Postablation Tg concentration predicts disease recurrence in patients with low-risk differentiated thyroid cancer

Pelttari H, Valimaki M, Loyttyniemi E, Schalin-Jantti C. Post-ablative serum thyroglobulin is an independent predictor of recurrence in low-risk differentiated thyroid carcinoma: a 16-yr follow-up study. Eur J Endocrinol 2010;163:757-63. EJE-10-0553 [pii];10.1530/EJE-10-0553 [doi]

SUMMARY

BACKGROUND

The incidence of differentiated thyroid cancer has been increasing steadily for the past several decades, especially the incidence of papillary thyroid cancer (PTC) and, to a lesser extent, follicular thyroid cancer (FTC). The prognoses of PTC and FTC are particularly favorable, with 5- and 10-year survival rates of 90% and 95%, respectively, when patients are properly treated. The tumor–node–metastasis (TNM) staging system is the most widely used means of predicting survival. Still, recurrence rates for these tumors are relatively high, ranging from 35% to 50%, depending on the patient's age and tumor characteristics, which are not reliably identified by the TNM staging system. The retrospective study by Pelttari et al. is aimed at identifying the variables that predict tumor recurrence.

PATIENTS AND METHODS

The study subjects are individuals treated at the Helsinki University Central Hospital (HUCH) district over a 15-year period from January 1, 1983, through December 31, 1997. The study subjects were selected from the clinical records of 710 patients (571 women and 139 men), 495 (70%) of whom comprised the final study group of patients with TNM stage I or II PTC or FTC and were considered free of disease and in complete remission after surgery and thyroid remnant ablation (RRA). Follow-up data for this group were identified from the clinical records of the patients.

Follow-up

To verify the current patient status, a questionnaire concerning the recent follow-up of thyroid cancer was also sent to patients whose documents revealed no recent entries. An 11.6-year follow-up of the cohort was described previously. The current study assessed recurrences and cancer-specific mortality in the cohort of 495 patients after a median follow-up of 16 years, in which prognostic factors for disease recurrence were evaluated, including patient age, sex, primary tumor size, tumor infiltration at the time of initial surgery, and lymph-node metastases and postablation serum thyroglobulin (Tg) concentrations.

Thyroglobulin

Postoperative Tg concentrations were obtained 4 to 6 weeks after surgery, and post-RRA Tg measurements were performed in combination with a ^{131}I whole-body scan 4 to 6 months after the first RRA, which was performed under thyrotropin (TSH) stimulation induced by levothyroxine (L-T_4) withdrawal. Serum Tg was measured by an ^{131}I kit with a detection limit of 3 µg/L until 1989, after which Tg was measured by an immunometric assay with a detection level of 1 µg/L. Anti-Tg antibody (TgAb) was evaluated with a ≥80% recovery.

Study Variables

Disease recurrence was defined as new evidence of tumor after a 12-month period without verification of disease, which included all tumor sites reported and confirmed either by imaging studies or surgery. Disease-free outcome was defined as an undetectable Tg, with no clinical evidence of disease and no radiologic evidence of tumor. Clinical and histologic variables included in the study were tumor size, the presence of lymph-node metastases, locoregional infiltration of tumor, and completeness of surgery as estimated by the surgeon performing the procedure. Local tumor infiltration was defined as macroscopic adherence of tumor into the adjoining muscle or soft tissue or microscopic invasion of adjoining tissue. The biologic variables were Tg concentrations measured after surgery and after RRA and measurement of TgAb.

RESULTS

Patient Features and Initial Therapy

The study cohort comprised 415 women (83.8%) and 80 men (16.2%), with a mean age at diagnosis of 40.6 years. A total of 461 tumors were PTCs (93.1%) and 31 were FTCs (6.1%). Mean tumor size was 1.8 cm (range, 0.3 to 6.0); FTCs were larger than PTCs (mean, 3.0 vs. 1.6 cm; P = 0.16). Tumor was classified in 13 patients as TNM pT3 due to tumor size.

Initial Surgery

Primary surgery was total or near-total thyroidectomy in 448 (95%) of the 472 patients. Locoregional lymph-node metastases were found in 59 of the 472 patients (12.5%). Although systematic lymph-node dissection was not performed, patients with lymph-node metastases detected before or during surgery had lymph-node surgery. At initial surgery, locoregional tumor infiltration was detected in 37 patients (7.4%) and surgery was complete in all but 3 of 472 (0.6%) patients.

Thyroid Remnant Ablation

Of the 472 patients, 414 (87.7%) had RRA followed by repeat ^{131}I therapy as necessary. The median RRA ^{131}I activity administered was 3.7 GBq (100mCi; range, 2.2 to 25.9 [100 to 700 mCi]).

Criteria for Classifying Patients as Free of Disease

Patients were considered to be free of disease if the neck ultrasound (US) examination was negative, serum Tg was unmeasurable after L-T_4 withdrawal, and there was no uptake on a diagnostic whole-body scan. One patient had distant metastases at the time of diagnosis and was classified as TNM stage II on the basis of her young age. All patients had follow-up of at least 10 years (range, 10 to 24) with a median follow-up of 16 years.

Tumor Recurrence

A total of 51 of the 472 patients (10.8%) had a tumor recurrence. Five of the 51 (10%) had FTC and 46 (90%) had PTC. A total of 43 (84.3%) of the detected recurrences were identified within 10 years from the time of initial diagnosis and therapy. The majority of recurrences (94.1%) were cervical-lymph-node metastases, 54.9% of which were detected with neck ultrasound and confirmed by tumor histology. A smaller number of recurrences (31.4%) were confirmed with new ^{131}I uptake on a diagnostic whole-body scan. Two patients required more therapeutic ^{131}I because of a significant increase in serum Tg on L-T_4 therapy without radiologic findings of tumor. This was confirmed by a posttreatment ^{131}I whole-body scan (RxWBS). In one case each, recurrence was detected on the basis of an increase serum Tg concentration on L-T_4 therapy, combined with palpable lymph nodes and suspicious ultrasound findings, and the appearance of TgAb was indicated by a declining Tg recovery. Thyroid cancer was the cause of death in one patient who had FTC that metastasized at a young age.

Postsurgical Thyroglobulin and Tumor Recurrence

Postsurgical serum Tg levels were found in 468 (94.5%) of the 472 patients. After primary near-total or total thyroidectomy, 250 of 472 patients (52.9%) had postsurgical serum Tg levels greater than the detection limit. A total of 34 of the 51 patients with disease recurrence had a postoperative Tg above the detection limit, as compared with 225 (54%) of the 420 patients without tumor recurrence (P = 0.251). There was no correlation between postoperative Tg and serum TSH levels. Median postoperative TSH concentration (76 and 73 mIU/L) did not differ among patients with and without recurrence, respectively (P = 0.39).

Serum Thyroglobulin levels after Thyroid Remnant Ablation and Disease Recurrence (Figure 1)

RRA was performed in 413 of the 472 patients (97%) who had total or near-total thyroidectomy (49 patients with recurrence and 364 without recurrence) (Figure 1). Post-RRA Tg levels were found in 401 patients (96.6%) and were detectable after the first RRA in 51 patients (12.7%; median, 10.0 µg/L [range, 1 to 500]). All patients with detectable Tg after RRA were treated with repeated amounts of ^{131}I until Tg became undetectable on RxWBS. The amount of ^{131}I administered ranged from 2.2 to 25.9 GBq (60 to 700 mCi). After RRA, Tg was detectable in 36.4% of patients with subsequent recurrence as compared with 9.8% without recurrence (P<0.0001). Median TSH concentrations of corresponding thyroid post-RRA were 44 and 36 mIU/L, respectively (P = 0.021). Of the 79 patients with undetectable serum Tg after RRA, a low recovery (<80%) was an indication of positive serum TgAb levels, and 9 of these patients had tumor recurrence.

Multivariate Logistic-Regression Analysis (Figure 2)

The independent predictors of disease recurrence were elevated postablation serum Tg concentrations, lymph-node metastases, and local tumor invasion (Figure 2).

CONCLUSION

Postablation Tg concentration is a robust predictor of disease recurrence in patients with differentiated thyroid cancer.

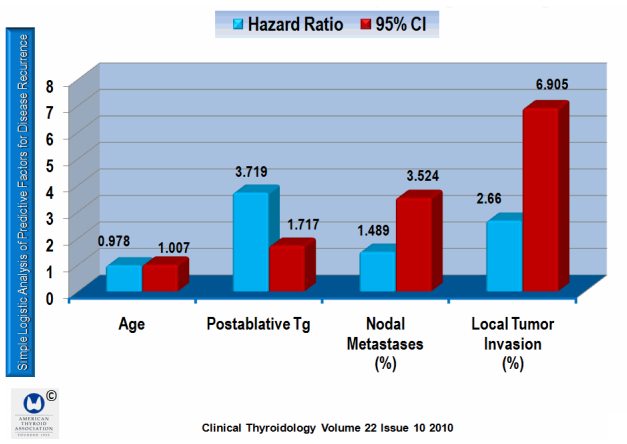

Figure 2. Figure 2 shows the independent variables, hazard ratio and 95% confidence intervals that identified the predictors of recurrence according to multivariate logistic regression analysis. CI = confidence interval.

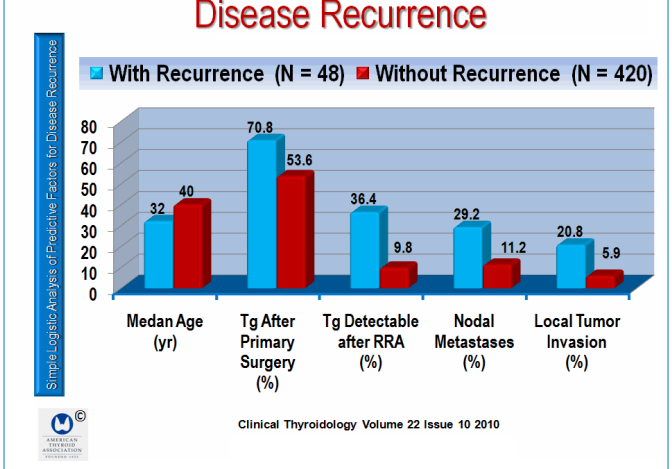

Figure 1. This figure shows the simple logistic analysis of predictive factors for disease recurrence. RRA = thyroid remnant ablation; Tg = thyroglobulin. This figure is derived from data in Table 2 of Pelttari et al.

COMMENTARY

The authors of this study initially reported the first set of data concerning the follow-up of this study cohort in 2008 (1) after a 5-year follow-up, during which the recurrence rate was 2.4%. However, after the current median follow-up of 11.6 years, the same study cohort of 495 patients at low-risk for thyroid cancer mortality found that one patient died of thyroid cancer and 51 patients had a nearly 11% (10.8%) rate of tumor recurrence. The authors point out that the recurrence rate has been steadily approaching that of the 14 to 15% reported after 30 years in a follow-up study from the Mayo Clinic (2). Pelttari et al. suggest that it is thus important to identify recurrence in this group of patients who may have recurrences many years after initial therapy. The authors found that tumor invasion at the time of initial surgery and detectable serum Tg concentrations after RRA (off L-T_4) were the only independent predictors of a late recurrence. This is particularly important, as the TNM classification fails to identify patients at risk for tumor recurrence.

Only a few studies have addressed this problem, showing that serum Tg levels at the time of RRA just after thyroidectomy are useful in predicting clinical recurrence in patients with low-risk tumors (3-5).

These studies underscore the importance of recurrence in patients with low-risk tumors, especially those with PTC and FTC and the utility of TSH-stimulated serum Tg levels within a short time after initial surgery has been performed.

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