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Medullary Carcinoma of the Thyroid: Prognostic Factors and Treatment Recommendations

Pascal R. Fuchshuber, MD, PhD, Thom R. Loree, MD, FACS, Wesley L. Hicks, Jr., DDS, MD, Richard T. Cheney, MD, and Donald P. Shedd, MD, FACS

Background: Because medullary thyroid carcinoma accounts for only 7% of all thyroid malignancies, data to support treatment strategies are scarce.

Methods: We retrospectively reviewed treatment and outcome in 34 patients with MTC treated at Roswell Park between 1961 and 1995. Univariate analysis was performed using the variables age, sex, tumor size, N stage, and M stage.

Results: Median survival was 4.7 years, with 51% and 32% of patients alive at 5 and 15 years, respectively. Nodal metastases were seen in 76% and distant metastases in 67% of all patients. More than 60% of the patients with nodal metastases survived longer than 10 years. Once diagnosed with distant metastases, 90% of the patients died within 5 years. Local failure rate with lobectomy was 44%, compared to 10% after total thyroidectomy ($P < .02$). Age, extrathyroid extension, and M stage portend a poor outcome. Nodal status had no statistically significant impact on survival.

Conclusion: Survival with tumors confined to the thyroid gland is independent of nodal status. Long-term survival in patients with distant metastases is rare. This study underscores the role of total thyroidectomy in the initial treatment and the need to develop effective adjuvant therapy for MTC.

Key Words: Medullary thyroid cancer—Thyroid cancer.

Medullary thyroid carcinoma (MTC) is a tumor of the parafollicular cells (C-cell), which secrete calcitonin.[1] It accounts for only 5% to 10% of all thyroid malignancies.[2] Therefore, clinical data to characterize the behavior of and establish treatment strategies for this disease remain limited. Despite its low incidence, MTC has attracted considerable interest because of its distinct clinical and pathologic features as well as its association with the MEN syndromes.

At Roswell Park Cancer Institute we treated 34 patients with MTC over a period of 34 years. This report presents our clinical experience, establishes prognostic factors, and evaluates our treatment strategies. Special emphasis is paid to the impact of regional and distant disease on survival, as well as the clinical importance of serum calcitonin levels in the treatment of MTC.

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From the Department of Head and Neck Surgery, Division of Surgical Oncology (PRF, TRL, WLH, DPS), and Division of Pathology (RTC), Roswell Park Cancer Institute, Buffalo, New York.

Address correspondence and reprint requests to Thom. R. Loree, MD Roswell Park Cancer Institute, Elm & Carlton Sts., Buffalo, NY 14263, USA.

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MATERIALS AND METHODS

The charts of all patients with histologically confirmed medullary thyroid carcinoma treated at Roswell Park Cancer Institute from January 1961 to December 1995 were reviewed (n = 34). Follow-up by letter or clinic visit was available on all 34 patients. Univariate analysis using the variables age, gender, tumor size, nodal status, and distant metastases was performed. All palpable or imageable disease within the thyroid bed was considered a local recurrence. Extrathyroid extension was defined as extension of local disease beyond the thyroid capsule on histologic examination. Superior mediastinal lymph node involvement was considered regional disease. Perihilar and lower mediastinal metastases were counted as distant disease. Basal serum calcitonin levels were correlated with the clinical course. Basal calcitonin levels were measured with radioimmunoassay. All available histo-

logic material was reviewed for C-cell hyperplasia. Patterns of failure were analyzed and correlated to treatments given.

Survival data was analyzed by the method of Kaplan and Meier.[3] Differences between groups were based on the log rank test and the Wilcoxon matched-pairs signed-rank test.[4]

RESULTS

The study included 34 patients with a mean age of 48 years (range 12 to 76 years) and a male-to-female ratio of 1.6 to 1. Five patients (15%) had MEN syndrome. Three of those patients had MEN IIa; the other two had MEN IIb. All patients in the MEN group were younger than 30 years (mean age 18 years, range 12 to 28 years). In contrast, all but one of the sporadic MTC patients were older than 30 years (mean age 53 years, range 27 to 76 years). In 12 of 29 non-MEN patients, histology material was available and was reviewed by one pathologist (RTC). None of the patients showed C-cell hyperplasia. Only one patient in the non-MEN group presented with bilateral disease, again with no evidence of C-cell hyperplasia.

Median follow-up was 18.7 years (range 1.6 to 32.9 years). Eleven patients (32%) were alive at the time of last follow-up, eight without evidence of disease and three with nodal disease. Twenty-two patients (65%) died of disease, one patient died of unrelated cause (leukemia), and two patients died of treatment complications related to chemotherapy. Two patients had no evidence of disease (NED) after treatment of metastatic disease outside the neck, one in the superior mediastinum and one with isolated lung metastases. All patients alive with disease had involvement of either the cervical or superior mediastinal lymph nodes, or both. Of the 22 patients who died of disease, 19 (85%) succumbed because of distant metastases. Only one patient died of locoregional disease, secondary to erosion of a major neck vessel after chemotherapy and radiation treatment.

The distribution of distant metastases is shown in Table 1. Lung, bone, and liver are the most common sites. Table 2 depicts the classification of the patients according to the TNM system. Sixty-five percent of the patients presented with N1 disease, and 33% had distant metastatic disease. Of the patients with distant metastases, 50% presented with palpable regional nodal disease.

The overall risk of regional nodal disease was 76%. This includes all patients who presented with or subsequently developed cervical or superior mediastinal nodal metastases. Similarly, the overall risk for distant metastatic disease was 67%, including all patients who presented with or eventually developed distant metastases.

TABLE 1. *Organ distribution of distant metastases in MTC patients*[a]

Lung	15
Bone	14
Liver	11
Mediastinum	8
Adrenal	2
Pituitary	2
Brain	1
Spleen	1
Kidney	1

[a] Multiple sites in one patient are listed separately.

Initial treatment consisted of total or subtotal thyroidectomy in 21 patients and lobectomy in seven patients (Table 3). All patients treated with combination chemotherapy and radiation alone had progression of disease. Local recurrences were significantly higher in patients undergoing lobectomy (4 out of 7) compared to patients treated with total or subtotal thyroidectomy (2 out of 21; $p = 0.02$, see Table 3).

Observation alone in clinically node-negative patients resulted in regional nodal recurrences in 36%. The only N0 patient who underwent elective neck dissection remains disease free. In patients with palpable cervical nodal disease, the recurrence rate was 41% even after a therapeutic neck dissection. There were no differences between MEN patients and patients with sporadic MTC in overall local, regional, and distant failure rates.

Figure 1 compares survival of patients with locoregional versus distant failures. Most patients with distant metastases succumb to their disease within 5 years. In contrast, long-term survival (>10 years) was seen in about two thirds of patients with locoregional failure only. Survival in patients with clinically detected multiple metastatic sites was uniformly poor (mean 23 months, range 2 to 48 months). Three out of four patients with distant disease who survived longer than 5 years had isolated bone metastases. All patients with superior mediastinal metastases are alive. One patient with an

TABLE 2. *TNM classification of 34 patients with medullary thyroid carcinoma*

	T1	T2	T3	T4	Total (%)
N0 M0	—	4	3	—	7 (20)
N1 M0	1	8	1	6	16 (47)
N0 M1	2	2	1	—	5 (15)
N1 M1	—	2	1	3	6 (18)

TABLE 3. *Initial treatment of 34 patients with medullary thyroid carcinoma and local recurrence rate for each treatment category*

Treatment	Total no. patients	Local failure	
		No. patients	Percentage
Total thyroidectomy	19	2	2/21 (9.5%)
Subtotal thyroidectomy	2	0	$P = .02$
Lobectomy	7	4	4/7 (57%)
Chemo- and radiotherapy only	3	3	6/6 (100%)
No treatment	3	3	

isolated lung metastasis is free of disease 16 years after wedge resection.

Overall median survival was 4.7 years, with 51% and 26% of patients alive at 5 and 20 years, respectively. Disease-free survival at 5 and 20 years was 41% and 16%, respectively (Fig. 2). Survival according to TNM stage is shown in Figure 3. In patients with tumor confined to the thyroid gland there were no survival differences between N0 and N1 patients. Survival was significantly worse in patients presenting with T4 disease ($P < .05$) and distant metastases ($P < .01$). Overall survival in MEN patients versus sporadic MTC patients was not significantly different.

By univariate analysis, age >50 years ($P < .025$), extrathyroidal extension ($P < .05$), and M stage ($P < .001$) attained significant negative prognostic value. Gender, N stage, and tumor size did not influence survival significantly. The distribution of extrathyroidal extension and distant metastases was not significantly different in the younger patients (<50 years of age) as compared to those patients over 50 years of age (33% versus 23% for extrathyroid extension and 66% versus 61% for metastases, respectively).

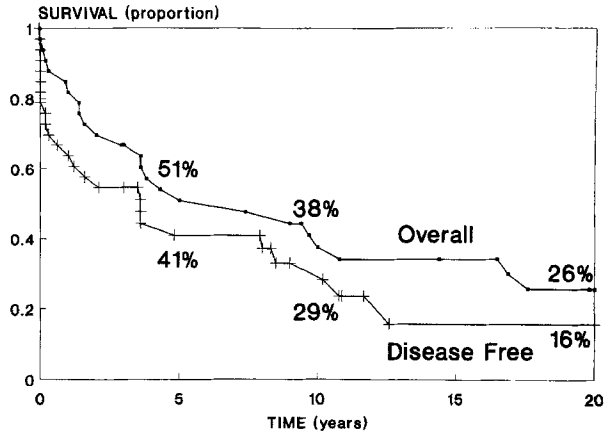

FIG. 2. Disease-free and overall survival for 34 patients with medullary thyroid carcinoma.

Multiple serum calcitonin levels were obtained in 21 patients. These results were correlated to clinical course (Table 4 and 5). In 14 of 15 patients, in whom disease recurred or progressed, calcitonin levels increased by a mean of 7-fold (see Table 4). In this group serum calcitonin levels remained the same in only one patient; no decrease was observed. The increase of serum calcitonin secondary to disease progression or recurrence was significant ($P < .02$) (see Table 5). If no disease progression or recurrence occurred (NED patients), serum calcitonin levels decreased in five out of six patients (see Table 4). The mean serum calcitonin level for this group of patients was 1133 pg/mL (range 8 to 3913). A normal calcitonin level (<300 pg/mL) was seen in only two of the six NED patients. Surgical treatment, either an initial thyroidectomy or a secondary procedure such as neck dissection for disease recurrence, significantly lowered serum calcitonin levels ($P < .002$) (see Table 5).

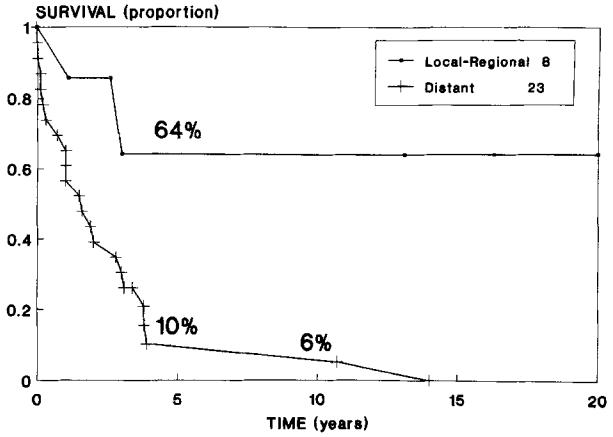

FIG. 1. Overall survival of patients with locoregional (N1) and distant (M1) disease.

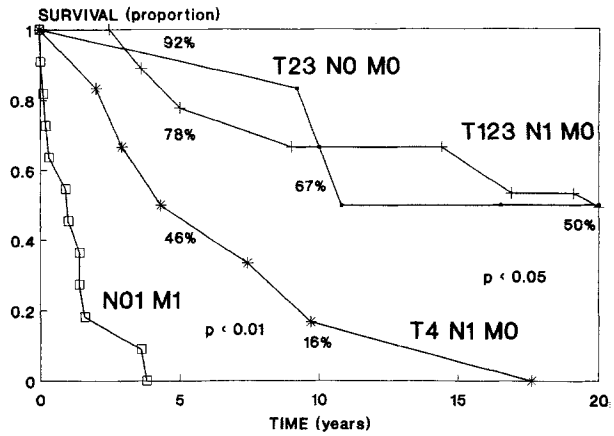

FIG. 3. TNM stage and survival. For tumors confined to the thyroid there were no significant differences between N0 and N1 patients.

TABLE 4. *Correlation of calcitonin levels adn clinical course in 34 patients with medullary thyroid carcinoma*

Serum calcitonin	Recurrence/progression	
	Yes	No
Raised	14 (7)[a]	1 (2)
Decreased/same	1 (2)	5 (5)

[a] No. patients (mean fold increase/decrease).

DISCUSSION

Early diagnosis and complete thyroidectomy for medullary thyroid carcinoma are well-established clinical treatment strategies.[5–11] There are several reasons for performing a complete thyroidectomy in MTC.[6,7] First, the sporadic nature of the disease may not have been established at the time of surgery. If the patient has the hereditary form of the disease, C-cell hyperplasia left behind in the contralateral lobe may progress to carcinoma. Second, intrathyroidal metastases do occur in sporadic MTC. Furthermore, detection of metastatic disease may be rendered difficult if residual tumor is present in the remaining thyroid gland.

Differentiation between sporadic and familial forms of the disease is facilitated by genetic testing for specific exons of the RET proto-oncogene.[12,13] However, it appears in this study that in the absence of genetic testing most patients are correctly assigned to each group by age at presentation. The cut-off age of 30 years confirms findings by other researchers.[6,7] Because of the occasional sporadic or familial MTC patient who manifests at an earlier or later age, respectively, genetic testing is recommended.[6,7,12,13]

Age has been recognized in several studies as a significant prognostic factor for survival, and that observation confirmed in this study.[5,14] The cut-off reported for age varies between 40[5,15,16] and 60[14] years, with 50 years reported in this study. The range reported for age is probably a reflection of the bias introduced by the retrospective nature of the analysis. Although gender has been identified by others as a significant prognostic factor,[5,14,16] it did not have a significant impact on survival in this study.

TABLE 5. *Change in mean basal serum calcitonin levels after surgical treatment (thyroidectomy and/or neck dissection) and after occurrence of disease recurrence/progression in medullarythyroid carcinoma*

Change in clinical course	Serum calcitonin level (mean and range in pg/mL)
Surgical treatment	
Before	14637 (5000–41900) $P < .002$
After	6460 (300–19220)
Recurrence progression	
Before	20566 (261–180000) $P < .02$
After	68475 (1262–500000)

P value by Wilcoxon matched-pairs signed-rank test.

The significantly higher local recurrence rate found in the lobectomy group in this study does suggest that complete thyroidectomy is the most appropriate initial treatment for most patients with MTC. On occasion, a microscopic MTC is found on pathologic evaluation after thyroid lobectomy. If the specimen does not show C-cell hyperplasia, further thyroid resection may not be needed.[17] However, currently we do perform a completion thyroidectomy in all patients diagnosed with MTC. The data presented here show that patients with tumors confined to the thyroid gland do significantly better than do patients with extrathyroidal extension. The importance of extrathyroidal extension as a prognostic factor in MTC has been established in similar studies by others.[5,8,14,15,18]

Metastases at presentation or subsequent to initial therapy significantly affect survival in patients with MTC.[14] Survival beyond 5 years with distant metastases was rare, and was seen only in patients with metastases confined to one organ site. Patients with distant metastases in multiple organs had a mean survival of only 23 months. Similar findings have been reported by others.[5] In this study, most patients with long-term survival after surgical treatment for distant metastases had disease confined to the superior mediastinum, thus supporting surgical resection of superior mediastinal metastases. In one study, patients with mediastinal nodal disease did worse than did those with cervical nodal metastases.[15] However, improved outcome following aggressive surgical resection of cervical and anterior superior mediastinal nodal groups in patients with MTC has been demonstrated by others.[18,19]

It has been proposed that occult liver metastasis represents a particular entity of MTC[19–22] and is one of the reasons for persistently elevated calcitonin levels in long-term survivors.[15,20,23–25] In one study, clinically undetectable liver metastases were found in 8 of 41 MTC patients following liver biopsy by laparotomy or laparoscopy.[22] All patients had hypercalcitonemia following initial surgical treatment of MTC. However, only one patient had sporadic MTC. The remaining seven patients had MEN-associated MTC. Although specific efforts to detect subclinical micrometastatic disease in our patients were not made, our data suggest that recurrent or persistent sporadic MTC is more likely to reside in lymph nodes. Only one patient with liver metastases has survived longer than 5 years. Most patients in this study who are alive with disease do not have organ metastases

but, rather, have involvement of regional and mediastinal nodal basins. In addition, our data do not suggest a predilection of MTC to metastasize to the liver more often than to other organ sites (see Table 1). Extensive diagnostic work-ups including MRI, CT, and a variety of nuclear scans in patients with metastatic MTC have revealed predominantly local soft tissue involvement.[26] In this other study, bone and lung metastases also were seen, but the study failed to show liver metastases. These findings indicate a higher probability for the presence of clinically occult nodal metastases in patients with persistent calcitonin elevations and in the absence of clinically detectable disease. We do acknowledge the existence of a micrometastatic form of liver metastasis in long-term survivors of MTC. It appears to occur more often in patients with MEN-associated MTC. However, in the absence of effective systemic therapy, further studies are needed to establish the clinical relevance of this form of MTC.

Interestingly, one patient in this series is free of disease 16 years following resection of a single lung metastasis. Resection of organ metastases usually is not advocated in this disease,[27] but in the unusual circumstance of a single isolated lung metastasis, it might be beneficial to perform surgical resection.

Our results confirm the fact that regional lymph node metastases occur in 60% to 80% of patients with MTC.[8,28,29] Nevertheless, the question of how to address the regional nodal basin in MTC remains controversial. In previous studies the presence of nodal disease in MTC has been identified as a significant prognostic factor.[5,14,15,17] In contrast to these studies, our analysis shows no significant impact on survival for nodal disease in patients with MTC. Most authors advocate therapeutic neck dissection for clinically detectable lymph node involvement,[5,6,8,27] and our data support this recommendation. However, this study demonstrates a substantial regional failure rate of 41% following therapeutic neck dissection for palpable regional disease. Furthermore, observation in clinically N0 patients leads to a 36% rate of subsequent regional nodal metastases. Hence, although limited by the small number of patients, our data suggest a role for elective nodal dissection in MTC patients without palpable regional disease. This suggestion is based on the observations that micrometastatic disease in the regional nodal basin is prevalent and salvage rates after development of palpable regional disease are limited. Similar recommendations have been made by others.[5,8,10,30] Some authors recommend a central node dissection in all patients with MTC, regardless of the clinical nodal status.[5,6,8,10,13]

We were not able to demonstrate a significant prognostic value for tumor size on univariate analysis. Other reports have shown that tumors over 3 cm^{31} or 4 cm^{14} do carry a significantly poorer prognosis. However, in the series reported by Scopsi et al.,[14] the prognostic significance for tumor size disappeared after multivariate analysis.

Serum calcitonin has been established as a valuable marker for screening as well as for detection of recurrent disease.[5,15,16] It is not as sensitive as pentagastrin stimulation[32] and clearly is being supplanted by molecular markers in the screening for familial MTC.[8,10] However, serum calcitonin levels in the majority of patients with MTC correlate closely with the clinical course and can be used to monitor disease recurrence and progression. Postoperative persistent elevations of calcitonin are seen in more than half of patients with MTC,[25] even in the absence of clinically detectable disease.[19] In this study only two patients with no evidence of disease (NED) had normal calcitonin levels (<300 pg/mL). However, only one NED patient had a calcitonin level higher than 1200 pg/mL. None of the patients with recurrent disease had calcitonin levels below 1200 pg/mL. The clinical significance of persistent stable calcitonin elevations in clinically disease-free patients with MTC remains uncertain.[15,23,24] Any attempt at reoperation should probably take into account the higher proportion of nodal disease in long-term survivors. Selective venous sampling techniques may be helpful in ruling out distant metastatic disease.[6,20,22] In several studies in which selective venous sampling was used to plan repeat surgical exploration, most patients were found to have disease recurrence in the neck region.[10]

We did not see differences in outcome between sporadic MTC patients and MEN patients. This may be due to the fact that in our patient population most MEN patients were diagnosed with metastatic disease. Other investigators have shown that patients with familial forms of MTC, once metastases are present, do not appear to have a different outcome compared to patients with sporadic MTC.[15,33]

Medullary carcinoma of the thyroid remains particularly intriguing to the surgical oncologist because of its locally aggressive behavior and high proportion of regional metastases. Several conclusions can be drawn from this retrospective clinical study. Extrathyroid extension, age, and M stage have adverse prognostic value for survival. Gender, N stage, and tumor size do not affect survival. Initial attempts at complete surgical removal of disease remain the key treatment strategy and should include total thyroidectomy and neck dissection. Evidence suggests that aggressive surgical therapy is beneficial in recurrent nodal disease. In selected patients,

resection of isolated lung metastases may be appropriate. The clinical data presented here suggest a role for elective node dissection in clinically N0 patients. Currently the role for chemotherapy and radiotherapy seems limited to unresectable disease and for palliative intent. Persistent low serum calcitonin elevations suggest residual nodal disease rather than distant metastases.

REFERENCES

1. Williams ED. Histogenesis of medullary carcinoma of the thyroid. *J Clin Pathol* 1966;19:114–8.
2. Norman T. Medullary thyroid carcinoma in Norway: epidemiological and genetic data. *Acta Pathol Microbiol Scand* 1977;85: 775–86.
3. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–86.
4. Wilcoxon F. Individual comparison by ranking methods. *Biometrics* 1945;1:80–3.
5. Kallinowski F, Buhr HJ, Meybier H, Eberhardt M, Herfarth C. Medullary carcinoma of the thyroid—therapeutic strategy derived from fifteen years of experience. *Surgery* 1993;14:491–6.
6. Thompson NW. Thyroid cancer. In: Niederhuber JE, ed. *Current Therapy in Oncology*. Philadelphia: BC Decker, 1993:240–8.
7. Thompson NW. Surgery for medullary thyroid carcinoma. In: Fee WE, Goepfert H, Johns ME, eds. *Head and Neck Cancer.* Vol. 2. Philadelphia: BC Decker, 1990:196–8.
8. Block MA. Surgical treatment of medullary carcinoma of the thyroid. *Otolaryngol Clin North Am* 1990;23:453–73.
9. Simpson WJ, Palmer JA, Rosen IB, Mustard RA. Management of medullary carcinoma of the thyroid. *Am J Surg* 1982;144:420–2.
10. Moley F. Medullary thyroid cancer. *Surg Clin North Am* 1995;75: 405–20.
11. Duh QY, Sancho JJ, Greenspan FS, et al. Medullary thyroid carcinoma. The need for early diagnosis and total thyroidectomy. *Arch Surg* 1989;124:1206–10.
12. Marsh DJ, Leanoyd DL, Andrews SD, et al. Somatic mutations in the RET proto-oncogene in sporadic medullary thyroid carcinoma. *Clin Endocrinology* 1996;44:249–57.
13. Callender DL, Sherman SI, Gagel RF, Burgess MA, Goepfert H. Cancer of the thyroid. In: Meyers EN, Suen JY, eds. *Cancer of the Head and Neck.* Philadelphia: WB Saunders, 1996:485–515.
14. Scopsi L, Sampietro G, Borachi P, Del Bo R, Gullo M, Placucci M, Pilotti S. Multivariate analysis of prognostic factors in sporadic medullary carcinoma of the thyroid. A retrospective study of 109 consecutive patients. *Cancer* 1996;78:2173–83.
15. Ellenhorn GD, Shah JP, Brennan MF. Impact of therapeutic regional lymph node dissection for medullary carcinoma of the thyroid gland. *Surgery* 1993;114:1078–81.
16. Saad MF, Ordonez NG, Rashid RK, Guido JJ, Hill S, Hickey RC, Samaan NA. Medullary carcinoma of the thyroid. A study of the clinical features and prognostic factors in 161 patients. *Medicine* 1984;63:319–42.
17. Foster RS. Thyroid gland. In: Davis JH, Sheldon GF, eds. *Surgery: A Problem-Solving Approach,* 2nd ed. St. Louis: Mosby, 1996: 2183–2247.
18. Moley JF, Wells SA, Dilley WG, Tisell LE. Reoperation for recurrent or persistent medullary thyroid cancer. *Surgery* 1993;114: 1090–5.
19. Block MA, Jackson CE, Tashjian AH. Management of occult medullary thyroid carcinoma. *Arch Surg* 1978;113:368–72.
20. Gautvik KM, Talle K, Hager B, Jorgensen OG. Early liver metastases in patients with medullary carcinoma of the thyroid gland. *Cancer* 1989;63:175–80.
21. Ahuja S, Ernst H. Dormant metastases in medullary thyroid carcinoma. A case report. *Exp Clin Endocrinol* 1991;98:37–41.
22. Tung WS, Vesely TM, Moley JF. Laparoscopic detection of hepatic metastases in patients with residual or recurrent medullary thyroid cancer. *Surgery* 1995;118:1024–9.
23. Van Heerden JA, Grant CS, Gherib H, Hay ID, Ilstrup DM. Long-term course of patients with persistent hypercalcitonemia after apparent curative primary surgery for medullary thyroid carcinoma. *Ann Surg* 1990;212:395–400.
24. Raue F, Winter J, Frank-Raue K, Lorenz D, Herfarth C, Ziegler R. Diagnostic procedure before reoperation in patients with medullary thyroid carcinoma. *Horm Metab Res Suppl* 1989;21:31–4.
25. Block MA, Jackson CE, Greenwald KA, Yott JB, Tashjian AH. Clinical characteristics distinguishing hereditary from sporadic medullary thyroid carcinoma. *Arch Surg* 1980;115:142–8.
26. Ugur O, Kostaglu L, Guler N, et al. Comparison of 99 mTc-DMSA, 201Tl and 99 Tc MIBI imaging in the follow-up of patients with medullary carcinoma of the thyroid. *Eur J Nucl Med* 1996;23:1367–71.
27. Soybel DI, Wells SA. Medullary thyroid carcinoma. In: Cady B, Rossi RL eds. *Surgery of the Thyroid and Parathyroid Glands.* Philadelphia: WB Saunders, 1991:152–78.
28. Simpson WJ, Palmer JA, Rosen JB, Mustard RA. Management of medullary carcinoma of the thyroid. *Am J Surg* 1982;144:420–2.
29. Tissels LE, Hansson G, Jansson S, Salander H. Reoperation in the treatment of asymptomatic metastasizing medullary thyroid carcinoma. *Surgery* 1986;99:60–6.
30. Pomorski L, Rybinski K. Lymphadenectomy in thyroid gland carcinoma—staging and therapy [in German]. *Zentralblatt fuer Chirurgie* 1996;121:455–8.
31. Bergholm U, Adami HD, Bergstroem R, et al. Clinical characteristics in sporadic and familial medullary thyroid carcinoma. *Cancer* 1989;63:1196–1204.
32. Gautvik KM. Medullary carcinoma of the thyroid. An update of diagnostic and prognostic factors. *Scand J Clin Lab Invest* 1991;206(Suppl):85–92.
33. Kullberg BJ, Nieuwenhuijzen Kruseman AC. Multiple endocrine neoplasia type 2b with a good prognosis. *Arch Intern Med* 1987; 47:1125–7.