Differentiated thyroid carcinoma : diagnostic and therapeutic studies

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Chapter 3

Serum Thyroglobulin Concentrations Predict Disease-free Remission and Death in Differentiated Thyroid Carcinoma

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Abstract

Objective: Most studies on the diagnostic value of serum thyroglobulin (Tg) concentrations in differentiated thyroid carcinoma (DTC) use fixed cut-off levels in heterogeneous groups of patients with respect to initial therapy and do not provide prognostic data. The objective of this study was to investigate the prognostic values of serum Tg for disease free remission and death, measured at fixed time points after initial therapy using receiver operator curve (ROC) analyses.

Design: Single-centre observational study with 366 consecutive patients with DTC, who had all been treated according to the same protocol for initial therapy and follow-up.

Methods: Tg concentrations were measured at five fixed time points after initial surgery. Tg cut-off values with highest accuracy were calculated with ROC analyses.

Results: During follow-up of 8.3±4.6 years, 84% of the patients were cured.

Pre-ablative Tg levels were an *independent* prognostic indicator for disease free remission (Tg cut off value 27.5 ug/L, positive predictive value 98%). Highest diagnostic accuracies of serum Tg for tumour presence were found during TSH stimulated Tg measurements, 6 months after initial therapy (Tg cut-off value 10 ug/L: sensitivity 100%, specificity 93%).

DTC related mortality was 14%. TSH stimulated Tg levels before ablation and 6 months after initial therapy were independent prognostic indicators for death.

Conclusion: Optimal institutional Tg cut-off levels for diagnosis and prognosis should be defined using ROC analyses for each condition and time point. Tg measurements 6 months after initial therapy during TSH stimulation had an excellent diagnostic value. Tg levels are independent prognostic indicators for disease free remission and death. Using this strategy, high-risk patient groups can be selected based on Tg levels, in addition to conventionally used prognostic indicators.

Introduction

Differentiated thyroid carcinoma (DTC) has an excellent prognosis with 10-year survival rates of 85-93 % (1). The purpose of follow-up protocols in DTC is the early detection of tumour recurrence or metastatic disease in order to optimize additional treatment. Most patients during follow up have been cured definitively, and, as a consequence, have a low pre-test probability for recurrent disease. Therefore, the sensitivity of the diagnostic test must be adequate to detect the few patients with evident thyroid carcinoma, whereas specificity must also be high to avoid unnecessary treatments in patients without recurrent disease. In addition, the burden of diagnostic tests for the patient should be kept at a minimum.

Serum thyroglobulin (Tg) measurements are the cornerstone in the follow-up in DTC. Numerous studies have been performed on the diagnostic value of Tg measurements. We recently published a structured meta-analysis on the diagnostic value of Tg including 46 articles (2). The interpretation of many studies on Tg performed so far is difficult, because in most studies i) Heterogeneous patient groups with respect to initial therapy are included, ii) The time points of Tg measurements after diagnosis are not clearly indicated, and iii) Fixed Tg cut-off levels are used, without receiver operator curve (ROC) analyses. The application of ROC data is essential, as a chosen cut-off level is a subjective choice based on the balance between a desired percentage of missed recurrences versus unnecessary therapies. Therefore, in a recent European consensus paper, it was recommended to define institutional Tg cut-off levels (3). Only a few studies have been published on the interpretation of Tg levels during follow up of DTC using ROC analyses. However, in those studies, heterogeneous patient groups were included and the time-points of Tg measurements were not clearly indicated (4;5;6). In addition, most studies provide data on the diagnostic value of Tg for tumour presence, but do not give data on the *prognostic* significance for disease free remission or death. One large study (7) studied the prognostic significance of 1-month post-surgical Tg levels and found a significant prognostic cut-off level of 10 ug/L. The few studies that were published on the prognostic significance of Tg measurements used fixed cut-off levels, contained selected subgroups of patients and included either Tg measurements at one time point or at undefined time points (8;9;10;11;12).

We therefore performed a study on the diagnostic and prognostic value of Tg in a homogeneous group of DTC patients with respect to initial therapy, using Tg measurements at 5 defined time-points after diagnosis, in combination with ROC analyses. In addition, we studied the diagnostic and prognostic value of Tg antibodies for tumour presence or death.

Patients and methods

Three-hundred-and-sixty-six consecutive patients were included in the study. These patients had received initial therapy for DTC between January 1986 and January 2000. All follow up data were collected until January 1, 2003. January 1986 was chosen as a starting date, because from that date forward, all relevant patient data were registered in a computerized database. Initial surgery and radioiodine ablation therapy were performed at the Leiden University Medical Centre or at one of the connected general hospitals. All hospitals are affiliated in the Regional Comprehensive Cancer Centre, using the same standardized protocol for the treatment and follow-up of DTC (Table 1).

Table 1. Patient characteristics

Parameter	N	Cured Patients N (%)	Patients Relapse after Cure N (%)	Deaths N (%)
Total	366	305 (84)	46 (13)	52 (14)
Gender (Male/ Female)	91 / 275	72 (80) /233 (85)	13 (14)/33 (13)	13 / 39 (14 / 14)
Stages				
T1	22	21 (96)	1 (5)	0 (0)
T2	188	176 (94)	17 (9)	10 (5)
T3	56	51 (91)	9 (16)	8 (14)
T4	96	53 (55) * #	17 (18)	32 (33) * #
T unknown	4	0 (0)	0 (0)	2 (50)
N1	107	76 (71) *	15 (14)	22 (21) *
M1	52	19 (36) * #	6 (11)	27 (54) * #
Histology				
Papillary	203	173 (86)	28 (14)	25 (12)
Follicular	72	58 (81) *	11 (15)	17 (24) *
Follicular variant papillary carcinoma	68	56 (82)	5 (7)	6 (9)
Hürthle Cell	23	18 (78)	2 (9)	4 (17)
Age (continuous)				
< 55 yr	210	221 (95)* #	18 (8)	3 (1)* #
> 55 yr	156	84 (64)* #	28 (21)	49 (31)* #

* Significant at univariate analysis
# Significant at multivariate analysis (see Table 4)

All patients were treated by near-total thyroidectomy, followed by routine radioiodine ablative therapy with 2800 MBq I-131.

Follow-up was performed according to a standard protocol. Serum Tg levels were measured at the following time points: 1) After initial surgery during thyroxin withdrawal just before radioiodine ablation, 2) Six months after initial surgical therapy during thyroxin therapy, 3) Six months after initial surgical therapy after thyroxin withdrawal ("off") and 4) Yearly during thyroxin therapy. Although additional TSH stimulated Tg measurements were performed in selected subgroups of patients at other time points after initial therapy, we did not include those data as these tests were not uniformly done in all patients, and calculations of diagnostic values would thus be biased. Thyroxin therapy was aimed to suppress TSH levels (below 0.1 mU/L). Six months after initial therapy a diagnostic 185 MBq I-131 scintigraphy was performed after thyroxin withdrawal.

Tumour presence during follow-up was defined as histologically or radiologically (X-ray, CT-scan, MRI-scan, FDG-PET scan or I-131 scintigraphy) within a 1-year interval before or after the time of Tg measurements. Although we realize that Tg is considered the best parameter for tumour presence, Tg was not used as a golden standard for tumour presence, as the diagnostic value of Tg was the subject of this study.

Disease free remission was defined as the absence of thyroid carcinoma for a minimum of 3 years according to the above mentioned parameters.

The following data were registered: age at diagnosis, sex, date of diagnosis, histology, TNM stage, date of cure, date of recurrence, tumour localization, death cause, Tg levels, TSH levels, Tg antibody levels and date of last follow up or death. TNM stage was registered according to the 5th edition (13). This was done because most patients were analysed before the latest edition of the TNM classification. We used the following end-points of follow-up: date of death (82 patients), date of emigration (12 patients) and date of most recent contact (272 patients).

Death causes were analysed in all 82 patients who had died during follow-up. Death cause was investigated using medical records, death certificates, enquiries with other physicians involved in the treatment of each patient, enquiries in other hospitals, enquiries with general practitioners and autopsy findings. Death causes were divided into thyroid cancer related death and other causes.

Analyses were performed in evaluable patients defined as patients in whom all of 4 conditions were fulfilled: Alive at the time-point of Tg measurement, documented serum Tg measurements, documented serum TgAb measurements *and* documented golden standard parameters for presence or absence of disease. If Tg-antibodies were present, the Tg measurement at this time was excluded from the calculations because of possible interference with the Tg assay. The numbers of these patients are given in Table 2.

Table 2. Diagnostic Values of Serum Tg Measurements for Active Tumour Calculated with Receiver Operator Curve Analysis. Patients with Tg antibodies were excluded

		Evaluable patients (N) #	Positive TgAb N (% of Evaluable Patients)	Tumor Location	Patients with Tumor N (% of Patients Negative TgAb)	Tg Cut-Off µg/L	Sensitivity (%)± SE	Specificity (%)± SE	PPV (%)	NPV (%)
Pre-Ablation		*304*	82 (27.0)	All	33 (15.1)	27.5	87.9 ± 5.7	90.3 ± 2.2	61.7	97.7
				Distant Metastases	21 (9.6)	27.5	85.7 ± 7.6	85.3 ± 2.5	38.3	98.2
Six Months After Initial Therapy	*Suppressed TSH*	287	79 (27.5)	All	37 (18.0)	2.5	89.2 ± 5.1	93.5 ± 2.0	75.0	97.5
				Distant Metastases	24 (11.7)	2.5	87.5 ± 6.8	87.3 ± 2.5	47.7	98.1
	Stimulated TSH	287	79 (27.5)	All	37 (18.0)	10.0	100.0 ± 0.0	93.1 ± 2.1	76.7	100.0
				Distant Metastases	24 (11.7)	10.0	100.0 ± 0.0	86.0 ± 2.8	48.8	100.0
Two Years After Initial Therapy	*Suppressed TSH*	244	32 (13.1)	All	43 (20.6)	2.0	85.0 ± 5.4	85.7 ± 2.7	60.6	95.7
				Distant Metastases	33 (15.8)	2.0	72.7 ± 7.8	88.6 ± 2.4	54.5	94.5
Five Years After Initial Therapy	*Suppressed TSH*	182	23 (12.6)	All	35 (22.6)	2.5	82.9 ± 6.4	96.7 ± 1.6	87.9	95.1
				Distant Metastases	30 (19.4)	2.5	83.3 ± 6.8	93.6 ± 2.2	75.8	95.9

Patients who were alive at the time points of measurements and in whom both Tg, TgAb and documentation of disease state according to the criteria for golden standard (see Methods) could be evaluated. PPV= positive predicted value, NVP = negative predicted value

Measurements of Tg and Tg-AB

Until January 1997 serum Tg was measured using an immunoradiometric assay (IRMA), the Dynotest TG (Brahms Diagnostica GmbH, Germany) with a sensitivity of 0.3 μg/L. From January 1997, the Dynotest TG-s (Brahms Diagnostica GmbH, Germany) was used, with a sensitivity of 0.05 μg/l. Inter-assay variability of 0.3 μg/l. The comparability of the 2 methods is excellent: R^2: 0.99, slope 0.99, intercept 0.09 (14). Serum Tg-antibodies were also measured at these specific time points by the Ab-HTGK-3 IRMA (DiaSorin Biomedics, Italy).

Statistical analyses

Data are presented as mean ± SD. All statistical analyses were performed using SPSS for windows version 12.0 (SPSS Inc., Chicago, IL). Data are expressed as number of patients (percentages), as mean ± Standard Deviation (SD) or as median (range). Receiver operator curves (ROC) were used to find the cut-off value with highest accuracy. Prognostic indicators for recurrence or death were calculated using univariate- and multivariate Cox-regression analyses: Indicators that were identified as significant for survival in univariate analysis were entered into a stepwise multivariate model. A p-value of < 0.05 was considered significant.

Results

Characteristics of the patients are shown in Table 1. Mean age at time of surgery was 48 ± 18 years. Mean follow-up was 8.3 ± 4.6 years. Significant prognostic factors for disease free remission and death are given in Table 4.

Diagnostic value of Tg

The diagnostic values of Tg measurements at the different time points are given in Table 2.

The diagnostic value of Tg before ablation therapy was reasonable in our analysis, with a sensitivity of 87.9% and a specificity of 90.3% at a cut-off value of 27.5 ug/L.

When a cut-off level of 2 ug/L was used, sensitivity increased to 93.9%, whereas specificity dropped to 45% with a positive predictive value of only 23% instead of 62%, with similar negative predictive value.

The highest diagnostic value of Tg was found during TSH stimulated Tg measurements 6 months after initial therapy (see Figure 1). The Tg cut-off value with highest accuracy was 10.0 ug/L, with sensitivity and specificity of 100.0 and

93.1%, respectively. When the more commonly used cut-off value of 2 ug/L was used, sensitivity remained similar, but specificity dropped to 82% with a positive predictive value of only 54%, instead of 73% (Figure 1). We analysed the course of 9 patients with Tg values > 10 ug/L, 6 months after initial therapy during TSH stimulation: in 3 patients, tumour was detected 2-5 years after initial therapy. In 4 patients Tg became undetectable and they were cured. Two patients had persistent measurable Tg, but no tumour was detectable up to 15 years after initial therapy.

Tg measurements on thyroxin, 2 and 5 years after initial therapy had lower sensitivities, but had comparable specificities and negative predictive values albeit at lower Tg cut-off values.

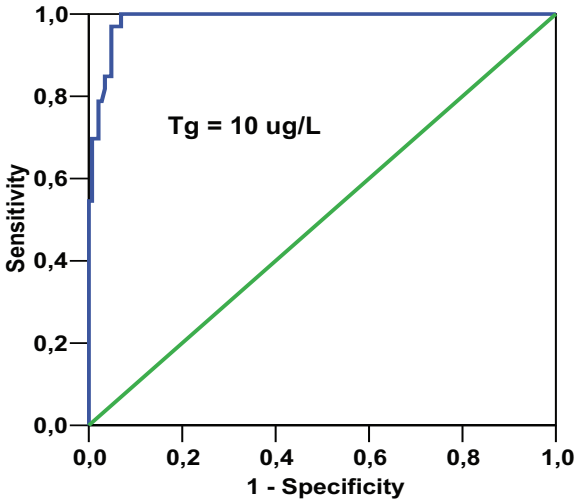

Figure 1. Receiver Operator Curve six months after initial therapy during stimulated TSH to obtain optimal cut-off levels of serum Tg measurements for the diagnosis of active tumour in patients with differentiated thyroid carcinoma.

Prognostic value of Tg

Disease free remission

The prognostic value of Tg for disease free remission is given in Tables 3 and 4. Interestingly, Tg before ablation had a high predictive value of 97.8% for disease free remission at a cut-off value of 27.5 ug/L. Tg appeared to be an independent prognostic marker for disease free remission (likelihood ratio for disease free remission 43.2 for Tg < 27.5 ug/L, $p<0.001$), irrespective of T4, M1 and age.

Thyroid Specific Death

The prognostic values for Tg measurements for DTC related death are given in Tables 3 and 4 and Figure 2. The negative predictive value was high for all time-points of Tg measurements.

Tg was an independent predictor for thyroid related death during TSH stimulation, 6 months after initial therapy (hazard ratio for Tg ≥ 10.0 ug/L 10.9, p=0.008, Table 4, Figure 2), 2 years after initial therapy (hazard ratio for Tg ≥ 2.0 ug/L 12.9, p<0.001) and 5 years after initial therapy (hazard ratio for Tg ≥ 2.0 ug/L 29.1, p=0.001).

Table 3. Prognostic Value of Serum Tg Measurements for Disease free remission and Thyroid Carcinoma Related Death. Patients with Tg antibodies were excluded

		Outcome	Tg µg/L Cut-Off	Sensitivity (%) ± SE	Specificity (%±) SE	PPV (%)	NPV (%)
Pre-Ablation		Disease free remission	27.5	84.4 ± 2.6	88.9 ± 5.6	97.8	49.1
		Death	21.5	66.7 ± 9.6	81.3 ± 2.8	30.2	95.3
Six Months After Initial Therapy	*Suppressed TSH*	Death	2.5	72.0 ± 9.0	85.7 ± 2.6	40.9	95.7
	Stimulated TSH	Death	10.0	85.0 ± 8.0	83.5 ± 2.9	39.5	97.8
Two Years After Initial Therapy	*Suppressed TSH*	Death	2.0	85.0 ± 8.0	85.7 ± 2.5	38.6	98.2
	Suppressed TSH	Death	2.0	82.4 ± 9.2	92.8 ± 2.2	58.3	97.7

PPV= positive predictive value, NVP = negative predictive value

Tg antibodies

The percentage of patients with Tg antibodies dropped from 27% immediately after initial surgery to 12% 5 years after initial therapy (see Table 2). There were no significant differences in tumour presence between patients with and without Tg antibodies: 15 – 23% in patients without Tg antibodies and 16 – 33% in patients with Tg antibodies. The presence of Tg antibodies did not have a significant prognostic for disease free remission or death.

Table 4. Likelihood Ratios for Serum Tg values for Outcome (Disease free remission or Thyroid Carcinoma Related Death) as calculated with Cox-survival Analysis. Patients with Tg antibodies were excluded

		Outcome	Univariate Analysis		Multivariate Analysis		Other Significant Parameters
			p	Likelihood Ratio (CI)	p	Likelihood Ratio (CI)	
Pre-Ablation		Disease free remission	<0.001	43.2 (15.0 – 124.3) #	<0.001	29.9 (5.2 – 171.5) #	Age, M1, T4
		Death	<0.001	8.0 (3.4 – 18.7)*	N.S.	--	Age, M1, T4
Six Months After Initial Therapy	*Suppressed TSH*	Death	<0.001	14.4 (5.7 – 36.7) *	N.S.	--	Age, T4
	Stimulated TSH	Death	<0.001	31.2 (7.1 – 136.7) *	0.008	10.9 (1.9 – 63.5) *	Age, T4
Two Years After Initial Therapy	*Suppressed TSH*	Death	<0.001	30.9 (9.0 – 105.7) *	<0.001	12.9 (3.4 – 49.2) *	Age, M1
	Suppressed TSH	Death	<0.001	24.2 (5.0 – 116.2) *	0.001	29.1 (3.6 – 232.2)*	Age

Likelihood Ratio for Tg value < Cut-Off * Likelihood Ratio for Tg value ≥ Cut-Off
Tg Cut Off values are given in Table 3

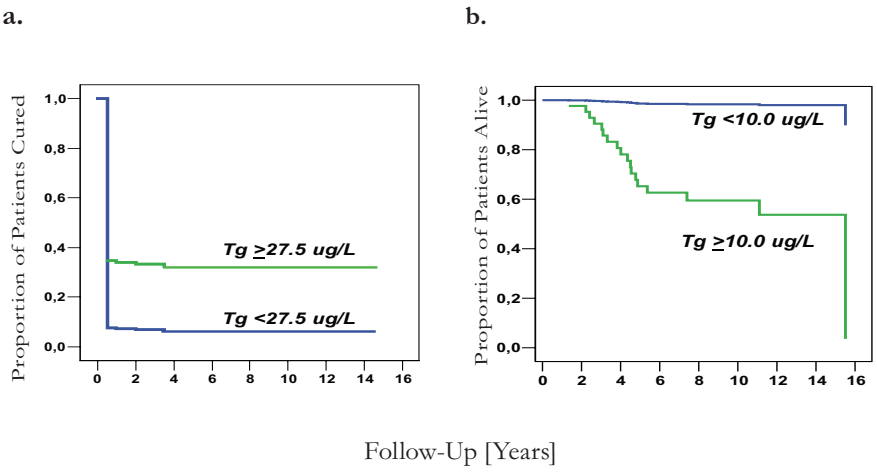

Figure 2. Prognostic value of Tg measurements for Differentiated Thyroid Carcinoma related disease free remission and mortality.
a. Disease free remission, Tg levels pre-ablation, four weeks after surgery; X-axis: years after initial therpy, Y-axis: Disease free remission
b. Survival according to TSH stimulated Tg, 6 months after initial therapy; X-axis: years after initial therapy, Y-axis: cumulative survival with death as endpoint.

Discussion

In the present study we investigated the diagnostic and prognostic value of serum Tg measurements for tumour presence, disease free remission and death in the follow-up of DTC by ROC analysis in a homogeneous group of patients with respect to initial therapy.

The study differed from earlier investigations with respect to the homogeneity of the patient group with respect to initial therapy, the fact that multiple Tg measurements were analysed at fixed time points during follow-up and the use of ROC analyses.

We found an excellent diagnostic accuracy of serum Tg values during TSH stimulation 6 months after initial therapy (sensitivity 100%), with a higher Tg cut-off level (10.0 ug/L) than commonly reported (2;15;16;10;8). When we used the more commonly used cut-off value of 2 ug/L, the specificity and positive predictive values dropped considerably (52% instead of 72%). We also found that Tg cut-off levels are dependant on the time-point of follow-up, which is an important finding, as in most papers on Tg, the time after diagnosis is not considered.

Tg levels are not only diagnostic indicators of tumour presence, but also predict disease free remission or death. We found that serum Tg levels before radioiodine ablation are an independent predictor for disease free remission, irrespective of the classical prognostic indicators. In our series a patient with Tg level pre-ablation of < 27.5 ug/L has an almost 98% chance to be definitely cured irrespective of the prognostic indicators stage T4, follicular histology, metastases and higher age.

TSH stimulated Tg measurements 6 months after initial therapy and at 2 and 5 years after initial therapy were independent predictors of thyroid carcinoma related death. Negative predictive values for DTC related death were high (95.3 – 98.2%) at all 5 time points of follow up, albeit with different Tg cut-off values.

In the discussion about the diagnostic value of Tg, specificity is a controversial issue. It has been argued that the specificity of Tg is per definition 100%. Although from a biological point of view it is undoubtedly correct that Tg is only synthesized by thyroid cells, in the clinical practice, the meaning of measurable Tg levels is not always clear, even more so with the advent of high sensitive Tg assays. A less than 100% specificity of Tg for thyroid carcinoma can be explained by the limitations of current imaging techniques to detect thyroid carcinoma. In this respect, it is advocated to administer a high dose of radioiodine to patients with elevated Tg levels, a policy that we agree with (17;18;19;20). However, we also observed that in only 3 of the 9 patients with TSH stimulated Tg levels > 10 ug/L and without detectable tumour, tumour became apparent during follow up, which is in line with the observation of Baudin et al (8). Therefore, in our opinion, a potential solution to circumvent the debate about specificity of Tg is to consider Tg as a risk indicator. The independent prognostic value of serum Tg values for disease free remission and death are arguments to include Tg in the conventional panel of risk factors. A potential consequence could be to administer higher dosages of radioiodine for ablation in patients with Tg levels higher than the above mentioned thresholds. As such we do not advocate that patients with Tg levels below institutionally defined cut-off levels should not be followed up carefully, but we belief that the elimination of Tg should not be a goal in itself.

Tg cut-off levels are not only influenced by clinical considerations, but also by analytical aspects. Analytical problems include the lack of universal standardisation of the Tg assays (21), intra-assay variability, "Hook" effects and the presence of Tg auto-antibodies(22;23). Another important point, not addressed in this study, is the observation that Tg rises may be more informative than absolute Tg levels (24;8).

The percentage of patients with Tg antibodies (initially 27%) is in line with previous studies (25;23;26). The percentages of active tumour in patients with and without Tg antibodies were comparable, conforming the lack of diagnostic value of Tg antibodies.

Because our study involved a large cohort of patients studied before the introduction of rhTSH, we did not include rhTSH stimulated Tg measurements in our series. However, recent reports indicate that the diagnostic accuracy is comparable (2;15;3). It has been suggested that Tg cut-off levels for rhTSH should be lower than for thyroid hormone withdrawal (27). However, no systematic analyses have been published comparing optimal Tg cut-off levels for both strategies. Furthermore, in a large study, similar Tg cut-off values were used for rhTSH and thyroxin withdrawal (16).

Because our analysis is based on retrospective data, we believe that the prognostic Tg cut-off values as found in our study should be interpreted with some caution, as they should be confirmed in a prospective study. We believe however that the main message, that Tg cut-off values should not be adopted from the literature, that Tg cut-off levels are dependant on the time of follow-up and that Tg has a prognostic value is valid.

In conclusion, our studies illustrate the importance of the definition of institutional Tg cut-off levels. We analysed the diagnostic value of Tg at specific time points and detected an excellent prognostic value 6 months after initial therapy during TSH stimulation. Our analyses allow the definition of groups of patients with an increased risk for residual disease or mortality, in addition to conventionally used prognostic indicators. Based on our analysis we recommend to subject every patient, who has undergone thyroid surgery and thyroid remnant ablation at least once to TSH stimulated Tg measurements.

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