Landsvater RM, Höppener JW, et al. Clinical screening as compared with DNA analysis in families with multiple endocrine type 2A. *N Engl J Med* 1994;331:828-35.
  22. Machens A, Holzhausen HJ, Dralle H. Contralateral cervical and mediastinal lymph node metastasis in medullary thyroid cancer: systemic disease? *Surgery* 2006;139:28-32.
  23. Bergenfelz A, Jansson S, Kristoffersson A, et al. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. *Langenbecks Arch Surg* 2008;393:667-73.
  24. Sanso GE, Domene HM, Garcia R, et al. Very early detection of RET proto-oncogene mutation is crucial for preventive thyroidectomy in multiple endocrine neoplasia type 2 children: presence of C-cell malignant disease in asymptomatic carriers. *Cancer* 2002;94:323-30.
  25. Machens A, Niccoli-Sire P, Hoegel J, et al. Early malignant progression of hereditary medullary thyroid cancer. *N Engl J Med* 2003;349:1517-25.