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Prognostic Impact of Serum Thyroglobulin Doubling-Time Under Thyrotropin Suppression in Patients with Papillary Thyroid Carcinoma Who Underwent Total Thyroidectomy

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Background: Detectable serum thyroglobulin (Tg) in patients with papillary thyroid carcinoma (PTC) after total thyroidectomy implies unsuccessful surgery, indicating a high risk of recurrence. Serum Tg kinetics in such patients have not been extensively studied. We studied serum Tg kinetics in patients with suppressed serum thyrotropin levels and undetectable anti-Tg antibody to minimize the effects of these factors on Tg values, and evaluated the relationship of prognosis to the serum Tg doubling-time.
Methods: Between January 1998 and December 2004, 1515 patients with PTC underwent total thyroidectomy in Kuma Hospital. After excluding patients with other thyroid cancers and those positive tests for anti-Tg antibody, there were 426 patients with 4 or more serum Tg measurements at a time that serum thyrotropin concentrations were <0.1 mIU/L. These patients were selected for the present retrospective study. Tg doubling-time was computed using Tg values measured during routine follow-up. Patients were followed for a mean of 88.1 months and a median of 86.7 months.
Results: Of the 426 patients, 137 patients had 4 or more measurements that revealed detectable Tg in serum Tg. The Tg doubling-time (DT), calculated using all available data, varied widely, and were grouped into those that were <1 year (17 patients), those that were 1–3 years (21 patients), and those that were ≥ 3 years (30 patients), as well as those with a negative value due to decrease in serum Tg (69 patients). There were also 88 patients who had three or fewer serum Tg measurements that showed detectable Tg levels, as well as 201 patients in whom serum Tg measurements were below the lower limit of detection. In the group of patients with a Tg-DT of <1 year the cause specific survival at 10 years was 50%, and in the group with a Tg-DT of 1–3 years it was 95%. In all other groups it was 100%. Many classical prognostic factors (TNM stage, age, and gender) as well as the Tg-DT were significant indicators of survival by univariate analysis, but Tg-DT remained the only independent predictor by multivariate analysis. Tg-DT was also the only independent predictor of distant metastases and loco-regional recurrence on multivariate analysis. Tg-DT calculated using only the first four data [Tg-DT (first four data)] was also the only independent predictor of survival, distant metastases, and loco-regional recurrence on multivariate analysis.
Conclusions: Tg-DT (all data or first four data) is a very strong prognostic predictor superior to the classical prognostic factors in patients with PTC.

Introduction

The thyroid gland consists of two types of epithelial cells: follicular cells being the vast majority and C-cells being a small minority. The follicular cells produce thyroglobulin (Tg) and synthesize thyroid hormones, whereas the C-cells secrete calcitonin. The former cells give rise to papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), and the latter cells are the origin of medullary thyroid carcinoma (MTC). These tumors usually keep the nature and functions of their original cells to some extent. Thus, serum calcitonin is a very sensitive tumor marker for MTC. Serum Tg is a marker for PTC or FTC. After thyroidectomy, even if the goal of the surgeon is to perform a total

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thyroidectomy, Tg is often present in serum because of residual thyroid tissue, either normal or tumor tissue. In 1984, we found that serum calcitonin levels increased exponentially in patients with MTC who showed persistent hypercalcitoninemia after surgery and proposed calcitonin DT as a very strong prognostic factor (1). The prognostic values of calcitonin DT were recently confirmed by Barbet *et al.* (2) and others (3,4), and this parameter has been adopted as an independent prognostic factor in recently published American Thyroid Association (ATA) Guidelines for the management of MTC (5). However, the value of serum Tg as a prognostic indicator in patients with PTC or FTC has not been studied extensively though it is well recognized that detectable amounts of Tg in serum after total thyroidectomy for thyroid cancer frequently indicates the presence of metastatic foci (6,7). There are two major considerations or limitations when employing serum Tg measurements as an indicator of residual thyroid tissue. Serum Tg levels are dependent on circulating thyrotropin (TSH) concentrations, even if tumor tissue is the source of Tg (8). In addition, techniques for measuring serum Tg are not reliable in the presence of anti-Tg antibodies (8,9). In the present study we assessed the kinetics of serum Tg levels with time after total thyroidectomy for PTC, specifically looking at the serum Tg-DT. We thought that this might be a better indicator of prognosis than absolute serum Tg levels. This approach, however, does not deal with the problem of serum Tg assays being unreliable in patients with anti-Tg antibodies. Therefore, the study was performed in patients without anti-Tg antibodies. In addition, only data in patients in whom serum TSH levels were suppressed as a result of exogenous thyroid hormone therapy were used in the calculation of Tg-DT.

Materials and Methods

Selection of the patients

Between January 1998 and December 2004, a total of 1515 patients with PTC underwent total thyroidectomy as their initial surgery in Kuma Hospital. After excluding patients with FTC, MTC, anaplastic thyroid carcinoma, malignant lymphoma of the thyroid, and dishormonogenetic goiter including Tg gene mutation carriers (25, 3, 6, 2, 48 patients, respectively), 1431 patients remained. Of these 1431 patients, 362 patients had detectable anti-Tg antibodies and so were excluded. Another 367 patients did not have tests for anti-Tg antibodies and were therefore also excluded, leaving 702 patients for the present study. In a preliminary analysis, we found that at least 4 serum Tg measurements under suppression of serum TSH were necessary for a proper kinetic analysis in each individual patient. A total of 426 patients had 4 or more serum Tg measurements at a time that their serum TSH was suppressed to <0.1 mIU/L. There were 349 females and 77 males, aged from 14 to 81 years, with a mean age of 51.5 years. Their tumor status in TNM staging system was T1, T2, T3, and T4 in 43, 129, 119, and 135 patients, respectively. There were 188 patients who had their tumors confined within the thyroid capsule (Ex0), 102 patients who had tumors with minimal extrathyroidal extension (Ex1), and 136 patients who had tumors with massive extrathyroidal extension (Ex2). There were 218 patients who had no clinically detectable node metastases (N0), 113 patients who had node metastases in the central compartment (N1a), and 95 patients who had node metastases in the lateral compartment (N1b). There were 14 patients with distant metastases (M1). The TNM Stages were Stage I, II, III, IVa, and IVc in 33, 74, 130, 175, and 14 patients, respectively. All patients underwent surgery with intent to cure (total thyroidectomy and neck dissection as required) except for the 14 patients with distant metastases. Radioiodine was administered in 167 patients, including patients with distant metastases as a treatment or to ablate possible thyroid remnants. Metastatic foci were detected with radioiodine scintigraphy in 18 patients, and radioiodine treatments were repeated in these patients. Patients were followed for 20–143 months with a mean of 88.1 months and a median of 86.7 months. Serum Tg levels were measured 1 and 3 months after surgery, and two times per year thereafter in the majority of patients, more frequently in high risk patients and once a year in very low risk patients. Imaging studies included once-a-year ultrasonography examinations of the neck and chest roentogenography or computed tomography scan as well as other studies if indicated. In this series, when carcinoma recurrence was detected on imaging studies other than radioiodine scintigraphy, those patients were regarded as having recurrence. During the study period, 6 patients died of the disease, 58 patients developed loco-regional recurrences, and 25 patients developed distant metastases.

Measurements of serum Tg, TSH, and anti-Tg antibody

Measurements of serum Tg, TSH, and anti-Tg antibody were performed as routine follow-up studies during each patient's regular outpatient examination. During the study period, three assay systems for Tg, three assay systems for TSH, and two assay systems for Tg antibody were used sequentially. The assay methods for Tg were Thyroglobulin Radioimmunoassay (Eiken Chemical, Co. Ltd.), Ab Bead Thyroglobulin Radioimmunoassay (Eiken Chemical), and Elecsys Tg Electrochemiluminescence Immunoassay (Roche Diagnostics GmbH). Tg values of these three methods were evaluated when they were adopted by Kuma Hospital, and we confirmed that values obtained by the new method were comparable to those obtained by the previous method (10). The assay methods for TSH were TSH RIA Beads Radioimmunoassay (Abbott Laboratories), AxSYM Ultrasensitive hTSH-II Microparticle Enzyme Immunoassay (Abbott), and ARCHITECT TSH Chemiluminescent Microparticle Immunoassay (Abbott). Each TSH assay system had sensitivity >0.1 mIU/L. Therefore, change in the TSH assay system did not significantly influence the study. For anti-Tg antibody, TgAb radioimmunoassay (Roche) and Elecsys Anti-Tg Electrochemiluminescence Immunoassay (RSR Ltd.) were used, and patients having values higher than the reference values for the assay systems were excluded from the study.

Data analysis

Kinetic analysis of serum Tg levels was performed in patients who had four or more measurements obtained under suppression of serum TSH to <0.1 mIU/L. Serum Tg values obtained when the serum TSH was ≥ 0.1 mIU/L were excluded from analysis. Each patient had one or more anti-Tg antibody tests showing negative results. Since changes in Tg levels were exponential (as shown in the Results section), a regression line, $\log y = \log a + bx$, was computed by nonlinear

least square regression (x: years after surgery; y: Tg level). Tg-DT was given as (log 2)/b. Tg values below the detectable level were not used for the calculation. Some patients had decreases in their serum Tg values during the study period; therefore, Tg-DTs in these patients were expressed as negative values. Tg-DT was calculated using all available data to establish the prognostic impact of Tg-DT. Tg-DT was also calculated using only the first four data [Tg-DT (first four data)] to evaluate its prognostic value in a clinical practice setting. In patients who underwent major treatments such as surgical resection of recurrent tumors, radioiodine treatment, or external beam radiotherapy during the follow-up period, Tg-DT was calculated using the serum Tg data obtained before treatment. For patients with distant metastases at presentation who received radioiodine treatment, serum Tg values measured 6 or more months after the final treatment were used for the calculation.

Fisher's exact test was used to compare variables. The Kaplan–Meier method and log-rank test were adopted to analyze time-dependent variables. The Cox regression model was adopted for multivariate analysis. These analyses were performed with StatView-J 5.0. A p-value <0.05 was regarded as significant.

This study was approved by the Ethics Committee of Kuma Hospital.

Results

Distribution of Tg-DT

Of the 426 patients, 137 patients had four or more detectable serum Tg levels that increased, remained stable, or decreased over time. Some representative cases are demonstrated in Figure 1. Tg-DT calculated using all available data [Tg-DT (all data)] in these patients showed a wide variation, being <1 year, 1–3 years and ≥3 years in 17, 21, and 30 patients, respectively (Table 1). In 69 patients there was a decrease in serum Tg levels. The Tg-DTs calculated in these patients had negative values ranging from −368.6 to −117665.5 years (median −1817.9 years), consistent with a slight and gentle decline in serum Tg values over time. There were 88 patients who had a combination of undetectable serum Tg as well as three or less determinations in which serum

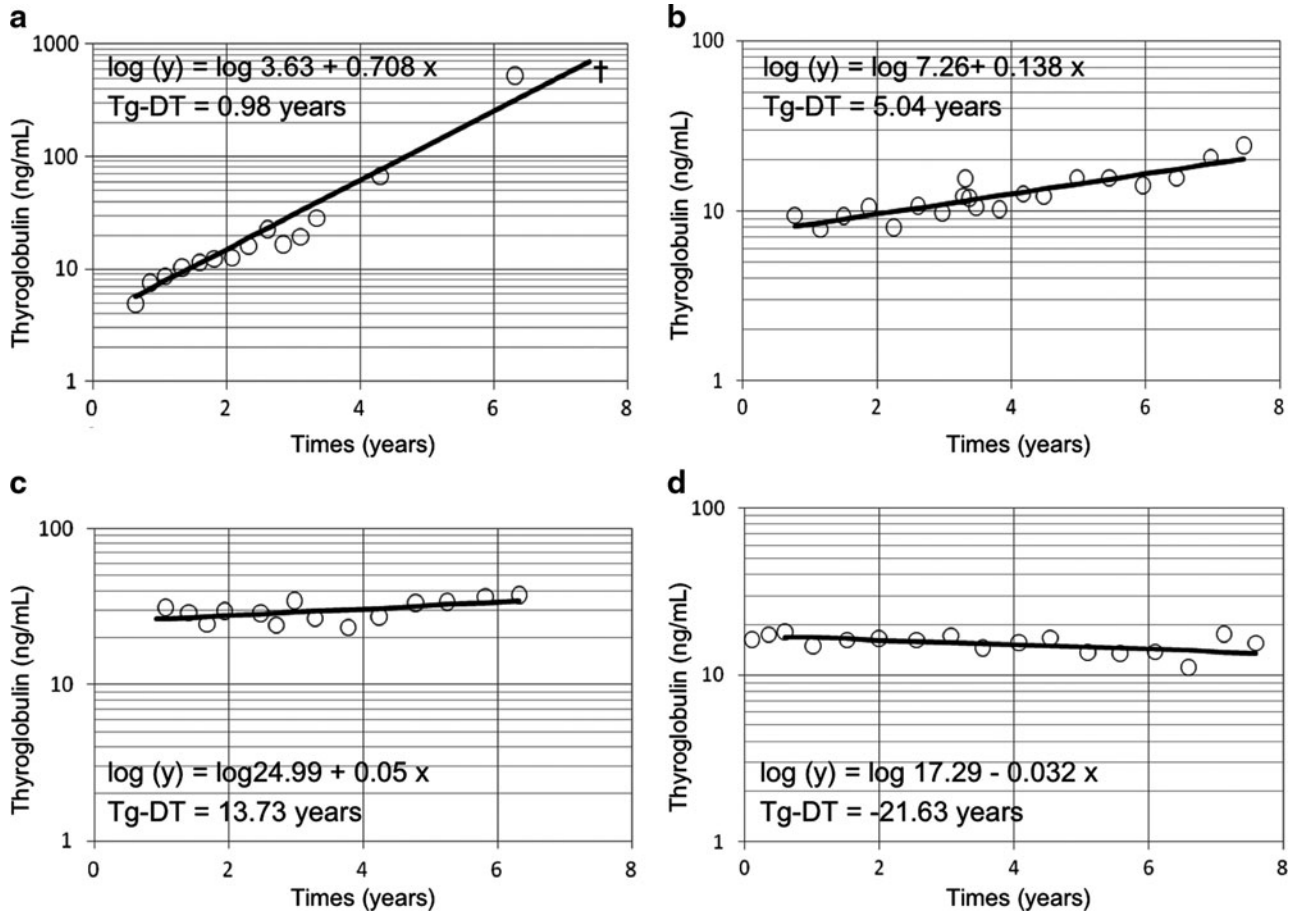

FIG. 1. Representative results of kinetic analyses of serial serum thyroglobulin (Tg) measurements. Tg was measured periodically after total thyroidectomy in patients with papillary thyroid carcinoma without detectable anti-Tg antibody. Since changes in serum Tg values measured under suppression of serum thyrotropin to <0.1 mIU/L were exponential, a regression line, $\log y = \log a + bx$, was computed by nonlinear least square regression (x: years after surgery; y: Tg level). Tg doubling-time (Tg-DT) was given as (log 2)/b. **(a)** A steep slope with a short Tg-DT of 0.98 years. +, died of cancer. **(b)** A gentle slope with a long Tg-DT of 5.04 years, **(c)** a flat slope with a very long Tg-DT of 13.73 years, and **(d)** a gentle declining slope of a negative Tg-DT value of −21.63 years.

Table 1. Distribution of the Patients According to Thyroglobulin Doubling-Time Status, Calculated Using All Available Data and Using Only the First Four Data

		No. of patients with Tg-DT calculated using	
Group	*Tg-DT status*	*All available data*	*Only first four data*
1	<1 year	17 (4.0%)	20 (4.7%)
2	1–3 years	21 (4.9%)	22 (4.9%)
3	≥3 years	30 (7.0%)	26 (6.1%)
4	Negative value	69 (16.2%)	69 (16.2%)
5	Not calculated[a]	88 (20.7%)	88 (20.7%)
6	Tg not detectable	201 (47.2%)	201 (47.2%)

[a]Patients with undetectable Tg levels and three or fewer detectable Tg levels.
Tg-DT, thyroglobulin doubling-time.

Tg was detectable. There were 201 patients in whom serum Tg was always undetectable. In these two groups of patients there was not attempt to calculate Tg-DT. According to the Tg-DT status, patients were divided into six groups (Table 1). Group 1 (Tg-DT <1 year) consisted only 4% of the cohort of the 426 patients and group 2 (Tg-DT 1–3 years) consisted of only 4.9% of this cohort. To evaluate the possible use of Tg-DT as a prognostic indicator in a practical setting, Tg-DT was also calculated using only the first four data points [Tg-DT (first four data)]. Distribution of the patients was quite similar in both calculation results (Table 1). The Tg-DT using the first four data points was consistent with Tg-DT using all data group in 70% of the patients, but in 32 patients (23.4%) this was not the case (Table 2).

Table 2. Comparison of Thyroglobulin Doubling-Time Calculated Using Only the First Four Data and Thyroglobulin Doubling-Time Calculated Using All Available Data

	Tg-DT (all data) (years)			
Tg-DT (first four data) (years)	*<1*	*1–3*	*≥3*	*Negative value*
<1	14	4	1	1
1–3	2	13	3	4
≥3	1	2	14	9
Negative value	0	2	12	55

Survival, prevalence of distant metastases, and loco-regional recurrence

Cause-specific survival, prevalence of new distant metastases, and first loco-regional recurrence at 5 and 10 years in the present series correlated clearly with TNM stages, Tg-DT (all data), and Tg-DT (first four data) (Table 3). None of the patients in stage I to III died of disease and only patients in stage IV died of disease. However, only 6 of 189 (3.2%) patients in stage IV died of disease, giving a 10-year cause-specific survival rate of 94.6%. When looking at Tg-DT (all data), 5 of 17 (29.4%) patients with Tg-DT ≤1 year and 1 of 21 (4.8%) patients with Tg-DT 1–3 years died of thyroid cancer, whereas none of the patients in the other Tg-DT groups died of cancer, giving 10-year cause-specific survival rates of 50%, 95%, and 100%, respectively. Tg-DT predicted survival more precisely than TNM staging. Higher prevalence rates of distant metastases and loco-regional recurrence were associated with shorter Tg-DT. Tg-DT also predicted these episodes more precisely than TNM staging. Tg-DT (first four data) gave similar results.

Table 3. Cause-Specific Survival, Appearance of Distant Metastasis, and Loco-Regional Recurrence According to Prognostic Variables

	Survival		*Distant metastasis*		*Loco-regional recurrence*	
	5-year	*10-year*	*5-year*	*10-year*	*5-year*	*10-year*
TNM stage						
I	100%	100%	0%	0%	3.0%	7.1%
II	100%	100%	0%	0%	0%	4.2%
III	100%	100%	1.6%	9.4%	4.7%	14.8%
IV	98.9%	94.6%	6.3%	18%	14.4%	30.2%
Tg-DT (all data) group						
1: <1 year	87.5%	50.0%	39.7%	59.8%	43.8%	78.6%
2: 1–3 years	95.0%	95.0%	11.5%	38.8%	23.5%	72.6%
3: ≥3 years	100%	100%	7.9%	47.1%	23.6%	42.5%
4: Negative value	100%	100%	6.1%	11.3%	10.6%	27.7%
5: Not calculated[a]	100%	100%	0%	0%	5.9%	8.7%
6: Tg not detectable	100%	100%	0%	0%	1.5%	2.2%
Tg-DT (first four data) group						
1: <1 year	89.5%	59.1%	27.6%	69.1%	36.8%	63.2%
2: 1–3 years	95.2%	95.2%	10.3%	37.2%	15.8%	42.4%
3: ≥3 years	100%	100%	8.3%	37.3%	29.2%	45.9%
4: Negative value	100%	100%	6.3%	9.0%	11.3%	32.8%
5: Not calculated[a]	100%	100%	0%	0%	5.9%	8.7%
6: Tg not detectable	100%	100%	0%	0%	1.5%	2.2%

[a]Patients with undetectable Tg levels and three or fewer detectable Tg levels.

Prognostic impact of Tg-DT (all data) on cause-specific survival

The prognostic impact of TNM stage on cause-specific survival is well established. In the present study cohort, Kaplan–Meier cause-specific survival curves for 426 patients with stage I to IV disease also showed clearly worse survival for patients in stage IV (Fig. 2a). Kaplan–Meier cause-specific survival curves according to Tg-DT (all data) and Tg-DT (first four data) also showed worse outcome in patients with short Tg-DT values with more striking discrimination of outcome (Fig. 2b, c). The results of univariate and multivariate analyses of cause-specific survival in relation to possible prognostic variables are summarized in Table 4. On univariate analysis, classical prognostic factors, such as ≥55 years age, male gender, tumor size >4 cm, massive extrathyroidal extension (Ex2), clinical node metastasis in the lateral compartment (N1b), distant metastasis (M1), advanced TNM stage, pathological node metastases and absence of radioiodine accumulation in metastatic foci, and Tg-DT (all data) were all significant prognostic factors. Multivariate analysis, however, demonstrated that only Tg-DT was a significant factor related to cause-specific survival. On univariate analysis, data from all patients were used, whereas data from only patients in Groups 1–4 were used for multivariate analysis, since Tg-DT was not calculated in Groups 5 and 6 (see Table 1 for definition of groups). Since only patients in stage IV died of the disease, TNM stage could not be included in multivariate analysis. However, Tg-DT discriminated worse outcome more clearly than TNM stage as described above and shown in Table 3 and Figure 2. During the present follow-up period over 10 years, 5 of 17 patients with Tg-DT <1 year and 1 of 21 patients with Tg-DT 1–3 years died of cancer, and none of the patients with Tg-DT longer than 3 years or those showing a negative value died of cancer. Among 14 patients with distant metastasis, only 1 patient died of cancer. She had Tg-DT <1 year, and 3 of the survivors had Tg-DT 1–3 years and the remaining 10 survivors showed Tg-DT longer than 3 years or a negative value. Similarly, among 189 patients with Stage IV disease, 6 patients died. Five of them had Tg-DT <1 year and the remaining patient had Tg-DT 1–3 years.

Prognostic impact of Tg-DT (all data) on the prevalence of distant metastases

Cumulative curves for distant metastases according to TNM stage, Tg-DT (all data), and Tg-DT (first four data) clearly showed a significantly higher prevalence in patients in advanced stages and those with shorter Tg-DT (Fig. 3a–c). Patients with M1 disease were excluded from the analysis. The results of univariate and multivariate analyses of distant metastases in relation to possible prognostic variables are summarized in Table 5. On univariate analysis, most of the classical prognostic factors described above and Tg-DT (all data) were significant prognostic factors. Multivariate analysis, however, demonstrated that only Tg-DT was a significant factor related to the incidence of distant metastases. On univariate analysis, data from all patients were used, whereas data from only patients in Groups 1–4 were used for multivariate analysis, since Tg-DT was not calculated in Groups 5 and 6.

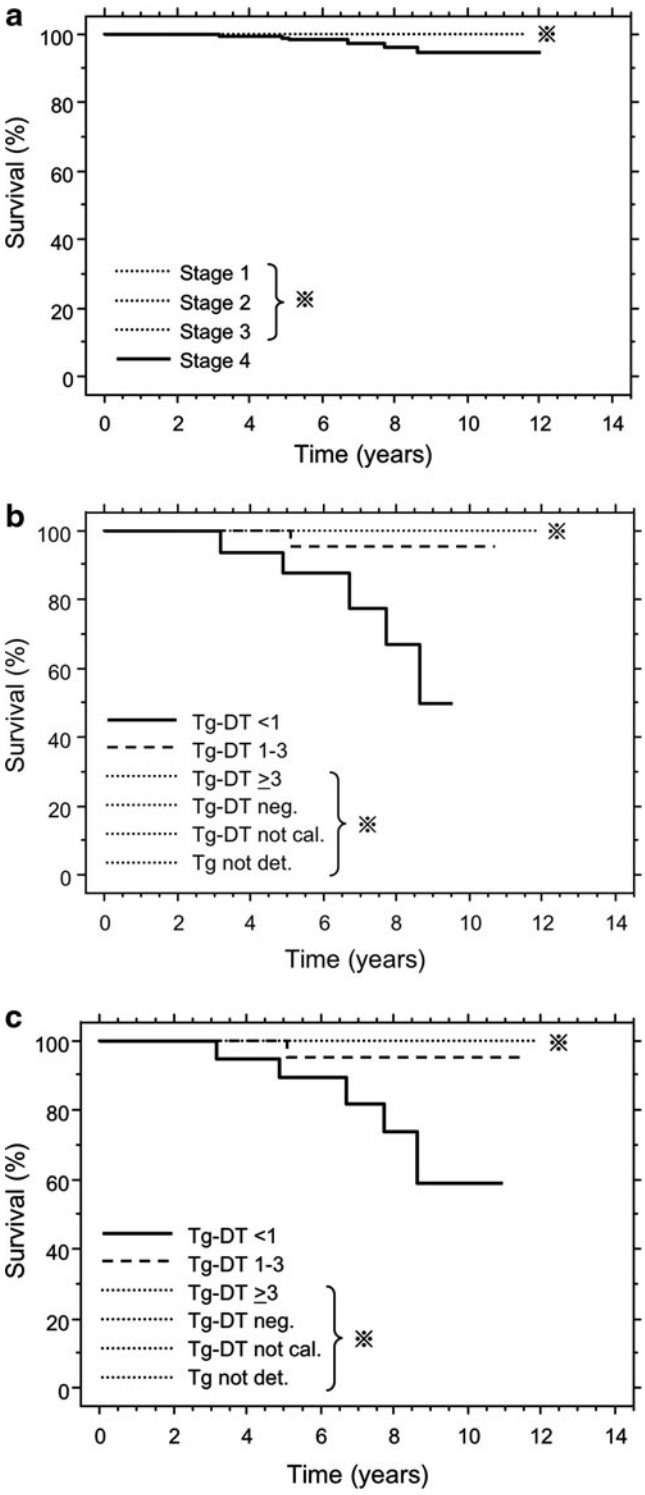

FIG. 2. Kaplan–Meier cause-specific survival curves according to TNM stage **(a)**, Tg-DT (all data) **(b)**, and Tg-DT (first four data) **(c)**.

Prognostic impact of Tg-DT (all data) on loco-regional recurrence

Cumulative curves for loco-regional recurrence according to TNM stage, Tg-DT (all data), and Tg-DT (first four data) clearly showed significantly higher recurrence rates in

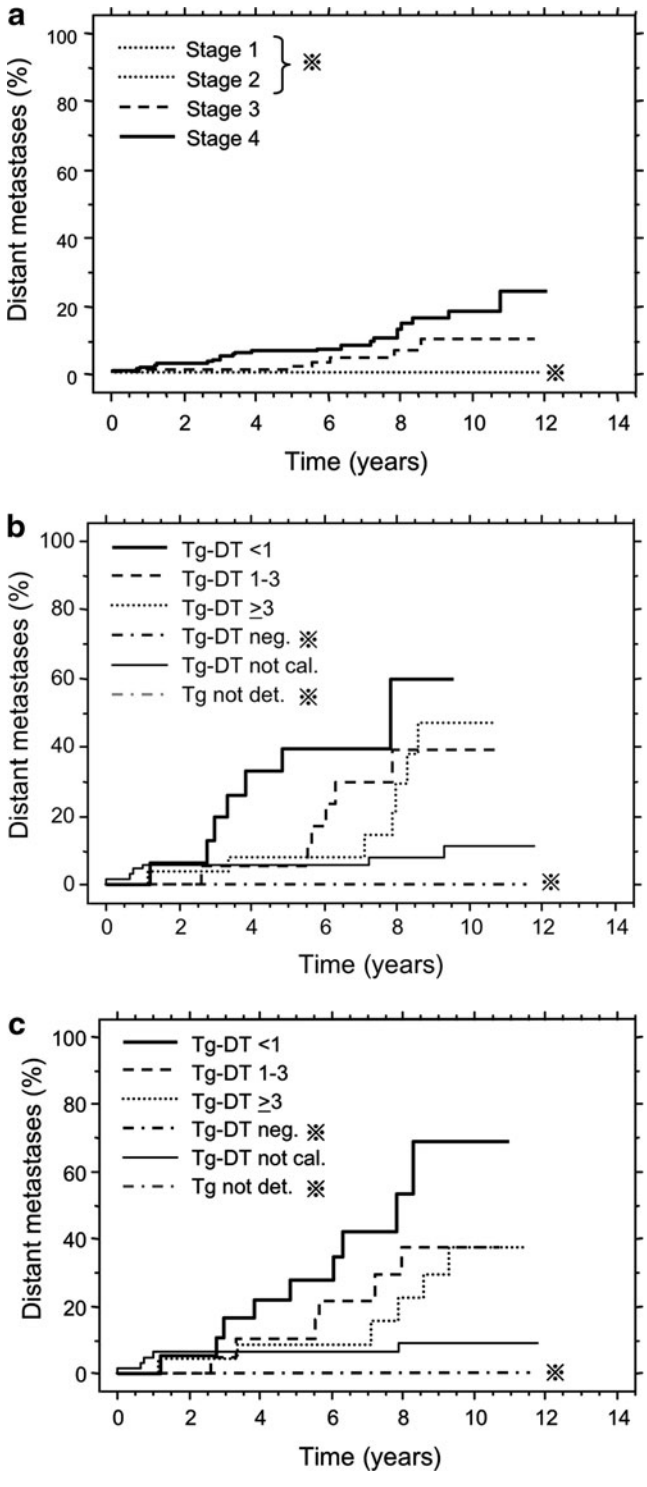

FIG. 3. Cumulative distant metastases according to TNM stage **(a)**, Tg-DT (all data) **(b)**, and Tg-DT (first four data) **(c)**.

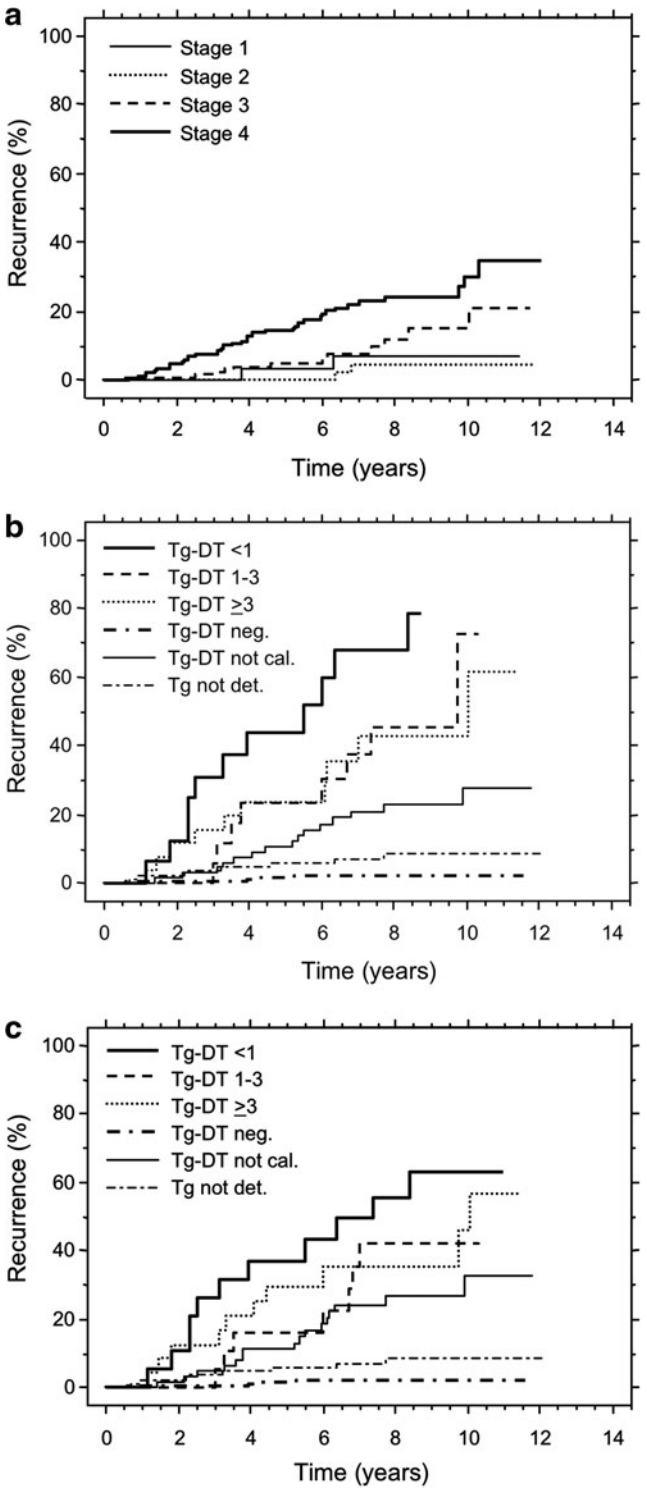

FIG. 4. Cumulative loco-regional recurrence according to TNM stage **(a)**, Tg-DT (all data), **(b)** and Tg-DT (first four data) **(c)**.

patients with advanced stages and shorter Tg-DT (Fig. 4a–c). Patients with M1 disease were excluded from analysis. The results of univariate and multivariate analyses of loco-regional recurrence in relation to possible prognostic variables are summarized in Table 6. On univariate analysis, most of the classical prognostic factors described above and Tg-DT (all data) were significant prognostic factors. Multivariate analysis, however, demonstrated that only Tg-DT was a significant factor in relation to loco-regional recurrence. On univariate analysis, data from all patients were used, whereas data from only patients in Groups 1–4 were used for multivariate analysis, since Tg-DT was not calculated in Groups 5 and 6.

Table 4. Cause-Specific Survival in Relation to Clinical, Pathological, and Biological Variables in Patients with Thyroglobulin Doubling-Time Calculated Using All Available Data

Variables	*Hazard ratio (95% CI)*	p-*Value*	*Multivariate*	p-*Value*
Age: ≥55 vs. <55	8.26 (0.96–70.97)	0.0543	NS	0.4751
Male vs. female	4.89 (0.98–24.36)	0.0525	NS	0.0671
T: ≥4 cm vs. <4 cm	4.15 (0.84–20.59)	0.0814	NS	0.3441
Ex: 2 vs. 0–1	12.52 (1.46–107.25)	0.0211	NS	0.0908
N: 1b vs. 0–1a	6.64 (1.22–36.26)	0.0289	NS	0.2688
M: 1 vs. 0	8.24 (0.94–72.35)	0.0571	NS	0.0876
pN: 1b vs. 0–1a	3.02 (0.54–16.73)	0.2063	NS	0.9303
Radioiodine accumulation: No vs. yes	4.64 (0.54–39.77)	0.1619	NS	0.8159
Tg-DT: Group 1 vs. 2–4	47.06 (5.47–405.13)	0.0005	S	0.0035

For each variable, the item on the left side shows worse outcome than that on the right. On univariate analysis, data from all patients were used, whereas data from only patients in Groups 1–4 were used for multivariate analysis, since Tg-DT was not calculated in Groups 5 and 6.

Ex, extra-thyroidal extension; Ex 0, no extension; Ex 1, minimal extension; Ex 2, massive extension; CI, confidence interval; NS, not significant; S, significant.

Table 5. Incidence of Distant Metastases in Relation to Clinical, Pathological, and Biological Variables in Patients with Thyroglobulin Doubling-Time Calculated Using All Available Data

Variables	*Hazard ratio (95% CI)*	p-*Value*	*Multivariate*	p-*Value*
Age: ≥55 vs. <55	NS	0.1587	NS	0.8068
Male vs. female	NS	0.4539	NS	0.7054
T: ≥4 cm vs. <4 cm	3.13 (1.45–6.74)	0.0037	NS	0.3593
Ex: 2 vs. 0–1	4.10 (1.90–8.86)	0.0003	NS	0.1840
N: 1b vs. 0–1a	3.55 (1.67–7.56)	0.0010	NS	0.3776
pN: 1b vs. 0–1a	3.25 (1.44–7.30)	0.0044	NS	0.3180
Stage IVa vs. I–III	4.85 (1.96–12.02)	0.0006	NS	0.4586
Tg-DT: Group 1 vs. 2–4	4.20 (1.73–10.21)	0.0015	S	0.0062

For each variable, the item on the left side shows worse outcome than that on the right. On univariate analysis data from all patients with M0 were used, whereas data from only patients in Groups 1–4 were used for multivariate analysis, since Tg-DT was not calculated in Groups 5 and 6.

Table 6. Loco-Regional Recurrence in Relation to Clinical, Pathological, and Biological Variables in Patients with Thyroglobulin Doubling-Time Calculated Using All Available Data

Variables	*Hazard ratio (95% CI)*	p-*Value*	*Multivariate*	p-*Value*
Age: ≥55 vs. <55	NS	0.1036	NS	0.7485
Male vs. female	NS	0.5980	NS	0.9587
T: ≥4 cm vs. <4 cm	2.2 (1.3–3.4)	0.0056	NS	0.3738
Ex: 2 vs. 0–1	1.87 (1.10–3.19)	0.0214	NS	0.3386
N: 1b vs. 0–1a	3.39 (2.00–5.75)	<0.0001	NS	0.8259
pN: 1b vs. 0–1a	2.35 (1.37–4.04)	0.0020	NS	0.4807
Stage: IVa vs. I–III	3.62 (2.03–6.47)	<0.0001	NS	0.5332
Tg-DT: Group 1 vs. 2–4	2.38 (1.20–4.71)	0.0129	S	0.0008

For each variable, the item on the left side shows worse outcome than that on the right. On univariate analysis data from all patients with M0 were used, whereas data from only patients in Groups 1–4 were used for multivariate analysis, since Tg-DT was not calculated in Groups 5 and 6.

Prediction of prognosis with Tg-DT (first four data)

To evaluate the possible use of Tg-DT as a prognostic indicator in a practical setting, prognostic value of Tg-DT calculated using only the first four data points [Tg-DT (first four data)] was analyzed in the same manner as Tg-DT (all data) analyses described above. Kaplan–Meier curves for cause-specific survival (Fig. 2c), cumulative curves for distant metastases (Fig. 3c), and loco-regional recurrence (Fig. 4c) according to Tg-DT (first four data) gave results quite similar to those derived from Tg-DT (all data). The results of univariate and multivariate analyses of cause-specific survival in relation to possible prognostic variables are summarized in Table 7. On univariate analysis, the classical clinicopathological prognostic factors and Tg-DT (first four data) were significant prognostic factors. Multivariate analysis, however,

Table 7. Cause-Specific Survival in Relation to Clinical, Pathological, and Biological Variables in Patients with Thyroglobulin Doubling-Time Calculated Using Only the First Four Data

Variables	*Hazard ratio (95% CI)*	p-*Value*	*Multivariate*	p-*Value*
Age: ≥55 vs. <55	8.26 (0.96–70.97)	0.0543	NS	0.4118
Male vs. female	4.89 (0.983–24.36)	0.0525	NS	0.4582
T: ≥4 cm vs. <4 cm	4.15 (0.84–20.59)	0.0814	NS	0.3468
Ex: 2 vs. 0–1	12.52 (1.46–107.25)	0.0211	NS	0.5301
N: 1b vs. 0–1a	6.64 (1.22–36.26)	0.0289	NS	0.0635
M: 1 vs. 0	8.24 (0.94–72.35)	0.0571	NS	0.1049
pN: 1b vs. 0–1a	3.02 (0.54–16.73)	0.2063	NS	0.2175
Radioiodine accumulation: No vs. yes	4.64 (0.54–39.77)	0.1619	NS	0.844
Tg-DT: Group 1 vs. 2–4	35.95 (4.18–309.1)	0.0011	S	0.0037

For each variable, the item on the left side shows worse outcome than that on the right. On univariate analysis data from all patients were used, whereas data from only patients in Groups 1–4 were used for multivariate analysis, since Tg-DT was not calculated in Groups 5 and 6.

demonstrated that only Tg-DT (first four data) was a significant factor in relation to cause-specific survival. On univariate analysis, data from all patients were used, whereas data from only patients in Groups 1–4 were used for multivariate analysis, since Tg-DT was not calculated in Groups 5 and 6. Similar to the analysis results for Tg-DT (all), multivariate analyses demonstrated that only Tg-DT (first four data) was a significant factor in relation to distant metastases and loco-regional recurrence (data not shown, $p = 0.0028$ and $p = 0.0188$, respectively).

Discussion

Age at surgery, gender, tumor size, extrathyroidal extension, node metastases, distant metastases, and TNM Stage are generally accepted prognostic factors for PTC and FTC (11–13). TNM Stage is defined by tumor size, extent of extrathyroid invasion of the tumor, presence or absence of node metastasis, and distant metastasis. TNM stage is the strongest prognostic factor among the factors described above, but it simply shows anatomical sites of tumor involvement. All of the above are also prognostic factors for MTC (14–16). All of these, however, are static factors at the time of surgery.

In 1984, we proposed calcitonin-DT to express the speed of tumor growth in individual patient with MTC and reported that calcitonin-DT was a very strong prognostic factor (1). In 2005, Barbet *et al.* confirmed the prognostic value of calcitonin-DT in patients with MTC (2). They reported that only calcitonin-DT remained an independent predictor of survival by multivariate analysis. The dynamic factors showing speed of tumor growth expressed as tumor marker-DT might indicate prognosis more accurately than static factors.

In 1956, Collins *et al.* introduced the concept that the growth of malignant tumors is exponential, and that the rate of growth can be described as the DT of the tumor (17). This concept fit changes in serum calcitonin levels in MTC very well. In 1988, we expanded the concept that tumor growth is exponential and proposed a method of estimating the duration of survival after surgery in each individual patient (18). The weight of residual tumor after surgery (W_2) can be estimated by the weight of the resected tumor (W_1) and serum calcitonin levels before and after surgery (S_1 and S_2, respectively). W_2 is given as $W_2 = W_1\, S_2/(S_1 - S_2)$. Survival index ($\beta$) is defined as the number of doublings of residual tumor until it weighs 1000 g (18), which would generally kill the host ((17). The expected duration of survival after surgery can be estimated using a simple formula, βDT (18). By this method, duration of survival can be estimated quantitatively in each individual patient. This formula clearly shows that only two factors, residual tumor weight and tumor growth rate, define survival. The residual tumor weight should be regarded as the number of doublings to become a certain weight and the tumor growth rate should be expressed as DT to understand tumor chronology. Patients in advanced TNM stage are more likely to carry residual tumor after surgery than patients in less advanced stage. However, TNM stage *per se* does not indicate residual tumor weight after surgery in each individual patient. This explains why calcitonin-DT has a much stronger prognostic impact than TNM stage.

In the present study on PTC, we showed that only Tg-DT remained an independent prognostic factor for cause-specific survival as well as distant metastases and loco-regional recurrence on multivariate analyses. Thus, Tg-DT is a highly potent dynamic prognostic factor in patients with PTC.

Serum Tg levels are influenced by circulating serum TSH concentrations (8). In the present study, we only used data for Tg levels that were obtained when serum TSH levels were lower than 0.1 mIU/L. The best serum TSH concentration for evaluation of Tg-DT as a prognostic indicator might differ for this but studies to determine if this were the case would be very difficult since there is no practical way to "clamp" serum TSH for long periods of time. Serum Tg values are unreliable in the presence of anti-Tg antibodies (8,9). Therefore, we excluded patients with anti-Tg antibody from the present study, which eliminated 362 patients or 34% of 1064 patients examined for the antibody. The cutoff values for anti-Tg antibody studies, however, were set for the diagnosis of Hashimoto thyroiditis (19), not for the evaluation of the appropriateness of Tg measurements. Is it necessary to exclude all patients with positive anti-Tg antibody from Tg kinetics studies? Further studies are needed to clarify the appropriate cutoff values for anti-Tg antibody when the test is performed for this purpose.

Identifying patients with rapidly growing tumors and a poor prognosis is very important in clinical practice. These patients require close follow-up and may require other treatments than their initial surgery. Recently, many new compounds, mostly tyrosine kinase inhibitors such as vandetanib

and sorafenib, have been under clinical trials for patients with advanced thyroid cancer (20,21). Patients with a short Tg-DT may be better candidates for these clinical trials than patients with advanced disease stage. In such trials, serum Tg kinetics might also be a useful indicator of the effects of these drugs. Conversely, for patients with long DTs or a negative value for DT, a watch-and-wait policy avoiding unnecessary treatment might be appropriate because these patients would be expected to show a very indolent clinical course.

For serum tumor marker DT to be useful in clinical practice, DT calculated from measurements obtained over a short period should reasonably predict the patient's prognosis. Barbet *et al.* evaluated calcitonin-DT as calculated using only the first 4 measurements and reported that it was also an independent predictor of survival in patients with MTC (2). In the present study, we obtained similar results for Tg-DT (first four data).

One might think that calculation of Tg-DT is difficult and Tg-DT is not easy to use in a clinical practice. However, in a clinical practice, an interval between the time of the most recent serum Tg measurement and the time of the measurement with a Tg level about half of the most recent value indicates Tg-DT. In the era of electronic medical recording systems, graphic demonstration of the change in serial serum Tg levels over time can be readily provided, as is the practice in Kuma Hospital. For easy and precise computing, a tumor marker DT calculator is available on the ATA website (www.thyroid.org) (5).

Conclusion

Tg-DT is a very potent dynamic factor for predicting cause-specific survival, distant metastases, and loco-regional recurrence in patients with PTC. We encourage its use in clinical practice and in designing research protocols.

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Disclosure Statement

The authors declare that there are no competing financial interests in relation to this article.

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