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MAIN ARTICLE

Elevated serum thyroglobulin levels at the time of ablative radioactive iodine therapy indicate a worse prognosis in thyroid cancer: an Australian retrospective cohort study

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Abstract

Background: Serum thyroglobulin is used as a surrogate marker for well-differentiated thyroid carcinoma recurrence. This study investigates whether thyroglobulin measured at the time of ablative radioactive iodine therapy predicts disease-free survival.

Methods: A retrospective review was conducted of patients with well-differentiated thyroid carcinoma presenting from 1989 to 2010 at the Royal Prince Alfred Hospital, New South Wales, Australia. Disease-free survival of patients with a significantly elevated stimulated thyroglobulin level (27.5 µg/l or higher) at the time of ablative radioactive iodine therapy was compared to that of patients without a significantly elevated thyroglobulin level using univariate analysis.

Results: Patients with a thyroglobulin level of 27.5 µg/l or higher had an increased relative risk of disease recurrence of 4.50 (95 per cent confidence interval = 1.35–15.04). If lateral neck dissection was required at the time of surgery, patients also had an increased relative risk of macroscopic disease recurrence of 4.94 (95 per cent confidence interval = 1.47–16.55).

Conclusion: An elevated thyroglobulin level of 27.5 µg/l or higher at the time of ablative radioactive iodine therapy is a prognostic indicator for macroscopic disease recurrence in well-differentiated thyroid carcinoma.

Key words: Thyroglobulin; Prognosis; Thyroid Neoplasms; Iodine; Biochemical Tumor Markers; Disease-Free Survival

Introduction

Although thyroid carcinoma is a rare disease, its incidence in Australia is increasing exponentially.[1] Well-differentiated thyroid carcinoma generally has an excellent prognosis, but it is difficult to predict which patients will have a poorer outcome.[2] The American Joint Committee on Cancer tumour–node–metastasis staging system for thyroid carcinoma is widely used to attempt to stratify a patient's prognosis and guide treatment. Such staging systems have, however, only been shown to explain less than one-third of the variation in prognosis between patients, struggling particularly to explain prognostic differences in low-risk patients.[3,4]

Other features known to correlate with a poorer prognosis in well-differentiated thyroid carcinoma are advanced age, male sex, extra-thyroidal extension and certain histological subtypes.[5] There has been an increase in research on the utility of molecular markers for prognostication.

Thyroglobulin is a pro-hormone involved in the synthesis of thyroxine (T4) and tri-iodothyronine (T3). It is produced both by normal thyroid tissue and in well-differentiated thyroid carcinoma. A detectable thyroglobulin level following total thyroidectomy and ablative radioactive iodine therapy of remnant thyroid tissue indicates likely persistent or recurrent carcinoma.

Thyroglobulin measurement is used to monitor well-differentiated thyroid carcinoma; however, its role as a prognostic tool is more controversial.[6,7] The American Thyroid Association recommends that thyroglobulin be used to monitor for disease recurrence, but there is no mention of its utility as a prognostic tool.[8]

Thyroglobulin levels may be elevated after total thyroidectomy as a result of residual thyroid tissue or

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carcinoma. It had been assumed that ablation of remnant normal thyroid tissue is required before positive thyroglobulin levels can be interpreted, though there is now evidence to the contrary.[9] Other studies in the literature have shown that the pre-ablative thyroglobulin level correlates with a poorer prognosis.[7,10] Additionally, the higher the cut-off point where an elevated thyroglobulin is considered significant, the more specific it is for future detection of macroscopic residual or recurrent disease.[11] It is important to be aware that patients with anti-thyroglobulin antibodies may have a false negative serum result for thyroglobulin levels.[12,13]

To date, there are still no studies to confirm the prognostic value of thyroglobulin levels among an Australian patient population with well-differentiated thyroid carcinoma. There is also a lack of consensus regarding the utility of pre-ablative serum thyroglobulin levels measured at the time of radioactive iodine therapy. This study aimed to assess the prognostic value of thyroglobulin measurement at the time of radioactive iodine therapy. The study was performed on patients presenting with well-differentiated thyroid carcinoma at a single metropolitan Australian teaching hospital.

Materials and methods

Ethics approval was obtained for this study from the Human Research Ethics Committee for the Royal Prince Alfred Hospital at the Sydney Local Health Network.

A retrospective cohort study of all patients presenting with well-differentiated thyroid carcinoma at the Royal Prince Alfred Hospital in Sydney was conducted. All patients with head and neck carcinomas presenting to surgeons in the unit have been entered prospectively into a head and neck database since 1987. Patients are added to this database at the time of their histopathological diagnosis, with relevant data updated at subsequent follow-up appointments. Patients with well-differentiated thyroid carcinoma that had been treated with total thyroidectomy and radioactive iodine therapy from 1989 to 2010 were studied. A comprehensive chart review of the patients was performed to ensure database accuracy. This involved reviewing clinician letters, operation notes, imaging findings (including details of radioactive iodine therapy), histopathology reports and results of blood tests performed at follow-up appointments.

All patients with well-differentiated thyroid carcinoma who underwent total thyroidectomy and ablative radioactive iodine therapy were reviewed. After the chart review, only patients with serum thyroglobulin levels measured at the time of radioactive iodine therapy were selected for study inclusion. Patients with positive thyroglobulin antibodies, insufficient follow up, evidence of metastatic disease on radioactive iodine therapy or missing data were excluded from the analysis (Table I). Disease recurrence was defined as histopathologically confirmed recurrent carcinoma occurring at least 12 months after radioactive iodine therapy.

TABLE I
INCLUSION CRITERIA

Thyroglobulin tested at time of radioactive iodine therapy
Thyroglobulin antibodies tested & negative at time of radioactive iodine therapy
No evidence of metastatic or residual disease on imaging at time of radioactive iodine therapy
Minimum follow up of 1 year
Confirmed histopathology diagnosis of well-differentiated thyroid carcinoma

Univariate analysis was used to assess whether an elevated thyroglobulin level at the time of radioactive iodine therapy was able to predict disease-free survival. Patients with a thyroglobulin level of 27.5 μg/l or higher were compared to those with a thyroglobulin level of less than 27.5 μg/l. This cut-off value was chosen as it has previously been shown to be optimal for prognostication.[11] The other clinical variables that were analysed separately were gender, age and lateral neck dissection performed at the time of thyroidectomy. The histological variables analysed were extrathyroidal extension, vascular invasion, higher tumour (T) stage and multifocal carcinomas.

Results

A total of 246 patients were identified in the head and neck database as having well-differentiated thyroid carcinoma treated with total thyroidectomy and radioactive iodine therapy. Of the patients excluded, 13 had positive thyroglobulin antibodies, 98 had incomplete data (including no thyroglobulin measurement at the time of radioactive iodine therapy), 8 had early recurrence (occurring within less than 12 months) and 27 had metastatic disease at the time of radioactive iodine therapy. This left 100 patients included in the study, with a mean age of 48.4 ± 15.6 years (Table II). Sixty-eight patients were female (68 per cent). The majority of patients had papillary carcinoma (70 per cent). Mean follow-up time was 3.0 years (range, 1.0–20.5 years). The median thyroglobulin level was 3.1 μg/l (ranging from undetectable to 244.0 μg/l). There were only 11 disease recurrences in the follow-up period; this meant that multivariate disease-free survival analysis was not possible.

Sixteen patients had a thyroglobulin level of 27.5 μg/l or higher and 84 patients had a thyroglobulin level of less than 27.5 μg/l at the time of radioactive iodine therapy. The relative risk of developing disease recurrence with a thyroglobulin level of 27.5 μg/l or higher was 4.50 (95 per cent confidence interval (CI) = 1.35–15.04). Having a thyroglobulin level of 27.5 μg/l or higher at the time of radioactive iodine therapy had a positive predictive value of 31.3 per cent (95 per cent CI = 11.0–58.7 per cent) for macroscopic disease recurrence. This had a statistically significant effect on disease-free survival ($p = 0.008$) as demonstrated by Kaplan–Meier curves (Figure 1). The only other tested variable (Table III) to show a

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TABLE II
PATIENTS' CHARACTERISTICS

Characteristic	Cases (*n* (%))
Sex	
– Male	32 (32)
– Female	68 (68)
Histological subtype	
– Papillary	70 (70)
– Follicular	29 (29)
– Tall cell	1 (1)
Histology	
– Vascular invasion	13 (13)
– Multifocal	37 (37)
Age (continuous); years	
– ≥45	58 (58)
– <45	42 (42)
TNM	
– T_1	45 (45)
– T_2	34 (34)
– T_3	13 (13)
– T_4	8 (8)
– N_1	31 (31)
– M_1	0 (0)
Neck dissection	
– Lateral neck	14 (14)
– Central only or no neck dissection	86 (86)

TNM = tumour–node–metastasis

TABLE III
UNIVARIATE ANALYSIS OF PROGNOSTIC VARIABLES

Variable	Odds ratio (95% CI)	*p*
Thyroglobulin ≥ 27.5 µg/l	4.50 (1.35–15.04)	0.008
Lateral neck dissection (± central)	4.94 (1.47–16.55)	0.005
Female gender	1.18 (0.30–4.59)	0.818
Age ≥ 45 years	1.58 (0.42–5.94)	0.491
T_1 or T_2	1.54 (0.33–7.22)	0.588
Extra-thyroidal extension	2.31 (0.68–7.9)	0.166
Vascular invasion	0	0.216
Multifocal tumour	0.93 (0.28–3.14)	0.909

CI = confidence interval; T = tumour

significant difference was whether lateral neck dissection was performed at the time of surgery, with a relative risk of disease recurrence of 4.94 (95 per cent CI = 1.47–16.55).

In the 11 patients with disease recurrence, the median thyroglobulin level was 19.0 µg/l (range, 3.1–244.0 µg/l). No residual or recurrent disease was detected during follow up in the 49 patients with a thyroglobulin level that was either 3 µg/l or lower or undetectable.

Discussion

This study shows an increased relative risk of developing recurrent thyroid carcinoma if serum thyroglobulin levels are 27.5 µg/l or higher at the time of radioactive iodine therapy. These results are comparable to those reported in the literature. For instance, thyroglobulin levels of 2 µg/l or higher at the time of remnant ablation has been shown to have a positive predictive value for disease recurrence of 23.1 per cent,[14] whilst in this study it was 31.3 per cent at levels of 27.5 µg/l or higher.

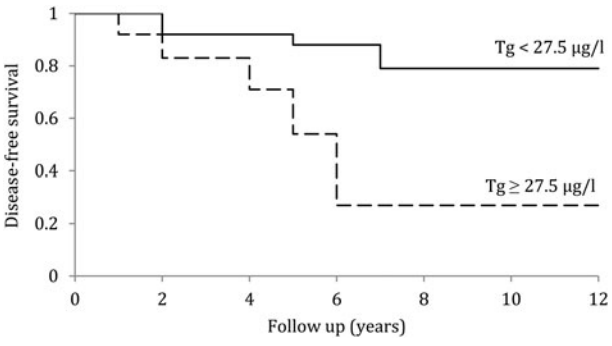

FIG. 1
Kaplan–Meier disease-free survival curves comparing thyroglobulin positive and negative patients. Tg = thyroglobulin

The low number of recurrences during the follow-up period was a major study limitation. This was not unexpected given that well-differentiated thyroid carcinoma may recur several years after initial treatment. Research of well-differentiated thyroid carcinoma is often limited by the relatively long follow-up period required, generally excellent prognosis and low recurrence rates. There are multiple commercial thyroglobulin assays available; given the retrospective nature of this study over three decades, there was heterogeneity regarding the assays used to measure serum thyroglobulin. The lowest detection limit of the thyroglobulin assays utilised in this study varied from 0.1 to 1 µg/l.

Prescribing a cut-off value to predict when an elevated thyroglobulin level reaches clinical prognostic significance is difficult. It has been reported in the literature that an elevated thyroglobulin level at the time of radioactive iodine therapy has a positive predictive value for residual disease.[9,11] Other factors that may affect the thyroglobulin level at the time of radioactive iodine therapy include residual normal thyroid tissue, positive thyroglobulin antibodies and thyroid carcinoma. Given the heterogeneity of thyroglobulin assays and individual institutions' treatment protocols, a single cut-off value is less useful than an overall assessment of a patient's risk of recurrence.

- **Prognosis in well-differentiated thyroid carcinoma is excellent**
- **Thyroglobulin is used as a surrogate marker for disease recurrence, but its role in prognosis is not established**
- **This retrospective cohort study showed a difference in macroscopic disease recurrence in patients with thyroglobulin levels of 27.5 µg/l or higher at the time of ablative radioactive iodine therapy**
- **Elevated thyroglobulin at the time of radioactive iodine therapy should be considered when stratifying risk of disease recurrence**

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The results from this study support the statement that an elevated thyroglobulin level at the time of radioactive iodine therapy cannot be dismissed as non-significant. These patients may represent a group with persistent microscopic metastases. The terms 'scan-negative, thyroglobulin positive' or 'thyroglobulin positive, no evidence of disease' have been used to make the distinction between this group of patients and those with complete remission.[14–16] Low-risk patients with persistent positive thyroglobulin should receive regular surveillance to detect any subsequent macroscopic disease. However, low-risk patients who have negative thyroglobulin at the time of remnant ablation may avoid radioactive iodine therapy and its associated risks.[17,18] Indeed, in a New Caledonian population of patients with well-differentiated thyroid carcinoma, a thyroglobulin level of 20 μg/l or higher at the time of radioactive iodine therapy was present in eight patients with no detectable macroscopic disease, and all eight patients developed macroscopic metastatic disease on subsequent scans.[19]

Conclusion

A significant difference in prognosis was evident in patients with an elevated thyroglobulin level of 27.5 μg/l or higher at the time of ablative radioactive iodine therapy. Further investigation may clarify whether increased surveillance of low-risk patients with a detectable elevation in serum thyroglobulin has an effect on patient outcomes.

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