Serum Carcinoembryonic Antigen as a Biomarker for Medullary Thyroid Cancer

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Background and Objectives: The lack of known elevated biomarkers in cancer surveillance is a challenge for diagnostics. However, few studies have assessed the proportion of patients with medullary thyroid cancer (MTC) that presented with elevated serum carcinoembryonic antigen (CEA) level. **Materials and Methods:** This was a retrospective study of 115 patients treated for MTC at Samsung Medical Center between 1995 and 2017. Serum calcitonin and CEA levels that were available at one of the following time points were included: (a) within 3 months before the initial surgery, (b) when a structural recurrence was confined to the neck, or (c) when a distant metastasis was identified during follow-up. Considering the high false-positive rate of serum CEA testing, 5 ng/mL was selected as the cut-off threshold. **Results:** The sensitivity of CEA at the time of diagnosis was 54%, but it significantly increased with anatomical stage, from 20% in stage I to 88% in stage IV (p for trend <0.001). At the time of diagnosis, larger tumor size, more frequent gross extra-thyroidal extension, more frequent N1b, and a higher number of metastatic lymph nodes were significantly observed in CEA-positive patients compared with CEA-negative patients ($p<0.05$). The sensitivity of CEA at the time of recurrence was 56% for local recurrence and 80% for distant recurrence. **Conclusion:** The CEA value was associated with anatomical stage as a biomarker for MTC and could be used to predict poor prognosis. However, serum CEA testing plays a limited role in diagnosis and follow-up of MTC because it can show normal values even in advanced disease.

Key Words: Thyroid neoplasms, Biomarkers, Carcinoembryonic antigen

Introduction

Medullary thyroid cancer (MTC) is a neuroendocrine tumor characterized by proliferation of para-follicular cells in the thyroid gland and was recognized and reported as a distinct tumor in 1959.¹⁾ Although it is a relatively rare disease with a prevalence of less than 5% among thyroid cancers, it has attracted research attention due to its characteristic clinical features and aggressiveness compared to differentiated thyroid cancers.²⁾

Para-follicular cells are classified as C-cells because they produce calcitonin,³⁾ which is a useful biomarker in MTC. Similar to other neuroendocrine tumors, MTC can produce other biochemical markers such as catecholamine, neuron-specific enolase, and chromogranin A.⁴⁾ Among them, carcinoembryonic antigen (CEA) is an established biomarker for MTC.⁵⁾ Current guidelines recommend measuring serum calcitonin and CEA together to evaluate MTC, and the serum levels of these markers directly correlate with the para-follicular or C-cell mass. The presence of serum calcitonin and CEA facilitate predictions for the

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likelihood of diagnosis or recurrence of MTC.⁶⁾ Consequently, the levels of these biomarkers and their doubling times are useful for predicting the risk of recurrence after surgical treatment and for evaluating the aggressiveness of metastatic disease.^{7,8)}

The lack of known elevated biomarkers in cancer surveillance is challenging for diagnostics. However, few studies have evaluated the proportion of patients with MTC that presented with elevated CEA level. Therefore, this study was conducted to determine the level of serum CEA compared with that of serum calcitonin for diagnosing and predicting recurrence in MTC patients and to identify limitations of serum CEA testing as a biomarker for MTC.

Materials and Methods

Patients

We retrospectively reviewed the medical records of patients treated for MTC at Samsung Medical Center between 1995 and 2017. Patients who underwent surgery for curative purposes were enrolled, and the initial anatomical stages of the patients were all below IVA. Patients with serum calcitonin and CEA values that were available at one of the following moments were eligible: (a) within 3 months before the initial surgery (n=94), (b) when structural recurrence was confined to the neck lymph nodes (n=25), or (c) when a distant metastasis was identified during follow-up (n=20). A total of 115 patients was enrolled, including those with a positive biomarker at the various time points. This study was approved by the Institutional Review Board of Samsung Medical Center (SMC 2020-07-134).

Measurements and Definitions

Serum calcitonin concentration was measured by an immunoradiometric assay using a commercialized assay kit (CT-U.S.-IRMA, DAsource ImmunoAssays S.A., Louvain-la-Neuve, Belgium). Serum CEA concentration was measured by a radiometric assay using a commercialized assay kit (CEA-RAICT, Cisbio Bioassays, Codolet, France). A serum calcitonin level

of 12 pg/mL or less was defined as normal at the initial MTC diagnosis,⁹⁾ and a level of 5 pg/mL or less

Table 1. Baseline characteristics of the study population (n=115)

Variable	Value
Age, years (mean±SD)	50.22±14.24
Sex, female (%)	72 (62.6)
Size, cm (mean±SD)	1.89±1.46
Multifocal tumors, number (%)	23 (20.0)
Bilateral tumors, number (%)	18 (15.7)
RET mutation, number (%)	
Positive	16/76 (21.1)
Negative	60/76 (78.9)
T stage, number (%)	
1a	40 (34.8)
1b	27 (23.5)
2	19 (16.5)
3a	7 (6.1)
3b	13 (11.3)
4a	9 (7.8)
N stage, number (%)	
0	47 (40.9)
1a	18 (15.6)
1b	50 (43.5)
AJCC 8th stage, number (%)	
I	37 (32.2)
II	10 (8.7)
III	18 (15.6)
IVA	50 (43.5)
Preoperative serum calcitonin, pg/mL	
Mean	1,188
Median	336
Range	4–17,200
Preoperative serum CEA, ng/mL	
Mean	32.3
Median	6.4
Range	0.5–475.7
Follow-up duration, years	
Median (IQR)	8.3 (4.9–10.8)
Clinical outcome, number (%)	
No evidence of structural recurrence confirmed by sonography	80 (69.6%)
Local metastasis confined to neck lymph nodes	15 (13.0%)
Distant metastasis confirmed by CT or PET scans	13 (11.3%)
Death	7 (6.1%)

AJCC: American Joint Committee on Cancer, CEA: carcinoembryonic antigen, CT: computerized tomography, IQR: interquartile range, MTC: medullary thyroid carcinoma, PET: positron emission tomography, SD: standard deviation

was considered undetectable after total thyroidectomy based on the functional sensitivity of the test. A serum CEA level of 5 ng/mL or less was regarded as normal before and after the initial surgery.

Genetic testing was performed by collecting DNA from peripheral blood with consent of the patients or their family members. White blood cells from patients were isolated, and DNA was extracted using a commercial kit (Wizard Genomic DNA Purification kit, Promega, WI, USA) and amplified by polymerase chain reaction using a 9600 thermal cycler (Applied Biosystems, CA, USA). Direct sequencing was performed using the MEN1 gene site (11q13.1) and the MEN2 gene site (10q11.2) ABI Prism 3100 Genetic Analyzer (Applied Biosystems, CA, USA).

Confirmation of MTC was based on the pathologic report after total thyroidectomy, and the size of the primary tumor was measured as the longest diameter of the largest mass. Anatomical staging was based on the 8th edition of the American Joint Committee on Cancer (AJCC) system. In cases of recurrence, local recurrence was diagnosed by sonographic fine-needle aspiration cytology. Distant metastasis was confirmed by chest, abdominal, or pelvis computerized tomog-

raphy (CT) scans with contrast or by fluoride-18 fluorodeoxy-glucose integrated with positron emission tomography/CT (18F-FDG PET/CT).

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation or median (interquartile range) depending on the type of distribution. Quantitative variables were summarized as count (percentage of the total). To visualize the biomarker levels, the values obtained by logging serum calcitonin and CEA concentrations were box plotted, and linear contrast was used to determine statistical significance. Cochran-Armitage trend tests were used to confirm the correlation between anatomical stage and positive result rates for biomarkers. Continuous variables were assessed using the t-test or Mann-Whitney U test to compare the clinico-pathologic features of CEA-positive and -negative patients, while quantitative variables were analyzed using the Chi-square test or Fisher's exact test. Statistical analysis was performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Table 2. Preoperative serum calcitonin and CEA rates correlated with anatomical stage

Total number	Positive patients		Sensitivity (%)		p for trend [†]		Increase in sensitivity by adding CEA	
	Calcitonin	CEA	Calcitonin	CEA	Calcitonin	CEA		
Stage I	35	31	7	88.6	20.0	0.035	<0.001	0%
Stage II/III	26	25	15	96.2	57.7			0%
Stage IV	33	33	29	100	87.9			0%
Total patients	94	89	51	94.7	54.3			0%

[†]p-values were calculated using the Cochran-Armitage trend test. CEA: carcinoembryonic antigen

Table 3. Clinical characteristics of calcitonin-negative MTCs at the time of diagnosis

Age	Sex	RET mutation	Size (cm)	mLN (Number)	N stage	AJCC stage	Ctn IHC	Ctn (pg/mL)	CEA (ng/mL)	Clinical outcome
52	F	-	0.4	0	0	I	(+)	11.0	1.0	No evidence of disease
60	M	-	0.7	0	0	I	(+)	9.0	3.9	No evidence of disease
50	F	-	0.5	0	0	I	(+)	4.0	1.4	No evidence of disease
52	M	Negative	0.5	5	1a	III	(+)	8.5	1.3	No evidence of disease
35	F	Positive	0.3	0	0	I	(+)	6.8	0.5	No evidence of disease

-: uninspected, AJCC: American Joint Committee on Cancer, CEA: carcinoembryonic antigen, Ctn: calcitonin, IHC: immunohistochemistry, mLN: metastatic lymph node

Results

Baseline Characteristics

The mean age of the 115 patients with MTC was 50 years, with a range from 13 to 84 years, and 72 patients (62.6%) were women. Among 76 patients tested for the RET mutation, 16 (21.1%) were confirmed to have the mutation. The mean tumor size was 1.9 cm, and the size ranged from 0.2 to 9.0 cm, and 18 patients (15.7%) had bilateral tumors. Lymph node metastasis was identified in 68 patients (59.1%). When the 115 patients were classified using the AJCC (8th edition) staging system, 37 (32.2%) were classed as stage I, 10 (8.7%) as stage II, 18 (15.7%) as stage III, and 50 (43.5%) as stage IVA. The median concentration of preoperative serum calcitonin was 336 pg/mL, and the value ranged from 4 to 17,200 pg/mL; the median concentration of preoperative serum CEA was 6.4 ng/mL and ranged from 0.5 to 475.7 ng/mL (Table 1).

Preoperative Serum Calcitonin & CEA Levels and Their Association with Tumor Stage

Preoperative serum calcitonin level was positive (>12 pg/mL) in most patients (89/94, 94.7%), but five (5.3%) had normal serum level at the initial diagnosis (Table 2). The five calcitonin-negative patients had tu-

mors that were less than 0.7 cm in size, and all except one were in stage I. These patients had normal serum CEA level and remained in remission after the initial surgery through the end of the study (Table 3). Preoperative serum CEA level was positive (>5 ng/mL) in 51 (54.3%) of 94 patients (Table 2). Preoperative serum calcitonin level was correlated with the serum CEA level ($R=0.78$, $p<0.001$, Fig. 1). Preoperative serum calcitonin and serum CEA levels increased significantly as tumor size increased (p for trend <0.001 , Fig. 2). Positive rates of preoperative serum calcitonin and CEA levels increased significantly with stage ($p=0.035$ and $p<0.001$, respectively; Table 2).

Fig. 1. Correlation between preoperative serum calcitonin and CEA levels.

Fig. 2. Preoperative serum calcitonin and CEA levels based on the primary tumor size quantile. (A) Serum calcitonin. (B) Serum CEA. Serum calcitonin and CEA levels are represented as logarithmic values. *Statistically significant with $p\leq 0.05$; **statistically significant with $p\leq 0.01$; ***statistically significant with $p\leq 0.001$.

Comparison of the Clinicopathologic Characteristics between Preoperative Serum CEA-Positive and Negative Patients

When the clinicopathologic characteristics of preoperative serum CEA-positive (>5 ng/mL) and CEA-negative patients were compared, there were no differences in age, sex, or multifocality between the two groups. However, larger tumor size, more frequent gross extrathyroidal extension, more frequent N1b, and a higher number of metastatic lymph nodes were significantly observed in the CEA-positive patients compared with the CEA-negative patients ($p < 0.05$, Table 4).

Serum Calcitonin & CEA Levels for Detecting Local or Distant Recurrence

Serum calcitonin and CEA levels have been used in postoperative surveillance to predict recurrence of MTC. Therefore, the sensitivity of each biomarker was evaluated at the time of detection of local or distant recurrence. The median levels of postoperative serum calcitonin and CEA were 427 pg/mL and 5.8 ng/mL, respectively, in patients with recurrence confined to the neck and 3200 pg/mL and 46.4 ng/mL in patients with distant recurrence. The postoperative serum calcitonin level was positive (>5 pg/mL) in all patients with local or distant recurrence (25/25 and 20/20, respectively), whereas postoperative serum CEA level was positive (>5 ng/mL) in 56.0% (14/25) of patients

Table 4. Comparison of the clinicopathologic characteristics between preoperative serum CEA-positive (>5 ng/mL) and CEA-negative patients

	CEA-positive patients n=51	CEA-negative patients n=43	p
Serum CEA			
Median (IQR)	21.5 (11.6–47.3)	2.3 (1.2–3.6)	<0.001
Age, years (mean ± SD)	53.22 ± 16.12	49.42 ± 12.56	0.206
Sex, female (%)	31 (60.8%)	25 (58.1%)	1.000
Multifocality	12 (23.5%)	7 (16.3%)	0.470
Size, cm (mean ± SD)	2.41 ± 1.48	1.13 ± 1.14	<0.001
Gross ETE, present (%)	13 (25.5%)	1 (2.3%)	0.004
N stage			<0.001
0	15	30	
1a	7	9	
1b	29	4	
Metastatic LN, number			
Median (IQR)	7 (0–11)	0 (0–1)	0.003
Clinical outcome, number (%)			0.026
No evidence of structural disease	42 (82.4)	41 (95.3)	
Structural recurrence	8 (15.7)	0 (0)	
Death	1 (1.9)	2 (4.7)	

CEA: carcinoembryonic antigen, ETE: extrathyroidal extension, IQR: interquartile range, LN: lymph node, SD: standard deviation

Table 5. Sensitivity of serum calcitonin and CEA levels at detection of recurrence

Total number	Number of positive patients		Sensitivity (%)		Increase in sensitivity by adding CEA	
	Calcitonin	CEA	Calcitonin	CEA		
Local recurrence	25	25	14	100	56.0	0%
Distant recurrence	20	20	16	100	80.0	0%

CEA: carcinoembryonic antigen

with local recurrence and in 80.0% (16/20) of patients with distant recurrence (Table 5). Even for the four patients who died due to progression of the disease, the serum CEA level was within the normal range (Table 6 and Fig. 3).

Discussion

In this study, serum CEA had lower sensitivity than

serum calcitonin not only at the initial diagnosis (94.7% vs. 54.3%), but also for detecting local recurrence (100% vs. 56.0%) and for confirming distant metastasis (100% vs. 80.0%). Serum calcitonin and CEA levels can be used as indicators, and guidelines recommend assessing both biomarkers when family members are screened for risk and for follow-up after thyroidectomy for MTC.¹⁰⁾ During patient surveillance and follow-up, it is important to assess the presence

Fig. 3. Serial changes in serum calcitonin (A) and CEA (B) levels of CEA-negative (<5 ng/mL) patients.

Table 6. Clinical outcomes of CEA-negative patients at detection of recurrence

Age	Sex	T stage	Size (cm)	mLN (Number)	N stage	Metastasis (site)	Calcitonin (pg/mL)	CEA (ng/mL)	Clinical outcome
Patients with local recurrence									
30	F	3a	4.0	10	1b	LN	185	1.3	Recur ^a
50	M	1a	1.6	2	1a	LN	399	2.4	Death
58	M	1b	1.4	3	1a	LN	312	0.5	Recur
49	F	3b	1.5	11	1b	LN	162	0.5	Recur
52	M	1b	0.9	2	1b	LN	66	2.8	Recur ^b
47	F	2	2.6	3	1a	LN	51	1.2	Death ^c
51	M	1a	1.0	3	1a	LN	131	2.0	Recur
21	M	1a	0.6	7	1a	LN	159	3.0	Recur
37	F	1b	1.5	24	1b	LN	549	0.7	Recur
57	F	1a	1.2	1	1a	LN	78	2.4	Recur
42	F	3a	5.6	14	1b	LN	4542	4.2	Recur
Patients with distant recurrence									
30	F	3a	4.0	10	1b	Lung	401	3.4	Recur ^a
52	M	1a	0.9	2	1b	Lung	770	3.8	Recur ^b
47	F	2	2.6	3	1a	Bone	3320	1.1	Death ^c
72	M	3a	6.5	46	1b	Liver	14826	3.6	Death

CEA: carcinoembryonic antigen, LN: lymph node, mLN: metastatic lymph node

^{a,b,c}Results observed for the clinical course of the same patient are indicated by the same letter.

of cancer to diagnose and treat patients early. Although the cost of CEA testing varies by country and healthcare system, the low sensitivity of serum CEA testing undermines the clinical significance of serum CEA level in terms of cost-effectiveness.

Preoperative serum calcitonin level was positively correlated with extent of disease and was related to postoperative biochemical normalization and prognosis.^{11,12)} Preoperative serum CEA is also well correlated with anatomical stage, and the level increases characteristically in advanced disease.^{13,14)} In this study, serum calcitonin level was significantly correlated with serum CEA level ($R=0.78$, $p<0.001$, Fig. 1), and both were significantly correlated with the extent of disease (Fig. 2). In addition, the sensitivity of biomarkers was higher in advanced disease because the level of biomarkers was associated with disease burden (Table 2).

Serum calcitonin has been emphasized as a diagnostic marker for MTC because of the low accuracy of cytologic diagnosis,¹⁵⁾ although routine screening of serum calcitonin in thyroid nodules is controversial when the actual prevalence of MTC is considered.¹⁶⁾ For calcitonin, the normal range varies depending on age and sex.¹⁷⁾ In this study, the preoperative calcitonin cut-off level was set to 12 pg/mL based on the results of our previous study.⁹⁾ In this study, five of 94 patients (5.32%) had calcitonin-negative MTC. Several studies have reported MTC patients with low serum calcitonin level. In their multicenter study, Frank-Raue et al.¹⁸⁾ analyzed 839 patients and reported that the prevalence of calcitonin-negative MTCs was 0.83% and suggested that the patients' prognoses were heterogeneous. The relatively high prevalence compared to previous studies is likely due to the involvement of many microcarcinomas, which were not included in other studies. The primary tumor size of all the calcitonin-negative cases in this study was less than 1 cm and ranged from 0.3 to 0.7 cm. All but one of the patients were diagnosed as stage I, and postoperative remission was maintained through the end of this study (Table 3).

Serum CEA is used for various types of cancers as an inexpensive and non-invasive blood-borne biomarker.¹⁹⁾ However, serum CEA level is increased in

various benign diseases, in smokers, and in cancer patients,²⁰⁾ and it is often within the normal range even when the patient is diagnosed with cancer.²¹⁾ Therefore, serum CEA measurement has low sensitivity and specificity and relatively low diagnostic value. It has been reported that serum CEA value is not useful in early diagnosis of MTC, and the positive rate of CEA in MTC was reported as 62% in a previous study.²²⁾ In consideration of the high false-positive rate of the CEA test, 5 ng/mL, which is the standard cut-off for smokers, was selected as the cut-off level in this study. The positive rate of CEA in MTC was confirmed to be 54.3% in this study, and the positive rate increased according to anatomical stage (p for trend <0.001 ; Table 2). Positivity of CEA was associated with known poor prognostic factors, such as primary tumor size, gross extrathyroidal extension, and N1b (Table 4). This explains the high positive rate in the patients with advanced MTC.

Some reports have suggested that measuring serum CEA is useful for follow-up in patients with MTC. In 1978, Wells et al.²²⁾ reported the value of serum CEA level for evaluating disease progression in MTC patients. In 1984, Mendelsohn et al.²³⁾ reported that some patients with aggressive disease had increasing serum CEA level despite stable or declining serum calcitonin level. In 2017, Zhou et al.²⁴⁾ suggested that CEA is useful because elevated level was observed in a group of calcitonin-negative patients. In the present study cohort, however, serum CEA increased with serum calcitonin, and some cases showed increased serum calcitonin without increased serum CEA (Table 6 and Fig. 3); the inverse case was not observed. Therefore, we suggest that measurement of serum CEA level plays a limited role in diagnosis and follow-up of MTC and cannot be substituted for serum calcitonin testing.

From a biological point of view, calcitonin and CEA have different pathways for production and excretion.²⁵⁾ Calcitonin is stored in the secretory granules of the parafollicular C cells that constitute MTC, and the level clearly increases in response to stimulation by compounds such as calcium or pentagastrin. CEA is expressed on the cell membrane, and the degree of ex-

pression on the cell membrane increases with differentiation of cancer.^{26,27)} Although CEA level is associated with aggressive features in many other carcinomas, metastasis can occur without CEA elevation.^{28,29)} This was confirmed in our study cohort of patients with MTC. The proportion of patients with positive serum CEA level at detection of distant metastasis on postoperative follow-up was 80% (Table 4), but serum CEA was not increased in all of those patients (Table 6 and Fig. 3). Serum CEA level is thought to be affected not only by CEA production by malignant cells, but also by the degree of excretion of CEA into systemic circulation, which might be associated with the tumor microenvironment.³⁰⁾

The primary limitation of this study was the retrospective design and that subjects were enrolled from a single institution. In addition, a fixed cut-off (5 ng/mL) of serum CEA was used for statistical analysis. This study was based on clinical experience with a relatively large number of patients with MTC, but other series might show different results from this study. The results should be considered and applied within these contexts.

The CEA value is associated with anatomical stage as a biomarker for MTC and could be used to predict poor prognosis. However, serum CEA testing plays a limited role in diagnosis and follow-up of MTC because it can show normal values even in advanced disease.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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