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Latent Subclinical Medullary Thyroid Carcinoma: Diagnosis and Treatment

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Abstract. Sporadic medullary thyroid carcinoma (SMTC) is usually diagnosed at a clinical stage often associated with lymph node involvement. Hence surgical treatment does not result in definitive cure in many patients. Studies have demonstrated that routine measurement of serum basal calcitonin (CT) in patients with nodular thyroid disease allows preoperative, early diagnosis of unsuspected SMTC. The aim of this work was to assess the results of surgery in patients operated on for subclinical SMTC detected preoperatively by measurement of serum CT. Results were compared with those obtained in patients with SMTCs diagnosed at a clinical stage and operated on during the same period. During a 4-year period (1993–1996) 24 SMTCs were diagnosed and treated in our department. They were diagnosed at a clinical stage in 13 patients (group 1): palpable thyroid tumor ($n = 11$), palpable metastatic lymph node ($n = 6$), distant metastases ($n = 4$). In nine cases the diagnosis was made by both fine-needle aspiration cytology and serum CT measurement. In the four other cases the initial cytology was incorrect, but the diagnosis was revised on the basis of elevated basal CT values. In 11 patients (group 2) presenting with nodular thyroid disease, SMTC was not clinically detectable. SMTC was preoperatively suspected by elevated CT levels: basal CT > 10 pg/ml and pentagastrin-stimulated CT peak > 100 pg/ml. One patient in group 1 with distant metastases was not operated on. All of the other 12 patients underwent total thyroidectomy and extensive lymph node dissection. The mean size of the tumors was 27 mm. Lymph node involvement was found in nine patients. After surgery, CT levels returned to normal in five patients but remained elevated in five others; the two remaining patients died of distant metastases. All 11 patients in group 2 underwent total thyroidectomy and central neck dissection. None of the 11 patients had nodal extension. All 11 patients are biochemically cured. It was concluded that routine measurement of basal serum CT in those with nodular thyroid disease allows early, preoperative diagnosis of subclinical SMTC and improves the results of surgery.

Sporadic medullary thyroid carcinoma (SMTC) is probably more common than previously suggested by the literature. Studies have indicated that the prevalence of SMTC in nodular thyroid diseases ranges between 0.57% and 1.37% [1–4]. SMTC is usually diagnosed at a clinical stage. Because lymph node involvement appears early and is related to the size of the primary tumor, in many cases surgical treatment does not provide a definitive cure. A lack of effective treatment other than surgery suggests that it is justified to detect and remove an SMTC when cure is possible, that is, in its earliest stage.

Procedures such as scintigraphy, ultrasonography, and fine-needle aspiration cytology (FNAC) are inadequate for detecting subclinical micro-SMTCs. We previously demonstrated that the routine measurement of basal serum calcitonin (CT) is sufficient to overcome this diagnostic failure [3, 4]. The aim of this study was to assess the results of surgery in patients operated on for latent subclinical SMTC detected only by routine measurement of serum CT. These results were compared with those obtained in patients with SMTCs diagnosed at a clinical stage and operated on during the same period.

Methods

Until 1993, our diagnostic strategy in patients with nodular thyroid diseases included thyroid examination, thyroid ultrasonography, and measurement of serum thyroid-stimulating hormone (TSH), free thyroid hormones, and thyroid antibodies. Radionuclide scanning was reserved for patients with thyrotoxicosis. FNAC with thyroid peroxidase immunodetection [5] was performed in patients with palpable solitary or dominant nodules.

Since 1993, measurement of basal serum CT was systematically included in our initial evaluation [3]. Serum CT is measured by an immunometric method (Elsa-CT; Cis-Bioindustries, Gif sur Yvette, France), including monoclonal antibodies that recognize the 11–17 and 24–34 regions of the CT molecule [6, 7]. CT values were considered normal according to the data of the French Medullary Thyroid Study Group (GETC), in which normal subjects have a basal serum CT level of less than 10 pg/ml [7, 8]. When the basal serum CT was more than 10 pg/ml, a pentagastrin (Pg) stimulation test was performed according to the GETC-recommended procedure. Briefly, an intravenous injection (0.5 μg/kg) of Pg (Peptavlon; ICF Pharma, Cergy, France) was conducted for 3 minutes. Blood samples were collected before and 3, 5, and 10 minutes after injection. The response is expressed as the maximum value of CT peaks 3 or 5 minutes after initiation of the Pg injection. The Pg-stimulated CT value was considered normal with reference to the data from the GETC, in which normal subjects had a peak CT value of less than 30 pg/ml [8]. Patients with a peak CT value over 100 pg/ml were suspected to have an SMTC [3, 4]. When an SMTC was suspected and FNAC was

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Table 1. Clinical presentation, pre- and postoperative CT levels, and cytologic and histologic findings in 13 patients with a clinical MTC (group 1).

Patient no.	Sex	Age (years)	Clinical presentation	Preop basal CT (pg/ml)	Cytologic diagnosis (initial/revised)	MTC (mm)	Lymph node metastases (N^+/N^-)	Distant metastases (M^+/M^-)	Postop CT (basal/Pg) (pg/ml)
1	M	33	Nodule	14,000	MTC	60	N^+	M^+	543/ND
2	M	65	Nodule	10,967	MTC	30	N^-	M^-	$< 10/< 10$
3	F	55	Nodule	4,066	MTC	30	N^-	M^-	$< 10/< 10$
4	F	82	Nodule	37,000	Anaplastic/MTC	45	N^+	M^+	†
5	M	67	Nodule	23,000	Anaplastic/MTC	40	N^+	M^+	†
6	M	57	Nodule	475	Papillary/MTC	13	N^+	M^-	$< 10/< 10$
7	F	67	Nodule	616	Thyroiditis/thyroiditis	12	N^+	M^-	58/ND
8	F	60	Nodule	2,352	MTC	25	N^-	M^-	$< 10/< 10$
9	M	58	Bone metastasis	13,465	MTC	2	N^+	M^+	7,734/ND
10	F	33	Lymph node metastasis	3,700	MTC	12	N^+	?	912/ND
11	M	84	Nodule	212,890	MTC	60	N^+	M^+	†
12	F	59	Nodule	1,294	MTC	15	N^+	M^-	119/ND
13	M	52	Nodule	4,645	MTC	35	N^-	M^-	$< 10/< 10$

Pg: pentagastrin stimulation test; ND: not done; †: died.

Table 2. Clinical presentation, pre- and postoperative CT levels, and histologic findings in the 11 patients with a latent subclinical MTC (group 2).

Patient no.	Sex	Age (years)	Clinical presentation cytology	Preop CT (basal/Pg)	MTC (mm)	Multicentricity	CCH
14	F	39	Sonographic nodule	45/97	7	—	—
15	F	73	Sonographic nodule	105/480	3	—	—
16	M	51	Nontoxic MNG	11/101	1,2	—	Bilateral
17	F	37	Nontoxic MNG	115/1958	9	—	—
18	F	66	Nontoxic MNG	139/3130	9	—	—
19	M	61	Nontoxic MNG	160/1152	8	—	—
20	F	45	Right solitary nodule; papillary carcinoma	26/1766	8 (left)	—	—
21	F	52	Solitary nodule; adenoma	36/186	2	Bilateral	Unilateral
22	F	51	Nontoxic MNG	77/3534	9	—	—
23	M	60	Nontoxic MNG	52/222	2	Bilateral	Unilateral
24	M	49	Nontoxic MNG	16/145	1,5	—	Unilateral

Pg: pentagastrin stimulation; MNG: multinodular goiter; CCH: C-cell hyperplasia.
There were no lymph node or distant metastases in any of the patients in group 2. In all cases the postoperative pentagastrin CT was less than 10.

feasible, CT immunodetection of cytologic samples was also performed.

The surgical specimens were examined histopathologically using a standard technique. Serial sections were obtained throughout the gland to detect microscopic MTCs. An extensive search for C-cell hyperplasia (CCH) or microscopic MTC loci was conducted by immunochemistry with an anti-CT polyclonal antibody (CT-205; Immunotech, Marseille, France). CCH was defined by immunohistologic criteria proposed by the pathologist of the GETC: either a C cell density of more than 40 cells/cm^3 ($\times$400) or at least three microscopic foci containing more than 50 C cells ($\times$100) [9].

Results

Among the 3384 patients presenting with a nontoxic nodular thyroid disease in our department over a 4-year period (1993–1996), 24 SMTCs were diagnosed and treated. There were 11 men and 13 women with a mean age of 56 years (33–84 years). None of these patients had clinical or biologic signs of multiple endocrine neoplasia (MEN) or a familial history of MTC or MEN. We excluded from this study patients who underwent surgery for MTC before being referred to our department.

An SMTC was discovered at a clinical stage (group 1) in 13 patients (Table 1): a palpable thyroid tumor in 11 cases, palpable metastatic lymph nodes in 6 cases, and distant metastases in 4 cases. SMTC was diagnosed in nine patients by FNAC and an elevated basal serum CT level. In the four other patients the initial cytology was incorrect, indicating malignancy in three cases (two anaplastic cancers, one papillary cancer) and chronic lymphocytic thyroiditis in one. On the basis of high basal serum CT values, the initial cytologic diagnosis was revised in three patients but remained unchanged in one (thyroiditis).

An SMTC was not clinically detectable (group 2) in 11 patients (Table 2). Seven of those patients presented with a nontoxic multinodular goiter with a predominant nodule in two, corresponding to a macrofollicular lesion at FNAC. Two other patients had a palpable solitary nodule assessed by FNAC (macrofollicular nodule and papillary cancer). SMTC was adjacent to the benign nodule in one patient and on the lobe opposite the papillary tumor in the other case. In the remaining two patients the SMTC was incidentally discovered by ultrasonography. FNAC performed

in one case was incorrect (papillary cancer) but was revised on the basis of abnormal serum CT levels. Thus for all 11 patients with latent subclinical SMTC, the diagnosis was suspected only by an elevated basal serum CT level ranging between 11 and 160 pg/ml and abnormal Pg-stimulated CT levels ranging between 97 and 3534 pg/ml. One patient in group 1 (Table 1), 83 years old with distant metastases, was not operated on and died 6 months later. All of the 12 other patients underwent total thyroidectomy and extensive lymph node dissection in the central and lateral neck areas. The mean size of the tumors was 27 mm (2–60 mm). Lymph node involvement was found in nine patients. Morbidity included two permanent recurrent laryngeal nerve palsies and one permanent hypoparathyroidism. After surgery, serum Pg-stimulated CT levels returned to normal in five patients and remained elevated in five. The remaining two patients died of distant metastases.

All 11 patients in group 2 (Table 2) underwent total thyroidectomy and lymph node dissection in the central neck area. The mean size of the SMTC was 5 mm (1.2–9 mm). The SMTC was unilateral in nine patients. Bilateral multicentricity was observed in two cases. An associated CCH was found in four patients: unilateral in three cases and bilateral in one case. A papillary cancer was associated in two cases. None of the 11 patients had lymph node extension or distant metastases. There was no mortality and no surgical morbidity. After surgery, serum Pg-stimulated CT levels returned to normal in all 11 patients with 1 to 4 years of follow-up.

Discussion

Large clinical series suggest that MTCs account for fewer than 10% of all thyroid carcinomas [10–12]. MTC occurs in both familial and sporadic forms. About 5% of thyroid carcinomas are SMTCs. Until now no studies reported the real prevalence of SMTC in nodular thyroid pathology. Studies indicate that routine measurement of serum CT is a useful screening test for SMTC [1–4]. In this series, the prevalence of SMTC in patients with nodular thyroid disease is 0.71%, which has led us, as other authors, to recommend that basal serum CT measurement become a routine procedure in the initial diagnostic strategy of nodular thyroid diseases.

Basal hypercalcitoninemia is not always due to an MTC [13], as nonspecific increases of basal serum CT have been reported in normal subjects [14]. The utilization of a two-site immunoradiometric assay eliminates this type of artifact. Some nonthyroidal neoplasms may also elevate the basal serum CT, but usually clinical features are different. In these cases a negative Pg test is a reliable means to eliminate the possibility of an SMTC.

In the experience of the GETC, basal serum CT values over 35 pg/ml suggest an MTC [4]. SMTCs, particularly micro-SMTCs, may be observed with mild basal hypercalcitoninemia, that is, between 10 and 35 pg/ml (three cases in our series). One must keep in mind that mild basal hypercalcitoninemia may also be related to CCH, and that CCH may occur adjacent to a follicular adenoma or carcinoma [15], a primary thyroid lymphoma [16], or chronic lymphocytic thyroiditis [9, 17]. Again, a Pg test is particularly useful in these circumstances. Indeed, according to the data of the GETC, a Pg-stimulated value over 100 pg/ml may be considered to be strongly related to the presence of an MTC. A mild CT peak is more likely to be related to the presence of a hepatocellular carcinoma (CCH).

In our series, five patients with a multinodular goiter exhibited a Pg peak over 100 pg/ml (between 118 and 340 pg/ml). They underwent total thyroidectomy for locoregional functional disorders, and no MTC (only CCH) was found in the specimens. It must be pointed out that the basal serum CT value was less than 35 pg/ml in each of these five patients (between 11 and 26 pg/ml). In short, latent subclinical SMTCs should be strongly suspected when the basal serum CT value is over 35 pg/ml, and the Pg-stimulated serum CT value is over 100 pg/ml. We have not observed any false-positive diagnoses of SMTC when the serum CT is higher than that.

No other procedure allows the diagnosis of SMTC as accurately as measurement of serum CT. Thyroid function tests, ultrasonography, and radionuclide scanning do not specifically indicate SMTC. FNAC, which can be performed only when the SMTC is clinically detectable, may fail to diagnose it [1–4, 10]. CT immunostaining of cytologic samples is usually not performed unless specifically requested. Serum CT evaluation is obviously the most sensitive and accurate predictor of SMTC. First, in patients with palpable SMTC initially assessed by FNAC, serum CT determination allows us to correct a false diagnosis. Second, and above all, it is the only procedure that allows detection of a latent subclinical SMTC.

In patients with familial MTC, family screening allows early diagnosis and leads to early radical surgery, resulting in a high cure rate [18–20]. Conversely, SMTCs are usually diagnosed late, at a clinical stage often associated with extensive lymph node involvement. They are sometimes diagnosed preoperatively by FNAC or during surgery by frozen section; but unfortunately diagnosis is too often after surgery by permanent section. This late, postoperative diagnosis results in inadequate initial surgical procedures, often requiring long and difficult reoperations with high morbidity. In many cases definitive cure is not obtained [21–24], which explains why SMTCs have a poor long-term prognosis with a 10-year-survival of around 60%. For familial MTC, one can expect that a preoperative diagnosis of SMTC at an early stage can improve the prognosis. Although our follow-up is short, our results seem to demonstrate the benefit of an early preoperative diagnosis. Routine measurement of serum CT facilitated or allowed the preoperative diagnosis of SMTC in all 24 patients of our series.

Finally, considering the prevalence of SMTC in nodular thyroid diseases in our experience (0.71%), routine measurement of the basal serum CT allowed detection of 1 SMTC for every 141 assays. In nine cases the diagnosis was also made by FNAC. One can conclude that CT measurement was the only diagnostic procedure that allowed detection of 15 SMTCs in this series. If we consider that currently a single serum CT assay costs about US $100, it can be calculated that approximately US $20,000 was spent on screening for each confirmed SMTC. This amount may seem high, but one must bear in mind that failure to measure the serum CT may delay or even miss the diagnosis, especially in patients with subclinical SMTC. This failure leads to a much more complicated, expensive subsequent course. Therefore the cost of initial basal CT screening should be weighed against the costs of additional hospital stays, examinations, and treatments.

Conclusions

Routine measurement of basal serum CT in patients with nodular thyroid disease improves the preoperative diagnosis of SMTC and allows early detection of latent subclinical SMTC. Even if the significance of micro-SMTCs is still unclear, early treatment should improve their prognosis. We recommend that basal serum CT measurement be included in the initial diagnostic evaluation of nodular thyroid diseases.

Résumé

Comme souvent on ne fait le diagnostic de cancer médullaire de la thyroïde sporadique (CMTS) que lorsqu'il existe des signes cliniques, fréquemment déjà associé à un envahissement ganglionnaire, le traitement chirurgical n'est pas toujours courronné de succès. Des études récentes semblent indiquer que le dosage systématique de calcitonine (CT) dans le sang chez les patients ayant une maladie nodulaire de la thyroïde peut permettre un diagnostic préopératoire précoce du CMTS nonsoupçonné auparavant. Le but de ce travail a été d'évaluer les résultats de la chirurgie chez les patients opérés pour un CMTS infraclinique, détecté en préopératoire par la CT (Elsa CT, Cis-Bioindustries—N< 10 pg/ml). On a comparé les résultats à ceux des patients ayant un CMTS diagnostiqué à un stade clinique et opérés pendant la même période. Méthodes: Pendant 4 ans (1993–96), 24 CMTS ont été diagnostiqués et traités dans notre département. Chez 13 patients (Groupe 1), le CMTS a été diagnostiqué à un stade clinique: tumeur de la thyroïde palpable (n = 11), ganglion métastatique palpable (n = 6), métastases à distance (n = 4). Chez 9 patients, le diagnostic a été fait par cytologie transcutanée à l'aiguille fine et par le dosage de la CT. Chez les 4 autres patients, le diagnostic initial par cytologie était érronée mais le diagnostic a été révisé en fonction de la CT élevée. Chez 11 patients (Groupe 2), présentant une maladie nodulaire de la thyroïde, le CMTS n'était pas cliniquement détectable. La tumeur CMTS a été suspectée en préopératoire par une CT basale élevée> 10 pg/ml et un taux de CT après stimulation par la pentagastrine >100 pg/ml. Résultats: Dans le groupe 1: un patient ayant des métastases à distance n'a pas été opéré. Les 12 autres patients ont eu une thyroïdectomie totale avec lymphadénectomie étendue. La taille moyenne des tumeurs était de 27 mm. Un envahissement ganglionnaire a été retrouvé chez 9 patients. Après chirurgie, les niveaux de la CT sont revenus à la normale chez 5 patients mais sont restés élevés chez 5 autres; les 2 patients restants sont décédés de métastases à distance. Dans le groupe 2, les 11 patients ont eu une thyroïdectomie totale avec lymphadénectomie médiane. Aucun de ces patients n'avaient un envahissement ganglionnaire. Les 11 patients ont été guéris d'un point de vue biochimique. Conclusion: Le dosage systématique de la CT basale dans la maladie nodulaire de la thyroïde permet un diagnostic précoce préopératoire du CMTS infraclinique et améliore les résultats de la chirurgie.

Resumen

En general el carcinoma medular esporádico de la glándula tiroides (CMET) se diagnostica tardíamente cuando ya se halla en estado clínico, estado que frecuentemente aparece asociado con extensión ganglionar. Por ello, en muchos pacientes el tratamiento quirúrgico no resulta en curación definitiva. Estudios recientes han demostrado que la determinación rutinaria de los niveles basales de calcitonina (CT) en pacientes con enfermedad nodular tiroidea, permite el diagnóstico preoperatorio y precoz de un CMET no sospechado. El propósito de este trabajo fue evaluar los resultados de la cirugía en pacientes operados por CMET en estado subclínico detectado por la determinación preoperatoria de CT-sérica (Elsa CT, Cis-Bioindustries N< 10 pg/ml). Los resultados fueron comparados con los logrados en pacientes en quienes se diagnosticó el CMET ya en un estado clínico y que fueron operados en el mismo periodo. Métodos: 24 CMET fueron diagnosticados y tratados en nuestro departamento en un periodo de 4 años (1993–1996). En 13 pacientes el CMET fue diagnosticado en un estado clínico: tumor palpable (9), ganglio linfático metastásico palpable (6), metastásico distante (4). En 9 casos el diagnóstico fue establecido por citología por aspiración con aguja fina y determinación de la CT sérica. En los otros 4 casos, la citología inicial resultó errada, pero el diagnóstico fue revisado con base en los valores elevados de CT. En 11 pacientes (grupo 2) que presentaban enfermedad nodular de la glándula tiroides, el CMET no era clínicamente detectable, pero preoperatoriamente se sospechó un CMET por la presencia de niveles elevados de CT: CT basal>10 pg/ml y nivel máximo de CT estimulada por pentagastrina > 100 pg/ml. Resultados: En el grupo 1: Un paciente con metástasis distantes no fue operado. La totalidad de los restantes 12 pacientes fue sometida a tiroidectomía total con disección ganglionar amplia. El tamaño medio del tumor fue 27 mm. Se encontró extensión ganglionar linfática en 9 pacientes. Luego de la cirugía, los niveles de CT retornaron a valores normales en 5 pacientes, pero se mantuvieron elevados en 5; los 2 pacientes restantes murieron por enfermedad metastásica. En el grupo 2: todos los 11 pacientes fueron sometidos a tiroidectomía total con disección cervical central. Ninguno de los 11 presentó extensión ganglionar linfática. Todos resultaron bioquímicamente curados. Conclusión: La determinación rutinaria de la CT sérica basal en la enfermedad nodular de la glándula tiroides permite el diagnóstico preoperatorio y precoz del CMET subclínico y mejora los resultados de la cirugía.

References

1. Pacini, F., Fontanelli, M., Fugazzola, L., Elisei, R., Romei, C., Di Coscio, G., Miccoli, P., Pinchera, A.: Routine measurement of serum calcitonin in nodular thyroid diseases allows the preoperative diagnosis of unsuspected sporadic medullary thyroid carcinoma. J. Clin. Endocrinol. Metab. *78*:826, 1994
2. Rieu, M., Lame, M.C., Richard, A., Lissak, B., Sambort, B., Vuong Ngoc, P., Berrod, J.L., Fombeur, J.P.: Prevalence of sporadic medullary thyroid carcinoma: the importance of routine measurement of serum calcitonin in the diagnostic evaluation of thyroid nodules. Clin. Endocrinol. (Oxf.) *42*:453, 1995
3. Henry, J.F., Denizot, A., Puccini, M., Niccoli, P., Conte-Devolx, B., De Micco, C.: Early diagnosis of sporadic medullary cancer of the thyroid: contribution of routine calcitonin assay. Presse Med. *25*:1583, 1996
4. Niccoli, P., Wion-Barbot, N., Caron, P., Henry, J.F., De Micco, C., Saint André, J.P., Bigorgne, J.C., Conte Devolx, B.: Interest of routine measurement of serum calcitonin: study in a large series of thyroidectomized patients. J. Clin. Endocrinol. Metab. *82*:338, 1997
5. Henry, J.F., Denizot, A., Porcelli, A., Villafane, M., Zoro, P., Garcia, S., De Micco, C.: Thyroperoxidase immunodetection for the diagnosis of malignancy on fine-needle aspiration of thyroid nodules. World J. Surg. *18*:529, 1994

6. Motté, P., Vauzelle, P., Gardet, P.: Construction and clinical validation of a sensitive and specific assay for serum mature calcitonin using monoclonal anti-peptide antibodies. Clin. Chim. Acta. *174*:35, 1988
7. Guilloteau, D., Perdrisot, D., Calmettes, C., Baulieau, J.L., Lecomte, P., Kaphan, G., Milhaud, G., Besnard, J.C., Jallet, P., Bigorgne, J.C.: Diagnosis of medullary carcinoma of the thyroid by calcitonin assay using monoclonal antibodies. J. Clin. Endocrinol. Metab. *71*:1064, 1990
8. Barbot, N., Calmettes, C., Schuffenecker, I., Saint André, J.P., Franc, B., Rohmer, V., Jallet, P., Bigorgne, J.C.: Pentagastrin stimulation test and early diagnosis of medullary thyroid carcinoma using an immunoradiometric assay of calcitonin: comparison with genetic screening in hereditary medullary thyroid carcinoma. J. Clin. Endocrinol. Metab. *78*:114, 1994
9. Guyetant, S., Wion-Barbot, N., Rousselet, M.C., Franc, B., Bigorgne, J.C., Saint André, J.P.: C-cell hyperplasia associated with chronic lymphocytic thyroiditis: a retrospective quantitative study of 112 cases. Hum. Pathol. *25*:514, 1994
10. Bergholm, V., Adami, H.O., Bergstrom, R., Swedish MTC Study Group: Clinical characteristics in sporadic and familial medullary thyroid carcinoma: a nationwide study of 249 patients in Sweden from 1959 through 1981. Cancer *63*:1196, 1981
11. De Bustros, A.C., Baylin, S.B.: Medullary carcinoma of the thyroid. In: The Thyroid: A Fundamental and Clinical Text (6th ed.), L.E. Braverman, R.D. Utiger, editors. Philadelphia, Lippincott, 1991, pp. 1166–1183
12. Ziegler, R.: Sporadic medullary thyroid carcinoma: clinical features and diagnosis. Recent Results Cancer Res. *125*:91, 1992
13. Niccoli, P., Conte Devolx, B., Lejeune, P.J., Carayon, P., Henry, J.F., Roux, F., Wion-Barbot, N., Bigorgne, J.C.: Les hypercalcitoninémie en dehors des cancers medullaires de la thyroïde. Ann. Endocrinol. (Paris) *57*:15, 1996
14. Body, J.J., Heath, H.: Nonspecific increases in plasma imunoreactive calcitonin in healthy individuals: discrimination from medullary thyroid carcinoma by a new extraction technique. Clin. Chem. *30*:511, 1984
15. Albores-Saavedra, J., Monforte, H., Nadji, M., Morales, A.R.: C-cell hyperplasia in thyroid tissue adjacent to follicular cell tumors. Hum. Pathol. *19*:795, 1988
16. Montesco, M.C., Pinarello, A., Ninfo, V.: Parafollicular C-cell hyperplasia: report of three cases in primary thyroid lymphomas. Tumori *74*:97, 1988
17. Biddinger, P.W., Brennan, M.F., Rosen, P.P.: Symptomatic C-cell hyperplasia associated with chronic lymphocytic thyroiditis. Am. J. Surg. Pathol. *15*:599, 1991
18. Wells, S.A., Chi, A.D., Toshima, K., Dehner, L.P.: Predictive DNA testing and prophylactic thyroidectomy in patients at risk for multiple neoplasia type 2a. Ann. Surg. *220*:237, 1994
19. Decker, R.A., Peacock, M.L., Borst, M.L., Borst, M.J., Sweet, J.A., Thompson, N.W.: Progress in genetic screening of multiple endocrine neoplasia type 2a: is calcitonin testing obsolete? Surgery *118*:257, 1995
20. Pacini, F., Romei, C., Miccoli, P., Elisei, A., Molinaro, E., Mancusi, F., Iacconi, P., Basolo, F., Martino, E., Pinchera, A.: Early treatment of hereditary medullary thyroid carcinoma after attribution of multiple endocrine neoplasia type 2a gene carrier status by screening for ret gene mutations. Surgery *118*:1031, 1995
21. Van Heerden, J.A., Grant, C.S., Gharib, H., Hay, I.D., Ilstrup, D.M.: Long-term course of patients with persistent hypercalcitoninemia after apparent curative primary surgery for medullary thyroid carcinoma. Ann. Surg. *212*:395, 1990
22. Moley, J.F., Wells, S.A., Dilley, W.G., Tisell, L.E.: Reoperation for recurrent or persistent medullary thyroid cancer. Surgery *114*:1090, 1993
23. Wells, S.A.: New approaches to the patient with medullary thyroid carcinoma of the thyroid gland. Thyroid Today *4*:1, 1994
24. Moley, J.F.: Medullary thyroid cancer. In: Textbook of Endocrine Surgery, O.H. Clark, Q.Y. Duh, editors. Philadelphia, Saunders, 1997, pp. 108–118

Invited Commentary

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According to the literature prior to 1994, sporadic medullary thyroid carcinoma (SMTC) accounts for 3% to 10% of all thyroid carcinomas [1]. In these large clinical series no specific or characteristic clinical feature of SMTC was described. Most of the patients showed palpable nodules, "cold" on scintigraphy. Sometimes ultrasonography depicted SMTCs as hypoechogenic, but this pattern is not pathognomonic or specific. Other thyropathies (local inflammation, thyrocyte tumors) may also be hypoechogenic. If the nodules were large enough or superficially situated in such a way as to guarantee a reliable evaluation, fine-needle aspiration, cytology, and immunochemistry were performed, which were sometimes helpful in diagnosing the SMTC preoperatively. The cytologists stress that the morphologic pattern of SMTCs is variable. Thus the characteristic pleomorphism, on the one hand, may lead to overdiagnosis and, on the other, may be suggestive of SMTC. Calcitonin assay was not recommended for "cold" nodules or routinely used in all patients with thyroid nodules because this diagnostic tool was thought not to be cost-effective [2].

The SMTC is described as a malignant tumor which from an early stage spreads to lymph nodes (palpable metastases 13–31%, micrometastases 37–75%) and shows distant metastases in up to 20% of cases [2].

A late, postoperative diagnosis results in an inadequate initial surgical procedure, especially in respect to lymph nodes. It results in a poor prognosis and a high rate of biochemically persistent disease, requiring a high rate of (sometimes unsuccessful) reoperations.

Recent prospective studies indicate that routine measurement of plasma calcitonin (CT) levels in all patients with thyroid disease allow the diagnosis of SMTC in 0.47% to 1.37% [3–6]. The results of the study by Henry et al. (prevalence of SMTC in patients with nodular disease 0.71%) are in accordance with our own results published recently by Vierhapper et al. [7], showing SMTC in 0.56%, respectively.

The CT screening and careful meticulous pathologic examinations result in a higher detection rate of SMTCs leading to a significant increase of SMTCs detected. In our own analysis the SMTC rate was 8% before and 19% during the period of routine CT screening [9]. Pacini et al. [3] described SMTCs in 17% and Rieu et al. [4] in 25% of all thyroid carcinomas. As concluded by Henry et al., only routine CT measurements offer the chance to diagnose all (micro)SMTCs, which would be missed in thyroid specimens obtained from other thyroid disorders without knowing the basal and pentagastrin (PG)-stimulated CT levels.

In agreement with Henry et al., basal serum CT levels (bCT) >10 pg/ml *in combination with* PG-stimulated serum CT levels (sCT) >100 pg/ml (=abnormal PG test; commercially available

radioimmunoassay (Cis-Biointernational, Gif-sur-Yvette, France) are *always* related to "abnormal" C cells.

We have analyzed 34 patients with an "abnormal" PG test. Altogether, 21 of these 34 patients (62%) showed C cell hyperplasia (CCH—at least one area with more than 50 C-cells per one low power field [100× magnification; [8] in both thyroid lobes]) only, while 13 patients (38%) had SMTCs, and 8 patients had SMTC plus CCH. By definition, all patients with SMTCs showed "subclinical" microcarcinoma (diameter ≤ 10 mm). In three patients (23%) with micro-SMTCs, lymph node micrometastases were documented at the time of surgery.

In contrast to the findings of Henry et al., our preliminary biochemical correlation [10] revealed that all patients with bCT > 64 pg/ml, sCT > 560 pg/ml, or both had SMTCs. These patients must undergo total thyroidectomy, central neck dissection, and lateral neck dissection because of the possibility of positive lymph nodes. In 5 of our 21 patients with a bCT > 35 pg/ml and < 64 pg/ml, only CCH could be documented. In patients with bCT < 64 pg/ml and sCT < 139 pg/ml, CCH may be predicted. Total thyroidectomy should be the minimal surgical procedure. Because CCH has a preneoplastic potential also in sporadic cases [8], central neck dissection is recommended. Patients with bCT < 64 pg/ml and sCT between 139 and 560 pg/ml may demonstrate CCH *or* SMTC. Further studies are necessary to specify this patient group more reliably. We recommend total thyroidectomy and central neck dissection; and in patients with visible tumors (tumor diameter > 3 mm) bilateral neck dissection is mandatory for removing possible micrometastases in lymph nodes, as found in 3 of 13 patients with micro-SMTCs. Following these surgical strategies, we were able to cure biochemically 93% of our screened SMTC patients.

We want to stress the conclusions by Henry et al., documented by this excellent study comparing screened and unscreened patients with SMTC, that routine determinations of CT must be included in the initial diagnostic evaluation of all patients with morphologic and functional thyroid disorders. It should be supplemented by PG stimulation if the basal CT concentration exceeds 10 pg/ml. Patients with an "abnormal" PG test must be operated because they run a substantial risk of suffering either SMTC or CCH, a potentially precancerous condition [7, 8]. This procedure increases the possibility of an early diagnosis of SMTC and provides the chance of early curative surgery. Balanced against a missed diagnosis and against the costs of a potential reoperation, such routine measurements of bCT may even be cost-effective.

References

1. Rosai, J., Carangui, M.L., DeLellis, R.A.: Atlas of Tumor Pathology: Tumors of the Thyroid Gland: 3rd Series. Washington, D.C., Armed Forces Institute of Pathology, 1992, pp. 247–258
2. Ziegler, R.: Sporadic medullary thyroid carcinoma: clinical feature and diagnosis. Recent Results Cancer Res. *125*:91, 1992
3. Paccini, F., Fontanelli, M., Fugazzola, L., Elisei, R., Romei, C., Di Cosia, G., Miccoli, P., Pinchera, A.: Routine measurement of serum calcitonin in nodular thyroid disease allows the preoperative diagnosis of unsuspected sporadic medullary thyroid carcinoma. J. Clin. Endocrinol. Metab. *78*:826, 1994
4. Rieu, M., Lame, M.C., Richard, A., Lissak, B., Sambort, B., Vuong-Ngoc, P., Berrod, J.L., Fombeur, J.P.: Prevalence of sporadic medullary thyroid carcinoma: the importance of routine measurement of serum calcitonin in the diagnostic evaluation of thyroid nodules. Clin. Endocrinol. (Oxf.) *42*:453, 1995
5. Henry, J.F., Denizot, A., Puccini, M., Niccoli, P., Conte-Devox, B., De Micco, C.: Early diagnosis of sporadic medullary cancer of the thyroid: contribution of routine calcitonin assay (in French). Presse Med *25*:1583, 1996
6. Niccoli, P., Wion-Barbot, N., Caron, P., Henry, J.F., De Micco, C., Sain Andre, J.P., Bigorgne, J.C., Mondigliani, E., Conte-Devolx, B.: Interest of routine measurement of serum calcitonin: study in a large series of thyroidectomized patient. J. Endocrinol. Metab. *82*:338, 1997
7. Vierhapper, H., Raber, W., Bieglmayer, C., Kasderer, K., Weinhäusl, A., Niederle, B.: Routine measurement of plasma calcitonin in nodular thyroid diseases. J. Clin. Endocrinol. Metab. *82*:1589, 1997
8. Kaserer, K., Scheuba, C., Neuhold, N., Weinhäusl, A., Vierhapper, H., Haas, O.A., Niederle, B.: C cell hyperplasia and medullary thyroid carcinoma in patients routinely screened for serum calcitonin. Am. J. Surg. Pathol. *22* (in press), 1998
9. Scheuba, C., Pandev, R., Kaserer, K., Prager, M., Passler, C., Vierhapper, H., Raber, W., Niederle, B.: Clinical effects of routine calcitonin measurements: preliminary results of a prospective study in surgical patients. Acta Chir. Austriaca *29*(Suppl. 135):2, 1997
10. Scheuba, C., Pandev, R., Kaserer, K., Prager, M., Passler, C., Niederle, B.: Medullary thyroid carcinoma (MTC): calcitonin levels and tumor staging—can metastases be predicted before surgery? Acta Chir. Austriaca *29*(Suppl. 135):5, 1997