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Changes in risk factors and Tumor Node Metastasis stage of sporadic medullary thyroid carcinoma over 41 years, before and after the routine measurements of serum calcitonin

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Abstract

The measurement of serum calcitonin (CT) in all thyroid nodules for the detection of medullary thyroid carcinoma (MTC) is controversial. We compare several prognostic factors, Tumor Node Metastasis (TNM) stage, and survival in sporadic MTC patients operated on before and after the use of routine measurements of serum CT in combination with thyroid ultrasonography (US). Thirty-seven patients had been operated on between 1969 and 1989 (group I), before the use of routine measurements of serum CT and the routine use of thyroid US, and 39 (group II) had been operated on between 1990 and 2009, after the introduction of routine use of serum CT and thyroid US. There were no between-group differences concerning age and sex. Group I had larger tumors at the time of operation ($P < .001$) and higher postoperative serum CT levels ($P < .001$). Cervical lymph node and distant metastases were found more frequently in group I in comparison with group II. The cases with TNM stage I were significantly higher in group II than in group I, in contrast with the cases with TNM stage IV that were significantly higher in group I. Univariate analysis revealed a significantly higher 15-year survival rate in group II than in group I ($P = .002$). The postoperative CT levels were positively correlated with tumor size ($P < .001$). During the last 2 decades, the diagnosis of sporadic MTC at an earlier stage has been made possible by the routine use of serum CT in combination with thyroid US. The significant increase of the 15-year survival rate shows better outcome in these patients.

1. Introduction

Medullary thyroid carcinoma (MTC) is a neuroendocrine neoplasm arising from the parafollicular C cells and represents 2% to 5% of all cases of thyroid malignancies [1]. The tumor is more aggressive than differentiated thyroid carcinoma, and the death rate due to MTC accounts for 13.4% of all thyroid cancer–related deaths [2]. A number of different staging systems have been proposed for the evaluation of patients with MTC [3,4]. On the other hand, numerous independent studies have evaluated the outcomes of treatment of MTC and have defined several separate prognostic factors for overall survival. For example, capsular infiltration is an independent bad prognostic factor regardless of tumor size and node metastases [5]. The extrathyroidal extension and the stage at diagnosis are independent predictors of life expectancy [6]. The normalization of postoperative serum calcitonin (CT) is associated with significant improvement of survival [7], and the postoperative CT doubling time seems to be a significant predictor of survival [8].

Basal serum CT level is a useful marker for the diagnosis of MTC. In some centers, after the introduction of routine serum CT measurement in all patients with thyroid nodules, a significant down-staging of the MTC was shown [9,10]. An improvement of the 10-year survival of these patients was also shown [9]. However, the routine measurement of serum CT is still controversial [11,12]. In addition, because of the wide use of thyroid ultrasonography (US) and color Doppler over the last 20 years, nonpalpable thyroid nodules can be detected and small lesions with malignant potential can be identified [13].

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The aim of this study was to compare several significant prognostic factors, tumor staging, and survival rate in all sporadic MTCs that were diagnosed in a single institution over a 41-year period before and after the use of serum CT as a routine test in combination with thyroid US in all thyroid nodules.

2. Methods

The files of patients diagnosed with MTC over the last 41 years were retrospectively evaluated. Among 102 patients treated for MTC in the Second Endocrine Unit of Alexandra Hospital during the period from 1969 to 2009, 80 had sporadic MTC and 22 patients were members of families with multiple endocrine neoplasia. From 80 patients with sporadic MTC, 76 with long-term follow-up and data before and after the operation were studied. Sporadic cases were documented from the absence of clinical signs, symptoms, and laboratory findings of pheochromocytoma and/or hyperparathyroidism either in patients with MTC or in their first- or second-degree relatives. After 1993, the familiar or sporadic nature of MTC was defined by DNA-based analysis. Thirty-seven patients (group I) were diagnosed before 1990 when CT measurement and thyroid US screening were not routinely performed in our institution. These patients underwent thyroidectomy for nontoxic multinodular goiter, and MTC was diagnosed postoperatively. In 18 of 37 patients from group I, the sporadic MTC was also confirmed by DNA analysis during the reexaminations, after 1993. The follow-up was 41 years (range, 1-41). Group II consisted of 39 patients with MTC diagnosed between 1990 and 2009 with a follow-up of 1 to 20 years. Group II cases were preoperatively diagnosed by clinical examination, thyroid US, and elevated basal CT levels (>40 pg/mL) and were operated on regardless of the results of fine needle aspiration cytology; and all had been evaluated by genetic screening. In our experience, basal CT levels more than 40 pg/mL indicate MTC. Before surgery, conditions other than MTC that were associated with elevated CT were excluded [14-16]. In patients with mildly elevated basal CT levels (>14 and ≤40 pg/mL), the calcium stimulation test was performed [17]. Serum CT was measured before and at the end of the 10-minute infusion of calcium gluconate (2.7 mg Ca per kilogram). Results were considered indicative of MTC when peak CT levels exceeded 10 times the basal levels. The same CT stimulation test was used to assess postsurgical cure. *Postoperative biochemical remission* was defined as undetectable serum CT levels before and after the calcium stimulation test. The postoperative CT was measured at least 1 month after the operation and every 6 months thereafter. In our center, serum CT was determined with commercial kits. Before 1990, we used a polyclonal radioimmunoassay method. Between 1990 and 2005, CT was determined using a 2-site chemiluminescence immunoassay (Advantage; Nichols Institute Diagnostics, San Juan Capistrano, CA). The sensitivity of the assay was 0.3 pg/mL. The within-assay coefficient of variation (CV) was 3.3% and the between-assay CV 9.5% at the 9-pg/mL level. Between 2006 and 2009, CT was determined by chemiluminescence immunoassay (Immulite 2000, Siemens Medical Solutions Diagnostics, LA, USA). The sensitivity of the assay was 2.0 pg/mL. The within-assay CV was 15.7% and the between-assay CV was 15.7% at the 11.5-pg/mL level. Undetectable CT was assigned the value of 0.05 pg/mL for the purpose of calculations. For the thyroid US examinations, commercially available scanners with capability to visualize lesions as small as 2 mm were used. The tumor staging was documented according to the Tumor Node Metastasis (TNM) classification recommended by the American Joint Committee on Cancer in 2002 [4]. The research was approved by the local ethical and scientific committee, and all patients have signed inform consent.

2.1. Statistical analysis

Age, tumor size, and CT values are expressed as mean ± SD. Categorical data are summarized using frequencies. Statistical evaluation was carried out using SPSS 13 (SPSS, Chicago, IL). Mean values between the 2 groups were compared by the nonparametric Mann-Whitney *U* test for continuous variables. Comparison of 2 groups of categorical variables was performed using the χ^2 test. The time of diagnosis was analyzed as a categorical variable. The correlation between variables is expressed as Spearman rank correlation coefficient. The difference in the proportion and 95% confidence intervals (CIs) were estimated for separated risk factors between the 2 groups. The 15-year disease-specific deaths were calculated by the nonparametric generalized Wilcoxon test (Gehan test). $P < .05$ was considered statistically significant.

3. Results

At the time of diagnosis, the 2-way comparison did not show significant differences in the patients' age and sex between the 2 groups ($P = .249$, not significant [NS] and $P = .987$, NS, respectively) (Table 1). Consistent with other studies for sporadic MTC, the mean age at surgery was 53 ± 8 and 55 ± 9 years in groups I and II, respectively [6]. The tumor size was recorded taking into account the primary tumor diameter at gross pathologic examination. There was a significant difference in tumor size between the 2 groups ($P = .001$) (Table 1). Of note, in group I, 10 (27%) of 37 patients had tumors of at least 4 cm; and 2 had 0.5-cm tumors. In contrast, in group II, only 3 (8%) of 39 patients had tumor of at least 4 cm ($\chi^2 = 8.1$, $P = .004$). Interestingly, compared with group I, there was a significant increase in the proportion of microscopic MTC (<1 cm) in group II (Table 1), where the preoperative diagnosis was based on thyroid US in combination with elevated basal CT levels; and 8 of them revealed an increase in CT levels after calcium

Table 1
Comparison of patients and tumor characteristics between the 2 groups

	Group I	Group II	*P* value
n (total)	37	39	
Age (y)	55 ± 6	56 ± 8	NS
Female/male	30/7	31/8	NS
Tumor size (cm)	3.5 ± 1.7	0.9 ± 1.4	=.015
Subclinical MTC (%)	5	33	<.001
Capsular invasion (%)	75	43	<.001
Lymph node metastasis (%)	56	35	<.01
Distant metastasis (%)	32	15	<.001
Tumor stage (%)			
I	14	49	<.001
II	24	18	NS
III	10	15	NS
IVA	25	2	<.001
IVC	29	15	<.01
IVA + IVC	54	18	<.001
Disease-specific death 15 y after thyroidectomy (%)	65 (24/37)	15 (6/39)	=.002

Group I: patients with MTC diagnosed before the introduction of the routine measurement of CT in all thyroid nodules. Group II: patients with MTC after the routine measurement of CT. The TNM staging system was adopted from the American Joint Committee on Cancer in 2002 [4]. Statistical analysis was performed by Mann-Whitney *U* tests and by Pearson χ^2 tests.

stimulation test. The postoperative serum CT levels were significantly higher in group I (mean = 2121 pg/mL, SD = 5420, range = 0.05-24000, median = 300) than in group II (mean = 665 pg/mL, SD = 2189, range = 0.05-12000, median = 17.5) ($P < .01$). This was in accordance with larger tumor size and more extensive disease demonstrated by the lymph node or distant metastases at the time of diagnosis in group I (Table 1). Consistent with these results was the observation of a strong positive correlation between preoperative CT in group II and tumor size (data not shown) as well as between postoperative CT values and tumor size in both groups (Fig. 1). Moreover, the percentage of biochemical cure, as it was assessed by undetectable basal and calcium-stimulated serum CT, was significantly higher in group II, reaching 64% in comparison with 30% of group I ($\chi^2 = 6.9$, $P = .008$). It is notable that, in both groups, all but one of the cases with tumor size less than 1 cm had undetectable serum CT postoperatively. In addition, in group II, most microscopic MTCs (10 of 13) were diagnosed during the last 12 years (data not shown). Regarding the prognostic factors for more advanced disease, the odds ratio for both node and distant metastases at the time of diagnosis was significantly higher in group I than in group II ($\chi^2 = 7.347$, $P = .007$) (odds ratio = 5.7; 95% CI, 2.3-14.0; $P < .001$).

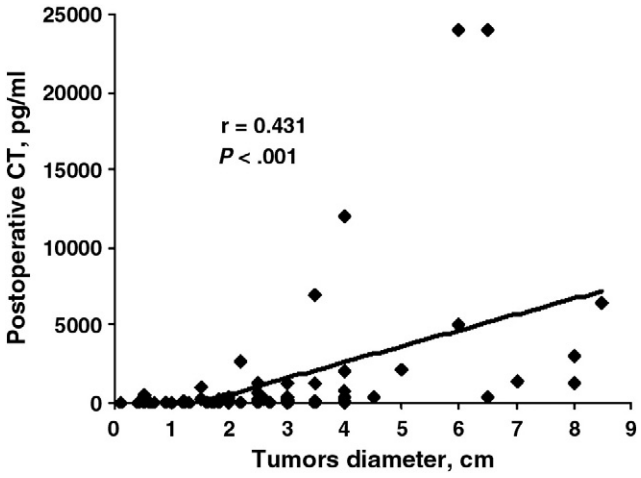

Fig. 1. Correlation between postoperative serum CT levels and tumor diameter in both groups. Undetectable CT was assigned the value of 0.5 pg/mL for the purpose of calculations.

Table 2
Comparison of the mean age of the 2 groups of patients belonging to the same TNM stage of MTC

	Age (y)		
	Group I	Group II	*P* value
Tumor stage			
I	56 ± 7	57 ± 7	NS
II	57 ± 8	56 ± 6	NS
III	58 ± 6	56 ± 3	NS
IVA + IVC	57 ± 7	56 ± 6	NS

Stratification of the mean age of patients and the TNM.

The overall analysis showed significant differences in tumor TNM stages between the 2 groups. The prevalence of patients with stage I disease was significantly higher in group II than in group I ($P < .001$); and again, the number of patients classified as having stage IV disease was significantly higher in group I than in group II ($P < .01$) (Table 1). Furthermore, analysis was stratified according to the mean

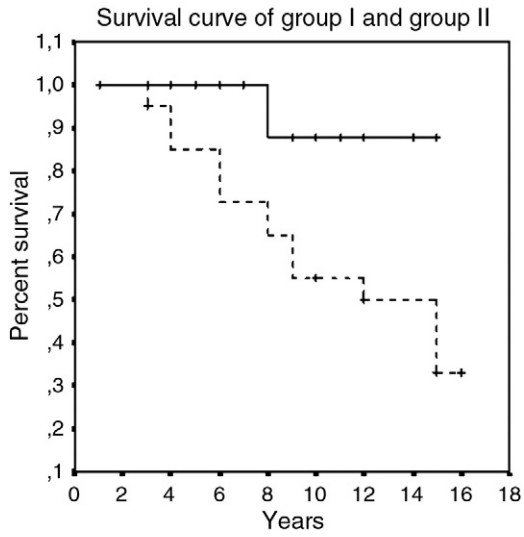

Fig. 2. Kaplan-Meier survival plots of the patients with sporadic MTC diagnosed before (group I) and after (group II) the introduction of routine measurement of serum CT in combination with thyroid US. Broken line = group I; solid line = group II. A significantly better outcome is shown in group II than in group I. The 15-year survival rate was 32% for group I and 87% for group II ($\chi^2 = 9.49$, $P = .002$, by Gehan test).

age of patients and the TNM. The comparison of the mean age of the 2 groups of patients belonging to the same stage did not show any significant difference (Table 2). In both groups with distant metastasis, the liver was most commonly involved. The 15-year survival rate of the patients in group II was significantly higher from that of patients in group I (χ^2 = 9.46, P = .002, Fig. 2). Thus, the above clearly shows a move toward less advanced tumor stage at the time of diagnosis in our center over the last 2 decades.

4. Discussion

This single-center retrospective study confirmed previous reports of earlier diagnosis of MTC as judged by the TNM stage, survival rate, or other prognostic factors as have been listed from several authors [4,6,9,18]. Our series includes a historical group of MTC patients that had been operated on between 1969 and 1989 and a group that underwent surgery after 1990 based on elevated serum CT levels even in patients with small unpalpable nodules recognized only by US. All researches have shown that the earlier the operation of MTC, the better the prognosis.

Although in studies covering a wide period the risk of biasing factors is high, the study was appropriately designed to avoid such a risk. For example, there was no "dropout bias" because only 4 patients were missing, the referral patterns to the institution has not significant change over time, the time of diagnosis was analyzed as a categorical variable, and the criteria for histology were homogeneous over time, allowing comparable staging and grading between the 2 groups. The impact of the various surgical options on postsurgical outcome in both groups is mentioned separately.

It is well known that serum CT levels are a very useful marker for both preoperative diagnosis and postsurgical follow-up of MTC [16]. However, for several reasons, controversial opinions are present in the literature regarding CT screening for patients with thyroid nodules [19,20]. In our cases, after 1990, the use of basal or basal plus stimulated CT levels in combination with thyroid US allowed us to identify smaller-sized MTCs in comparison with those before 1990. This combination was useful especially for subclinical MTCs that evade palpation and where fine needle aspiration cytology is usually unsuccessful. This is demonstrated by the increased proportion of MTC less than 1 cm in size in group II. The tumor size is important in the classification of tumor staging (T category) as well as for the chance of postoperative biochemical cure [21]. The average size of tumors in our group II was also much smaller than the average of the group of 1252 patients studied by Roman et al [2]. Twenty years ago, thyroid US was not routinely performed; and small MTCs were probably not detected, an issue which was raised by Elisei et al [9]. The fact that, in our study, almost all small tumors had no metastases and all had biochemical cure shows the importance of the early detection of MTC [2].

Besides biochemical cure in small tumors, we found that more cases, even with larger lesions, had undetectable postoperative CT levels in group II compared with group I, which seems to be associated with good prognosis [7]. At this point, we can suggest that most individuals in group II had complete surgical resection by expert surgeons who have, during the last decades, realized that even small MTCs could be associated with lymph node metastases and that a more extensive surgery is associated with better prognosis [2,19,22,23]. This is particularly critical in group II patients because they underwent surgery because of elevated preoperative CT levels that have influenced the surgical options. The fact that the postoperative CT levels were significantly lower in group II, apart from the overall smaller size of MTCs, reflects the overall earlier stage at the time of operation in group II. In this regard, we found a strong positive correlation between tumor size and postoperative CT levels in both groups, showing that the larger tumors are associated with more advanced disease at the time of diagnosis with less chance for complete remission, although according to Cohen et al [21] a higher preoperative CT does not predict absence of postoperative CT normalization. In addition, in accordance with other studies, the preoperative basal CT levels were strongly and positively correlated with tumor size and TNM stage [21,24].

Many authors have emphasized the problems of interpretation of CT levels because of the relative lack of an absolute threshold value for elevated basal or stimulated CT that discriminates malignant from benign disease. It is noteworthy that the vast majority of small MTCs in our center were found during the last decade, showing the continuing improvement in the interpretation of serum CT levels and the diagnosis of MTC. It could be hypothesized that more careful histopathologic analysis with the more frequent use of CT immunohistochemistry by the pathologist may have uncovered more occult MTCs in group II, but this is not the issue of our study because all patients of group II had abnormal CT levels preoperatively and an MTC was expected. It seems that the measurement of CT in all thyroid nodules is mandatory for the potential of underlying medullary carcinoma [25]. In our patients, no false-positive cases were reported after the histopathologic results. Detectable serum CT levels postoperatively indicate persistent disease, and the proportion of our patients who continued to have persistent disease was significantly lower in group II than in group I. In some studies, the values of postoperative serum CT levels are considered to be an independent prognostic factor [7], although they are not included in the calculation of TNM stage. Lymph node involvement (N category), extension beyond the thyroid capsule, and distant metastases are crucial in the demonstration of TNM stage. In our study, the significant decrease of cases with lymph node metastasis or thyroid capsule invasion in group II compared with group I advocates a better prognosis. Miccoli et al [5] showed in a prospective study of 70 MTC patients that the outcome of encapsulated tumors was significantly better regardless of tumor size and node

metastases. In addition, all studies demonstrate that distant metastases are an important bad prognostic factor and that the number of our cases with metastases was much lower in the last 2 decades. We have expected that group II patients would be, on average, younger than group I patients because of the earlier diagnosis. The lack of age differences between the 2 groups could be explained partially by the fact that only sporadic cases were included because, following the advances in molecular biology over the last 17 years in familial MTC, subjects at risk for MTC undergoes surgery at an earlier age [26]. Because of the relatively small number of patients, we cannot hypothesize that the natural history of the disease is changing with time to a less aggressive form. Again, from this study, it is not possible to answer questions about the changes in the incidence of MTC from 1969 to 2009.

The study of the above-mentioned risk factors shows clearly the dramatic decrease of TNM stage as well as the improvement of other prognostic factors over the last 20 years in our cases of sporadic MTC. The rapid increase in the proportion of small early-stage MTC reflects the clinical benefits of applying CT screening and thyroid US. Consistent with those findings is the observation of an increased 15-year survival rate during the last decades in patients with sporadic MTC; and our data are in agreement with the studies showing that patients with MTC, after the introduction of routine serum CT measurement in nodular goiters, had better outcome in comparison with older cases where the measurement of CT was not applied [9,27].

In conclusion, we have shown a significant improvement of TNM stage at the time of diagnosis over the last 20 years and an increased 15-year survival of patients with sporadic MTC. The most profound explanation is that, in our center, for the last 2 decades, serum CT screening alone or combined with CT provocative test and thyroid US has become an integral part of the clinical workup for patients with thyroid nodules.

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