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Evaluation of Surgical Results and Prediction of Prognosis in Patients with Medullary Thyroid Carcinoma by Analysis of Serum Calcitonin Levels

Akira Miyauchi, M.D., Fumio Matsuzuka, M.D., Kanji Kuma, M.D., Shin-ichiro Takai, M.D., Kembu Nakamoto, M.D., Kenji Nakamura, M.D., Satoru Nanjo, M.D., and Masazumi Maeda, M.D.

Second Departments of Surgery, Kagawa Medical School, Kagawa; Kuma Hospital, Kobe; and Osaka University Medical School, Osaka, Japan

Serum calcitonin levels before (S_1) and after (S_2) surgery were measured in 67 patients with medullary thyroid carcinoma and the patients were followed with serial calcitonin measurements for a mean duration of 7 years. The calcitonin doubling time (T_2) was calculated in patients with elevated postoperative calcitonin levels. Assuming that the serum calcitonin level is linearly correlated with tumor weight, the residual tumor weight (W_2) is estimated as $W_1S_2/(S_1-S_2)$ where W_1 is the weight of the resected tumor. The reduction index (α) is defined as $W_2/(W_1 + W_2) = (1/2)^{\alpha}$. αT_2 indicates the expected prolongation in survival (EPS) by surgery. The survival index (β) is defined as the number of doublings of residual tumor until it weighs 1,000 g, which would generally kill the host. The expected duration of survival (EDS) after surgery is estimated as βT_2. Death within 3 years after surgery or recurrence within 5 years was best associated with short EPS followed by short T_2 or small α. S_2 had a rather weak correlation and S_1 had almost no correlation with the prognosis. The duration of survival in 3 patients who died of the disease was very close to the EDS. T_2 indicates growth rate of the tumor, α indicates degree of radicality of the surgery, EPS indicates the effects of the surgery, and EDS indicates duration of survival after surgery. These parameters allow quantitative judgment of the effect of surgery and quantitative prediction of the prognosis in each patient.

Serum calcitonin is a very sensitive tumor marker of medullary thyroid carcinoma [1]. Preoperative calcitonin levels correlate roughly with tumor weight or extent of the disease [2]. Thus, both pre- and postoperative calcitonin levels appear to have prognostic value. Wells et al. [3] reported that distant metastases or death occurred only in patients with preoperative calcitonin levels higher than 10 ng/ml. Stepanas et al. [4] described that high postoperative calcitonin levels implied extended disease in general, but not always poor prognosis. We reported that the postoperative calcitonin levels increased exponentially in patients with medullary thyroid carcinoma, and that the doubling time of the levels correlated well with life expectancy and recurrence [5].

Collins et al. [6] reported that malignant tumors grow exponentially, and that the rate of growth can be described by the doubling time of the tumor. According to this concept, tumor growth is defined by only 2 factors: the tumor doubling time and the initial tumor volume or residual tumor volume after surgery.

In this study, we estimated residual tumor weight, and calculated the calcitonin doubling time in patients with medullary thyroid carcinoma. With these parameters, we estimated the expected prolongation in survival by surgery and the expected duration of survival after surgery, which best correlated with life expectancy and recurrence.

Material and Methods

The serum calcitonin level of 67 patients with medullary thyroid carcinoma seen at our hospital was measured serially. Twenty-six patients exhibited the hereditary type and 41 the sporadic type. Fifty-six patients were of primary cases and the remaining 11 patients underwent surgery for a recurrent tumor. Five patients underwent a total of 7 operations for recurrent disease during the follow-up period. Patients were treated with mainly surgery alone, although some received additional chemotherapy or radiotherapy. Plasma calcitonin levels were measured before and within 1 month after surgery and periodically thereafter including intravenous calcium or the tetragastrin loading test, described previously [5]. In 35 patients with abnormally high calcitonin levels after surgery, the doubling time of calcitonin levels (T_2) was calculated individually, as described previously [5]. Fifty-four patients, including 15 with recurrent disease, were examined both preoperatively and postoperatively. In 65 patients, including 16 operated for recurrent tumor, the first postoperative measurement was made within 1 month after surgery. Mean duration of follow-up was 7.0 ± 5.8 years (mean ± SD); mean duration of serial calcitonin measurements, 4.3 ± 3.4 years; and a mean number of measurements, 10.7 ± 8.3 per patient.

Assuming that the serum calcitonin level is linearly correlated with tumor weight in a particular patient, the residual tumor weight (W_2) is estimated as $W_1S_2/(S_1 - S_2)$ where W_1 is resected tumor weight, and S_1 and S_2 are calcitonin levels before and after surgery, respectively (Fig. 1). S_2 was regarded as zero if

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Reprint requests: Akira Miyauchi, M.D., Second Department of Surgery, Kagawa Medical School, Miki-cho, Kita-gun, Kagawa 761-07, Japan.

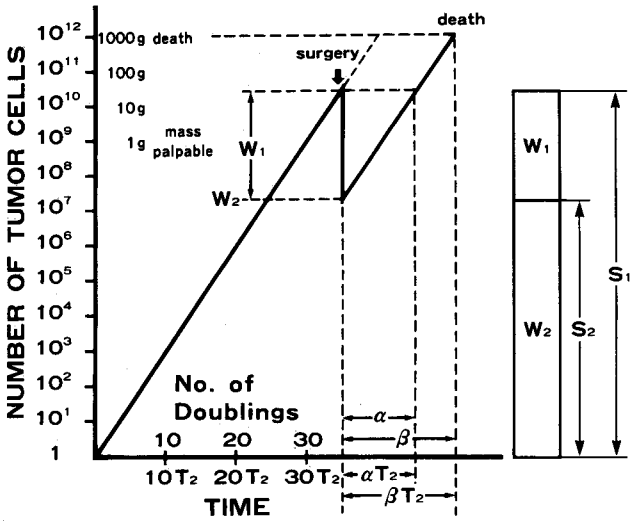

Fig. 1. Quantitative estimation of prognosis with an ideal tumor marker. W_1 = resected tumor weight, W_2 = residual tumor weight, S_1 = serum calcitonin level before surgery, S_2 = serum calcitonin level after surgery, T_2 = doubling time, α = reduction index, αT_2 = expected prolongation in survival, β = survival index, βT_2 = expected duration of survival.

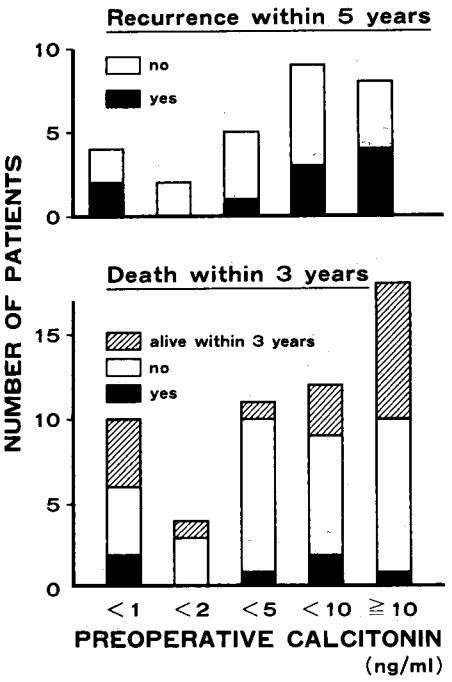

Fig. 2. Preoperative serum calcitonin levels and prognosis in 54 patients with medullary thyroid carcinoma, including 15 operated on for recurrent disease. Shaded area represents patients who are alive but with postoperative periods of less than 3 years.

there was no change in calcitonin level during calcium or tetragastrin loading. The residual tumor ratio, $W_2/(W_1 + W_2)$, is calculated as S_2/S_1. The reduction index (α) is defined as $W_2/(W_1 + W_2) = (1/2)^{\alpha}$. Then, $\alpha = \log(S_1/S_2)/\log 2$. Since the residual tumor (W_2) will increase to the preoperative tumor weight ($W_1 + W_2$) after α time doublings, αT_2 indicates expected prolongation in survival (EPS) by surgery (T_2 = calcitonin doubling time) (Fig. 1).

The survival index (β) is defined as a number of doublings of the residual tumor (W_2) until it becomes 1,000 g, since a tumor of this weight would generally kill the host [6]. By definition, $2^{\beta} \times W_2 = 1{,}000$; then, $\beta = \log(1{,}000/W_2)/\log 2$. The expected duration of survival (EDS) after surgery is estimated as βT_2.

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

Results

Preoperative Calcitonin Levels and Prognosis

There was no significant correlation between preoperative serum calcitonin level and death within 3 years or recurrence within 5 years after surgery in 54 patients, including 15 operated for recurrent disease (Fig. 2). However, patients with preoperative calcitonin levels higher than 10 ng/ml were less likely to exhibit normal calcitonin levels after surgery compared to those with a lower calcitonin level ($\chi^2 = 7.891$, $p < 0.005$), indicating extended disease in these patients. Patients operated for recurrent disease were less likely to have a normal calcitonin level after surgery compared to those with primary disease ($\chi^2 = 5.709$, $p < 0.05$).

Postoperative Calcitonin Levels and Prognosis

Figure 3 shows the relation between postoperative calcitonin level and death within 3 years or recurrence within 5 years after surgery in 65 patients, including 16 operated for recurrent disease. Patients with postoperative calcitonin level higher than 2 ng/ml had a higher risk of death or recurrence compared to those with a lower calcitonin level ($\chi^2 = 2.247$, $p < 0.2$; $\chi^2 = 11.100$, $p < 0.002$, respectively). However, even in patients with a postoperative calcitonin level lower than 1 ng/ml, death or recurrence was not rare except for those with a normal calcitonin level after calcium or tetragastrin loading.

Calcitonin Doubling Time and Prognosis

Doubling time of calcitonin levels ranged from 0.12 year to more than 16 years. In 5 patients, the calcitonin levels decreased during the observation period and the calcitonin doubling time in these patients had a negative value (Fig. 4). Patients with a calcitonin doubling time shorter than 0.5 year had a significantly higher incidence of death within 3 years or recurrence within 5 years after surgery ($\chi^2 = 16.854$, $p < 0.002$; $\chi^2 = 7.429$, $p < 0.01$, respectively).

Residual Tumor Ratio

The residual tumor ratio ranged from 0 to more than 0.5 (Table 1). The residual tumor ratio was zero, indicating complete removal of the tumor in 46% of the patients with hereditary disease, 56% of those with sporadic disease, in 62% of the primary cases, and in 15% of the recurrent cases. In only primary cases, 53% of the patients with hereditary disease and

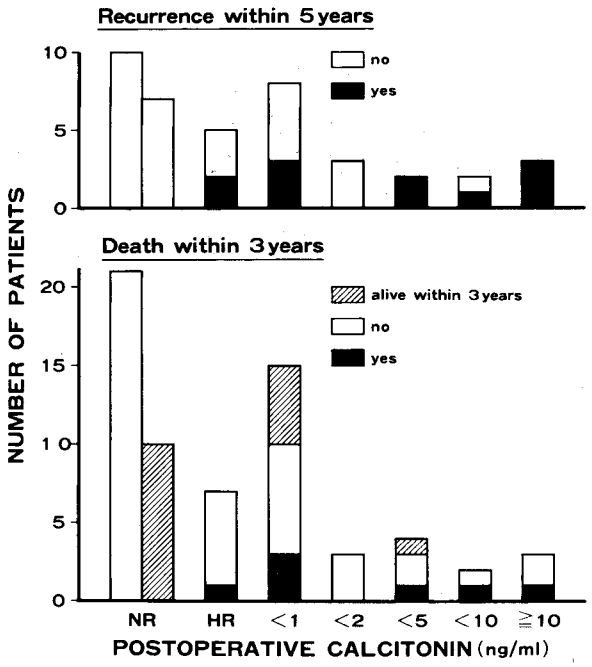

Fig. 3. Postoperative serum calcitonin levels and prognosis in 65 patients with medullary thyroid carcinoma, including 16 operated on for recurrent disease. NR = normal response to calcium or tetragastrin loading, HR = normal basal value with increased response.

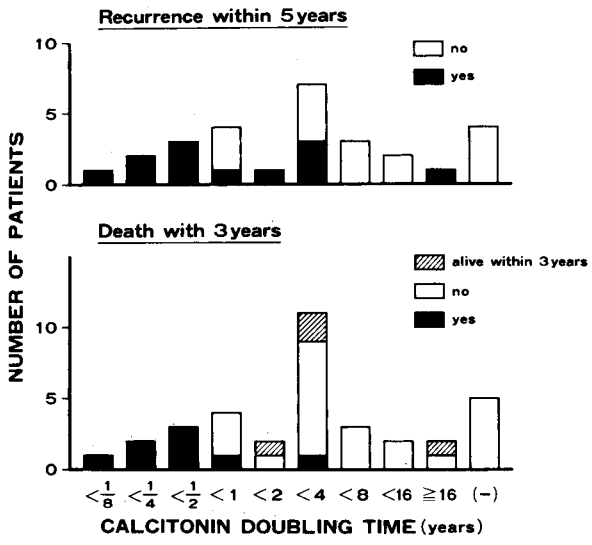

Fig. 4. Calcitonin doubling time (T_2) and prognosis in 35 patients with medullary thyroid carcinoma. (—) denotes patients with negative T_2 value, indicating a decrease in calcitonin levels during the follow-up period.

69% of those with sporadic disease had a residual tumor ratio of zero.

Reduction Index and Prognosis

The reduction index in 29 patients ranged from 0.32 to 8.9 and was infinite in 31 patients (Fig. 5). Patients with a reduction index of less than 3 were more likely to die within 3 years after surgery or to have recurrence within 5 years compared to those with a reduction index more than 3 ($\chi^2 = 18.801$, $p < 0.002$; $\chi^2 = 17.803$, $p < 0.002$, respectively).

Table 1. Distribution of residual tumor ratio.

	No. of patients	Residual tumor ratio 0	<0.01	<0.05	<0.1	<0.2	<0.5	≥0.5
Type of disease								
Hereditary	24	11	2	2	5	0	3	1
Sporadic	36	20	2	3	3	2	3	3
Surgery								
Primary	47	29	4	3	5	0	4	2
Nonprimary	13	2	0	2	3	2	2	2

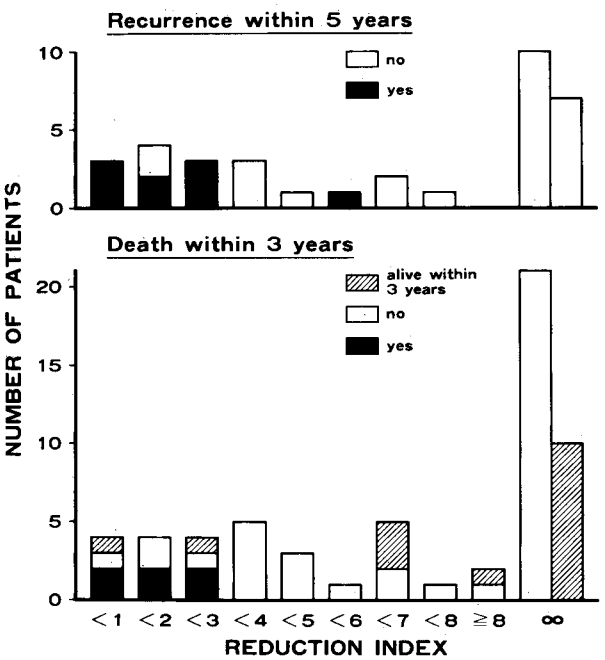

Fig. 5. Reduction index and prognosis in 60 patients with medullary thyroid carcinoma.

Expected Prolongation in Survival (EPS)

Distribution of expected prolongation in survival (EPS) calculated from reduction index and calcitonin doubling time is shown in Table 2. (If the reduction index is infinite, EPS is also infinite irrespective of calcitonin doubling time.) Five patients with a negative calcitonin doubling time were put into EPS for more than 10 years. EPS was more than 5 years in patients with hereditary disease, except for 2 patients. In 91% of the primary cases and in 71% of the patients operated for recurrent disease, EPS was more than 5 years,indicating effectiveness of surgery in these patients.

Expected Prolongation in Survival and Prognosis

EPS had a high correlation with prognosis as shown in Fig. 6. None of the 5 patients with an EPS shorter than 1 year survived for 3 years, whereas all but one with an EPS longer than 1 year

Table 2. Distribution of expected prolongation in survival by surgical therapy.

	No. of patients	Expected prolongation in survival (yr)					
		<1	<2	<5	<10	≥10	∞
Type of disease							
Hereditary	21	2	0	0	1	7	11
Sporadic	36	4	1	1	4	6	20
Surgery							
Primary	43	3	1	0	1	9	29
Nonprimary	14	3	0	1	4	4	2

survived more than 3 years ($\chi^2 = 27.252$, $p < 0.002$). Recurrence occurred within 5 years after surgery in all 7 patients with an EPS shorter than 5 years but in only 2 of the 29 patients with an EPS longer than 5 years ($\chi^2 = 21.340$, $p < 0.002$).

Expected Duration of Survival and Prognosis

The expected duration of survival (EDS) after surgery was estimated in 12 patients with elevated postoperative calcitonin levels, indicating residual tumor elsewhere (Table 3). In these patients, the estimated residual tumor weight ranged from 0.03 g to 55 g, and the survival index ranged from 4.2 to 15.0. Calcitonin doubling time ranged from 0.18 year to 71.2 years in 9 patients and was of negative value in 3. EDS ranged from 0.8 year to more than 50 years. Interestingly, the duration of survival after surgery in 3 patients who died of the disease was very close to the estimated EDS (1 year 7 months versus 0.8 year, 1 year 2 months versus 1.4 year, and 2 year 2 months versus 3.9 years). Nine patients with a long EDS were alive with no clinical evidence of recurrence. Thirty-one patients with a normal postoperative calcitonin level and, therefore, theoretically infinite EDS were alive with no evidence of recurrence, except for one who died of unrelated disease.

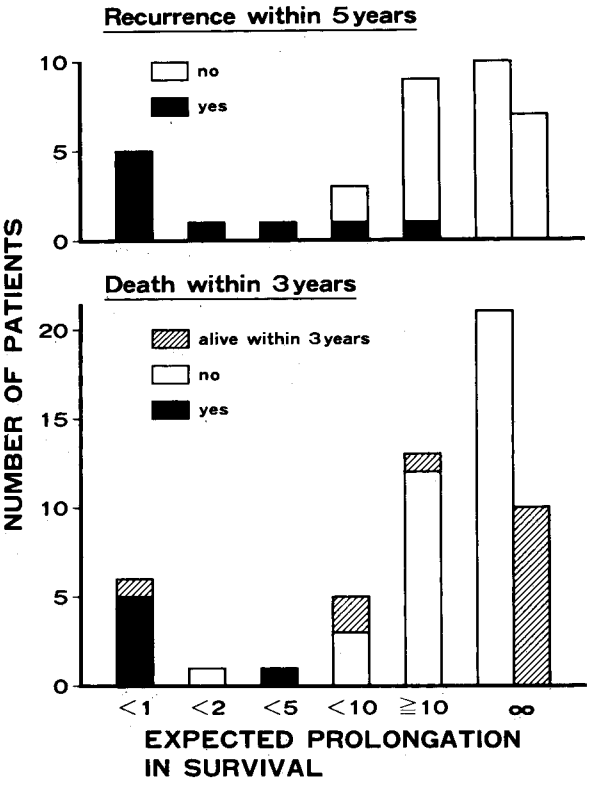

Fig. 6. Expected prolongation in survival and prognosis in 57 patients with medullary thyroid carcinoma.

Discussion

Previously, we have demonstrated that doubling time of calcitonin levels has a much better prognostic value than preoperative or postoperative calcitonin levels in patients with medullary thyroid carcinoma [5]. This is confirmed in the present article. Herein, we have tried to predict the prognosis more precisely and more quantitatively, and to evaluate the prognostic benefit of surgical therapy.

According to Collins' concept that growth of the malignant tumor is exponential [6], growth of the tumor is defined by only 2 factors: tumor doubling time (t_2) and initial tumor volume. The time period (T) necessary for initial tumor of volume V_1 to grow up to volume V_2 is very simply expressed as $T = \chi t_2$, where χ is defined as $2^\chi = V_2/V_1$. As we have shown previously, change in calcitonin levels in patients with residual tumor was exponential and calcitonin doubling time (T_2) had a good correlation with prognosis [5].

We estimated residual tumor ratio by the ratio of postoperative calcitonin level to preoperative calcitonin level and expressed as $(1/2)^\alpha$. α is called the reduction index. Expected prolongation in survival (EPS) after a particular surgery in a particular patient is estimated in a simple formula as αT_2. The reduction index also had a good correlation with the prognosis and EPS had a better correlation with the prognosis. T_2 indicates growth rate of the tumor, α indicates degree of radicality of surgery, and EPS indicates prognostic benefit of surgery.

The tumor bearer will generally die when the tumor grows to about 1,000 g [6]. We can estimate the duration of survival after surgery if we could know the residual tumor weight and tumor doubling time in a particular patient. We estimated the residual tumor weight by resected tumor weight and calcitonin levels before and after surgery. The expected duration of survival (EDS) was calculated from the estimated tumor weight and calcitonin doubling time. The duration of survival was surprisingly very close to EDS in 3 patients who died of the tumor. EDS − EPS indicates duration of survival without surgery.

Growth of medullary thyroid carcinoma seems to fit well with Collins' tumor growth concept, and changes in calcitonin levels seem to reflect well changes in tumor weight in each patient. From the point of view of tumor chronology, an ideal tumor marker should be very sensitive and its serum level should have a linear correlation with tumor weight. Calcitonin for medullary thyroid carcinoma is one of the best tumor markers in this regard. Several factors are, however, known to cause fluctuations in calcitonin levels [7, 8], necessitating a long observation period and multiple measurements in order to obtain a good regression line of calcitonin levels to calculate calcitonin doubling time. Saad et al. [9] reported that the carcinoembryonic antigen (CEA) level was better for calculating the doubling time

Table 3. Expected duration of survival (EDS) and prognosis.

Patient	Age (yr), Sex	Residual tumor weight (g)	Survival index	Calcitonin doubling time (yr)	EDS (yr)	Actual survival[a]
1	58, M	55	4.2	0.18	0.8	1 yr 7 mo, D
2	52, M	19	5.7	0.25	1.4	1 yr 2 mo, D
3	62, F	3.3	8.2	0.48	3.9	2 yr 2 mo, D
4	63, F	9	6.8	3.0	20	3 yr 8 mo, A
5	60, F	0.39	11.3	2.9	33	5 yr 3 mo, A
6	32, F	0.42	11.2	3.1	35	4 yr 7 mo, A
7	62, M	1.4	9.5	6.1	58	6 mo, A
8	38, M	0.4	11.3	26.9	>100	1 yr 11 mo, A
9	42, F	0.31	11.6	71.2	>100	5 yr 6 mo, A
10	66, F	0.76	10.4	−9.6	∞	7 yr 9 mo, A
11	33, M	0.03	15.0	−9.7	∞	8 yr 1 mo, A
12	58, F	0.2	12.3	−8.2	∞	3 yr 6 mo, A

[a]D = died of tumor, A = alive without clinical recurrence of tumor.

in patients with medullary carcinoma because there is less fluctuation. This is confirmed by our study [10]. CEA doubling time was, however, longer than calcitonin doubling time in our cases, and CEA is not sensitive enough to calculate residual tumor weight [10].

Our concept, mentioned above, may fit cases with other malignant tumors having good tumor markers. The tumor marker doubling time indicates the growth rate of tumor, the reduction index indicates degree of radicality of surgery, EPS indicates prognostic benefit of surgical therapy, and EDS indicates duration of survival after surgery. These parameters allow quantitative judgement of surgical benefit and quantitative prediction of the prognosis in each patient.

Résumé

Le taux de calcitonine sérique avant (S_1) et après (S_2) l'acte chirurgical ont été mesurés chez 67 patients ayant un cancer médullaire de la thyroïde; on a ensuite mesuré les taux de calcotonine de façon répétée pendant 7 ans en moyenne. Le temps de doublement de calcitonine a été calculé chez les patients ayant des taux élevés de calcitonine en postopératoire. En assumant que le taux de calcitonine augmente proportionnellement au poids tumoral, le poids tumoral résiduel ($W_2 = W_1S_2/(S_1 - S_2)$ où W_1 = poids de la tumeur réséquée. L'index de réduction (α) est défini par $W_2/(W_1 + W_2) = (1/2)$ puissance α. Le produit αT_2 indique la prolongation de survie procurée par l'acte chirurgical (PSP). L'index de survie (β) se définit par le nombre de doublements de la tumeur résiduelle jusqu'à ce qu'elle pèse 1,000 g, ce qui provoque en général la mort du patient. La durée espérée de survie après chirurgie (DES) = βT_2. La survenue de mort avant 3 ans, ou de récidive avant 5 ans était corrélée au mieux avec une PSP courte, suivie d'un T_2 court ou d'un α petit. S_2 était peu corrélé et S pratiquement pas corrélé du tout avec le pronostic. La durée de survie chez 3 patients morts de leur maladie était très près de la DES. T_2 indique le taux de croissance de la tumeur, α indique le degré de radicalité de la chirurgie, PSP indique les effets d la chirurgie, et DES la durée de survie après chirurgie. Ces paramètres permettent d'évaluer quantitativement les effets de la chirurgie et d'établir le pronostic de chaque patient.

Resumen

Los niveles de calcitonina sérica fueron medidos antes (S_1) y después (S_2) de la cirugía en 67 pacientes con carcinoma medular de tiroides y los pacientes fueron seguidos con mediciones seriadas de calcitonina durante un promedio de 7 años. El tiempo de doblaje de la calcitonina fue calculado en los pacientes con niveles postoperatorios elevados de calcitonina. Bajo la presunción de que el nivel sérico de calcitonina se correlaciona en forma linear con el peso del tumor, el peso residual del tumor (W_2) puede ser estimado como $W_1S_2/(S_1 - S_2)$, donde W_1 es el peso del tumor resecado. El índice de reducción (α) es definido como $W_2/(W_1 + W_2) = (1/2)^{\alpha}$. αT_2 indica la prolongación esperada de la supervivencia (PES) por la cirugía. El índice de supervivencia (β) es definido como el número de doblajes del tumor residual hasta un peso de 1,000 g, el cual generalmente mata al paciente. La duración esperada de la supervivencia (DES) después de la cirugía es definida como βT_2. La muerte dentro de los 3 años despues de la cirugía o la recurrencia dentro de los 5 años apareció más íntimamente asociada con una corta PES, seguida de una corta T_2 o pequeño α. S_2 presentó una correlación débil, y S_1 casi ninguna, con el pronóstico. La duración de la supervivencia en 3 pacientes que murieron de la enfermedad apareció muy cercana a la DES. T_2 indica la tasa de crecimiento del tumor, α indica el grado de radicalidad de la cirugía, PES indica los efectos de la cirugía, y DES indica la duración de la supervivencia después de la cirugía. Estos parámetros permiten una apreciación cuantitativa del efecto de la cirugía y una predicción cuantitativa del pronóstico en cada paciente.

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Invited Commentary

Lars-Erik Tisell, M.D., Ph.D.

Department of Surgery, Sahlgren's Hospital, Göteborg, Sweden

A laboratory test which would indicate the prognosis for surgical therapy and long-term survival in patients with malignant disease would be welcomed by all surgeons. Miyauchi et al. have designed such a method which is applicable to medullary carcinoma of the thyroid. They can calculate the expected duration of survival and also the expected prolongation of survival by surgery. This method is based on the concept that the origin of cancer is the mutation of a single cell and that the growth of the tumor can be described by its doubling times [1]. Miyauchi et al. ingeniously used the pre- and postoperative calcitonin levels and the weight of the resected tumor tissue to estimate the residual amount of tumor. In their series, they found that this method could allow quantitative judgment of the effect of surgery and quantitative prediction of the prognosis of the patients.

A reservation as to the validity of this method concerns the assumption that the growth rate of cancer is constant throughout its course. There are observations indicating that this is not always the case [2]. Furthermore, determination of the weight of the resected tumor must imply difficulties and uncertainty, especially in patients with infiltrating tumors and with numerous metastases to the lymph nodes, with varying involvement.

There are some points in this article that need to be clarified. For example, the authors do not state whether basal or provoked calcitonin levels were used for the calculations. Several figures presenting the patients of the series include the heading "Death within 3 years" and the patients are separated into 3 groups according to whether they survived 3 years or not. I cannot imagine more than 2 alternatives, yes or no.

In conclusion, this article is an important contribution to our knowledge of the biology of medullary thyroid carcinoma. The authors have demonstrated a way to predict the prognosis of this tumor. Whether their method can be applied to all cases of medullary thyroid carcinoma cannot be known until it has been tested in larger series with longer observation times.

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