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Incidentally Found Medullary Thyroid Cancer: Treatment Rationale for Small Tumors

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Abstract. The object of this study was to assess the extent of surgery required for small sporadic medullary thyroid cancers (sMTCs). We retrospectively studied 261 patients with MTCs treated in our institution between 1986 and 2002 and identified 15 patients with small pT1 or pT2 sMTCs. The tumors were diagnosed incidentally, so surgical therapy was less than total thyroidectomy. Total thyroidectomy with or without neck dissection was applied to all other patients as standard surgical treatment of care. Patients were systematically followed up by postoperative ultrasonography, calcitonin, carcinoembryonic antigen levels, and pentagastrin stimulation tests. On long-term follow-up over a period of 4.6 years, the rate of biochemical cure in these patients who underwent less than total thyroidectomy for a sporadic incidentally diagnosed tumor was 100%. We concluded that completion thyroidectomy and neck dissection are not mandatory in patients in whom a solitary small sMTC is incidentally discovered by histologic diagnosis following operation so long as a genetic background is excluded. Nevertheless, such patients require systematic careful long-term follow-up.

Medullary thyroid cancer (MTC) originates from parafollicular calcitonin-secreting cells (C-cells) and accounts for only 3% to 10% of all thyroid malignancies [1–3], although it is responsible for up to 13.4% of death-related thyroid cancers [4]. The sensitivity and specificity of calcitonin as a tumor marker can be enhanced by performing a pentagastrin test [5, 6]. The tumor's occurrence is either sporadic or hereditary due to germline mutation in the *RET* protooncogene [7, 8], where it is part of a number of hereditary malignant diseases, such as multiple endocrine neoplasia type 2A (MEN-2A), MEN-2B, and familial (non-MEN type) MTC [9].

Hereditary MTC presents as a bilateral, multicentric process [6, 10, 11] that requires total thyroidectomy and neck dissection for cure [12, 13]. In contrast, sporadic MTC, which comprises 70% to 80% of all MTCs, tends to be unicentric and confined to one lobe [14, 15]. The extent of lymph node dissection for this entity remains controversial [15–17].

When operating on a cold nodule without a specified fine-needle aspiration (FNA) diagnosis, the surgeon may encounter the postoperative situation of a previously unrecognized, incidentally found MTC in a patient in whom less than total thyroidectomy has been performed. As yet there is no evidence-based treatment guideline for this problem. We therefore report our outcomes for a series of 15 small, incidentally discovered sporadic MTCs in a group of 261 patients.

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Patients and Methods

A total of 261 patients with MTC were treated between April 1986 and September 2002 at our institution. Patients were classified as having (1) sporadic MTC; (2) MEN; or (3) familial non-MEN MTC.

A retrospective evaluation of the tumor staging revealed 15 patients with a small sporadic MTC. TNM classification was done according to the 1997 recommendation of the International Union Against Cancer (UICC) [18]. In all 15 cases the pathologic diagnosis was incidental and based on immunohistochemical analysis of calcitonin, chromogranin A, carcinoembryonic antigen (CEA), cytokeratin, and (for differential diagnosis) thyroglobulin. The cohort consisted of 12 women and 3 men with an average age of 51 years (range 35–75 years) at the time of operation. No patient had a family history of MTC, and none had symptoms typical for MEN-II.

Following surgery, all 15 patients with incidentally found MTCs were examined for germline mutations of the *RET* protooncogene. DNA samples were extracted from their peripheral blood cells, and polymerase chain reaction (PCR) products for exons 10, 11, and 13 of the *RET* protooncogene were analyzed [19, 20]. None of these patients showed any mutation in the described exons. Additional basal and pentagastrin-stimulated calcitonin and CEA were measured immediately after operation and 3, 6, and 12 months later. When patients had no signs or symptoms of tumor persistence, a yearly follow-up was performed. Plasma calcitonin was measured in blood samples before and 2, 5, and 10 minutes after an intravenous bolus injection of pentagastrin (0.5 μg/kg). For evaluation we used a chemiluminescence antibody assay (Calcitonin, Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) [21]. The normal ranges for basal calcitonin was < 5 ng/ml for women and < 12

Table 1. Clinical presentation and therapeutic features in 16 patients with incidentally found sMTCs.

Patient	Initials	Date of operation	Clinical presentation	Operation
1	F.F.	October 1992	toxic adenoma left	subtotal resection left
2	C.H.	January 1995	bilateral multinodular goiter	subtotal resection bilateral
3	U.K.	April 1996	bilateral multinodular toxic goiter	subtotal resection bilateral
4	B.S.	September 1996	cold nodule right, FNA: suspected malignancy	lobectomy right
5	L.R.	February 1997	bilateral multinodular goiter	subtotal resection bilateral
6	M.S.	July 1997	bilateral multinodular toxic goiter	subtotal resection bilateral
7	I.G.	October 1997	cold nodule left	lobectomy left
8	H.B.	November 1999	bilateral multinodular goiter	subtotal resection bilateral
9	W.T.	March 2000	bilateral multinodular goiter	subtotal resection bilateral
10	C.K.	September 2000	bilateral multinodular goiter	subtotal resection bilateral
11	M.K.	September 2000	bilateral multinodular goiter	subtotal resection bilateral
12	R.K.	January 1995 (2×)	bilateral multinodular goiter	1. lobectomy left/near-total right/LN-ext. 2. resection right
13	B.W.	March 2002	cold nodule left	subtotal resection bilateral
14	E.B.	January 2001 March 2001	bilateral multinodular goiter	1. subtotal resection bilateral 2. thyroidectomy + neck dissection right
15	B.Z.	May 1995	bilateral multinodular goiter, FNA: suspected papillary carcinoma left	lobectomy left + lymph node dissection left/near-total resection right

FNA: fine-needle aspiration; LN-ext.: lymph node-extirpation; sMTCs: sporadic medullary thyroid carcinomas.

Table 2. Clinical features and pathologic findings in 15 patients with incidentally found sMTCs.

Patient	Initials	Gender	Age (years)	Tumor side	Tumor size (cm)	UICC stage
1	F.F.	M	60	Left	0.1	T1
2	C.H.	F	52	Left	0.1	T1
3	U.K.	F	42	Left	0.5	T1
4	B.S.	F	36	Right	2.5	T2
5	L.R.	F	56	Left	0.3	T1
6	M.S.	F	67	Right	0.7	T1
7	I.G.	F	35	Left	1.8	T2
8	H.B.	M	57	Right	2.2	T2
9	W.T.	M	75	Left	0.6	T1
10	C.K.	F	53	Left	0.5	T1
11	M.K.	F	48	Right	0.8	T1
12	R.K.	F	47	Right	0.3	T1
13	B.W.	F	48	Right	0.5	T1
14	E.B.	F	53	Right	0.5	T1
15	B.Z.	F	40	Right	0.7	T1N1

ng/ml for men; the normal values for stimulated calcitonin in women and men were < 20 and < 125 ng/ml, respectively. The normal range for CEA was < 4 ng/ml.

Table 3. Last follow-up of patients with incidentally found small sMTCs; 1992–2002.

Patient	Initials	Last follow-up	Maximum stimulated calcitonin (ng/ml)	Follow-up (years)
No completion operation				
1	F.F.	September 2002	2.3	10
2	C.H.	April 2001	< 0.01	7
3	U.K.	April 2002	0.1	6
4	B.S.	December 2000	0.53	6
5	L.R.	September 2002	< 0.01	5
6	M.S.	September 2001	0.8	5
7	I.G.	December 2001	2.7	5
8	H.B.	January 2002	42	3
9	W.T.	July 2002	0.42	2
10	C.K.	September 2002	0.18	2
11	M.K.	September 2002	< 0.15	2
12	R.K.	September 2002	< 0.01	7
13	B.W.	September 2002	< 0.01	0.5
Completion operation (Tx + neck dissection)				
14	E.B.	September 2001	20.7	1.5
15	B.Z.	May 2002	< 0.01	7

Median follow-up was 4.6 years.
Tx: thyroidectomy.

Results

Clinical data and operative procedures of all patients with incidentally found sporadic MTCs are presented in Tables 1 and 2.The indications for surgery were a bilateral multinodular goiter without any signs of malignancy in 10 patients (nos. 2, 3, 5, 6, 8–12, 14). In eight of these cases a bilateral subtotal resection was performed. One patient was operated on twice because of elevated pentagastrin-stimulated calcitonin and CEA results 3 months after the first operation (patient 14). Thyroidectomy and ipsilateral neck dissection were performed. One patient was treated in another hospital (patient 12). He was initially treated by lobectomy and contralateral near-total resection with additional local lymph node extirpation. Following the unexpected histopathologic result, the thyroid remnant of the right side was removed a few days after the first

Table 4. Review of the literature for positive lymph nodes in T1 and T2 sMTCs: 1993–1998.

	T1 sMTCs		T2 sMTCs	
Study	No.	With positive nodes (no.)	No.	With positive nodes (no.)
Kallinowski [23]	19	7 (37%)	4	2 (50%)
Pacini [24]	2	0	5	0
Wagner [25]	2	1 (50%)	16	1 (6%)
Niccoli [26]	11	0	3	1 (33%)
Gimm [16]	5	3 (60%)	3	1 (33%)
Beressi [17]	55	17 (31%)		
Henry [27]	11	0		
	105	28	31	5

Table 5. Review of the literature: complications after completion thyroidectomy: 1993–1997.

Study	Patient (no.)	Transient hypoparathyroidism (%)	Permanent hypoparathyroidism (%)	Transient recurrent nerve palsy (%)	Permanent recurrent nerve palsy (%)	Transient Horner syndrome (%)
Goretzki [28]	110	5.6	3.0	8.5	4.0	—
Pezullo [29]	35	—	2.8	—	2.8	—
Gimm [30]	36	—	25	—	8.4	5.6
Moley [5]	52	—	5.8	3.8	—	3.8

operation.Three patients were operated on because of an isolated cold node (patients 4, 7, 13). In two cases a lobectomy was performed. In the third case bilateral subtotal resection was done because of the intraoperative finding of multiple nodules.

One patient (no. 1) was operated on for a 3.2 cm diameter toxic adenoma in the left lobe that was confirmed by postoperative histology. Independently, a 0.1 cm medullary thyroid carcinoma was found next to the toxic adenoma.

Patient 15 had a bilateral multinodular goiter with a pathologic result after FNA biopsy of a cold nodule that was suspected to be a papillary carcinoma. For this reason the surgical procedure was lobectomy with lymph node dissection on the left side and near-total resection on the right side. Pathology revealed a 3 cm microfollicular adenoma in the left lobe and, unexpectedly, a small MTC (0.7 cm) in the right lobe. In addition, there was a single micrometastasis in a lymph node of the central compartment.

Pathology examination classified 11 of the tumors as pT1, 3 as pT2, and 1 as pT1pN1. There were no postoperative complications, especially no recurrent nerve palsy or hypocalcemia.

The follow-up of all 15 patients, with an average duration of 4.6 years (range 1.5–10.0 years), consisted of a history, clinical examination, and blood tests. We analyzed free triiodothyronine (fT_3), free thyroxine (fT_4), thyroid-stimulating hormone (TSH), CEA, and basal and pentagastrin-stimulated calcitonin at yearly intervals. During follow-up, one of these patients (no. 14) presented with tumor recurrence, evidenced by elevated calcitonin and CEA. Ultrasonography showed a local tumor mass. Liver ultrasonography and chest radiography revealed no pathologic findings; therefore a second operation was performed. On long-term follow-up over a median of 4.6 years, the rate of biochemical cure was 100% (Table 3). No other patients had elevated calcitonin or CEA levels, nor did they develop any other signs of tumor recurrence.

Discussion

Surgery is the treatment of choice for curing patients with MTCs. Chemotherapy is insufficient, and external radiotherapy is of doubtful benefit. In patients with an established diagnosis of MTC pre- or intraoperatively, radical surgery that may include thyroidectomy and ipsilateral lymph node dissection is performed. The argument behind this strategy is a tendency toward a multicentric presentation and early lymph node involvement, especially with heredity MTCs, where the frequency may reach 80% to 90% [6, 12]. Total thyroidectomy has also been recommended as the procedure of choice for sporadic MTCs [3, 6, 12] because of their possible hereditary nature, which may not be proven before surgery, and the possibility of bilateral disease. Most sporadic MTCs (80–90%), however, tend to be unilateral, being restricted to one lobe [14, 22]. Therefore some groups perform only hemithyroidectomy with central and ipsilateral neck dissection as an appropriate procedure for patients with an apparently sporadic MTC tumor if preoperative germline *RET* oncogene mutation analysis supports its nonhereditary nature [22].

The nature of MTCs, sporadic or hereditary, can be reliably established by germline *RET* mutation analysis using sequencing methods previously reported. This practice should lead to new surgical concepts in the treatment of incidentally found small sporadic MTCs. The frequency of lymph node metastasis associated with small sporadic MTCs has not yet been reported in the literature. A review of the literature concerning lymph node metastases with small sporadic MTCs is shown in Table 4 [6, 17, 23–27]. There are marked differences among the results of various studies. Gimm et al. [16] reported five patients with pT1 MTCs, three of them with lymph node metastases. Surgical treatment was thyroidectomy and dissection of the centrocervical compartment. Beressi et al. [17] described lymph node metastases in 17 of 55 patients with a pT1 MTC. The surgical procedure was thyroidectomy and complete or incomplete central dissection. This study, however, was not based on genetic analysis. Niccoli et al. [26] reported 11 patients with a pT1 MTC, five of them with bilateral C-cell hyperplasia. All were treated with thyroidectomy and central lymph node compartment dissection. None of the 11 patients showed lymph node metastases. Pacini et al. [24] reported two patients and Henry et al. [27] reported 11 patients with a pT1 MTC. After thyroidectomy and lymph node dissection no metastases were found.In our patients the centrocervical compartment was not systematically removed in case of an unknown malignancy. Only one patient (no. 15) showed one central lymph node metastasis incidentally.

The most important argument against a completion thyroidectomy is the increased morbidity after a second operation (for more details see Table 5) [5, 28–30]. The patients can benefit by avoiding the risk of hypoparathyroidism, recurrent nerve palsy, or the need for lifelong supplementation of thyroid hormone after a second operation.

Our procedure of choice is hemithyroidectomy with intraoperative frozen section examination in patients with a cold nodule or bilateral resection in patients with a multinodular goiter. If a sporadic MTC is suggested preoperatively (e.g., by FNA biopsy in combination with an elevated calcitonin level), total thyroidectomy with central lymph node dissection and at least lateral lymph node dissection on the tumor side is our surgical procedure of choice. The need for unilateral or bilateral lymph node dissection for sporadic MTC is still unclear according to the literature. Our current standard surgery for an unexpected postoperatively diagnosed sporadic MTC (negative *RET* protooncogene and negative family history) is shown in the surgical decision tree in Figure 1. In the case of tumor staging higher than pT1, a completion operation with thyroidectomy and central and at least lateral lymph node dissection on the

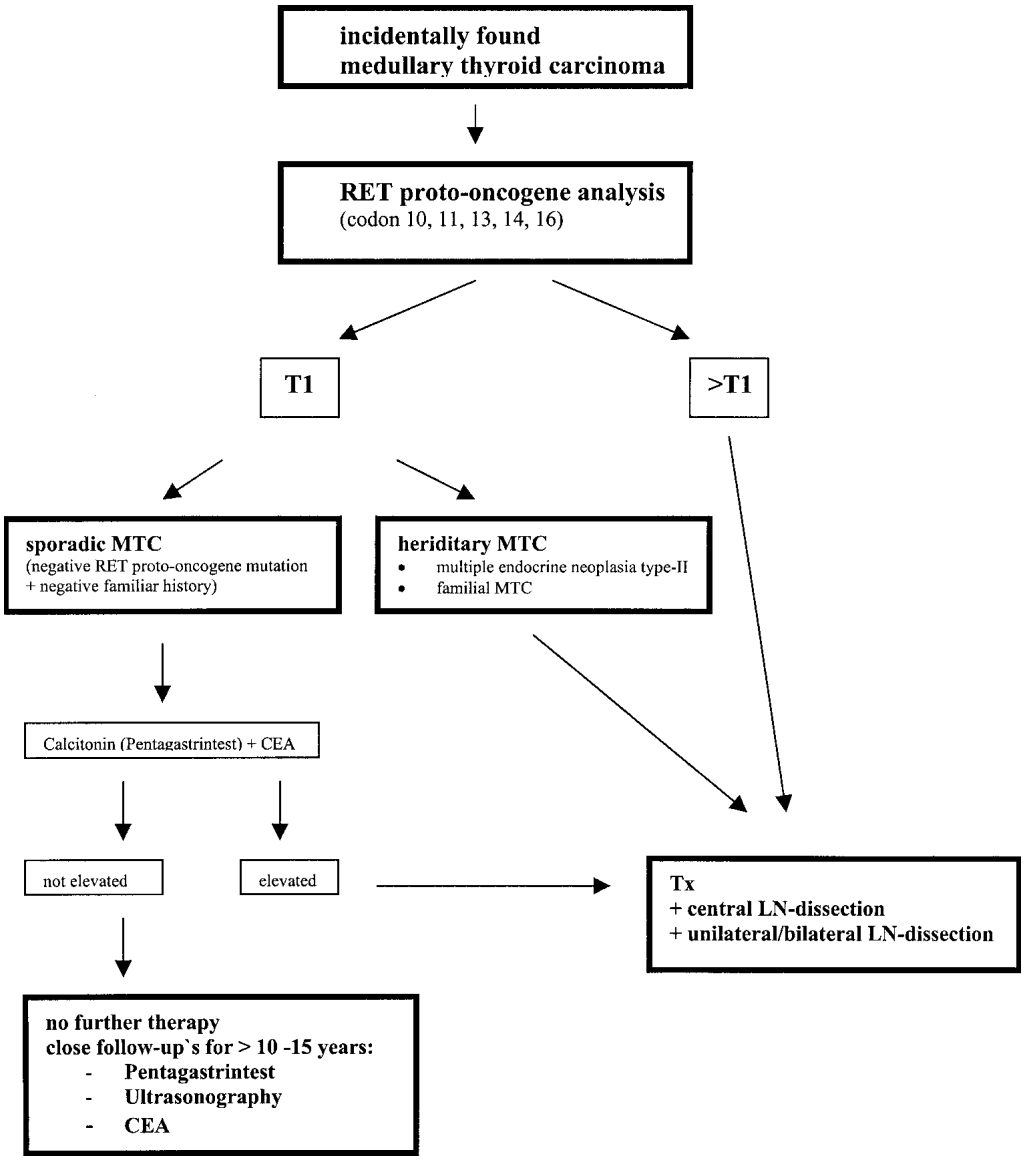

Fig. 1. Surgical decision tree for an incidentally found medullary thyroid carcinoma (MTC). Tx: thyroidectomy; CEA: carcinoembryonic antigen; LN: lymph node.

tumor side is performed. If invasive tumor growth and lymph node metastases exist, bilateral lymph node dissection is indicated. In the case of a pT1 tumor, basal and pentagastrin-stimulated calcitonin and CEA are measured. If the values are elevated, a completion operation, as described before, is performed. If the levels are not elevated, no further surgical therapy is necessary. Because of the unknown outcome, a close, long follow-up of at least 10 years (better lifelong) is mandatory.

Our data show that less surgery for pT1 sporadic MTCs may be sufficient. Further reasons are (1) its tendency to be unilateral and restricted to one lobe (80–90%) [10, 14, 15] (Miyauchi et al. [22] reported 40 patients with an sMTC, all of them unilateral); and (2) developing metastases at an advanced tumor stage.

Over the 10 years of our study, only one patient developed tumor recurrence a short time after the first operation. The procedure in patients 4, 7, 8, and 15 was not in accordance with our proposed treatment scheme. However, therapeutic decisions especially were carried out only after detailed discussions and at the request of the patients themselves.

Résumé. L'objectif de cette étude a été d'évaluer la nécessité d'une chirurgie étendue chez le patient porteur de cancer médullaire de la thyroïde dit sporadique (sMTC) de petite taille. Nous avons étudié de façon rétrospective 261 patients porteurs de MTC traités dans notre institution entre 1986 et 2002 et nous avons identifié 15 patients porteurs de sMTC de petite taille, pT1 ou pT2. Le diagnostic de MTC était de découverte fortuite et ainsi le geste thérapeutique n'a toujours pas été une thyroïdectomie totale. La thyroïdectomie totale avec ou sans lymphadénectomie cervicale a été réalisée chez tous les patients comme un traitement chirurgical standard. Les patients ont été suivis de façon systématique par une échographie postopératoire, un dosage de la calcitonine, un dosage des taux d'antigène carcino-embryonnaire et les tests de stimulation à la pentagastrine. En ce qui concerne le suivi à long terme sur 4.6 ans, le taux de cure biochimique chez les patients ayant eu une thyroïdectomie sub-totale pour cancer médullaire sporadique de découverte fortuite a été de 100%. Nous concluons que la totalisation de la thyroïdectomie et la lymphadénectomie ne sont pas nécessaires en cas de découverte fortuite postopératoire par l'histologie de tumeur sMTC solitaire à la condition qu'une histoire génétique peut être exclue. Néanmoins, de tels patients nécessitent un suivi à distance systématique.

Resumen. El propósito del presente estudio fue evaluar la necesidad de cirugía ampliada en casos de pequeños cánceres medulares esporádicos

(PCMT). Analizamos en forma retrospectiva 261 pacientes con CMT tratados en nuestra institución en el periodo 1986–2002, entre los cuales identificamos 15 con pcMT. Estos pacientes se presentaron con tumores pT1 o pT2. El diagnóstico de CMT fue incidental, y por consiguiente la intervención operatoria fue menos que una tiroidectomía total. En todos los otros pacientes se practicó tiroidectomía total con o sin disección cervical como modalidad estándar de tratamiento quirúrgico. El seguimiento sistemático postoperatorio de los pacientes operados se hizo mediante ultrasonografía, determinación de niveles de calcitonina y de antígeno carcinombrionario y pruebas de estímulo con pentagastrina. En el seguimiento a largo plazo sobre un periodo de 4.6 años, la tasa de curación bioquímica en los pacientes que recibieron menos de tiroidectomía total en casos de tumores esporádicos incidentales fue 100%. Nuestra conclusión es que no es mandatorio realizar reoperación para completar la tiroidectomía y hacer la disección cervical en pacientes con el hallazgo histológico incidental de pCMT siempre y cuando se haya excluido un antecedente genético. Sin embargo, tales pacientes requieren un cuidadoso y sistemático seguimiento.

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