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Serum Thyroglobulin Levels at the Time of ^{131}I Remnant Ablation Just after Thyroidectomy Are Useful for Early Prediction of Clinical Recurrence in Low-Risk Patients with Differentiated Thyroid Carcinoma

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We investigated whether serum thyroglobulin (Tg) measured at the time of remnant ablation (ablation-Tg) could be a prognostic indicator complementary to serum Tg levels at the time of the first diagnostic whole-body scan (WBS) after thyroid hormone withdrawal (control-Tg; approximately 6–12 months after ablation-Tg) and whether ablation-Tg could predict the persistence or recurrence of disease in low-risk patients with differentiated thyroid carcinoma.

Patients with differentiated thyroid carcinoma (n = 268) treated with total or near-total thyroidectomy followed by immediate ^{131}I remnant ablation were studied. Patients with anti-Tg autoantibodies and those showing evidence of extracervical metastases were excluded. Two patients showing remnant uptake on follow-up diagnostic WBS received a second ablation. We found significant correlation between ablation-Tg and control-Tg levels; 114 of 143 patients (80%) with ablation-Tg greater than 2 μg/liter showed detectable (≥1 μg/liter) control-Tg, and 70 of 125 (56%) patients with ablation-Tg 2 μg/liter or less showed undetectable (<1 μg/liter) control-Tg [odds ratio 5.1, 95% confidence interval (CI) 3.0–8.9, $P < 0.001$]. When the 268 patients were followed up for a mean period of 5.7 ± 1.4 yr (range 2.8–8.3 yr), 35 (13%) had recurrences; 73 (27%) were classified as "Tg positive, no evidence of disease"; and 160 (60%) showed complete remission. Of 143 patients with ablation-Tg greater than 2 μg/liter, recurrence was observed in 33 cases (23%); "Tg positive, no evidence of disease," was observed in 52 cases (36%); and complete remission was observed in 58 cases (41%). Of 125 patients with ablation-Tg 2 μg/liter or less, two patients (2%) showed recurrence during the follow-up; 21 patients (17%) were regarded as "Tg positive, no evidence of disease"; and 102 patients (81%) showed complete remission. The positive predictive value for recurrence in patients having ablation-Tg greater than 2 μg/liter was found to be 23.1% (33 of 143 patients, 95% CI 16.4–30.8%). The negative predictive value for recurrence in patients having ablation-Tg 2 μg/liter or less was found to be 98.4% (123 of 125 patients, 95% CI 94.4–99.8%).

These data indicate that serum Tg levels measured at the time of immediate postoperative ^{131}I remnant ablation correlated well with serum Tg levels at the time of the initial diagnostic WBS and had a complementary role for predicting persistence or recurrence of disease in the earliest postoperative period. (*J Clin Endocrinol Metab* 90: 1440–1445, 2005)

CURRENTLY THE TREATMENT of differentiated thyroid carcinoma consists of total or near-total thyroidectomy followed by ^{131}I remnant ablation and thyroid hormone suppression (1). During the follow-up, serum stimulated thyroglobulin (Tg) measurement is the best means for detecting the presence of normal and/or malignant thyroid tissue, which is the only source of Tg. Serum Tg measured during thyroid hormone withdrawal (THW) or recombinant human TSH stimulation after remnant ablation may help identify patients with persistent cancer (2, 3). A recent report (4) proposed that hypothyroid and euthyroid recombinant human TSH-stimulated serum Tg levels are comparably effective in detecting metastases when a cutoff value of 2 μg/liter is used. Some studies have suggested the possibility of using high Tg values measured just before ^{131}I remnant ablation as a prognostic marker (5, 6). However, critics of this plan have indicated that total thyroid ablation is necessary to exclude the influence of residual normal thyroid tissue (4) and that Tg may remain detectable for up to 1 yr after remnant ablation (2). Thus, we hypothesized that serum Tg measured at the time of remnant ablation could be a prognostic indicator in low-risk patients with differentiated thyroid cancer, complementing serum Tg values measured at the first-year follow-up after THW.

We investigated the clinical significance of serum Tg levels measured immediately after ^{131}I remnant ablation in low-risk patients with differentiated thyroid carcinoma. Serum Tg levels measured at the time of remnant ablation were evaluated for correlation with corresponding serum Tg values measured 6–12 months after remnant ablation, at the time of the initial diagnostic whole-body scan (WBS) after THW. Using these data, we were able to assess postablation Tg

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Abbreviations: Ablation-Tg, Tg measured at the time of remnant ablation; CI, confidence interval; control-Tg, serum Tg measured 6–12 months after remnant ablation at the time of first diagnostic WBS after THW; FDG, ^{18}F-deoxyglucose; NPV, negative predictive value; PET, positron emission tomogram; PPV, positive predictive value; Tg, thyroglobulin; THW, thyroid hormone withdrawal; WBS, whole-body scan.

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levels as a novel early prognostic indicator for predicting persistent or recurrent disease.

Patients and Methods

Initial treatment and early follow-up with diagnostic WBS

This study included 394 consecutive patients with differentiated thyroid carcinoma who underwent total thyroidectomy followed by immediate ^{131}I remnant ablation between 1996 and 1998 according to the protocol established by the endocrinology division of the Asan Medical Center (Seoul, Korea). We obtained informed consent from all subjects, and the local ethics committee approved the protocol. All operations were performed by a single experienced surgeon (S.J.H.), and no grossly visible thyroid remnants were left. Five to six weeks after surgery, during which time thyroid hormone was withheld, each patient received an ablative dose of ^{131}I (3.7–5.55 GBq, 100–150 mCi). At that time, the TSH level was above 30 mU/liter, and serum Tg was measured (ablation-Tg). A postablation WBS was performed 5–7 d after the administration of ^{131}I. No quantitative measurement of thyroid uptake was performed. Six patients had preoperative clinical evidence of extracervical metastases, 13 patients had uptake outside the thyroid bed noted in the postablation ^{131}I WBS, and 97 patients had positive anti-Tg autoantibodies. These 116 patients were excluded. Thyroid hormone suppressive treatment was initiated just after the remnant ablation, with the aim of decreasing serum TSH to subnormal levels without inducing clinical thyrotoxicosis. Thyroid hormone levels were titrated every 3 months by measurement of serum free T_4 and TSH levels. Diagnostic WBS with 148 MBq ^{131}I after THW was performed 6–12 months after remnant ablation, with a simultaneous measurement of serum Tg (control-Tg) performed. At that time, TSH was above 30 mU/liter. Patients showing remnant uptake on initial diagnostic ^{131}I WBS received an additional 5.55 GBq dose of ^{131}I for a second ablation; stimulated Tg levels measured after the second ablation were used as the control-Tg value in these individuals. Of the initial patient population, 10 patients were lost to follow-up or refused to take further workups and were excluded from the analysis. This left a study population of 268 patients with no visible remnant uptake on control WBS.

Subsequent follow-up and localization of persistent or recurrent lesions

During the follow-up period, physical examinations were regularly performed on all patients every 3–6 months. Plain chest radiographs were obtained yearly. Diagnostic WBS with 148 MBq ^{131}I and measurement of Tg levels during THW were carried out every 1–2 yr on the basis of clinical suspicion. In 131 patients, spontaneous changes in serum Tg levels during THW were noted during at least 2 yr of follow-up. When serum Tg during THW was above 2 μg/liter or there was clinical suspicion of recurrence, one or more nonradioiodine imaging methods [including neck ultrasonography, technetium-99m methoxyisobutyl isonitrile scan, ^{18}F-deoxyglucose (FDG) positron emission tomogram (PET), or chest computed tomogram] were performed to localize normal and/or malignant thyroid tissues. In nine patients, therapeutic trials of 5.55 GBq ^{131}I were performed and posttreatment WBS were obtained.

Definition of clinical outcome

In terms of clinical outcome, the 268 patients were distributed into the following groups: 35 recurrence (13%); 73 "Tg positive, no evidence of disease" (27%); and 160 complete remission (60%). Recurrence was defined as the reappearance of disease after complete ablation of thyroid remnants (as determined by cytological or histopathological information) or persistently definite or extracervical ^{131}I uptake on posttreatment WBS after administration of 5.55 GBq ^{131}I. "Tg positive, no evidence of disease" was used to designate patients in which one or more instances of detectable serum Tg during THW were documented without visualization of disease by extensive additional nonradioiodine imaging. Complete remission was defined as undetectable Tg levels after THW or spontaneous disappearance of serum Tg after THW during the follow-up, with negative diagnostic WBS and negative neck ultrasonographic results.

Measurement of Tg, anti-Tg autoantibody, and TSH

Serum Tg measurements and anti-Tg assays were performed at the times of diagnostic ^{131}I WBS or administration of therapeutic doses of ^{131}I during THW. Serum Tg levels were measured by immunoradiometric assay (ELSA-hTG kit; Schering-CIS Bio International, Gif-sur-Yvetee, France) with a functional sensitivity of 1 μg/liter. We were unable to standardize serum Tg against CRM-457 but instead developed our own Tg-reference interval according to the laboratory medicine practice guidelines suggested by the National Academy of Clinical Biochemistry (available at http://www.nacb.org/lmpg/main.stm). Our generated Tg-reference interval was approximately 1.0–27.4 μg/liter (mean 5.2 μg/liter). The anti-Tg levels were measured by radioligand assay (HENNING test anti-Tg; BRAHMS Diagnostica, Berlin, Germany), and anti-Tg values above 100 U/ml were considered positive. Serum TSH was measured by radioimmunometric assay (SPAC-S TSH kit, Daiichi, Tokyo, Japan; normal range 0.5–5.0 mU/liter; intraassay coefficient of variation, 2.1%; interassay coefficient of variation, 2.5%).

^{131}I WBS

Diagnostic ^{131}I WBS was routinely scheduled 6–12 months after remnant ablation and every 1–2 yr thereafter. After 4 wk of THW, 148 MBq ^{131}I was administered, and WBS was obtained 48–72 h later using a dual head γ-camera (BiadXL24; Trionix, Twinsburg, OH) equipped with a high-energy collimator. The used scan speed was 12 cm/min, with a total count of at least 100,000 cpm. Afterward we administered periodic diagnostic WBS with Tg measurement after THW throughout the follow-up period. In addition, we performed WBS 2 and 7 d after administration of therapeutic doses of 5.55 GBq ^{131}I. All patients were advised to restrict dietary iodine intake for at least 15 d before the administration of radioiodine.

Statistical analysis

Associations between variables were analyzed using contingency tables and Fisher's exact test. The 95% confidence intervals (CI) were calculated using the binomial distribution. The positive predictive value (PPV) for recurrence was calculated as follows: the number of patients with recurrence and ablation-Tg level greater than 2 or greater than 10 μg/liter was divided by the total number of patients with ablation-Tg greater than 2 or greater than 10 μg/liter. The negative predictive value (NPV) for recurrence was calculated as follows: the number of patients without recurrence and ablation-Tg 2 or less or 10 μg/liter or less was divided by the total number of patients with ablation-Tg 2 or less or 10 μg/liter or less. These analyses were performed using the InStat software program (GraphPad Software Inc., San Diego, CA). $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

The study population included 268 patients (40 men and 228 women) with no remnant uptake visible at the diagnostic WBS (there were 266 negatives on the first diagnostic WBS and two negatives on the second diagnostic WBS). The mean age of enrolled patients was 44.4 $\pm$ 13.2 yr (range, 13.3–80.4 yr). The histopathological types included 254 papillary carcinomas and 14 follicular carcinomas (including three Hürthle cell carcinomas). The frequencies of size above 4 cm, multifocality, extrathyroidal invasion, and lymph node metastases were 9, 16, 56, and 58%, respectively. None of the patients showed distant metastases at the time of remnant ablation (this was an inclusion criterion). The stagings by tumor, lymph node, metastasis classification system of the International Union Against Cancer and the American Joint

Committee on Cancer, revised in 1997, were I in 147 patients, II in 37 patients, III in 84 patients, and IV in no patients.

Diagnosis of recurrence

As shown in Table 1, 35 patients showed recurrence confirmed by cytological and/or histopathological information, or definite ^{131}I uptake on posttreatment WBS after administration of 5.55 GBq ^{131}I. The mean interval between the time of control-Tg measurement and diagnosis of recurrence was 3.3 ± 2.3 yr (range, 0.5–8.3 yr). PET scans were able to localize disease in 11 patients, and ultrasonography-guided fine-needle aspiration was used to detect disease in 20 patients, with seven overlapping cases in which both tests were positive. Recurrence was identified in the remaining 11 patients by physical examination (four cases), posttreatment WBS after therapeutic trial of 5.55 GBq ^{131}I (three cases), methoxyisobutyl isonitrile scan (two cases), diagnostic ^{131}I WBS (one case), and chest computed tomography (one case).

Correlation between serum Tg level at the time of remnant ablation (ablation-Tg) and serum Tg level at the time of first diagnostic WBS (control-Tg)

As shown in Fig. 1, of 64 patients with ablation-Tg greater than 10 μg/liter, the control-Tg was above 2 μg/liter in 56 patients (87.5%), between 1 and 2 μg/liter in five patients (7.8%), and undetectable in three patients (4.7%). Interestingly, all 30 patients with ablation-Tg greater than 30 μg/liter showed control-Tg greater than 2 μg/liter. Among 79 patients with ablation-Tg greater than 2 and 10 μg/liter or less, the control-Tg was above 2 μg/liter in 26 patients (32.9%), between 1 and 2 μg/liter in 27 patients (34.2%), and undetectable in 26 patients (32.9%). Among 125 patients who had ablation-Tg 2 μg/liter or less, three patients (2.4%) had control-Tg greater than 2 μg/liter, 52 patients (41.6%) had control-Tg levels between 1 and 2 μg/liter, and 70 patients (56.0%) had undetectable control-Tg. There was significant correlation between groups according to the level of abla-

TABLE 1. Patients with recurrence confirmed by cytological or histopathological information, or by persistently definite or extracervical ^{131}I uptake on posttreatment whole body scan

No.	Age (yr)/sex	Ablation-Tg (μg/liter)	Control-Tg (μg/liter)	Duration before localization (months)[a]	Main diagnostic maneuver[b]	Site of recurrence	Additional treatment modalities
1	37/F	592	27	14	RxWBS (+)	Cervical LN	^{131}I
2	24/F	514	623	6	DxWBS (+)	Cervical LN, lung	^{131}I, surgery, radiation
3	33/F	342	244	14	PET (+)	Mediastinum	^{131}I, surgery, radiation
4	37/F	315	281	9	MIBI (+), PET (−)	Cervical LN	Surgery
5	33/M	210	118	35	PET (+), USFNA (−)[c]	Cervical LN	Surgery
6	50/M	205	121	33	USFNA (+)	Cervical LN	Surgery, ^{131}I
7	50/M	203	170	10	Palpation (+)	Cervical LN	Surgery, ^{131}I
8	38/M	186	318	7	RxWBS (+)	Cervical LN	Surgery, ^{131}I, radiation
9	32/F	109	45.8	14	PET (+)	Cervical LN	Surgery, radiation
10	41/M	103	118	90	PET (−), USFNA (+)	Cervical LN	Surgery
11	40/F	97	93.8	56	USFNA (+)	Cervical LN	Surgery
12	74/F	91.3	36.4	33	USFNA (+)	Cervical LN	Refused further Tx
13	15/F	70.2	174	12	PET (+), USFNA (+)	Cervical LN	Surgery
14	39/F	51.9	39.6	20	PET (+)	Cervical LN	Surgery, radiation
15	33/F	47.9	25.9	99	USFNA (+)	Cervical LN	Surgery
16	46/M	47.7	58.6	7	Palpation (+)	Cervical LN	Surgery
17	50/F	38.3	11.3	27	MIBI (+)	Mediastinal LN	Surgery
18	43/M	35.5	17.3	6	PET (+), USFNA (+)	Cervical LN	Surgery, ^{131}I, radiation
19	20/F	33.3	23.6	62	PET (+), USFNA (+)	Cervical LN	Surgery
20	56/F	32.8	31.4	63	PET (+), USFNA (+)	Cervical LN	Surgery
21	49/F	30.9	29.3	80	PET (+), USFNA (+)	Cervical LN	Surgery
22	21/F	29.6	37.4	50	USFNA (+)	Cervical LN	Surgery
23	13/F	29.3	45.5	13	RxWBS (+)	Cervical and mediastinal LN	^{131}I
24	43/F	19	11	79	USFNA (+)	Cervical LN	Surgery
25	28/M	17.2	14.9	71	USFNA (+)	Cervical LN	Surgery
26	52/F	16.1	8.4	9	USFNA (+)	Cervical LN	Surgery, ^{131}I, radiation
27	59/M	12.7	11.9	19	USFNA (+)	Cervical LN	Surgery
28	55/M	6.6	2.3	69	USFNA (+)	Cervical LN	Surgery, ^{131}I
29	65/F	6.1	5.7	54	Palpation (+)	Neck mass	Surgery, ^{131}I, radiation
30	34/F	5.1	5.6	60	PET (+), USFNA (+)	Cervical LN	Surgery
31	74/F	4.7	0	41	CT (+)	Lung	Supportive treatment only
32	24/F	4.5	2.2	59	USFNA (+)	Cervical LN	Surgery
33	23/M	3.9	3.6	65	USFNA (+)	Cervical LN	Surgery
34	42/F	1.8	1.2	60	Palpation (+)	Neck mass	Surgery, ^{131}I
35	57/M	1.6	0	57	PET (+), USFNA (+)	Cervical LN	Supportive treatment only

F, Female; M, male; RxWBS, posttherapy WBS after administration of therapeutic dosage of 5.55 GBq ^{131}I to detect source of elevated serum Tg; DxWBS, diagnostic WBS; USFNA, ultrasonography-guided fine-needle aspiration; MIBI, technetium-99m methoxyisobutyl isonitrile WBS; LN, lymph node; Tx, treatment.

[a] Duration between the time of first diagnostic scan and the time of clinical recurrence found by the additional listed diagnostics.

[b] All patients except one (no. 2) showed no uptake on one or more diagnostic WBS.

[c] Ultrasonography localized 0.8 cm-sized lymph nodes, but cytology revealed lymphocytes only.

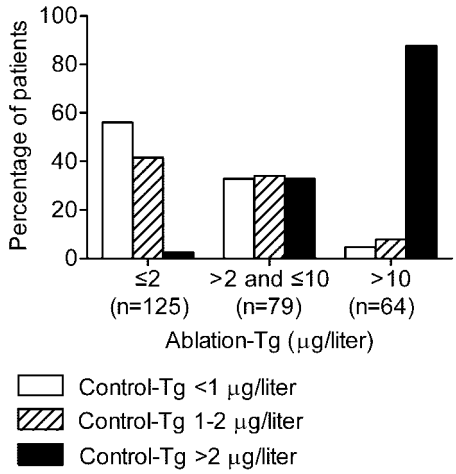

FIG. 1. Correlation between serum Tg at the time of remnant ablation and serum Tg level measured at the time of first diagnostic WBS after THW. There was significant correlation between groups according to level of ablation-Tg and control-Tg (three by three χ^2 test, $\chi^2 = 143.1$, $df = 4$, $P < 0.001$).

tion-Tg and control-Tg (three by three χ^2 test, $\chi^2 = 143.1$, $df = 4$, $P < 0.001$).

Clinical outcome of patients with ablation-Tg greater than 10 μg/liter

As shown in Fig. 2, of 64 patients with ablation-Tg greater than 10 μg/liter, 27 patients (42.2%) showed recurrence during the follow-up period. In three of these patients, a therapeutic dosage of 5.55 GBq ^{131}I was administered to detect the source of elevated serum Tg. One patient showed cervical

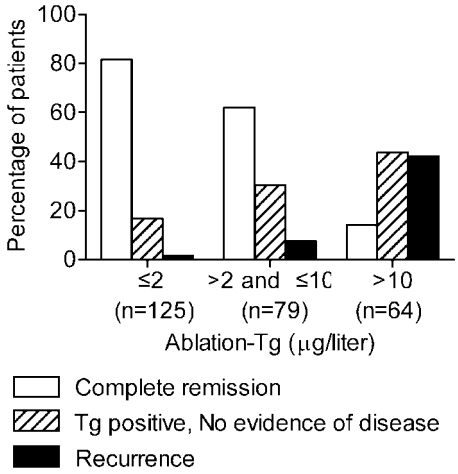

FIG. 2. Clinical outcome according to serum Tg at the time of remnant ablation. Complete remission, no detectable serum-Tg after THW or spontaneous disappearance of serum-Tg after THW was documented during the follow-up with negative diagnostic WBS; "Tg positive, no evidence of disease," one or more measurements of detectable serum Tg during THW were documented without visualization of disease by additional nonradioiodine imaging; recurrence, clinical reappearance of disease confirmed by cytological or histopathological information or persistently definite or extracervical ^{131}I uptake on posttreatment WBS after administration of 5.55 GBq ^{131}I. There was significant correlation between groups according to level of ablation-Tg and control-Tg (three by three χ^2 test, $\chi^2 = 100.1$, $df = 4$, $P < 0.001$).

lymph node uptake and received an additional dosage of ^{131}I up to a total dosage of 202.2 GBq, whereupon the stimulated serum Tg levels decreased from 592 to 27 μg/liter. Another patient showed cervical lymph node uptake and received additional radical neck dissection and external radiation therapy, whereupon the stimulated Tg decreased from 318 to 7 μg/liter. The third patient, a 13-yr-old girl, showed cervical and mediastinal lymph node uptake in posttreatment WBS but refused additional treatment; her serum Tg increased from 29.3 to 45.5 μg/liter during the 40 months of the observation period.

Of the remaining patients with ablation-Tg greater than 10 μg/liter, 28 patients (43.7%) were designated "Tg positive, no evidence of disease" because they did not show any evidence of disease despite extensive nonradioiodine imaging studies. During the follow-up, 21 of these patients showed serum Tg greater than 2 μg/liter during THW, five patients revealed follow-up serum Tg between 1 and 2 μg/liter after THW, and Tg levels were not measured in two patients with initial control-Tg levels of 1.3 and 1.1 μg/liter, respectively.

And finally, nine patients (14.1%) with ablation-Tg greater than 10 μg/liter showed complete remission. Of these, three patients showed undetectable Tg levels after THW during the follow-up period, and six patients showed detectable control-Tg levels after THW at initial follow-up but achieved spontaneous negative conversion during the follow-up period.

Clinical outcome of patients with ablation-Tg above 2 and no greater than 10 μg/liter

Of 79 patients with ablation-Tg greater than 2 and 10 μg/liter or less (Fig. 2), six patients (7.6%) showed recurrence during the follow-up, and 24 patients (30.4%) were "Tg positive, no evidence of disease." An additional six patients showed follow-up serum Tg during THW of greater than 2 μg/liter, 13 patients revealed follow-up serum Tg after THW between 1 and 2 μg/liter, and follow-up Tg levels were not measured in five patients with initial control Tg levels ranging from 1.0 to 1.6 μg/liter. Finally, 49 patients (62.0%) achieved complete remission. Of these, 23 patients showed undetectable Tg levels after THW during the follow-up period, and 26 patients showed detectable control-Tg levels after THW at initial follow-up but achieved spontaneous negative conversion during the full follow-up period.

Clinical outcome of patients with ablation-Tg 2 μg/liter or less

Of 125 patients with ablation-Tg 2 μg/liter or less (Table 1), two (1.6%) showed clinical recurrence during the follow-up. One patient presented with a palpable neck mass 60 months after initial treatment. In the other patient, recurrence was detected by FDG-PET and confirmed by ultrasonography-guided aspiration cytology 57 months after initial treatment.

"Tg positive, no evidence of disease" was determined in 21 patients (16.8%). Four of these patients showed follow-up serum Tg during THW of greater than 2 μg/liter. Four patients (with control-Tg values of 1.2, 1.6, 2.7, and 6.1 μg/liter,

respectively) showed no evidence of clinical disease by extensive imaging studies and had serum Tg levels during THW of 5.5, 2.9, 2.3, and 2.7 μg/liter, respectively (4.9, 2.4, 3.0, and 2.0 yr after the initial diagnostic WBS, respectively). An additional 12 patients had follow-up serum Tg levels after THW between 1 and 2 μg/liter, and follow-up Tg was not measured in five patients whose control-Tg values ranged from 1.1 to 1.5 μg/liter.

Complete remission was observed in 102 of these patients (81.6%); 63 patients showed undetectable stimulated serum Tg during the entire follow-up period, and 39 showed spontaneous negative conversion of serum Tg during THW after 2.7 ± 1.3 yr of follow-up (range, 1–5.5 yr).

Predictive value of ablation-Tg

The PPV for recurrence in patients with ablation-Tg greater than 2 μg/liter was found to be 23.1% (33 of 143 patients, 95% CI 16.4–30.8%). The NPV for recurrence in patients with ablation-Tg 2 μg/liter or less was calculated to be 98.4% (123 of 125 patients, 95% CI 94.4–99.8%). The PPV for recurrence in patients with ablation-Tg greater than 10 μg/liter was calculated to be 42.2% (27 of 64 patients, 95% CI 31.0–56.7%). And finally, the NPV for recurrence in patients with ablation-Tg 10 μg/liter or less was found to be 96.1% (196 of 204 patients, 95% CI 92.4–98.3%).

Discussion

Recent studies have begun to investigate the use of control-Tg values (stimulated Tg measured at the time of diagnostic WBS 6–12 months after remnant ablation) to predict recurrent or persistent disease (3, 7). To find earlier parameters for predicting persistence or recurrent disease, we evaluated the prognostic value of ablation-Tg (the serum Tg level measured at the time of ^{131}I remnant ablation just after thyroidectomy). We studied the clinical outcome of 268 patients with low-risk differentiated thyroid carcinoma who were treated with total thyroidectomy followed by high-dose ^{131}I remnant ablation. Serum Tg levels were measured at the time of remnant ablation and compared with those taken 6–12 months thereafter during THW. We hypothesized that these values might be comparable in predicting long-term remission, persistent disease, or early recurrence when a cutoff value of 2 μg/liter was used.

Three major findings in this work suggest that ablation-Tg might be a valuable prognostic factor. First, a significant correlation was observed between ablation-Tg and control-Tg levels (Fig. 1). All enrolled patients received total thyroidectomies by a single skilled surgeon who left no visible remnants within the operation field. This strategy might minimize the influence of residual normal thyroid tissue on ablation-Tg. Thus, the source for ablation-Tg might reflect remnant or residual disease after remnant ablation. Second, the clinical outcome was significantly affected by the level of ablation-Tg. As shown in Fig. 2, patients grouped according to ablation-Tg showed significantly different clinical outcomes; the PPV was 23.1% and the NPV was 98.4% when a cutoff of 2 μg/liter was applied. Third, the proportion of patients with ablation-Tg greater than 2 μg/liter and clinical recurrence was comparable with that of patients with control-Tg 1 μg/liter or greater. In the present study, 33 of 143 patients (23.1%) with ablation-Tg greater than 2 μg/liter showed clinical recurrence during the follow-up period. In previous reports, 19–24% of patients with control-Tg 1 μg/liter or greater showed recurrence (3, 7).

In this work, we defined recurrence as the clinical reappearance of disease after complete ablation of thyroid remnants, as confirmed by cytological or histopathological information or definite ^{131}I uptake on posttreatment WBS after administration of 5.55 GBq ^{131}I. However, although not visualized, detectable Tg levels should be considered a sign of potential malignant disease or persistent normal thyroid residue. Several recent articles point toward very low serum Tg levels (1–2 μg/liter on TSH stimulation) as the cut-off for considering a patient at risk of disease (8–10). If we define clinical outcome as recurrence or no recurrence, we might mistakenly classify patients with small residual malignancies as being in remission. Accordingly, we herein classified patients as belonging to one of three clinical outcome groups: recurrence; "Tg positive, no evidence of disease"; or complete remission. The middle of these, "Tg positive, no evidence of disease," is a gray zone harboring patients with potential malignant disease or persistent normal thyroid remnants.

No reference exists in the literature regarding the normal distribution of postoperative Tg values in patients receiving thyroidectomies, complicating our determination of the ablation-Tg cutoff levels. A wide range of threshold levels have been suggested, ranging from 10 to 69.7 μg/liter (5, 6, 11–13). A recent report (5) proposed 30 μg/liter as a cutoff for ablation-Tg and showed that more frequent clinical progression was observed in patients with ablation-Tg equal to or above 30 μg/liter (33%) *vs.* patients with ablation-Tg levels less than 30 μg/liter (4%). Our data showed that the PPV for ablation-Tg greater than 30 μg/liter or greater than 10 μg/liter was 70.0% (21 of 30 patients; data not shown) or 42.2% (27 of 64 patients), respectively. However, the PPV of ablation-Tg at cutoff values of 30 μg/liter or 10 μg/liter was not applicable due to the rarity of patients showing high ablation-Tg levels; ablation-Tg was above 10 μg/liter in 23.9% patients and above 30 μg/liter in 11.2%. Previously, Ronga *et al.* (6) showed that when a cutoff ablation-Tg value of 2.25 μg/liter was used, the NPV was 99% in excluding recurrence. In the present study, we used a cutoff serum Tg level of 2 μg/liter after THW at the time of remnant ablation to predict clinical recurrence and found that ablation-Tg 2 μg/liter or less was observed in 46.9% of patients, and the NPV for ablation-Tg 2 μg/liter or less was 98.4%.

Of the 64 patients with ablation-Tg greater than 10 μg/liter, 42.2% had persistent disease or recurrence during the follow-up period. The effect of remnant ablation was not sufficient to control the residual malignant tissue in many of the patients. We have to closely monitor changes in stimulated Tg level in these patients. When elevated Tg is found, we should thoroughly search for the source and apply appropriate additional treatments. In patients with ablation-Tg greater than 2 and 10 μg/liter or less, 62% showed negative conversion of stimulated Tg after remnant ablation, and recurrence was detected in 7.6% of cases. Thus, remnant ablation seems to have the most powerful beneficial impact on

the prognosis in patients with minimal residual disease, and aggressive high-dose ablation therapy might be mandatory in this group of patients. Among patients with ablation-Tg 2 μg/liter or less, recurrence was detected in only 1.6% of patients. Because stimulated serum-Tg 2 μg/liter or less could be considered as a minimal burden of remnant normal tissue rather than malignant residual disease, these patients might be almost cured by surgery alone, so the incremental benefit of remnant ablation in these patients might be less evident. It is possible that T_4 suppression without remnant ablation might be sufficient in this category of patients, but additional studies are needed to confirm this possibility.

There are no definite guidelines with regard to additional imaging for detection of recurrence. A consensus report suggested an algorithm for follow-up using neck ultrasonography in patients with detectable suppressed Tg or stimulated Tg above 2 μg/liter (4). Another study even suggested a first follow-up based on routine thyroid ultrasonography (14). The utilities of FDG-PET scan in patients with elevated serum Tg and negative WBS have been confirmed in several studies (15–17) in which the reported sensitivities for detecting metastases ranged from 71 to 94%. Although the present study was not designed to determine superior methods for detecting clinical recurrence in patients with elevated serum Tg, our results suggest that ultrasonography was somewhat superior and/or more cost effective, compared with FDG-PET, because the sites of 11 clinical recurrences defined by positive FDG-PET scanning were restricted to the neck area, and eight of 11 FDG-PET-detected recurrences underwent ultrasonography-guided aspiration to confirm recurrence before surgery (with cytological confirmation in seven patients) (Table 1).

In conclusion, we herein showed that serum Tg levels measured at the time of ^{131}I remnant ablation in low-risk patients with differentiated thyroid carcinoma could be correlated with serum Tg measured 6–12 months later, during THW, and could reliably predict persistent or recurrent disease in the earliest postoperative time period.

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