CLINICAL STUDY

Non-suppressed thyrotropin and elevated thyroglobulin are independent predictors of recurrence in differentiated thyroid carcinoma

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Abstract

Objective: Although in most cases differentiated thyroid carcinoma (DTC) responds to surgery and radioiodine (RaI) therapy, some patients will have recurrence and eventually cancer-related death. However, although various prognostic factors of DTC have been identified (e.g. staging, suppressed thyrotropin), none of the previous studies have assessed simultaneously their role in multivariate analysis.

Design and Methods: In this retrospective population-based study, we reviewed the clinicopathological data of 254 DTC patients treated in eastern Finland during the years 1976–1995, for clinical characteristics, primary treatment, follow-up and cancer recurrence. Tumor stage was based on pathological tumor-node-metastasis (pTNM) classification, and histopathological specimens were re-evaluated.

Results: DTC recurrence occurred in 33 patients (13%). In univariate analyses, the predictors of recurrence were older age (>60 years, $P < 0.05$), follicular tumor type ($P < 0.01$), pTNM classification system ($P < 0.05$) and post-ablative radioiodine uptake outside the neck ($P < 0.05$). Non-suppressed serum thyrotropin (TSH) and elevated serum thyroglobulin ($>3 \mu\text{g/l}$) measured one year after operation were both related to tumor recurrence ($P < 0.05$ and $P < 0.001$ respectively). In multivariate analysis the independent predictors for recurrence were both elevated thyroglobulin ($P < 0.001$) and non-suppressed TSH ($P < 0.05$) independent of histology, pTNM stage and RaI uptake. Adjusted risk ratio for recurrence of DTC for unsuppressed thyrotropin was 2.3, for elevated thyroglobulin 14.0 and, if both conditions were present, the risk ratio increased to 45.1.

Conclusion: Our results suggest that both non-suppressed serum TSH and elevated serum thyroglobulin are related to an increased risk of DTC recurrence independent of tumor type and pTNM stage.

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Introduction

Differentiated thyroid carcinoma (DTC) is a rather common malignancy with generally favorable prognosis, but it can also be aggressive, leading to recurrent disease or even death. Evidently some patients require aggressive therapy, but their identification remains problematic, and aggressive thyrotropin (TSH) suppression therapy has potential drawbacks, especially on the cardiac and circulatory systems (1) and possibly also on bone mineral density (2).

The tumor-node-metastasis classification (TNM) (3) is a widely accepted classification system for staging of

DTC. When pathological characteristics of primary tumor are available for staging, it is considered as pTNM. So far, scant data are available on the independent prognostic value of pTNM for DTC recurrence. Of the currently available classification systems, pTNM is reported to have the highest prognostic value regarding recurrence-free survival (4). However, in a retrospective analysis, the pTNM was less accurate in predicting relapse-free survival than death (5).

From the other prognostic factors of DTC, the negative post ablative radioiodine (RaI) scan is found to be associated with more favorable prognosis (6). The

independent prognostic value of this procedure has not yet been defined. One of the clinical goals in the treatment of DTC is to suppress the TSH secretion by levothyroxine (L-T₄). Although, theoretically, TSH suppression has evident benefits, the clinical value of TSH suppression in preventing DTC recurrence has, so far, been documented in two studies (7, 8). Thyroglobulin (Tg) measurement is an important test in the follow-up of DTC. The presence of thyroglobulin in the serum indicates the persistence of DTC. However, there are some patients whose serum Tg can be as low as 3 ng/ml and still have recurrent or metastatic disease (9). The interaction of TSH suppression (treatment-related factor) and thyroglobulin (indicator of residual thyroid tissue) has not been assessed.

We have performed a population-based retrospective review and analysis of consecutive series of patients with DTC in order to assess the prognosis of DTC patients. Specifically, we clarified the independent prognostic role of age, stage, tumor infiltrating lymphocytes (TILs), the uptake of RaI, the degree of serum TSH suppression and serum Tg to DTC recurrence.

Subjects and methods

Patients

The study population consisted of all consecutive patients with DTC who were treated according to a

similar protocol and followed-up between 1976 and 1995 in a defined area in the eastern part of Finland. The total population of the area is 500 000 persons, and our data were collected from hospitals that are the only ones that treat thyroid carcinoma in this area. Data files of the Finnish Cancer Registry revealed a total of 373 potential patients with International Classification of Diseases (ICD)-8 (193.99) and ICD-9 (193) codes (10, 11). Those whose clinical follow-up data were inadequate or were for less than 6 months, whose pathological specimens were not available or were not confirmed at re-evaluation, were excluded. Formation of the study population is illustrated by the flow diagram in Fig. 1.

All the relevant patient records were reviewed for tumor characteristics, metastases, primary treatment and follow-up, and cancer recurrence. Evidence of recurrence was based on either ultrasound, RaI or magnetic resonance image findings and recurrence was defined as a new evidence of local disease or distant metastases occurring more than 6 months after the primary operation (12). Tumor stage was assessed retrospectively according to the pTNM classification system based on the 1987 International Union Against Cancer (UICC) classification (3).

Treatment

All the patients in this study underwent thyroidectomy. The type of operation was total or near total

Figure 1 Formation of the study population.

thyroidectomy in 219 (86%) patients, palliative resection in 18 (7%) patients, and 12 (5%) patients whose quality of operation could not be assessed from the patients' files. The standard procedure was always to perform as complete a thyroidectomy as possible. Hemithyroidectomy was performed on 5 (2%) patients with occult DTC. After surgical operation, a low-dose RaI scan was performed. The ablation therapy was given if there was an accumulation of radioiodine. The whole-body scan was performed a few days after RaI ablation and the uptake was recorded. In our study group, 198 (78%) patients received radioiodine ablation therapy. Fifty-eight patients received ablation therapy twice or more. The median of post-operative radioiodine ablation dose was 105 mCi (mean 105.4 and mode 80 mCi, range 50–150 mCi). After these procedures the TSH suppression treatment with thyroxine was started for every patient to prevent tumor residual growth.

TSH and thyroglobulin

From 1976 to 1981, serum TSH was determined using the TSH radioimmunoassay (RIA) kit (Amersham, Amersham, Bucks, UK) and from 1981 to 1986 using the TSH(¹²⁵I) RIA kit (Farnos Diagnostica, Turku, Finland). After 1986, the Spectria TSH immunoradiometric assay (IRMA) ¹²⁵I kit (Farnos Diagnostica) was used. The suppression of serum TSH one year after operation was defined as ≤ 1.0 mU/l and/or no response to thyrotropin releasing hormone (TRH) during the years 1976–1986, and as serum TSH ≤ 0.1 mU/l during 1986–1995. Two hundred micrograms TRH were given i.v. and the levels of TSH were measured at zero time and 20 min and 30 min after TRH administration. TSH was considered suppressed when the difference between TSH values at baseline and 20 min after injection was lower than 2 mU/l (7).

Likewise, serum thyroglobulin was assessed one year after operation. Serum thyroglobulin values were determined in a central laboratory (Oy Medix Ab, Kauniainen, Finland) using an RIA kit (HTGK2, Biosorin, Saluggia, Italy). The cut-off level was 3 μ g/l; levels over that were considered elevated. Thyroglobulin was measured during the follow-up on L-T₄ treatment. All thyroglobulin measurements were checked for interfering serum antibodies and due to their presence six patients were excluded from the analyses concerning serum thyroglobulin.

Histopathological classification

Two experienced histopathologists (V-MK and SH) re-examined hematoxylin and eosin stained sections simultaneously, being unaware of the clinical data. Histopathological diagnosis was confirmed by reviewing one to four original sections of the primary tumor.

Papillary carcinomas were subdivided as common type, follicular variant and occult carcinomas. Follicular

carcinomas were subdivided as minimally invasive or widely invasive.

The infiltration of lymphocytes and plasma cells in close vicinity of the tumor as well as inside the tumor area were estimated from all the papillary carcinoma specimens and graded as absent or present. Histopathological specimens of different metastases were also reviewed.

Statistical analysis

The SPSS program package (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The association between the tumor recurrence and other factors was tested by Mantel-Haenzel or Pearson chi-square tests. Cox regression model was used for multivariate analyses. A *P* value < 0.05 was considered statistically significant. The relapse-free survival was defined as the time from surgical resection to the time of cancer recurrence. Life tables were constructed using an actuarial method which takes into account the differences in actual observation periods (13). The expected five-year mortality rate of DTC patients was determined by adjusting the general population of the same geographical area by gender and age to the DTC patients. When comparing the outcome of DTC patients with the general population, the standardized mortality ratio (the ratio between the actuarial and expected mortality) was used to express the increased mortality.

Results

Clinical characteristics

Clinical characteristics of the study population are shown in Table 1 according to DTC recurrence. Women outnumbered men, and the mean follow-up time of the study population was 7.2 years, with a range of less than 1 year to 20 years. Histopathological re-examination confirmed the diagnosis of 216 papillary and 38 follicular carcinomas. The mean age at diagnosis was 46.8 years (range 8–92 years) for papillary and 61.6 years (range 27–84 years) for follicular carcinoma.

Predictors of the recurrence of DTC

Univariate analyses Thirty-three out of two hundred and fifty-four patients had local or distant recurrences (13%) (Table 1).

In univariate analyses, the gender did not predict the recurrence of DTC. The mean age of the whole study group was 49.0 years, but the frequency of older patients (> 60 years) was markedly higher in those with recurrence than in those without (39% vs 23%, *P* < 0.05). Likewise, the follicular type of tumor was associated with a higher risk of tumor recurrence

Table 1 Characteristics of study population according to the recurrence (REC) of DTC. Number of patients with percentage in parentheses are given.

	REC – (n = 221)	REC+ (n = 33)	P value
Gender			
Men	35 (16)	9 (27)	0.1
Women	186 (84)	24 (73)	
Age			
≤60 years	170 (77)	20 (61)	<0.05
>60 years	51 (23)	13 (39)	
Histology			
Papillary	193 (87)	23 (70)	<0.01
Follicular	28 (13)	10 (30)	
Tumor size			
T ₁ : ≤10 mm	42 (20)	3 (9)	<0.001
T ₂ : 10–40 mm	124 (58)	11 (33)	
T ₃ : >40 mm	15 (7)	8 (24)	
T ₄ : extra thyroidal invasion	34 (16)	11 (33)	
Nodal metastases			
N ₀ : negative	182 (85)	18 (56)	< 0.001
N _{1a} : ipsilateral	24 (11)	11 (35)	
N _{1b} : bilateral	8 (4)	3 (9)	
Distant metastases			
M ₀ : negative	207 (95)	25 (81)	<0.01
M ₁ : positive	11 (5)	6 (19)	
Stage			
I	119 (56)	12 (40)	<0.05
II	63 (30)	9 (30)	
III	22 (10)	5 (17)	
IV	8 (4)	4 (13)	
Papillary carcinoma			
Inflammatory cell infiltration			
Absent	108 (56)	15 (65)	0.13
Present	85 (44)	8 (35)	
Subtype			
Common type	141 (73)	16 (70)	0.20
Occult	25 (13)	1 (4)	
Follicular variant	27 (14)	6 (26)	
Follicular carcinoma			
Invasion type			
Minimally invasive	10 (37)	3 (33)	0.84
Widely invasive	17 (63)	6 (67)	

For explanation of Stage I, II, III, IV see reference (3).

($P < 0.01$). Most of the tumors (54%) were 1–4 cm in diameter and the size of the tumor was also related to the higher risk of tumor recurrence ($P < 0.001$). Histology revealed 46 patients (19%) with nodal metastasis and 17 (7%) patients with distant metastasis. The presence of nodal and distant metastases was predictive of recurrent disease ($P < 0.001$ and $P < 0.01$ respectively). Higher stage of tumor was found to be associated with higher incidence of tumor recurrence ($P < 0.05$). The degree of inflammatory cell infiltration in tumor tissues did not associate with cancer recurrence.

The non-suppressed TSH one year after the primary operation was related to higher risk of tumor recurrence ($P < 0.05$) (Fig. 2). In univariate analysis, the strongest predictor for tumor recurrence was the elevated serum thyroglobulin ($> 3 \mu\text{g/l}$) (median 21.0, range 4–5684 $\mu\text{g/l}$) measured one year postoperatively (71% vs 14%, $P < 0.001$) (Fig. 3). Fifteen patients had elevated serum

thyroglobulin level at the same time as unsuppressed TSH. Eight (53%) of these patients had recurrence during the follow-up.

The RaI uptake after the first ablative dose was observed in the neck in 156 (90%) patients and also elsewhere in 24 patients (11%). The RaI uptake in the neck was not predictive of recurrence, but uptake outside the neck increased the risk significantly ($P = 0.01$).

Multivariate analyses In multivariate analysis ($n = 132$, including age, gender, treatment center, tumor type, stage, RaI uptake, TSH suppression and serum thyroglobulin), the strongest predictor for DTC recurrence was elevated serum thyroglobulin ($P < 0.001$) and serum TSH suppression ($P < 0.05$) (Table 2). The analysis was performed after exclusion of subjects with occult DTC and the conclusion regarding main risk factors remained identical (data

Figure 2 Frequencies of suppressed serum TSH one year after operation in patients with recurrence (REC+) ($n = 28$) and in those without recurrence (REC-) ($n = 185$) during the follow-up. P value is shown.

not shown). In order to further illustrate the impact of serum TSH and thyroglobulin on the risk of recurrence of DTC, Fig. 4 here shows that the risk ratio (adjusted for age, sex and stage) for elevated TSH alone (without elevated serum thyroglobulin) was 2.23 (95% confidence interval (CI) 0.36–13.90), for thyroglobulin alone (with suppressed serum TSH) 13.96 (95% CI 3.30–59.08) and for both conditions (elevated serum TSH and thyroglobulin) the risk ratio increased markedly (up to 45.11, 95% CI 7.54–269.84).

Mortality of patients with DTC

All-cause mortality as compared with the general population Twenty-four patients (9.4%) died within 5 years after the primary operation, and the actuarial mortality was 11.2% (28 deaths). The standardized mortality ratio was 1.2 (28 actuarial deaths/23 expected deaths; CI 0.71 to 2.02).

Predictors of disease-specific and all-cause mortality in patients with DTC Twenty-three patients (9.1%) died because of DTC during the follow-up. Type of tumor, age older than 60, TNM stage and serum thyroglobulin level were strongly associated with cancer-related and all-cause mortality. In addition, gender and TSH suppression were associated only with all-cause mortality, and post-ablative RaI uptake with cancer-related mortality (Table 3).

Figure 3 Frequencies of serum thyroglobulin levels one year after operation in patients with recurrence (REC+) ($n = 20$) and in those without recurrence (REC-) ($n = 143$) during the follow-up. P value is shown.

Discussion

The data provided by this study reveal that the serum thyroglobulin and serum TSH suppression are both statistically independent predictors of DTC recurrence, despite adjusting for age, gender, and pTNM stage. The older age (>60 years), the type of tumor, post ablative RaI uptake and pTNM stage were related to the increased incidence of DTC recurrence. In addition, our patients' characteristics are comparable to previous hospital or register based cohorts (7, 14). Moreover, female-to-male ratio, percentage of follicular tumors or frequency of recurrences in our study group do not differ markedly from previous studies (7, 15, 16).

The histology of the tumor is one of the major prognostic factors identified. The follicular type of tumor is reported to have a poorer prognosis than the papillary type (12, 17). However, after controlling for other factors, the type of tumor was not an independent predictor for DTC recurrence in the present study. Frequent occurrence of focal lymphocytic infiltration in the thyroid gland is documented in papillary thyroid carcinoma patients (18). Matsubayashi *et al.* (19) found that lymphocytic infiltration of the tumor was related to favorable prognosis in 95 Japanese patients, which contradicts the results of Kamma *et al.* (20). The mean age of our patients was closer to that of patients studied by Matsubayashi *et al.* (19), but we could not show any significant difference between TILs and tumor recurrence.

Table 2 Multivariate analysis for the recurrence of DTC.

	Hazards ratio	95% CI	P value
Age (≤ 60 yr = 0, > 60 yr = 1)	0.41	(0.07–2.24)	0.301
Gender (0 = man, 1 = woman)	2.24	(0.40–12.48)	0.357
Histology (0 = papillary, 1 = follicular)	0.75	(0.11–5.31)	0.771
Stage			
I	Reference		0.229
II	4.42	(0.96–20.43)	0.057
III	1.95	(0.26–14.87)	0.519
IV	6.12	(0.60–62.21)	0.126
Ral uptake (0 = no, 1 = yes)	0.89	(0.08–9.92)	0.922
TSH suppression (0 = no, 1 = yes)	3.46	(1.02–11.74)	0.046
Thyroglobulin level (≤ 3 $\mu\text{g/l}$ = no, > 3 $\mu\text{g/l}$ = yes)	12.28	(3.55–42.41)	<0.001
Treatment center (0 = Kuopio, 1 = others)	0.38	(0.08–1.73)	0.213

For explanation of Stage I, II, III, IV see reference (3).

Several studies (14, 15, 21) have shown that an unfavorable outcome is associated with age. We found that age over 60 years was related to a higher risk of tumor recurrence and cause-specific mortality, confirming previous findings (14, 17). The size of the tumor and the presence of distant metastases were strongly linked with the recurrence of tumor in the current study. These tumor characteristics have been confirmed to be related to unfavorable outcome in several reports (12, 14, 21). The pTNM staging system is considered to be a useful system for discriminating the high and low risk patients. Loh *et al.* (12) have performed a retrospective analysis of 700 patients with DTC. They found the pTNM staging system to be an independent prognostic factor for tumor recurrence. However, serum TSH suppression or serum thyroglobulin levels were not taken into account in their analysis. We found that the pTNM stage associated with poor outcome, although it was not an independent prognostic factor for relapse-free survival.

TSH increases adenylate cyclase activity and cAMP levels *in vitro*, thereby leading to thyroid cell growth (22). The clinical value of TSH suppression has been documented by a retrospective study by Pujol *et al.* (7).

They showed that the difference between constantly suppressed TSH and unsuppressed TSH increases the risk of recurrence significantly whatever the cut-off value (0.05–0.1 mU/l) used for defining TSH suppression. TSH suppression was also an independent predictor of relapse-free survival in their study. The minor draw-back of our study was that serum TSH was evaluated from one point only. However, the tolerability to suppressive therapy with l-T_4 is evident 1 year after treatment and only minor fluctuations (data not shown) were seen with a longer follow-up. This single point assessment, if anything, will lead to a conservative estimate of the true association. Thus, our study is in agreement with the findings of Pujol *et al.* (7) and further implies that the role of TSH suppression is statistically independent even after taking serum thyroglobulin into account. However, at present the optimal degree of TSH suppression by ultrasensitive TSH measurement is not known (23). We assume that one of the reasons for unsuppressed TSH in the present study was poor tolerance of suppressive l-T_4 doses, which can cause thyrotoxic symptoms such as weight loss and heart arrhythmias (1).

Figure 4 Risk ratios for the recurrence of DTC (Cox regression analysis) for non-suppressed TSH only, elevated thyroglobulin only and for both occurring simultaneously.

Table 3 Risk factors for all-cause mortality (ACM) and cancer-related mortality (CRM). The number of patients with percentage in parentheses are given.

	ACM			CRM		
	+(n = 40)	– (n = 214)	P value	+(n = 23)	– (n = 231)	P value
Histology						
Papillary	24 (60)	192 (90)	<0.001	13 (56)	203 (88)	<0.001
Follicular	16 (40)	22 (10)		10 (44)	28 (12)	
Age						
≤60 years	8 (20)	182 (15)	<0.001	3 (13)	187 (81)	<0.001
>60 years	32 (80)	32 (85)		20 (87)	44 (19)	
Sex						
Male	12 (30)	32 (15)	<0.05	6 (26)	38 (17)	0.2
Female	28 (70)	182 (85)		17 (74)	193 (83)	
Stage						
I	2 (6)	129 (62)	<0.001	0 (0)	131 (58)	<0.001
II	11 (33)	61 (29)		3 (18)	69 (31)	
III	11 (33)	16 (8)		5 (29)	22 (10)	
IV	9 (27)	3 (1)		9 (53)	3 (1)	
TSH suppression						
Suppressed	13 (46)	123 (66)	<0.05	6 (43)	130 (65)	0.09
Unsuppressed	15 (54)	62 (34)		8 (57)	69 (35)	
Thyroglobulin						
≤3 µg/l	3 (23)	125 (83)	<0.001	1 (11)	127 (83)	<0.001
>3 µg/l	10 (77)	25 (17)		8 (89)	27 (17)	
RaI uptake						
No uptake	4 (12)	10 (6)	0.07	1 (5)	13 (7)	<0.001
Uptake in the neck	20 (59)	136 (85)		8 (42)	148 (85)	
Distal uptake	10 (29)	14 (9)		10 (53)	14 (8)	

For explanation of Stage I, II, III, IV see reference (3).

Serum thyroglobulin has been proven to be a sensitive tumor marker in DTC after RaI ablation therapy (24). In our analyses, thyroglobulin values measured during L-T₄ treatment were used. The sensitivity of thyroglobulin measurement decreases but specificity increases compared with values measured when off L-T₄ treatment (25). When on L-T₄ therapy, a consistent level of 2 µg/l during the follow-up period has proved to be highly indicative of the cancer-free state, although only a minority of patients meets this criteria (9). Our cut-off value for serum thyroglobulin level was 3 µg/l, which has also been used in some other studies (7, 25, 26). In our study, one year after operation, 35 patients (21%) had thyroglobulin over 3 µg/l, of whom 15 (43%) had recurrent disease. In multivariate analysis, the elevated serum thyroglobulin proved to be the most powerful independent predictor for tumor recurrence.

Theoretically, patients with DTC are exposed not only to the risk of recurrence of the cancer, but also to subclinical hyperthyroidism, which may have adverse effects on bone and cardiac and circulatory systems, as well as multiple high dose RaI therapies which may potentially cause increased mortality (1, 27). To assess the possible excess mortality associated with DTC, we used as a control group the general population of eastern Finland. In the current study the mortality rate of DTC patients was only 1.2 times that of the general population. Our follow-up time for survival analysis was five years which is a rather limited time to assess DTC

mortality. Deaths caused by DTC are reported to occur for 40 years after primary treatment (16). Our age-adjusted survival analysis shows that mortality caused by DTC tended to increase slightly for 4 years after primary treatment decreasing subsequently almost to the same level as the mortality of the general population. In the present study a slight increase in mortality seems to be caused by DTC itself rather than by treatment procedures.

In conclusion, both serum thyroglobulin level and serum TSH suppression one year after primary treatment are independent prognostic factors for DTC recurrence. Our results confirm the role of age, type of tumor, distal RaI uptake and TNM stage of primary tumor as predictors of DTC recurrence. Finally, DTC does not cause a statistically significant increase in all-cause mortality as compared with the general population.

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