CLINICAL STUDY

Post-ablative serum thyroglobulin is an independent predictor of recurrence in low-risk differentiated thyroid carcinoma: a 16-year follow-up study

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Abstract

Objective: To study whether post-surgical and/or post-ablative thyroglobulin (Tg) concentrations may serve as independent predictors of disease recurrence in patients treated for TNM stage I or II well-differentiated thyroid carcinoma (WDTC).

Design: An observational retrospective study with a median follow-up of 16 years (range 10–24).

Patients and measurements: Post-operative and post-ablative Tg concentrations, age, tumour size, local infiltration and nodal metastasis at primary surgery as well as disease recurrences and cancer-specific deaths were evaluated in 495 low-risk (TNM stages I and II) patients, the majority of whom had total thyroidectomy and radioactive iodine remnant ablation as initial treatment.

Results: Fifty-one patients (10.3%) experienced disease recurrence during follow-up. In multiple logistic regression analysis, post-ablative Tg concentrations (odds ratio (OR) 3.72, confidence interval (CI) 1.71–8.05, $P=0.0009$) and local infiltration on primary surgery (OR 2.66, CI 1.03–6.90, $P=0.04$) were the only independent predictors of recurrence.

Conclusions: Post-ablative Tg concentration is a strong predictor of disease recurrence in WDTC.

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Introduction

Differentiated thyroid carcinoma (DTC) is the most common endocrine malignancy (1) and the incidence has even increased during the past decades (2, 3). Most patients are diagnosed at a relatively young age and the prognosis is good, with 5- and 10-year survival rates of 90–95% (2, 3). Despite the low risk of DTC-related death, disease recurrence rates as high as 35% have been reported after 40 years of follow-up (2). The number of patients who need monitoring for possible disease recurrence is therefore considerable. While recent guidelines favour lighter follow-up schemes, identification of prognostic risk factors for disease recurrence would help to identify high-risk patients.

Several staging systems have been proposed based on clinical and pathological variables (4–6). However, these systems were created and validated using cancer-specific survival as the outcome and not recurrent disease, which still requires significant intervention. In 2006, the American Thyroid Association recommended the use of pathological TNM (pTNM) staging for all patients with DTC (7, 8). This staging system depends heavily on patient age (<45 or ≥ 45 years) and primary tumour size (≤ 2 , >2 to ≤ 4

and >4 cm) (6), both of which have been shown to predict cancer-specific survival.

This study therefore aimed to identify factors that predict recurrence after long-term follow-up. We assessed recurrences and cancer-specific deaths in a cohort of 495 patients with well-differentiated thyroid carcinoma, initially treated with both surgery and radioactive iodine remnant ablation (RRA) after a median follow-up of 16 years. We studied possible prognostic factors for disease recurrence in this cohort, including age, gender, primary tumour size, infiltration at primary surgery, nodal metastasis at primary surgery and post-surgical and post-ablative serum thyroglobulin (Tg) concentrations.

Patients and methods

Patients

The clinical records of 710 patients (571 females and 139 males) diagnosed with papillary or follicular thyroid carcinoma at the Helsinki University Central Hospital (HUCH) district in a 15-year time period from 1st January 1983 through 31st December 1997 were reviewed. This study material of 495 patients (70.0% of all) comprises those differentiated papillary or follicular

thyroid carcinoma TNM stage I or II patients who were considered to be disease free and in complete remission after primary surgery and RRA therapy. All patients were managed at the HUCH. The follow-up data of this cohort was retrieved by reviewing the clinical records of all patients. A questionnaire regarding the present follow-up of thyroid cancer was additionally sent to patients whose documents showed no recent entries. The 11.6-year follow-up data of the cohort have been described previously (9).

Thyroglobulin

Data on post-operative and post-ablative serum Tg concentrations were obtained from the original documents. Post-operative Tg was measured before initiation of thyroxine therapy at the time the patient was evaluated for RRA, e.g. 4–6 weeks after surgery. Post-ablative Tg measurements in combination with ^{131}I whole-body scan (WBS) were performed 4–6 months after the first RRA, under TSH stimulation induced by thyroxine withdrawal.

Until 1989, serum Tg was measured by an RIA kit (Medix Laboratories Ltd, Kauniainen, Finland) with the detection limit of 3 µg/l, and after that by an immunometric sandwich assay using two MABs (AutoDelfia, Perkin Elmer, Wallac, Turku, Finland) with the detection limit of 1 µg/l. Prevalence of anti-Tg antibodies was evaluated using the recovery method according to the manufacturer's instructions (Delfia Tg (hTG), Perkin Elmer). Briefly, 0.25 µg human purified Tg was added to 250 µl of each patient's sera in 25 µl buffer and mixed well. Tg was measured from serum with and without added Tg and the recovery was calculated. A recovery of $\geq 80\%$ was considered normal and excluded the presence of anti-Tg-antibodies. The analytical sensitivity for the Tg measured was 0.2 µg/l.

Study design

Disease recurrences and cancer-related deaths were recorded and possible predictive variables for disease recurrence were evaluated. A disease recurrence was defined as new evidence of disease after a disease-free period of 12 months or more. It included all sites of disease reported and confirmed either by imaging or by surgery. Disease free was defined as undetectable Tg, no clinical presentation of disease and no radiological evidence of disease. Clinical and histopathological variables included tumour histology, size, presence of nodal metastasis, local infiltration and mode and completeness of surgery (estimated by the performing surgeon) and patient age and gender. Local infiltration was defined as macroscopic adherence of the tumour to the adjoining muscle or soft tissue or microscopic invasion of the adjoining tissue. Biologic variables included Tg concentrations measured after surgery and after RRA and measurement of Tg antibodies.

Statistical analysis

The relationship between recurrence and explanatory factors (age, gender, detectable Tg after primary surgery, detectable Tg after RRA, post-operative non-detectable Tg in the presence of Tg antibodies, size (cm), follicular histology, total thyroidectomy, complete surgery, nodal metastasis in primary surgery, local infiltration in primary surgery and RRA given) was first examined using simple logistic regression for each factor separately. A multiple logistic regression model including all significant factors in the first analysis was then created. The 95% confidence intervals (CI) were programmed to hazard ratios. A P value < 0.05 was considered statistically significant. All tests were performed as two-sided tests. S+ software was used for statistical analyses. To compare recurrence-free time between patients with detectable and non-detectable Tg, a Kaplan–Meier plot was drawn and log rank test was performed.

Ethics

The study was reviewed and approved by the ethical committee at the HUCH. Written, informed consent was obtained from all patients if additional information was needed after their follow-up at the HUCH had ended.

Results

Patient characteristics and primary therapy

The study cohort consisted of 415 (83.8%) female and 80 (16.2%) male patients. Mean age at diagnosis was 40.6 years. Thirty-one (6.1%) tumours were of follicular histology, 461 (93.1%) of papillary and 3 of mucopapillary histology. Mean tumour size was 1.8 (range 0.3–6.0) cm, with the follicular tumours being larger than the papillary (mean 3.0 vs 1.6 cm, $P = 0.1326$). Thirteen patients had a tumour classified as T3 due to size. Total or near total thyroidectomy was performed as primary treatment in 95% of the patients. Of these 472 patients, 414 (87.7%) received RRA treatment, and repeat doses were administered if necessary. The patient was considered disease free if the neck ultrasound (US) examination was negative and, after the withdrawal of T4, Tg was unmeasurable and there was no uptake on WBS. The median RRA activity administered was 3.7 (range 2.2–25.9) GBq. Local tumour infiltration at surgery was detected in 7.4% of the cases ($n = 37$). Surgery was complete in all but three cases. Locoregional nodal metastases were present in 12.5% of the cases. Systematic dissection of the cervical lymph node compartments was not performed but pathologic nodes detected before or during surgery were removed. One patient had evidence of distant metastasis at the time of diagnosis, and she was classified as TNM stage II because of her young age. At the time of the present analysis, each patient had a follow-up of at least 10 years (range 10–24) with a median follow-up of 16 years.

Disease recurrences

During the median follow-up of 16 years, 51 patients (10.3%) experienced a disease recurrence. Five of them had a tumour of follicular histology and 46 of papillary. The duration of the disease-free period after primary treatment, the primary diagnostic tool of the recurrence, localisation of the recurrence and post-ablative Tg concentrations for each patient, is presented in Table 1.

Forty-three of the detected recurrences (84.3%) occurred within 10 years from diagnosis and initial treatment.

The majority of recurrences were located in the cervical lymph nodes (94.1%) and were detected with the neck US examination (54.9%) and were confirmed histopathologically. The diagnosis of a smaller number of recurrences (31.4%) was confirmed with a definite new uptake on diagnostic WBS (Table 1). In two cases,

Table 1 The characteristics of patients with recurrence.

Number	Age	Gender	Location of recurrence	Primary diagnostic method	Post-ablative Tg	Time to recurrence (months)
10	49	Female	Cervical LN	US/FNAB	<1	21
13	39	Female	Cervical LN	US	NA	60
31	53	Female	Cervical LN	US/FNAB	NA	25
42	31	Female	Cervical LN	US/FNAB	<1	18
49	26	Female	Cervical LN	DxWBS	<1	59
57	25	Female	Cervical LN	US/FNAB	<1	58
61	21	Female	Cervical LN	US	<3	24
68	21	Male	Cervical LN	US/FNAB	<1	69
76	19	Female	Cervical LN	Tg/US	2.0	108
88	39	Male	Cervical LN	DxWBS	NA	35
90	54	Female	Cervical LN	TG/WBS	<3	108
95	30	Male	Cervical LN	DxWBS	4.0	16
97	19	Female	Cervical LN	NA	<1	132
98	27	Female	Cervical LN	US/FNAB	<1	52
109	33	Female	Cervical LN	DxWBS	3.0	38
119	26	Female	Cervical LN	US/FNAB	5.0	92
125	53	Female	Cervical LN	US/FNAB	<1	18
149	16	Female	Cervical LN	US/FNAB	23.0	131
168	20	Female	Mediastinal LN	Tg-on-T4	84.0	65
172	52	Female	Cervical LN	DxWBS	<1	27
210	36	Female	Cervical LN	US/FNAB	3.0	16
212	51	Female	Cervical LN	US/FNAB	<1	48
218	69	Male	Cervical LN	DxWBS	<1	58
223	17	Female	Cervical LN	DxWBS	84.0	60
225	27	Female	Cervical LN	US/FNAB	<1	149
228	73	Female	Cervical LN	DxWBS	<1	67
229	42	Female	Cervical LN	US/FNAB	NA	30
244	27	Male	Cervical LN	US	28.0	36
260	43	Male	Cervical LN	US/FNAB	<1	33
274	44	Female	Cervical LN	US/FNAB	<1	144
279	24	Female	Cervical LN	US	<1	21
282	30	Female	Cervical LN	US	<1	18
284	20	Male	Cervical LN	US/FNAB	58.0	21
286	42	Female	Cervical LN	DxWBS	NA	24
300	27	Male	Cervical LN	US/FNAB	NA	110
316	6	Female	Cervical LN	US/FNAB	<1	121
319	40	Female	Cervical LN	US/FNAB	NA	66
357	60	Male	Cervical LN	DxWBS	<3	59
370	16	Female	Cervical LN	Tg + palpation	18.0	22
406	35	Female	Cervical LN	DxWBS	<3	93
419	32	Male	Cervical LN	DxWBS	<3	263
420	18	Female	Cervical LN	DxWBS	<3	24
434	41	Female	Cervical LN	New Tg-AB	<1	113
441	19	Female	Cervical LN	DxWBS	<1	71
470	34	Male	Cervical LN	US/FNAB	28.0	108
474	27	Male	Cervical LN	US/FNAB	5.0	26
475	43	Female	Cervical LN	US/FNAB	3.0	116
478	40	Female	Cervical LN	DxWBS	<1	48
485	32	Male	Cervical LN	US/FNAB	8.0	144
524	65	Female	Cervical LN	Tg-on-T4	2.0	212
584	53	Female	Cervical LN	DxWBS	<3	35

LN, lymph node; US, ultrasound examination; FNAB, fine-needle aspiration biopsy; DxWBS, diagnostic whole body scan with ¹³¹I; NA, not available.

Table 2 Simple logistic analysis of predictive factors for disease recurrence. Thyroglobulin (Tg) concentrations were available for 468 patients and data are expressed as number (percentage) or median (range).

	With recurrence (n=48)	Without recurrence (n=420)	P
Age (years) (median with range)	32 (15–73)	40 (12–80)	0.0057
Male gender	13 (27.1)	62 (14.8%)	0.0305
Tg detectable after primary surgery	34 (70.8%)	225 (53.6%)	0.0251
Tg detectable after RRA ablation	16 (36.4%) ^a	35 (9.8%) ^b	<0.0001
Post-ablative non-detectable Tg with Tg antibodies	6 (12.5%)	78 (18.6%)	0.3029
Size (cm) (median with range)	2.0 (0.3–5.0)	1.8 (0.1–7.0)	0.1326
Follicular histology	4 (8.3%)	24 (5.7%)	0.4769
TTE	48 (100%)	406 (96.7%)	0.958
Complete surgery	48 (100%)	419 (99.8%)	0.9745
Nodal metastasis in primary surgery	14 (29.2%)	47 (11.2%)	0.0008
Local infiltration in primary surgery	10 (20.8%)	25 (5.9%)	0.0005
RRA given	46 (95.8%)	357 (85.0%)	0.0564

TTE, total or near total thyroidectomy.

^an=44.^bn=357.

the therapeutic activities of radio-iodine were given because of a significant rise in Tg on thyroxine without the radiological findings. The recurrence was confirmed with treatment dose WBS. In one case each, recurrence was detected based on increased Tg concentration on T4 combined with palpable nodes, a suspect US finding and the appearance of Tg antibodies indicated by declining recovery respectively.

Thyroid carcinoma was registered as cause of death for one patient (data provided by Statistics Finland), who was diagnosed with a metastasised follicular carcinoma at a young age. This case, which initially had been wrongly classified, was reported previously (9).

Post-surgical Tg concentrations and disease recurrence

Post-surgical Tg levels were recorded in 468 cases (94.5%). After primary total or near total thyroidectomy, 250 cases (52.9%) demonstrated post-surgical Tg levels above the detection limit. Of the 51 patients with disease recurrence, 71% (n=34) had a post-operative Tg level above the detection limit as compared with 54% (n=225) of the 420 patients without recurrence (P=0.0251; Table 2). Post-operative Tg did not correlate with post-operative TSH concentrations (r=0.056). The post-operative median TSH concentrations did not differ between patients with and without recurrence (76 and 73 mU/l respectively, P=0.39).

Tg concentrations after radio-iodine ablation and disease recurrence

RRA was performed in 414 cases of the 472 patients who had undergone total or near total thyroidectomy (49 patients with subsequent recurrence and 365 without recurrence). Post-ablative Tg levels were recorded in 401 cases (96.9%) and were detectable after the first RRA therapy in 51 cases (12.7%, median

10.0 µg/l, range 1–500). All patients with detectable Tg after initial RRA received repeat doses until Tg became undetectable and there was no evidence of disease on post-therapy WBS. Total ¹³¹I activity administered varied between 2.2 and 25.9 GBq (60–700 mCi). After ablation, Tg was measurable in 36.4% of patients with subsequent recurrence compared with 9.8% of patients without recurrence (P<0.0001; Table 2). The corresponding post-ablative median TSH concentrations were 44 and 36 mU/l respectively (P=0.36). Disease recurrence was diagnosed significantly more often in patients with detectable Tg after initial RRA compared to patients in whom Tg was undetectable (Fig. 1; P=0.021).

In seventy-nine cases with undetectable Tg after RRA, a low recovery (<80%) indicated Tg antibodies. Nine of these patients subsequently developed disease recurrence. There was no statistically significant

Figure 1 Percentage of recurrence-free patients without (n=350) and with (n=51) detectable Tg after first ablative radio-iodine treatment as a function of time.

Table 3 Predictors of recurrence in multiple logistic regression analysis.

	Hazard ratio	95% CI	P value
Age	0.978	0.978–1.007	0.1369
Post-ablative Tg	3.719	1.717–8.054	0.0009
Nodal metastasis	1.489	0.629–3.524	0.3651
Local infiltration	2.66	1.025–6.905	0.0444

difference in the prevalence of Tg antibodies between patients with and those without recurrence ($P=0.3029$; Table 2).

Characteristics of patients with and without recurrence

Simple logistic analysis of predictive factors for disease recurrence is presented in Table 2. Compared with patients without recurrence, patients who experienced disease recurrence were younger ($P=0.0057$), more often males ($P=0.035$) and more often had detectable post-surgical and post-ablative Tg levels ($P=0.0251$ and $P<0.0001$ respectively). Patients with recurrence also had more nodal metastasis ($P=0.0008$) and local infiltration ($P=0.005$) at primary surgery.

Of the 37 patients who presented with infiltration at primary surgery, 8 (21.6%) had detectable Tg concentrations after RRA compared to 9.4% patients without infiltration. Six of the eight patients (80%) were subsequently diagnosed with a recurring carcinoma.

Multiple logistic regression analysis

Multiple logistic regression analysis including all statistically significant variables in Table 2 revealed that only infiltration at primary surgery (odds ratio (OR) 2.66, CI 1.03–6.90, $P=0.04$) and post-ablative detectable Tg concentrations (OR 3.7, CI 1.71–8.05, $P=0.009$) were independent predictors of disease recurrence (Table 3).

Discussion

We present here long-term follow-up data on a cohort of 495 patients at low risk of thyroid cancer-specific death and report the significant association of local infiltration on primary surgery and post-ablative Tg concentrations with disease recurrence after a median follow-up of 16 years. Strengths of this study are a rather great number of patients, all patients uniformly belonging to the favourable TNM classes I–II, and a long follow-up.

During the follow-up, only 1 patient died, but 51 patients (10.3%) experienced a recurrence. The recurrence rate thus increased by 2.4% during this prolonged follow-up of 5 years compared with the recurrence rate of 8.9% at median follow-up of 11.6 years in the

previous report of the same cohort (9). The recurrence rate is steadily approaching that of 14–15% after 30 years of follow-up in the Mayo Clinic cohort (10). The numbers demonstrate that the follow-up indeed should aim to detect disease recurrences, as the majority of these patients are at low risk of thyroid cancer-specific death. It is therefore important to identify good predictors of well-differentiated DTC recurrences, which could help identify high-risk patients and, on the other hand, enable lighter follow-up schemes for suitable cases. This would also increase the cost-effectiveness of the surveillance system.

In the revised TNM staging classification of thyroid carcinoma, infiltrative tumours are classified either as T3 or T4 depending on the grade of invasion (6). In this study, infiltration *per se* at primary surgery and detectable serum Tg concentrations after the first RRA (off thyroxine) were the only independent predictors of a later recurrence. Local infiltration is included in nearly all classification systems for predicting cancer-specific death, but only a few studies have examined the possible role of post-surgical or post-ablative Tg concentrations on disease outcome (11–13). In a study of 268 patients (TNM stages I–III) with a median follow-up of 5.7 years (11), the recurrence rate was 13% and the authors concluded that post-operative serum Tg has a complementary role in predicting disease persistence or recurrence. They found a good correlation between post-surgical and post-ablative Tg concentrations, but did not relate post-ablative concentrations to recurrence rate (11). In the 5.1-year follow-up study of 212 TNM stages I–III patients by Toubreau *et al.* (12), recurrence rate was 9% and, in line with this study, post-ablative, but not post-surgical Tg, emerged as a strong predictive factor of disease recurrence, in addition to lymph node invasion. Hall *et al.* (13) studied 213 DTC patients (TNM stages I–IV) for a median of 47 months, and 12% experienced recurrence at 11 months. They found that post-surgical Tg > 20 pmol/l together with advanced tumour stage was an independent predictor of disease recurrence (13). Taken together, in line with this study, these studies implicate post-surgical/ablative Tg as a predictor of disease recurrence or progression.

Recently, Sciuto *et al.* (14) reported that the response to RRA was the strongest predictor of both morbidity and mortality in a cohort of 1503 DTC patients (TNM stages I–IV) with a follow-up of 5 years (14). Although the authors did not report the Tg values in their cohort, a good response to RRA also implies low Tg levels (14). In line with this, recurrence rate (2.4%) of 509 patients successfully treated with RRA as evidenced by non-detectable Tg concentrations and negative WBS 8 months after ablation did not differ between low- and high-risk DTC patients during 12–59 months of follow-up (15). The authors concluded that follow-up should not be based on tumour classification but on the basis of initial treatment response (15).

The role of RRA in well-differentiated DTC patients at low risk of cancer-specific death has been much debated. An obvious consensus exists that by destroying all the thyroid tissue, RRA not only simplifies the follow-up based on serum Tg measurements but also increases its reliability (7, 8, 16, 17). The patients of the present cohort were treated according to a uniform scheme including total or near total thyroidectomy and RRA if not contraindicated. As previously described (9), the cornerstones of the follow-up were neck US examination and fine needle biopsy where indicated and measurements of Tg concentrations on T4 therapy. In this uniformly treated patient sample, a detectable post-ablative Tg concentration measured during thyroxine withdrawal was an independent predictor of later recurrence. The data imply that, in patients treated according to this protocol, more emphasis should be put on the follow-up of patients with detectable post-ablative Tg concentrations, while a lighter follow-up scheme probably is indicated in patients with undetectable post-ablative Tg.

That stimulated Tg concentrations measured 6–12 months after initial treatment should be included in the surveillance scheme of DTC patients is strongly emphasised in a number of recent guidelines, not only to control the outcome of primary therapy but also to guide further surveillance (7, 16, 18). The post-ablative Tg concentrations predicting recurrence in this study were measured after endogenous TSH stimulation and the results are in line with the present recommendations of the European guidelines (16, 18). The guidelines recommend Tg measurements stimulated by recombinant human TSH (rhTSH) at 6–12 months after initial RRA. If Tg concentrations are undetectable, follow-up can thereafter be based on yearly evaluation of serum TSH and Tg on T4 treatment with or without neck US examination.

Naturally, the findings of this study are only applicable to patients being treated with RRA. Owing to fear of secondary malignancies, it has been proposed that RRA should be individually tailored (18). It has also been suggested to increase the use of routine prophylactic lymph node dissection and let the results from the node dissection guide the use of RRA (19). The latter suggestions are, however, still under debate (20).

In this study, most of the recurrences and especially the later ones were loco-regional lymph node metastases in the neck. This finding further supports the concept that low-risk patients with DTC can be safely followed up with neck US examination and serum Tg measurements on T4, without the use of rhTSH stimulation.

In conclusion, in this prolonged follow-up of 495 DTC patients at low risk of cancer-specific death, recurrence rate was 10.3% at a median follow-up of 16 years. Post-ablative serum Tg concentrations and local infiltration at primary surgery were the only independent predictors of recurrence.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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