Relation of Doubling Time of Plasma Calcitonin Levels to Prognosis and Recurrence of Medullary Thyroid Carcinoma

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Plasma calcitonin (CT) levels were measured serially in 54 patients surgically treated for medullary thyroid carcinoma. Patients with postoperative basal CT levels higher than 1 ng/ml measured within 1 month after surgery had a higher recurrence rate than those with lower CT levels ($p < 0.002$). Patients with postoperative basal CT levels higher than 2 ng/ml had a lower survival rate than those with lower CT levels ($p < 0.01$). However, preoperative basal CT levels had no significant correlation with life expectancy or recurrence during the present observation period. Serial measurements in 23 patients with elevated postoperative CT levels showed exponential increases in basal CT levels in 19 patients ($p < 0.05$ in nine patients, $0.05 < p < 0.1$ in four patients) and slight decreases in four ($p < 0.05$ in one patient). Doubling time of CT levels calculated from the regression line in each patient showed the highest correlation with 3-year survival, recurrence within 5 years, and time interval between surgery and clinical recurrence of the tumor, allowing quantitative prediction of the prognosis.

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PLASMA CALCITONIN (CT) is a very sensitive tumor marker of medullary thyroid carcinoma. The diagnostic value of the measurements of CT levels in patients suspected of the tumor is well established.[1,2] It has particular value in the diagnosis of affected members in groups at high risk.[3,4] An abnormal increase in CT levels after calcium or gastrin injection in patients with normal basal CT levels is diagnostic of C cell hyperplasia or early medullary carcinoma.[5,6] Preoperative CT levels correlate roughly with the tumor weight[7] or extent of the disease.[7,8] Abnormal CT levels after surgery imply residual tumor elsewhere.[7,9] Thus, both pre- and post-operative CT levels appear to have prognostic value. Stepanas et al.[10] described the usefulness of serial measurements in the long-term follow-up. High CT levels after surgery implied extended disease in general but not always poor prognosis, whereas a marked rise preceded metastases and death in their three patients. However, these investigators did not attempt to quantify the rate of changes in CT levels.

In this report, preoperative and postoperative CT levels as well as changes in CT levels in postoperative serial measurements were analyzed with respect to life expectancy and recurrence in 54 patients with medullary thyroid carcinoma. We found that the changes in CT levels were exponential and that the doubling time of CT levels, calculated with a computer, had the best correlation with life expectancy and recurrence, which allowed quantitative prediction of the prognosis.

Patients and Methods

Fifty-four patients with medullary thyroid carcinoma seen at our hospitals had serial measurements of CT levels. Twenty-four patients exhibited the hereditary type and thirty the sporadic type. Forty-two patients were of primary cases and the remaining 12 patients underwent surgery for recurrent tumor. Patients were treated with mainly surgery only, though some received additional chemotherapy or radiotherapy. Twenty-seven of the 42 patients with the primary disease had both preoperative and postoperative measurements. Fifty patients had the first postoperative measurement within 1 month after surgery. Mean duration of follow-up was 52.3 ± 50.9 months (mean ± SD), mean duration of serial CT measurements 33.3 ± 28.3 months, and a mean number of measurements 6.9 ± 5.6 for each patient.

Basal CT levels and stimulated CT levels with intravenous calcium or tetragastrin were determined by radioimmunoassay described elsewhere.[11] Venous blood was

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TABLE 1. *Preoperative Plasma Calcitonin Levels and Prognosis in Patients with Medullary Thyroid Carcinoma—Plasma Calcitonin and Tumor Status at End of Follow-up**

Preoperative Plasma Calcitonin (ng/ml)	NR†	HR‡	HB§	Recurrence‖	Number of Deaths‖	Total
0.2–1	2		1	1		4
1–2	4				1	5
2–5	1	2	3			6
5–10	4	1			1	6
>10		2	2	1	1	6
Total	11	5	6	2	3	27

* Primary cases only.
† NR = normal basal levels with normal responses to stimuli.
‡ HR = normal basal levels with high responses.
§ HB = high basal levels with high responses.
‖ All patients with recurrence or who died of the tumor had high basal calcitonin levels at the end of follow-up.

drawn before intravenous injection of 2% calcium chloride (0.6 ml/kg of body weight) for 10 minutes and at 0, 15, 30, and 60 minutes after the injection followed by intravenous tetragastrin (4 μg/kg of body weight) for 5 minutes, with additional blood samples being taken at 0 and 5 minutes after tetragastrin. The normal upper limit of the basal CT level is 0.2 ng/ml and that of the stimulated level is 0.4 ng/ml in our laboratory. Plasma calcitonin levels were classified into three categories according to basal and maximum stimulated levels: 1) normal response (NR), normal basal and normal stimulated levels; 2) high response (HR), normal basal and abnormally high stimulated levels; and 3) high basal (HB), abnormally high basal and stimulated levels.

TABLE 2. *Postoperative Plasma Calcitonin Levels and Prognosis in Patients with Medullary Thyroid Carcinoma—Plasma Calcitonin and Tumor Status at End of Follow-up**

Postoperative Plasma Calcitonin (ng/ml)	NR†	HR‡	HB§	Recurrence‖	Number of Deaths‖	Total
NR	19	2	1	1		23
HR		4	1			5
0.2–1			5			5
1–2				1		1
2–5			1		1	2
5–10			1		1	2
>10				1		1
Total	19	6	9	3	2	39

* Primary cases only.
† NR = normal basal levels with normal responses to stimuli.
‡ HR = normal basal levels with high responses.
§ HB = high basal levels with high responses.
‖ All patients with recurrence or who died of the tumor had high basal calcitonin levels at the end of follow-up.

Twenty-three patients had abnormally high basal CT levels after surgery and were followed up with serial measurements for more than 6 months (mean duration of serial measurements 39.9 ± 27.1 months with a mean number of measurements of 8.2 ± 3.9). Since changes in CT levels in these patients were found to be exponential (as shown in "Results") a regression line, $\log y = \log a + bx$, was calculated with a computer from the simultaneous equations, $\Sigma \log y = N \log + b\Sigma x$ and $\Sigma(x \cdot \log y) = (\log a)\Sigma x + b\Sigma x^2$ (y: CT levels, x: years after surgery, N: number of measurements) in each patient. Doubling time of CT levels (T2) was calculated as (log 2)/b.

Patients were followed up with physical examination, chest roentogenography, tomography, computerized axial tomography, bone or liver scintigraphy, or aortography when indicated. Clinical recurrence of the disease was defined as presence of evidence of tumor recurrence on these examinations.

Results

Preoperative Basal Plasma Calcitonin Levels and Prognosis

Table 1 shows the relation between basal CT levels before surgery and CT levels and tumor status at the end of follow-up in 27 patients of primary cases. At the end of follow-up, 11 patients had normal basal and normal stimulated CT levels (NR) and were free from the disease. Sixteen patients had abnormal CT levels suggesting residual tumor, of them only five had clinically overt recurrent disease, including three patients who died of the tumor. There was no significant correlation between preoperative basal CT levels and life expectancy or recurrence during the present observation period, though patients with preoperative basal CT levels higher than 10 ng/ml were less likely to exhibit normal CT levels after surgery compared to those with lower preoperative CT levels ($\chi^2 = 3.35$, $0.1 > p > 0.05$).

Postoperative Plasma Calcitonin Levels and Prognosis

Table 2 shows the relation between postoperative CT levels measured within 1 month after surgery and CT levels and tumor status at the end of follow-up in 39 patients of primary cases. Among 23 patients with normal basal and normal stimulated CT levels (NR) examined within 1 month after surgery, two patients became hyperresponsive to stimuli (HR), one developed abnormally high basal and stimulated CT levels (HB), and one had clinical recurrence of the tumor. Four of six patients with postoperative basal CT levels higher than 1 ng/ml developed clinically overt recurrence, two of whom died of the disease. Patients with basal CT levels higher than 1 ng/ml after surgery had a higher recurrence rate than

those with levels lower than 1 ng/ml (4/6 *versus* 1/33, $\chi^2 = 13.142$, $p < 0.002$). Patients with basal CT levels higher than 2 ng/ml after surgery had a higher mortality rate than those with lower CT levels (2/5 *versus* 0/34, $\chi^2 = 7.292$, $p < 0.01$). However, not all patients with high postoperative CT levels had recurrence or death. There was no relation between postoperative basal CT levels and time interval between surgery and recurrence or death.

Serial Measurements of Basal Plasma Calcitonin Levels

Serial measurements of plasma CT levels were determined for more than 6 months in 23 patients with abnormally high postoperative CT levels. The serial basal CT levels in the individual patients showed exponential changes, which were clearly seen, especially in patients with steep slopes. Some representative cases are shown in Figure 1. Each patient had a remarkably different slope of the regression line. The regression line, log y = log a + bx (y: basal CT level, x: years after surgery), and the doubling time of CT levels (T2) was computed for each patient (Table 3). The correlation coefficients relating CT levels to time after surgery were high and the correlations were significant in most of the patients with steep slopes, namely short T2 (Table 3). Among 14 patients with T2 shorter than 3 years, the correlation coefficients were higher than 0.750 in 11 patients and the correlations were significant ($p < 0.05$) in nine. Five patients with T2 longer than 3 years showed weak positive correlations that were not significant. Four patients showed negative correlations, *i.e.*, decreases in CT levels during the follow-up period, only one of which was significant. In four patients significance of the correlation was equivocal ($0.05 < p < 0.1$). Insignificant correlations were seen in patients with gentle slopes or long T2, in those with short periods of observation compared to T2, or in those with a small number of measurements. An observation period longer than two- to three-fold that of T2 appears necessary to obtain a significant correlation. The 95% confidence limits of the slope of the regression line (b) and T2 are shown in Table 3.

The calculated T2 values ranged from 0.12 to 13.6 years in 19 patients with positive correlations and they were −1.8, −9.6, −9.7, and −45.6 years in four patients with negative correlations (Fig. 2). Three of the four patients in whom CT levels decreased during the follow-up period had postoperative basal CT levels lower than 1 ng/ml. Patients with sporadic medullary thyroid carcinoma had shorter T2 (median, 1.1 years) than those with the hereditary type (median, 4.3 years).

Two patients under observation before and after reoperation exhibited similar T2 values; 0.59 year before reoperation and 0.53 year after reoperation in one patient, and 0.81 year and 1.54 years, respectively, in the other.

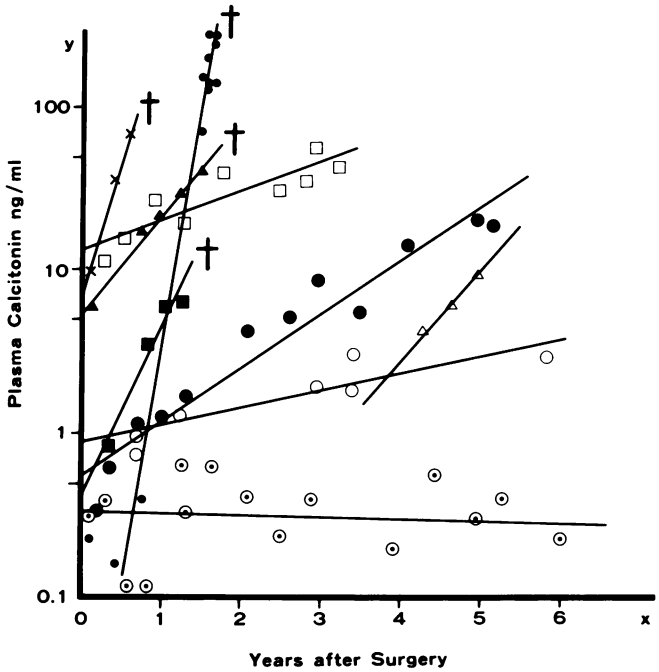

FIG. 1. Serial plasma calcitonin measurements and regression lines in representative patients with medullary thyroid carcinoma. Note remarkably different slope of regression line in each patient and early death in patients with steep slope. One patient had similar slopes before (△: log y = log 0.026 + 0.509x, T2 = 0.59 year) and after (▲: log y = log 5.8 + 0.566x, T2 = 0.53 year) reoperation.

Doubling Time of Basal Calcitonin Levels and Prognosis

All five patients with T2 shorter than 0.5 year died of the cancer within 3 years, whereas none of 13 patients with T2 longer than 0.5 year died within 3 years ($\chi^2 = 13.360$, $p < 0.001$, Table 4). A patient with T2 of 0.59 year died 7 years after the initial operation. Another patient with T2 of 5.6 years who bore recurrent tumor in the neck died of hepatocellular carcinoma 25 years after the initial operation. The ratio of postoperative survival duration to T2 in patients who died of the cancer was 11.1 ± 5.5 (mean ± SD) with a range from 5.5 to 20.9.

Five patients had massive metastases to the liver; one patient had massive bone metastases; and one had both. Six of them had T2 shorter than 0.6 year and died within 14 months after the discovery of the metastases, whereas the remaining one with T2 of 1.6 years is alive 5 years after the discovery of the liver metastases. Mean survival duration after discovery of the metastases was 9 ± 5 months in patients who died of the disease. The ratio of survival duration after the discovery of T2 in patients who died of the disease was 3.1 ± 1.7 (mean ± SD) with a range from 1 to 5.6.

Recurrence within 5 years after the initial surgery or reoperation for recurrent tumor occurred more frequently in patients with T2 shorter than 1 year ($p < 0.005$, Table

TABLE 3. *Serial Measurements in 23 Patients with Elevated Postoperative Calcitonin Levels*

Patient	Type	Period of Measurements (yr-mo)	Number of Measurements	Regression Line (log y = log a + bx)*	r†	p‡	95% Limits of Slope (b) of Regression Line (Upper	Lower)	T2§	95% Limits of T2 (Upper	Lower)
1	S‖	0-7	3	log y = log 0.16 + 2.490x	0.994	p < 0.1	5.935	−0.955	0.12	0.05	−0.32
2	S	1-7	14	log y = log 0.04 + 2.229x	0.965	p < 0.001	2.611	1.846	0.14	0.12	0.16
3	H¶	0-6	3	log y = log 7.22 + 1.687x	0.999	p < 0.01	2.020	1.354	0.18	0.15	0.22
4	S	0-9	6	log y = log 6.68 + 1.196x	0.683	NS	2.971	−0.578	0.25	0.1	−0.5
5	S	0-11	4	log y = log 0.43 + 1.007x	0.984	p < 0.05	1.562	0.452	0.30	0.2	0.7
6-1**	S	0-8	3	log y = log 0.03 + 0.509x	0.999	p < 0.05	0.832	0.186	0.59	0.4	1.6
6-2		1-5	5	log y = log 5.82 + 0.566x	0.994	p < 0.001	0.676	0.456	0.53	0.4	0.7
7-1	H	2-4	5	log y = log 0.14 + 0.370x	0.972	p < 0.01	0.536	0.205	0.81	0.6	1.5
7-2		3-4	7	log y = log 0.62 + 0.195x	0.889	p < 0.01	0.310	0.079	1.54	1.0	3.8
8	S	5-0	12	log y = log 0.58 + 0.324x	0.971	p < 0.001	0.381	0.267	0.93	0.8	1.1
9	S	1-2	5	log y = log 0.66 + 0.276x	0.863	p < 0.1	0.572	−0.020	1.1	0.5	−15.1
10	H	0-9	6	log y = log 0.15 + 0.213x	0.494	NS	0.733	−0.308	1.4	0.4	−1.0
11	S	3-1	9	log y = log 13.6 + 0.175x	0.897	p < 0.005	0.252	0.098	1.7	1.2	3.1
12	S	5-2	7	log y = log 9.83 + 0.185x	0.758	p < 0.05	0.368	0.002	2.6	0.8	136
13	H	2-9	7	log y = log 0.25 + 0.107x	0.883	p < 0.01	0.172	0.042	2.8	1.8	7.2
14	H	1-11	9	log y = log 0.83 + 0.104x	0.402	NS	0.315	−0.108	2.9	1.0	−2.8
15	S	6-3	8	log y = log 0.07 + 0.095x	0.685	p < 0.1	0.196	0.006	3.2	1.5	50
16	S	1-4	2	log y = log 0.39 + 0.094x	—	—	—	—	3.2	—	—
17	H	3-8	6	log y = log 0.61 + 0.053x	0.780	p < 0.1	0.113	−0.006	5.6	2.7	−50
18	S	2-7	8	log y = log 1.98 + 0.053x	0.431	NS	0.164	−0.058	5.7	1.8	−5.2
19	H	7-3	14	log y = log 0.25 + 0.022x	0.161	NS	0.108	−0.063	13.6	2.8	−4.7
20	H	5-11	16	log y = log 0.34 − 0.007x	−0.048	NS	0.073	−0.086	−45.6	4.2	−3.5
21	H	5-1	13	log y = log 0.48 − 0.031x	−0.359	NS	0.022	−0.084	−9.7	13.4	−3.6
22	H	4-9	10	log y = log 0.20 − 0.031x	−0.228	NS	0.077	−0.140	−9.6	3.9	−2.2
23	S	2-7	6	log y = log 8.15 − 0.169x	−0.855	p < 0.05	−0.027	−0.311	−1.8	−11.2	−1.0

* y = basal plasma calcitonin level (ng/ml); x = years after surgery.
† r = correlation coefficient.
‡ p = significance of correlation.
§ T2 = doubling time of basal plasma calcitonin level.
‖ S = sporadic.
¶ H = hereditary.
** Patients 6 and 7 were under observation before (6-1, 7-1) and after (6-2, 7-2) reoperation.

5). The intervals between surgery and recurrence in patients with T2 shorter than 0.5 year were also significantly shorter ($p < 0.05$, Table 6).

Discussion

Stepanas et al.[10] reported the importance of serial measurements of serum calcitonin (CT) in the long-term follow-up of patients with medullary thyroid carcinoma. They described that patients with high CT levels after surgery showed no clinical or radiological evidence of recurrence over a 3-year observation period; their three patients who died had relatively, but not absolutely, high CT levels and a marked rise in CT levels that preceded metastases and death. Similar observations were reported in isolated cases by several authors.[9,12] However, they all failed to demonstrate a clear correlation between postoperative CT levels and prognosis or recurrence, nor could they adequately explain the discrepancy between postoperative CT levels and prognosis observed in some cases. Though some authors reported that increase in CT levels preceded metastases or death, they did not attempt to quantify the rate of increase.[10,12]

Collins et al.[13] introduced the concept that growth of malignant tumors in man is exponential, and that the rate of growth can be described by the doubling time of the tumor. Assuming that secretion of calcitonin by a unit volume of tumor in a particular case is constant, changes in plasma calcitonin levels should be expected to reflect the change in tumor volume. As this study demonstrates, CT levels increased exponentially in patients with abnormal postoperative CT levels. Doubling time of CT levels calculated from the regression line in each patient showed the highest correlation with 3-year survival, recurrence within 5 years, and time interval between surgery and clinical recurrence. Interestingly, the durations of postoperative survival in patients who died of the disease were in a relatively narrow range, *i.e.*, 5.5- to 20.9-fold (mean 11.1-fold) of the doubling time of CT levels. Five doublings of a tumor will result in a 32-fold increase in volume compared to the initial volume, 10 doublings will make a 10^3-fold volume, and 20 doublings will make a 10^6-fold volume.

Doubling times of CT levels in our patients with medullary thyroid carcinoma were much longer than doubling times of tumor calculated from changes in size for breast cancer,[13-15] colon cancer,[13,16] or skeletal sarcomas.[13,17] This is consistent with the much more favorable prognosis in medullary thyroid carcinoma.[18,19]

Plasma calcitonin level after surgery is considered to

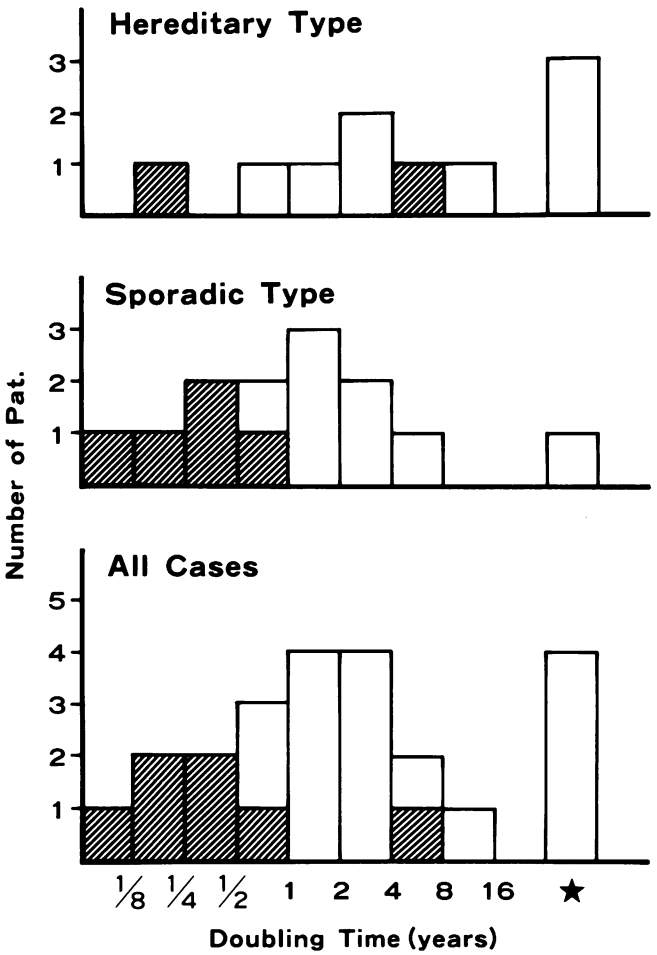

FIG. 2. Distribution of doubling time of plasma calcitonin levels (T2) in patients with medullary thyroid carcinoma. Solid column represents deceased patients. All five patients with T2 shorter than 0.5 year died within 3 years. ★ = patients with negative T2 values, indicating a decrease in plasma calcitonin levels during the follow-up period.

reflect residual tumor volume, since the preoperative CT level is reported to have a rough correlation with tumor weight in patients operated for medullary thyroid carcinoma.[7] In the present paper, a significant correlation was observed between basal CT levels after surgery and prognosis or recurrence. However, high CT levels were not always related to poor prognosis or early recurrence, as has been reported by several authors.[9-11]

Concerning tumor growth, two main factors should be considered that affect prognosis or recurrence. These are growth rate and initial tumor volume or residual tumor volume after surgery. As tumors grow exponentially, the growth rate, represented by doubling time, has much more impact on prognosis than the residual tumor volume.[13] Thus, it is reasonable that doubling time of CT levels had much more effect on prognosis than plasma calcitonin levels after surgery.

Trump et al.[8] reported a case of medullary thyroid carcinoma with widely disseminated metastases in which

TABLE 4. *Doubling Time of Plasma Calcitonin Levels (T2) and 3-year Survival in Patients with Medullary Thyroid Carcinoma*

T2 (year)	Number of Survivors	Number of Deaths	Total
<0.5	0	5	5
>0.5	13	0	13
Total	13	5	18

$\chi^2 = 13.360$; $p < 0.001$.

plasma calcitonin level was unexpectedly low. Growth of the tumor in that patient was rather rapid, and photomicrographs of the tumor presented in their paper apparently showed a poorly differentiated variant of medullary thyroid carcinoma. Several case reports demonstrated anaplastic variants of medullary thyroid carcinoma with poor prognosis,[20-23] poor staining property on immunohistochemistry with anticalcitonin serum,[21-23] low content of calcitonin in tumor tissue,[8] or a small number of secretory granules on electron microscopic studies.[22] The pathologic specimens from our patients with doubling time of CT levels shorter than 0.5 year showed poor differentiation and weak staining property on immunohistochemical studies with anticalcitonin serum (not demonstrated in the text; one case was reported elsewhere).[21] The ratio of plasma CT level to tumor weight estimated from angiography or computerized axial tomography in these patients was 0.15 ± 0.25 ng/ml/g (mean ± SD), which was lower than the ratio of preoperative basal plasma CT level to tumor weight, 0.76 ± 0.67 ng/ml/g, in 18 patients with well-differentiated tumor in whom plasma CT levels returned to normal or near normal after surgery (not shown in the text, $p < 0.02$). Thus, poorly differentiated medullary carcinoma may have inappropriately low CT levels and short doubling time of CT levels as a result of impaired secretion of calcitonin and rapid growth rate, respectively.

Wells et al.[24] reported that patients with preoperative stimulated plasma CT levels higher than 10 ng/ml had a higher incidence of regional lymph node metastases or residual tumor after surgery indicated by abnormal post-

TABLE 5. *Doubling Time of Plasma Calcitonin Levels (T2) and Recurrence Within 5 Years in Patients with Medullary Thyroid Carcinoma—Clinically Overt Recurrence*

T2 (year)	No	Yes	Total
<0.5	0	5	5*
0.5–1	1	4	5†
>1	12	3	15‡
Total	13	12	25

* <0.5 *vs.* >1: $\chi^2 = 6.944$, $p < 0.01$.
† <0.5 plus 0.5–1 *vs.* >1: $\chi^2 = 9.141$, $p < 0.005$.
‡ 0.5–1 *vs.* >1: $\chi^2 = 3.590$, $p = 0.06$.

TABLE 6. *Doubling Time of Plasma Calcitonin Levels (T2) and Interval Between Surgery and Recurrence*

T2 (years)	Number of Patients with Recurrence	Interval (mean ± SD; years)
<0.5	5	0.8±0.5*
0.5–1	5	3.3±1.8†
>1	10	10.5±10.0‡

* <0.5 *vs.* 0.5–1: $p < 0.05$.
† <0.5 *vs.* >1: $p < 0.05$.
‡ 0.5–1 *vs.* >1: $p < 0.1$.

operative CT levels than patients with lower CT levels. In their series, distant metastases or death occurred only in patients with stimulated CT levels higher than 10 ng/ml. They concluded that preoperative stimulated CT levels were of prognostic value. In the present study, preoperative basal CT levels had no significant correlation with life expectancy or recurrence during the observation period. However, none of our patients with preoperative basal CT levels higher than 10 ng/ml exhibited normal CT levels after surgery, suggesting extended disease in these patients.

Several factors were known to cause fluctuations in CT levels. Daily fluctuations[2] and an increase after meals[25] were reported in patients with medullary thyroid carcinoma. Maximum CT levels after meals were less than two-fold of those before meal.[25] Circadian variation of plasma calcitonin levels was also reported in normal subjects.[26] Thus, care should be taken to minimize the risk of misinterpretation in follow-up with serial CT measurements. Blood samples should be drawn before meal and at the same time of the day.

Serial measurements of CT levels provide quantitative prediction of the prognosis in each individual patient and help to elucidate important features of human tumor biology.

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