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# Thyroglobulin

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**Volume 3**

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## Thyroid Cancer – Diagnosis, Therapy & Follow Up

Diagn Cytopathol. 2007 Jul;35(7):439-43.

### **Fine needle aspiration cytology of unsuspected metastatic hurthle cell carcinoma of the thyroid and its pitfalls: A report of two cases.**

**Lallu S, Naran S, Bethwaite P.**

Department of Cytology, Anatomic Pathology, Capital and Coast Wellington Hospital, Wellington, New Zealand.

We discuss two cases of unsuspected metastatic thyroid carcinoma of Hurthle cell type, presenting as subcutaneous masses in the occipital scalp and supra-acetabular region of the right ilium; clinically suspected to be a lipoma and a vascular tumour, respectively. These two cases were initially investigated by fine-needle aspiration cytology. In case 1, a definitive diagnosis of metastatic Hurthle cell carcinoma was made based on cell block preparation and positive immunohistochemical stains for thyroglobulin and thyroid transcription factor-1. Case 2 was reported as suggesting an oncocyctic process, metastatic Hurthle cell lesion. The filter preparations from both cases showed compact sheets and individual large polygonal cells with voluminous granular cytoplasm, eccentric nuclei with minimal atypia and bland chromatin. Scattered haemosiderin-laden macrophages and cystic debris were also identified in both cases. These cases are of interest as the bland cytologic features may lead to an erroneous benign diagnosis. Immunohistochemistry aids the definitive diagnosis of metastatic Hurthle cell carcinoma of thyroid especially when the presence of a previous thyroid lesion is not communicated to the laboratory. *Diagn. Cytopathol.* 2007;35:439-443. (c) 2007 Wiley-Liss, Inc.

*Eur J Endocrinol.* 2007 Jul;157(1):101-7.

### **Thyroglobulin detection in fine-needle aspirates of cervical lymph nodes: a technique for the diagnosis of metastatic differentiated thyroid cancer.**

**Cunha N, Rodrigues F, Curado F, Ilhéu O, Cruz C, Naidenov P, Rascão MJ, Ganho J, Gomes I, Pereira H, Real O, Figueiredo P, Campos B, Valido F.**

Serviço de Patologia Clínica, Instituto Português de Oncologia de Coimbra Francisco Gentil, EPE, Av. Bissaya Barreto, 98, 3000 Coimbra, Portugal.

**BACKGROUND:** Fine-needle aspiration cytology is frequently used for differential diagnosis of neck masses of unknown origin. Inconclusive and even false-negative results are not uncommon. **Aim:** To evaluate the utility of thyroglobulin (Tg) measurement in fine-needle aspirates (FNA-Tg) for detecting cervical lymph node (CLNs) metastases from differentiated thyroid carcinomas. **METHODS:** An ultrasound-guided fine-needle aspiration was done in 67 patients with 83 suspicious enlarged CLNs to obtain material for cytology and Tg measurement in the needle washout, using an immunometric chemiluminescent assay. Measurement of anti-Tg antibodies (FNA-TgAb) was also carried out in half of all the aspirates. Subjects were divided into two groups: one of 16 patients awaiting thyroidectomy and the other of 51 patients in follow-up after surgery. **RESULTS:** The first group of patients had positive FNA biopsy (FNAB-Tg) in 14 out of the 18 studied CLNs with a range of 3.2-43 352 ng/ml, while FNAB-cytology indicated metastasis in only 8 out of the 14 CLNs with positive histology. A total of 65 CLNs were studied in the follow-up group. Lymphadenectomy was performed in 23 patients and 28 aspirated CLNs were removed. Histology confirmed the diagnosis of metastasis suggested by FNAB-Tg in 20 CLNs and of reactive lymphadenitis in the remaining 8 CLNs. FNAB-cytology was positive in only 11 CLNs. Sensitivity of FNAB-Tg was not affected by the studied FNAB-TgAb. **CONCLUSIONS:** The FNAB-Tg achieved a sensitivity of 100% in both groups. FNAB-Tg is an easy and inexpensive technique which proved to increase the diagnostic of cytology in the early diagnosis of papillary carcinoma recurrence to CLN even in the presence of serum TgAb.

*Eur J Nucl Med Mol Imaging.* 2007 Jul;34(7):1012-7. Epub 2007 Jan 26

### **Iodine-123 as a diagnostic imaging agent in differentiated thyroid carcinoma: a comparison with iodine-131 post-treatment scanning and serum thyroglobulin measurement.**

**Urhan M, Dadparvar S, Mavi A, Houseni M, Chamroonrat W, Alavi A, Mandel SJ.**

Division of Nuclear Medicine, Department of Radiology, Department of Medicine University of Pennsylvania Medical Center, Philadelphia, PA, 19104, USA.

**PURPOSE:** Using( 123)I for diagnostic purposes avoids the risk of stunning for subsequent radioiodine treatment and affords an excellent image quality. In this study we assessed the role of( 123)I in comparison with( 131)I post-treatment imaging in patients with thyroid cancer. **METHODS:** We compared a total of 292( 123)I scans with their corresponding post-treatment( 131)I images. Patients received a therapeutic dose of( 131)I following diagnostic scanning with 50-111 MBq of( 123)I. All patients were in a hypothyroid state (>30 mIU/l) before radioiodine administration for either diagnostic or therapeutic purposes. **RESULTS:** In 228 out of 263 patients with a positive diagnostic scan,( 123)I whole-body scan findings were concordant with those of corresponding post-treatment( 131)I images (concordance rate 87%). However, there were 44 additional foci of abnormal uptake on post-treatment( 131)I scans in 22 discordant cases with no impact on therapeutic management of the patients. In 13 patients, there was at least one new site on post-treatment images that had been missed on pretreatment( 123)I images. Twenty-nine patients with a negative diagnostic scan were treated with( 131)I owing to a high serum thyroglobulin level (range 11.3-480 ng/ml). Radioiodine uptake sites were seen in eight post-treatment scans. In 21 pairs of whole-body scans, both the pre- and the post-treatment scan were negative (concordance rate 72.4%). **CONCLUSION:** (123)I scanning is comparable to high-dose( 131)I post-treatment imaging in thyroid carcinoma patients, and (123)I offers

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excellent image quality as a diagnostic agent. It avoids disadvantages such as stunning before treatment and delivery of a high radiation dose to patients.

J Nucl Med. 2007 Jul;48(7):1043-6. Epub 2007 Jun 15.

### **Comparison of Outcomes After 123I Versus 131I Preablation Imaging Before Radioiodine Ablation in Differentiated Thyroid Carcinoma.**

**Silberstein EB.**

Division of Nuclear Medicine, Department of Radiology, and Division of Hematology/Oncology, Department of Medicine, University of Cincinnati Medical Center, Cincinnati, Ohio.

Detection of residual tissue after thyroidectomy for papillary or follicular thyroid carcinoma may be performed using diagnostic imaging with either (123)I or (131)I. The former is often preferred to avoid "stunning"-defined as a reduction in uptake of the therapeutic dose of (131)I caused by some form of cell damage from the diagnostic dosage of the radionuclide. Stunning could potentially reduce the therapeutic efficacy of (131)I given to ablate a postthyroidectomy remnant. This study examines the outcomes of ablative (131)I therapy after diagnostic studies with either (123)I or (131)I to determine if the diagnostic dosages of these radionuclides used in our Thyroid Cancer Center reduce the efficacy of (131)I given for remnant ablation. **METHODS:** Fifty patients with nonmetastatic papillary or follicular carcinoma of the thyroid received total thyroidectomy; this was followed by thyroid hormone withdrawal to achieve a serum thyroid-stimulating hormone level in excess of 30 mIU/mL. They were divided prospectively into 2 groups. Group 1 had diagnostic imaging with 14.8 MBq of (123)I followed by thyroid remnant ablation with 3.7 GBq of (131)I. Group 2 had empiric ablation with the same 3.7-GBq (131)I dosage, but the preceding diagnostic scan was performed with 74 MBq of (131)I. Comparisons of equivalence of the 2 population samples and of the postablation outcomes were evaluated by chi(2) analysis. Successful ablation required a negative follow-up thyroid scan 6-8 mo after ablation and also an undetectable serum thyroglobulin level in the absence of antithyroglobulin antibodies. **RESULTS:** There was no significant difference between the 2 groups demographically, in tumor burden or stage, or in the postthyroidectomy ablation rate (group 1, 81%; group 2, 74%;  $P > 0.05$ ). **CONCLUSION:** If thyroid remnant stunning occurs due to 74 MBq (131)I used as a diagnostic agent before (131)I ablation, it has no significant clinical correlate, as it yields the same ablation rate as that which occurs after 14.8 MBq of (123)I used for imaging.

Nat Clin Pract Endocrinol Metab. 2007 Jul;3(7):510-1. Epub 2007 May 22.

### **Can serum thyroglobulin levels predict patient outcome after treatment of differentiated thyroid carcinoma?**

**Sherman SI.**

Department of Endocrine Neoplasia and Hormonal Disorders, University of Texas MD Anderson Cancer Center, Houston, TX 77030-4008, USA. sisherma@mdanderson.org

Surg Oncol. 2007 Jun 26

### **Operative strategy for follicular thyroid cancer in risk groups stratified by pTNM staging.**

**Lin JD, Chao TC, Chen ST, Huang YY, Liou MJ, Hsueh C.**

Division of Endocrinology and Metabolism, Department of Internal Medicine, Chang Gung Memorial Hospital, Chang Gung University, Taiwan, ROC.

This study determined cancer survival rates and follow-up status at different pTNM stages to stratify risk groups in follicular thyroid carcinoma. Two hundred and fourteen follicular thyroid cancer patients (167 females, 47 males) who underwent surgery and followed-up treatment at a single medical center were enrolled in this retrospective study. Tumors were staged by UICC-TNM criteria (6th edition). Low risk for follicular thyroid cancer was defined as pT1N0M0. (Moderate-risk group) was defined as all other patients in pTNM stage I, and high risk as patients in stages II-IV. After mean follow-up of 9.6±0.3 years, 1.6% (2/120), 21.9% (7/32), 5.6% (1/18) and 52.3% (23/44) of patients in pTNM stages I-IV, respectively, died of thyroid cancer. Of 214 follicular thyroid cancer patients, 35 (16.4%), 85 (39.7%) and 94 (43.9%) were defined as low-, moderate- and high-risk groups at the time of surgery. None of the low-risk patients died, and all achieved disease-free status. In the moderate- and high-risk groups, 2.4% (2/85) and 27.7% (26/94) died of thyroid cancer. The moderate- and high-risk groups underwent near-total thyroidectomy and (131)I therapies, and 15 of 107 (14.9%) died of thyroid cancer while 18 (16.8%) had persistent disease at the end of the study period. Multiple regression analysis demonstrated that tumor size, radioactive iodide therapy and post-operative thyroglobulin level significantly differ between the mortality and survival groups. In conclusion, the low-risk follicular thyroid cancer group as defined by pTNM staging had excellent prognosis. Total thyroidectomy and post-operative radioactive iodide therapy are mandatory in moderate- and high-risk groups. Over one-fourth of the follicular thyroid cancer patients in the high-risk group died of thyroid cancer despite aggressive treatment.

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Clin Endocrinol (Oxf). 2007 Jun 11

### **Preoperative undetectable serum thyroglobulin in differentiated thyroid carcinoma: incidence, causes and management strategy.**

**Giovanella L, Ceriani L, Ghelfo A, Maffioli M, Keller F.**

Nuclear Medicine and Thyroid Unit, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland.

**Background** In recent years serum thyroglobulin (Tg) measurement during thyroxine (T4) treatment and/or after stimulation by endogenous TSH or recombinant human TSH (rhTSH) has eclipsed other diagnostic procedures in managing patients with differentiated thyroid cancer (DTC). However, preoperative undetectable Tg was reported in up to 12% of patients affected by DTC and recurrences of DTC with no increase in serum Tg have also been described. Clearly, a negative Tg measurement may falsely reassure both the patient and the clinician in these cases. **Aim** We retrospectively evaluated the incidence of undetectable or reduced preoperative serum Tg in a group of 436 patients affected by DTC. Additionally, we evaluated the role of Tg retesting by two different immunoassays in patients with low Tg at first measurement. **Methods** We retrospectively selected 17 patients with undetectable (i.e. less than functional sensitivity of assay method) or reduced Tg (i.e. between functional sensitivity and minimum normal value) among 436 patients with histologically proved DTC. The remaining 419 patients were used as control cases. Frozen sera from all patients were retested by two different Tg immunoassays. **Results** Globally, 17 out of 436 (3.8%) patients showed undetectable (n = 5, 1.1%) or reduced (n = 12, 2.7%) preoperative Tg. The Tg level was above the minimum normal value in 3 and 4 out of 5, and 8 and 9 out of 12 of these patients, respectively, when two different immunoassays were employed. On the other hand, undetectable or reduced Tg levels were found in 3.0%-5.1% of control cases when different immunoassays were used. **Conclusions** Regardless of the method employed, 3.0-5.1% of patients with DTC showed undetectable or reduced preoperative Tg. This fact must be recognized, as Tg cannot be used as a benchmark for DTC follow-up in these cases. However, Tg retesting with different immunoassays seems to be useful in ruling out these pitfalls in a large majority of patients, and also indicates the most effective assay to be employed in these cases.

Clin Nucl Med. 2007 Jun;32(6):440-4.

### **Papillary thyroid carcinoma: 35-year outcome and prognostic factors in 1858 patients.**

**Pelizzo MR, Boschin IM, Toniato A, Piotto A, Pagetta C, Gross MD, Al-Nahhas A, Rubello D.**

Department of Surgical Sciences, University of Padova, Italy.

**BACKGROUND AND AIM:** Papillary thyroid carcinoma (PTC) is universally regarded as a curable malignancy with a favorable prognosis. However, a minority of patients may present, or subsequently develop, locoregional and distant metastases that may adversely affect survival. The value of the various staging methods is complicated by different approaches to diagnostic, therapeutic and follow-up strategies. We aimed at assessing the prognostic factors and survival rate in a large cohort of patients treated and followed up in the same center. **MATERIALS AND METHODS:** A total of 1858 patients with PTC operated on by the same surgeon, and followed in the same center over a period of 35 years, were included. Total thyroidectomy was performed in the majority of patients after I-131 diagnostic scans and thyroglobulin assays. When the latter 2 were positive, therapy with I-131 was given. Follow-up was performed periodically and further therapy doses were administered when necessary. All patients were maintained on life-long thyroxine. **RESULTS:** Ninety-three patients (5%) developed evidence of locoregional or distant metastases after an average follow-up period of 7.9 years (range 1.53-30.5 years). Univariate analysis showed all variables (except for gender) to be significantly correlated with disease recurrence and survival. Multivariate analysis showed 4 variables to be significant and independent prognostic factors: patient age at first treatment, extent of disease, extent of surgery, and the presence of I-131 positive metastases. **DISCUSSION AND CONCLUSION:** Our data agree with other scoring systems in that patient age at first treatment and the extent of disease are significant and independent prognostic factors. However, and at variance with other methods, we found that the extent of primary surgery and the presence of I-131 positive or negative metastases have similar prognostic significance. In high risk patients, total thyroidectomy and lymphadenectomy followed by I-131 treatment and TSH-suppressive hormonal therapy are recommended.

J Nucl Med. 2007 Jun;48(6):879-88.

### **Total thyroidectomy and adjuvant radioiodine treatment independently decrease locoregional recurrence risk in childhood and adolescent differentiated thyroid cancer.**

**Handkiewicz-Junak D, Wloch J, Roskosz J, Krajewska J, Kropinska A, Pomorski L, Kukulska A, Prokurat A, Wygoda Z, Jarzab B.**

Department of Nuclear Medicine and Endocrine Oncology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland.

We sought to assess whether extensive surgical treatment, postsurgical radioiodine therapy, or both decrease the risk of locoregional recurrence (LR) after curative primary treatment in children and adolescents diagnosed with differentiated thyroid cancer (DTC) at age  $\leq 18$  y. **METHODS:** To determine the incidence of and identify predictive factors for thyroid bed recurrence (TBR) or lymph node recurrence (NR), we performed a chart review and retrospective multivariate Cox regression analysis on 235 patients with DTC diagnosed at age  $\leq 18$  y and managed with curative intent at our tertiary referral center from 1973 to 2002; 40 of these patients had distant metastases at diagnosis. We also determined overall and recurrence-free survival and generated curves for these variables using Kaplan-Meier and Cox univariate analysis. **RESULTS:** During a median follow-up of 82 mo (range, 5-402 mo), no DTC-related deaths occurred, 203 (86%) children remained recurrence-free,

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and 32 (14%) children had LR, including TBR in 9 (28% of LR), NR in 20 (63% of LR), and both in 3 (9% of LR). Among patients treated with radical intent and showing no distant metastases, the most recent thyroglobulin level was <1 ng/mL in all but 4% of cases. The median time from the first surgery to LR was 37 mo (range, 9-280 mo). In multivariate analysis, significant risk factors for TBR were less than total thyroidectomy and lack of postsurgical radioiodine treatment (respective risk increases of 9.5 [P = 0.04] and 11 times [P = 0.03]). For NR, classic papillary histology, incomplete primary lymph node management (i.e., lack of modified lymphadenectomy of affected lymph nodes or lack of confirmation of disease-free nodes by intraoperative staging), and absence of adjuvant radioiodine therapy were independent significant predictive factors that increased the recurrence risk by 1.9 (P = 0.02), 3.3 (P = 0.02), and 3.2 (P = 0.02) times, respectively. Age or sex did not correlate with LR risk. **CONCLUSION:** In DTC patients <or=18 y of age, extensive initial therapy-consisting of total thyroidectomy combined with modified lymphadenectomy performed in case of lymph node metastases and followed by radioiodine therapy--is associated with a substantial decrease of DTC LR risk.

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Q J Nucl Med Mol Imaging, 2007 Jun 1

### **Fluorodeoxyglucose positron emission tomography/computed tomography in patients with differentiated thyroid cancer and elevated thyroglobulin after total thyroidectomy and (131)I ablation.**

**Salvatore B, Paone G, Klain M, Storto G, Nicolai E, D'Amico D, Della Morte AM, Pace L, Salvatore M.**

Fondazione SDN, Naples, Italy.

**AIM:** The aim of this study was to evaluate the role of 18F FDG-PET, differentiated thyroid cancer and thyroglobulin in patients with differentiated thyroid carcinoma (DTC) treated with therapeutic (131)I because of elevated thyroglobulin (Tg) levels during follow-up. The results of FDG-PET/CT were compared with post-therapy (131)I whole-body scan ((131)I-t-WBS) and Tg at short-term follow-up. **METHODS:** Forty-five patients with DTC underwent a new therapeutic (131)I administration based upon Tg values >1.5 ng/mL. All patients underwent (131)I-t-WBS 5-7 days after (131)I therapy. A few days before (131)I administration, a FDG-PET/CT scan was performed in all patients. FDG-PET/CT was considered positive (PET+) when at least one abnormal focus of FDG uptake was found; likewise, (131)I-t-WBS was considered positive (WBS(+)) when at least one abnormal focus of uptake was found. Assessment of short-term response to radioiodine was performed by measuring Tg values. **RESULTS:** FDG-PET/CT was positive in 32 patients, 23 of which had a positive (131)I-t-WBS, and negative in 13, 8 of which had a negative (131)I-t-WBS. Overall agreement was 69%. Tg values were significantly higher in FDG-PET/CT positive (502+/-1 027 ng/mL) than in FDG-PET/CT negative patients (57+/-94 ng/mL). A significant difference emerged between (131)I-t-WBS positive (561+/-1 086 ng/mL) and (131)I-t-WBS negative (65+/-120 ng/mL) findings. In these 45 patients, Tg normalized in 36%, was reduced by at least 50% in 24%, and remained unchanged in the remaining 40%. Overall, at short-term follow-up, Tg values normalized in 77% of the 13 patients with negative FDG-PET/CT and in 19% of the 32 patients with positive FDG-PET/CT. **CONCLUSION:** FDG-PET/CT is a powerful and useful tool for assessing patients with DTC. It can provide additional information in those patients with high Tg at follow-up and eligible for (131)I therapy. A negative FDG-PET/CT could also represent a prognostic tool combined with serum Tg testing at short term follow-up.

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Thyroid, 2007 Jun;17(6):543-7

### **Impact of pregnancy on serum thyroglobulin and detection of recurrent disease shortly after delivery in thyroid cancer survivors.**

**Leboeuf R, Emerick LE, Martorella AJ, Tuttle RM.**

Endocrinology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York.

**Objective:** Since pregnancy can stimulate thyroid growth, we examined the effect of pregnancy on recurrence and serum thyroglobulin (Tg) shortly after delivery in thyroid cancer survivors. **Design:** Retrospective analysis of thyroid cancer survivors who became pregnant after completing initial therapy. **Main outcome:** 36 women (age 34 +/- 4 years) who became pregnant a median of 4.3 years after initial therapy for differentiated thyroid cancer were evaluated a median of 4 months after delivery. As part of their initial therapy, 23 women underwent total thyroidectomy with radioactive iodine remnant ablation (RRA), six had total thyroidectomy without RRA, and seven underwent lobectomy without RRA. Following total thyroidectomy with or without RRA, no evidence of recurrence was detected in the early postpartum period in women with negative prepregnancy ultrasound and either undetectable or low suppressed Tg levels. However, disease progression was documented as enlargement of a previously stable cervical lymph node in one of three patients and a marked rise in serum Tg without evidence of structural disease progression in a patient with previously stable distant metastases. When analyzed based on initial therapy, the mean suppressed Tg after delivery was not significantly different than the prepartum value. However, eight women had Tg values after delivery more than 20% higher than the baseline Tg before pregnancy (three with known disease, five with no clinical evidence of disease). **Conclusion:** In thyroid cancer survivors, pregnancy is unlikely to cause clinically significant disease recurrence in the early postpartum period when structural imaging studies confirm the absence of residual disease but can occasionally be associated with progression of known metastatic lesions. Even though the serum Tg did not differ significantly before and after pregnancy, the long-term implications of minor rise in serum Tg seen in some individual patients cannot be assessed without longer studies in larger cohorts.

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Am J Surg Pathol. 2007 May;31(5):729-36

### **Histologic variants of papillary and follicular carcinomas associated with anaplastic spindle and giant cell carcinomas of the thyroid: an analysis of rhabdoid and thyroglobulin inclusions.**

**Albores-Saavedra J, Hernandez M, Sanchez-Sosa S, Simpson K, Angeles A, Henson DE.**

Department of Pathology of Louisiana State University Health Sciences Center, Shreveport, LA 71130, USA.  
jalbor@lsuhsc.edu

We describe the histologic variants of papillary and follicular carcinomas associated with 109 spindle and giant cell carcinomas (SGCC) of the thyroid and determine the incidence of rhabdoid and thyroglobulin inclusions in these tumors. In addition, we searched for rhabdoid and thyroglobulin inclusions in 120 papillary carcinomas (PC) (all 15 variants included), 23 differentiated follicular carcinomas (DFC), (6 with insular pattern), 6 poorly differentiated follicular carcinomas (PDFC) and 34 follicular adenomas (FA). The following differentiated thyroid carcinomas coexisted with SGCC: 51 (46.8%) PC, (34 conventional type, 14 tall cell variant and 3 follicular variant), 6 (5.5%) DFC, 1 follicular carcinoma with insular pattern (0.9%), and 3 oncocytic carcinomas (2.8%). Eleven SGCC (10%) and 2 (33%) PDFC showed rhabdoid features, but lacked thyroglobulin inclusions. Thyroglobulin inclusions were found in 10 FA (29%), 8 (17%) follicular variants of PC and in 7 (30.4%) DFC. There were no rhabdoid inclusions in any of these differentiated thyroid tumors. Our findings support the hypothesis that most SGCC result from dedifferentiation or anaplastic transformation although the mechanisms that underlie this transformation remain unknown. The finding that only 1 (0.9%) SGCC was associated with follicular carcinoma with insular pattern contradicts the opinion that this tumor occupies an intermediate position between differentiated and anaplastic carcinomas. Rhabdoid features are markers of PDFC and SGCC while thyroglobulin inclusions are markers of FA and differentiated thyroid carcinomas with follicular phenotype.

J Pediatr Surg. 2007 May;42(5):853-6.

### **Cumulative doses of adjunct 131I treatment depend on location of residual thyroid tissue after total thyroidectomy in differentiated thyroid cancer.**

**Saint-Vil D, Emran MA, Lambert R, Alos N, Turpin S, Huot C.**

Division of Pediatric General Surgery, CHU Sainte Justine, Montreal, Quebec, Canada H3T 1C5. dickens\_saint-vil@sss.gouv.qc.ca

**PURPOSE:** The aim of this study was to review the outcome after adjunct postoperative 131I therapy in patients with differentiated thyroid carcinoma (DTC) treated with total thyroidectomy (excluding medullary thyroid carcinoma). **METHODS:** Retrospective chart review: Management protocol is total thyroidectomy with cervical node sampling, 131I whole-body scan 3 weeks postoperatively to document residual thyroid tissue or metastatic lesions. Adjunct treatment consists of one or more 131I (100-200 mCi/1.73 m<sup>2</sup>). Patients are considered disease free if 2 consecutive 131I whole-body scan are negative with undetectable thyroglobulin level. **RESULTS:** Twenty-one patients, 14 females and 7 males, with a mean age of 13.6 years were treated. Whole-body scan postoperatively revealed uptake in the thyroid bed (TB) in 10 patients, in cervical lymph nodes (CLN) in 9 patients, and in CLN and lungs in 2 patients. Patients with residual uptake in TB received a significantly lesser dose of 131I (mean, 122 +/- 53 mCi) than those with metastatic CLN (357 +/- 182 mCi) ( $P < .004$ ) (t test) or lung mets (523.5 mCi). With a mean follow-up of 7.8 years (range, 1-16 years), overall survival is 100% but disease-free survival is 100%, 66%, and 0% respectively for patients with residual disease in TB, CLN, and lungs. **CONCLUSION:** Patient with residual thyroid tissue in the TB required a significantly lesser number of treatments and doses of 131I compared to patients with cervical node metastases with a 100% disease-free survival. The best management of immediate postoperative residual cervical nodes (surgical excision vs 131I) remains to be defined. The efficacy of 131I therapy in patients with lung metastases remains controversial with complete remission unlikely.

Cancer Biother Radiopharm. 2007 Apr;22(2):289-95

### **Reinduction of Cell Differentiation and (131)I Uptake in a Poorly Differentiated Thyroid Tumor in Response to the Reverse Transcriptase (RT) Inhibitor Nevirapine.**

**Modoni S, Landriscina M, Fabiano A, Fersini A, Urbano N, Ambrosi A, Cignarelli M.**

Department of Nuclear Medicine, Centro di Riferimento Oncologico della Basilicata, Rionero in Vulture (PZ), Italy.

Our recent findings have shown that the reverse transcriptase (RT) inhibitors, nevirapine and efavirenz, used for 10 years in human immunodeficiency virus (HIV) disease, act as cytostatic and differentiating agents by modulating gene expression in several human tumor cell models. In dedifferentiated thyroid cancer, they reestablish thyroid-stimulating hormone (TSH) signaling, Na/I symporter (NIS), thyroglobulin peroxidase (TPO) expression, and even radioiodine uptake (RIU). In this paper, we describe the case of a 76-year-old woman who was affected by thyroid papillary carcinoma and who underwent a total thyroidectomy and a debulking of the right laterocervical region for lymph-node metastases, vessel infiltration, and neoplastic thrombosis of the internal jugular vein, followed by 3 radioiodine treatments. At restaging, a computed tomography scan revealed that distant metastases were mostly not taking up the radioiodine at the (131)I whole-body scan (WBS). An analysis of tumor cells obtained by fine-needle aspiration biopsy of a right laterocervical lymph-node revealed cell anisokaryosis, nuclear pleomorphism, and scanty colloid, as well as the undetectable expression of thyroglobulin and NIS proteins. After starting a nevirapine treatment (NT), higher thyroglobulin levels were observed and some metastases exhibited a significant increase in radioiodine uptake, which led us to again treat the patient with (131)I. Five (5) months later, the (131)I-WBS

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revealed the disappearance of RIU in some metastases and its significant reduction in other lesions, with a parallel drop in serum thyroglobulin. No new metastatic lesion was revealed by rh-TSH-stimulated <sup>131</sup>IWBS and (18)F-fluorodeoxyglucose positron emission tomography scan. Cells obtained from the right laterocervical lymph-node 2 months after NT exhibited a reduced nuclear pleomorphism, an increase in colloid production, and a significant upregulation of thyroglobulin and NIS protein expression. This first in vivo molecular and morphologic evidence of cell differentiation in human cancer and low toxicity of nevirapine strongly encourage its use in dedifferentiated thyroid cancer treatment.

Clin Chim Acta. 2007 Apr;379(1-2):101-4.

### **The clinical utility of Lens culinaris agglutinin-reactive thyroglobulin ratio in serum for distinguishing benign from malignant conditions of the thyroid.**

**Shimizu K, Nakamura K, Kobatake S, Satomura S, Maruyama M, Kameko F, Tajiri J, Kato R.**

Diagnosics Research Laboratories, Wako Pure Chemical Industries, Ltd., Japan. shimizu.kayoko@wako-chem.co.jp

**BACKGROUND:** Traditionally, the follow-up of differentiated thyroid carcinoma consists of periodic withdrawal from L-T4-suppressive therapy to allow performance of a highly sensitive serum Tg measurement to detect recurrences. We investigated Lens culinaris agglutinin-reactive thyroglobulin ratios in serum to evaluate in usefulness for detection of thyroid carcinoma. **METHODS:** The study was conducted on 93 serum sample from 23 healthy volunteers, 32 patients with benign thyroid tumor, 28 patients with thyroid carcinoma without metastasis, and 10 patients with thyroid carcinoma with lymph node metastasis. **RESULTS:** The Lens culinaris Agglutinin reactive thyroglobulin ratio in patients with thyroid carcinoma was significantly lower than in patients with benign thyroid tumor with serum thyroglobulin concentration >200 ng/ml. Among cases of thyroid carcinoma with lymph node metastasis, Lens culinaris Agglutinin reactive thyroglobulin ratios were significantly lower than in patient with thyroid carcinoma without metastasis and those with benign tumor regardless of serum thyroglobulin concentration. **CONCLUSION:** Measurement of Lens culinaris Agglutinin reactive thyroglobulin ratio in serum may be useful for distinguishing between thyroid carcinoma and benign thyroid tumor.

Nucl Med Commun. 2007 Apr;28(4):251-5.

### **A clinical study of all-trans-retinoid-induced differentiation therapy of advanced thyroid cancer.**

**Zhang Y, Jia S, Liu Y, Li B, Wang Z, Lu H, Zhu C.**

Department of Nuclear Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. zhangyifan1992@yahoo.com.cn

**OBJECTIVE:** To evaluate the changes in differentiation markers and therapeutic effects in all-trans-retinoic acid (ATRA)-treated patients with dedifferentiated thyroid cancer. **METHODS:** Between September 2001 and July 2004 eleven patients were analysed retrospectively. They had dedifferentiated thyroid cancers (DTC) (four follicular, five papillary, two oxyphilic) and were selected for treatment with ATRA (1.00+/-0.09 mg x kg x d) for 30 or 60 days. All patients had advanced stage tumours with prior operative and radioiodine treatment. Extensive tumour invasion, distant metastatic spread, and insufficient or non-existent uptake of radioiodine precluded conventional therapeutic options. Changes in I uptake, response of target lesions, and serum thyroglobulin (Tg) levels were measured and compared in these patients before and after ATRA therapy. **RESULTS:** In 11 patients with DTC, iodine uptake was increased in four and there was a partial response (PR) of target lesions in five patients as well as two patients with stable disease. Tg was assessed in eight patients, in whom two responders showed increased radioiodine uptake or no change and decreased Tg level, as well as PR after ATRA-induced differentiation therapy. **CONCLUSIONS:** ATRA has an effect on the differentiation status of DTC and deserves further investigation.

Cancer. 2007 Mar 15;109(6):1078-81.

### **Patients with differentiated thyroid cancer have a venous gradient in thyroglobulin levels.**

**Kebebew E, Reiff E.**

Department of Surgery, Mount Zion Medical Center, University of California-San Francisco, San Francisco, California 94143, USA. kebebewe@surgery.ucsf.edu

**BACKGROUND:** Although serum thyroglobulin (Tg) is an excellent marker for detecting recurrent or persistent differentiated thyroid cancer (DTC), it is unreliable in patients who have positive anti-Tg antibodies. Furthermore, a growing number of patients with DTC have elevated Tg levels but no detectable disease on radioiodine scanning or other imaging studies. The objective of this study was to determine whether a gradient in Tg protein level exists in patients with DTC. **METHODS:** Fifteen patients who underwent thyroidectomy and/or lymph node dissection for primary DTC (n = 10 patients) and recurrent or persistent DTC (n = 5 patients). A venipuncture was performed simultaneously from the internal jugular vein adjacent to the tumor and the ipsilateral antecubital vein. Venous Tg protein levels were measured by using a chemiluminescence assay. **RESULTS:** The average internal jugular-to-antecubital vein Tg protein ratio was 3.4:1.0 (median Tg ratio, 2.9:1; range, 0.8-62.2). Four patients had positive anti-Tg antibodies but still had a Tg gradient. Tg levels were significantly higher in the adjacent internal jugular vein than in the antecubital vein (P = .0019). The Tg ratio between the internal jugular and antecubital veins was significantly higher in patients with recurrent or persistent DTC than in patients with primary tumors (P = .0196). **CONCLUSIONS:** To the authors' knowledge, this is the first study to document a venous gradient in Tg protein levels in patients with DTC. The findings suggested that venous sampling for Tg may be used to localize DTC in some patients who have high or increasing serum Tg levels but negative radioiodine scans or imaging studies.

## Thyroid Cancer – Diagnosis, Therapy & Follow Up

Clin Endocrinol (Oxf). 2007 Mar;66(3):329-34

### **Should 'low-risk' thyroid cancer patients with residual thyroglobulin be re-treated with iodine 131?**

**Hindié E, Zanotti-Fregonara P, Duron F, Keller I, Bouchard P, Devaux JY.**

Department of Nuclear Medicine, Hôpital Saint-Antoine, Assistance Publique Hopitaux de Paris, Paris, France.  
elif.hindie@sls.aphp.fr

**OBJECTIVE:** The American consensus statement on patients with low-risk thyroid cancer, published in 2003, suggests repeat (131)I therapy if the thyroglobulin value is elevated at first follow-up. We evaluated this strategy in our practice. **METHODS:** Among 407 patients with thyroid cancer who had total thyroidectomy and (131)I ablation between January 2000 and December 2003, 12 patients with stage I thyroid cancer (any tumour (T), any node (N), metastasis (M)0 if < 45 years or T1, N0, M0 if > 45 years), were re-treated on the basis of their thyroglobulin level at first follow-up. Mean patient age was 32.8 years. None of them had a T4 tumour. Thyroglobulin levels after thyroid hormone withdrawal 'off-T4' ranged between 4.5 and 251 ng/ml (median 8). One to four courses of 3.7 GBq (131)I were given. **RESULTS:** Three patients had a negative (131)I therapy scan and an uneventful course. Two patients had slight residual uptake only in the thyroid bed and negative ultrasound examination. Four patients had isolated (131)I uptake in the mediastinal region. No abnormalities were found on complementary mediastinal imaging. This finding was interpreted as benign (131)I thymic uptake. The last three patients also had mediastinal thymic uptake associated with a slight thyroid bed uptake. One patient had a gradual increase in the thyroglobulin level, and underwent resection of nonfunctioning neck lymph nodes. Thyroglobulin levels declined in all other patients. **CONCLUSIONS:** No distant lesions were found in a group of young 'low-risk' thyroid cancer patients given empirical (131)I therapy for residual thyroglobulin. When blind (131)I therapy shows no uptake, or uptake limited to the thymus, (131)I therapy should not be repeated. The authors also briefly discuss the hypothesis that enhanced thymus might be a source of benign thyroglobulin secretion.

Eur J Nucl Med Mol Imaging. 2007 Mar;34(3):363-7.

### **Reproducibility of whole-body 131I scan and serum thyrotropin and stimulated thyroglobulin values in patients studied twice after injection of recombinant human thyrotropin.**

**Niederkoher RD, McDougall IR.**

Division of Nuclear Medicine, Stanford University Medical Center, 300 Pasteur Drive, Room H-0101, Stanford, CA 94305-5281, USA.

**PURPOSE:** Recombinant human TSH (rhTSH) is used to increase radioiodine uptake during imaging of thyroid cancer, obviating the need to render the patient hypothyroid. We assessed the reproducibility of radioiodine uptake, serum thyrotropin (TSH), and stimulated serum thyroglobulin (Tg) levels after rhTSH administration. **METHODS:** A retrospective review was performed of patients at Stanford who underwent whole-body (131)I scanning for surveillance of thyroid cancer twice after thyroidectomy and (131)I ablation, with rhTSH prior to each scan. Forty-eight hour radioiodine uptake, peak serum TSH, and stimulated serum Tg levels for each study were recorded. Paired t tests and correlation analysis were used to assess interexamination repeatability. **RESULTS:** Twenty-three patients underwent two scintiscans with rhTSH, for a total of 46 exams. There was no significant difference between percent uptake at 48 h in the paired exams ( $p=0.40$ ). Serum TSH level was measured in 45 of 46 exams; TSH exceeded 50 mIU/l in all cases, and there was no significant difference between paired TSH levels ( $p=0.93$ ). All patients had stimulated serum Tg levels measured, with no significant difference between paired Tg levels ( $p=0.40$ ); after excluding one patient whose Tg changed from 15.8 ng/ml to undetectable between scans without interval treatment, the p value rose to 0.95. There was a strong correlation among paired uptake values ( $r=0.85$ ,  $p<0.0001$ ), peak serum TSH ( $r=0.69$ ,  $p=0.0003$ ), and stimulated Tg levels ( $r=0.81$ ,  $p<0.0001$ ). No discordant scan interpretations were reported. **CONCLUSION:** Forty-eight hour radioiodine uptake, peak serum TSH, and stimulated serum Tg levels after administration of rhTSH are repeatable between studies, demonstrating reproducibility of diagnostic results without rendering patients hypothyroid.

J Endocrinol Invest. 2007 Mar;30(3):173-80

### **Possible reasons for different pattern disappearance of thyroglobulin and thyroid peroxidase autoantibodies in patients with differentiated thyroid carcinoma following total thyroidectomy and iodine-131 ablation.**

**Thomas D, Liakos V, Vassiliou E, Hatzimarkou F, Tsatsoulis A, Kaldrimides P.**

Department of Endocrinology, Diabetes and Metabolism, Metaxa Memorial Anticancer Research Hospital, Piraeus, Greece.  
thomasproge@endo.gr

The purpose of this study was to reveal some possible factors for the differences between the pattern of disappearance of thyroglobulin autoantibodies (anti-Tg) and thyroid peroxidase autoantibodies (anti-TPO) in patients with differentiated thyroid carcinoma following thyroidectomy and iodine-131 ablation. Patients with a history of follicular cell derived cancer (papillary, follicular, both papillary and follicular, Hürthle cell) and high pre-operative titers of anti-TPO and/or anti-Tg autoantibodies were retrospectively studied. Thyroglobulin (Tg) levels were measured using radio-immunometric assay (RIA). Anti-Tg and anti-TPO levels during the first 6 yr' follow-up were measured by passive agglutination, during the following 10 yr by ELISA method and during the last 2 yr by chemiluminescence assay. A statistically significant difference was observed between

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median time (72 months) of disappearance of anti-TPO and median time (39 months) of disappearance of anti-Tg in patients with complete ablation of thyroid tissue, following iodine-131 administration ( $p=0.0395$ , Logrank statistic=4.24, Kaplan-Meier method). A statistically significant difference was observed between median time (106 months) of disappearance of anti-TPO and median time (33 months) of disappearance of anti-Tg in patients >45 yr of age ( $p=0.034$ ) and between median time (111 months) of disappearance of anti-TPO and median time (41 months) of disappearance of anti-Tg in patients with tumor size <2 cm ( $p=0.0175$ ). We concluded that patients with differentiated thyroid carcinoma and pre-surgical elevated titers of both Tg and anti-TPO tend to become earlier anti-Tg seronegative. Although tumor size and age may influence the pattern of thyroid autoantibody reduction, the exact reasons for the different rhythm of autoantibodies decrease must further be evaluated.

Acta Otolaryngol Suppl. 2007 Feb;(557):55-7.

### **A rare case of hyperfunctioning papillary carcinoma of the thyroid gland.**

**Kim TS, Asato R, Akamizu T, Harada D, Nakashima Y, Higashi T, Yamamoto N, Tamura Y, Tamaki H, Hirano S, Tanaka S, Ito J.**

Department of Otolaryngology-Head and Neck Surgery, Graduate School of Medicine, Kyoto, Japan.

We report a rare case of hyperfunctioning papillary carcinoma of the thyroid. A 32-year-old man was referred to our hospital for the treatment of a painless mass in the left neck, which had been detected on routine physical check-up. Cervical ultrasonography and computed tomography showed a solid tumor with calcification in the left lobe of the thyroid gland. Serum examinations demonstrated hyperthyroidism with a high level of thyroglobulin. Fine needle aspiration biopsy revealed a cytological diagnosis of class II. Tc-99m scintigraphy showed a hot nodule in the left lobe, which implied that the tumor was a hyperfunctioning thyroid tumor. Left lobectomy of the thyroid gland was performed to treat the hyperfunctioning tumor. Postoperative pathological examinations revealed a follicular variant papillary carcinoma. Postoperative thyroid function became within the normal range. Although hyperfunctioning thyroid carcinomas are rare, it is important to correctly diagnose them and to perform appropriate surgical interventions.

Am J Clin Oncol. 2007 Feb;30(1):63-8

### **Predictive value of the preablation serum thyroglobulin level after thyroidectomy is combined with postablation 131I whole body scintigraphy for successful ablation in patients with differentiated thyroid carcinoma.**

**Lee HJ, Rha SY, Jo YS, Kim SM, Ku BJ, Shong M, Kim YK, Ro HK.**

Department of Internal Medicine, Chungnam National University Hospital, Daejeon, Korea.

**OBJECTIVES:** To investigate the clinical importance of the combined use of serum thyroglobulin (Tg) levels measured just before ablation (ablation-Tg) and postablation 131I whole body scintigraphy (WBS) patterns for predicting ablation success in patients with differentiated thyroid carcinoma who received total thyroidectomy and 131I ablation therapy. **METHODS:** We retrospectively studied the early clinical outcomes for 81 differentiated thyroid carcinoma patients treated with total thyroidectomy and high-dose 131I ablation therapy between June 2001 and July 2004. **RESULTS:** Ablation success was achieved in 42 (97.7%) of the 43 patients with uptake in the thyroid bed only and ablation-Tg levels less than 10 ng/mL, whereas successful ablation was achieved in 9 (75.0%) of the 12 patients with uptake in the thyroid bed only and ablation-Tg levels equal to or greater than 10 ng/mL ( $P = 0.029$ ). Among 15 patients with uptake including a lymph node and ablation-Tg levels less than 10 ng/mL, 14 patients (93.3%) showed ablation success, whereas successful ablation was achieved in only 2 (18.2%) of the 11 patients with uptake including a lymph node and ablation-Tg levels equal to or greater than 10 ng/mL ( $P < 0.001$ ). **CONCLUSIONS:** These data indicate that the combined use of serum Tg levels measured just before ablation and the 131I WBS patterns after ablation may be an early predictor of ablation success in patients with differentiated thyroid carcinoma who received total thyroidectomy and high-dose 131I ablation therapy.

Arq Bras Endocrinol Metabol. 2007 Feb;51(1):99-103

### **Management of low-risk patients with thyroid carcinoma and detectable thyroglobulin on T4 after thyroidectomy and ablation with iodine-131.**

**Rosário PW, Borges MA, Costa GB, Rezende LL, Padrão EL, Barroso AL, Purisch S.**

Endocrinology Service, Department of Thyroid, Santa Casa de Belo Horizonte, MG. pedrorosario@globo.com

**OBJECTIVE:** To evaluate the positive predictive value of detectable Tg during T4 therapy (Tg on T4) in patients with thyroid cancer after total thyroidectomy and remnant ablation, discussing the work-up in this situation and the empirical indication of 131I. **PATIENTS AND METHODS:** Initially, 234 low-risk patients [tumor < 5cm, completely resected, no extensive extrathyroid invasion (pT4)] submitted to total thyroidectomy and ablation with 131I (3.7-5.5 GBq) who presented no ectopic uptake on RxWBS were studied. Of these, 23 patients with detectable Tg on T4 (> 1ng/ml) during the first year after initial therapy were selected. **RESULTS:** Metastases were detected by neck US in 7 patients, by chest CT in 2 and by US and CT in 3. Four of five patients with lung metastases upon CT had a positive RxWBS. Eleven patients with negative US and CT received a new 131I dose (without DxWBS), and RxWBS showed ectopic uptake in 3 patients. Among the patients with negative RxWBS, 7 remained free of apparent disease and Tg was declining (5 with undetectable Tg on T4 at the end of the study). One patient presented an increase in Tg and FDG-PET was positive for lymph node and bone metastases. **CONCLUSIONS:** All patients with Tg on T4 > 5ng/ml presented apparent disease. In these cases, even when US and CT are negative, the administration of a therapeutic dose of 131I (without DxWBS) and FDG-PET are recommended. Among patients with

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detectable Tg on T4  $\leq$  5ng/ml and negative US and CT, only 12% presented ectopic uptake on RxWBS. These cases could be followed up by monitoring Tg on T4, and RxWBS and FDG-PET should only be performed if this marker does not decrease after 1-2 years.

Clin Endocrinol (Oxf). 2007 Jan;66(1):58-64

### **Serum thyroglobulin concentrations predict disease-free remission and death in differentiated thyroid carcinoma.**

**Heemstra KA, Liu YY, Stokkel M, Kievit J, Corssmit E, Pereira AM, Romijn JA, Smit JW.**

Department of Endocrinology and Metabolic Diseases, Leiden University Medical Centre, Leiden, The Netherlands.

**OBJECTIVE:** Most studies on the diagnostic value of serum thyroglobulin (Tg) concentrations in differentiated thyroid carcinoma (DTC) use fixed cut-off levels in heterogeneous groups of patients with respect to initial therapy and do not provide prognostic data. The objective was to investigate the prognostic values of serum Tg for disease-free remission and death, measured at fixed time-points after initial therapy using receiver operator characteristic (ROC) curve analyses. **DESIGN:** Single-centre observational study with 366 consecutive patients with DTC, who had all been treated according to the same protocol for initial therapy and follow-up. **METHODS:** Tg concentrations were measured at five fixed time-points after initial surgery. Tg cut-off values with the highest accuracy were calculated with ROC analyses. **RESULTS:** During the 8.3  $\pm$  4.6 years of follow-up, 84% of the patients were cured. Pre-ablative Tg levels were an independent prognostic indicator for disease-free remission (Tg cut-off value 27.5 microg/l, positive predictive value 98%). The highest diagnostic accuracies of serum Tg for tumour presence were found during TSH-stimulated Tg measurements, 6 months after initial therapy (Tg cut-off value 10 microg/l; sensitivity 100%, specificity 93%). DTC-related mortality was 14%. TSH-stimulated Tg levels before ablation and 6 months after initial therapy were independent prognostic indicators for death. **CONCLUSION:** Optimal institutional Tg cut-off levels for diagnosis and prognosis should be defined using ROC analyses for each condition and time-point. Tg measurements 6 months after initial therapy during TSH stimulation had an excellent diagnostic value. Tg levels are independent prognostic indicators for disease-free remission and death. Using this strategy, high-risk patient groups can be selected based on Tg levels, in addition to conventionally used prognostic indicators.

Q J Nucl Med Mol Imaging. 2006 Dec;50(4):348-54.

### **Value of thyroglobulin to 131I uptake ratio in selection of initial therapy dose of 131I in patients with differentiated thyroid carcinoma.**

**Zerva B, Koutsikos J, Palestidis C, Kounadi E, Gerali S.**

Department of Nuclear Medicine, Alexandra University Hospital, Athens, Greece.

**AIM:** To test the hypothesis that the ratio of thyroglobulin (Tg) to 131I uptake in the thyroid bed during the immediate post-thyroidectomy work-up could be used before first 131I treatment to detect patients with residual or metastatic thyroid cancer and justify the administration of a higher ablation dose in selected cases and a possibly better therapeutic effect. **METHODS:** We retrospectively studied 293 patients with differentiated thyroid carcinoma that received their first 131I treatment in our department. Patients with Tg  $>$ 100 ng/mL, 131I uptake  $>$ 10% and measurable Tg-specific autoantibodies, were excluded. According to the post-therapy total body scan (TBS), we divided them in 2 groups: group I, without metastases (negative TBS), and group II, with metastases (positive TBS). The ratio of Tg to 131I uptake measured before the first 131I treatment was calculated in both groups. **RESULTS:** A total of 248 patients were included in the study; 225 in group I and 23 in group II. Tg to 131I uptake ratio was significantly lower in group I (mean 2.17 ng/mL/%, range 0-36), than in group II (mean 32.7 ng/mL/%, range 2.14-220), ( $P < 0.01$ ). The sensitivity, specificity and accuracy (using a threshold ratio 7 ng/mL/% as normal) were all 95.6% for predicting a positive post-therapy TBS. **CONCLUSIONS:** The use of a threshold ratio 7 ng/mL/% as the upper limit of normal provides useful information with higher sensitivity and specificity in identifying patients with metastatic disease creating the possibility for the selective use of higher initial iodine therapy doses.

Surgery. 2006 Dec;140(6):1035-41; discussion 1041-2

### **Thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma in children.**

**Antonelli A, Miccoli P, Fallahi P, Ferrari SM, Grosso M, Boni G, Berti P.**

Department of Internal Medicine, Università di Pisa, Pisa, Italy.

Surgery. 2006 Dec;140(6):1000-5; discussion 1005-7

### **Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer.**

**Sywak M, Cornford L, Roach P, Stalberg P, Sidhu S, Delbridge L.**

Endocrine Surgical Unit, University of Sydney, Sydney, Australia. marksywak@nebsc.com.au

**BACKGROUND:** Lymphadenectomy in clinically node-negative papillary thyroid cancer (PTC) is controversial. The aim of this study is to determine whether routine ipsilateral level VI lymphadenectomy (LNDVI) has advantages over total thyroidectomy (TT) alone. **METHODS:** A retrospective cohort study was performed. Patients undergoing surgery for clinically node-negative PTC  $>$ 1 cm were included. Group A had TT and LNDVI. Group B had TT alone. The number of radioiodine

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treatments and postablative stimulated serum thyroglobulin (TG) levels were compared. RESULTS: From 1995 to 2005, 447 patients with clinically node-negative PTC underwent surgery. Group A (n = 56) had TT and LNDVI. Group B (n = 391) had TT alone. Tumor size was equivalent (group A, 20 mm; group B, 23 mm; P = .14) as were MACIS (metastasis, age, completeness of resection, invasion, and size) scores (group A, 4.70; confidence interval, 4.23-5.17; group B, 4.73; confidence interval, 4.4-5.05). Serum postablative TG levels were lower in group A (0.4 microg/L) compared with group B (9.3 microg/L), P = .02. More patients had undetectable TG levels in group A (72%) than in group B (43%) (P < .001). Long-term complications rates were the same. CONCLUSIONS: In PTC the addition of routine LNDVI results in lower postablation levels of TG and higher rates of athyroglobulinemia when compared with TT alone.

Surgery. 2006 Dec;140(6):960-6; discussion 966-7

### **A phase II trial of rosiglitazone in patients with thyroglobulin-positive and radioiodine-negative differentiated thyroid cancer.**

**Kebebew E, Peng M, Reiff E, Treseler P, Woeber KA, Clark OH, Greenspan FS, Lindsay S, Duh QY, Morita E.**

Department of Surgery, University of California, San Francisco, CA 94143, USA. kebebew@surgery.ucsf.edu

BACKGROUND: Rosiglitazone is a peroxisome proliferator-activated receptor gamma (PPARgamma) agonist that has been shown to induce differentiation, cell cycle arrest, and apoptosis in a variety of human cancers including thyroid cancer. METHODS: Ten patients with differentiated thyroid cancer were enrolled in an open-label, phase II trial of oral rosiglitazone treatment (4 mg daily for 1 week, then 8 mg daily for 7 weeks). The levels of PPARgamma receptor mRNA and protein expression were determined in the patient's neoplasm. RESULTS: Of 10 patients, 4 had positive radioiodine scans after rosiglitazone therapy with uptake in the neck in 3 patients and in the pelvis in 1 patient. After treatment, the serum thyroglobulin level decreased in 2 patients, increased in 5 patients, and was stable in 3 patients. No patient developed clinically important toxicity associated with rosiglitazone treatment. We found no relationship in the level of PPARgamma mRNA and protein expression in patients who had radioiodine uptake compared with those who did not. CONCLUSIONS: Our findings suggest that rosiglitazone treatment may induce radioiodine uptake in some patients with thyroglobulin-positive and radioiodine-negative differentiated thyroid cancer. We found no relationship between the expression level of the PPARgamma mRNA and protein in the neoplasm and radioiodine uptake status after rosiglitazone therapy, questioning the potential pathway of effect.

Thyroid. 2006 Dec;16(12):1273-8.

### **Sequential follow-up of serum thyroglobulin and whole body scan in thyroid cancer patients without initial metastasis.**

**Huang SH, Wang PW, Huang YE, Chou FF, Liu RT, Tung SC, Chen JF, Kuo MC, Hsieh JR, Hsieh HH.**

Department of Nuclear Medicine, Chang Gung Memorial Hospital-Ksohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan.

OBJECTIVE: To investigate the usefulness of whole body scan (WBS) and serum thyroglobulin (Tg) measurement after thyroxine withdrawal during sequential follow-ups in patients with differentiated thyroid cancer (DTC). Design: Two hundred and sixty-five consecutive DTC patients were enrolled. They were previously treated with near-total thyroidectomy and I-131 remnant ablation, without initial metastases or Tg antibodies. All had the first follow-up WBS and serum Tg measurement 6-12 months after initial treatment, and 165 patients received the second follow-up without further therapy. Positive/negative predictive values (PPV/NPV) were calculated by the outcome of patients being followed up for more than 8 years (mean +/-SD: 133 +/-26 months). Results: Serum Tg levels while the patients were off thyroxine therapy decreased spontaneously in 39.3% of the cases without further therapy. The NPV of the first follow-up serum Tg level was excellent: <2 microg/L and <0.5 microg/L were 95.1% and 98.2%, respectively. However, the PPV of the first follow-up serum Tg level was low: >10 microg/L and 2-10 microg/L were 40% and 9.6%, respectively. The trend of Tg levels was more informative; the PPV was 62.5% in cases with an increase of serum Tg of >10 microg/L and 16.6% with an increase of <5 microg/L. However, decreasing Tg levels may associate with rapid deterioration of disease, in which cases decrease of Tg indicated dedifferentiation of the tumor. The diagnostic WBS showed the same picture in 91.5% of the patients. Only one patient (0.6%) turned from negative study to positive during the follow-up. In the meanwhile his serum Tg levels increased from 0.56 to 13.6 microg/L. Conclusion: It is most informative when both the trend and the levels of Tg during sequential follow-up are considered. The diagnostic WBS may be performed for selected patients with indication based on Tg levels to localize the disease.

Nucl Med Commun. 2006 Nov;27(11):873-6.

### **Clinical importance of anti-thyroglobulin auto-antibodies in patients with differentiated thyroid carcinoma: comparison with 99mTc-MIBI scans.**

**Küçük ON, Aras G, Kulak HA, Ibiş E.**

Department of Nuclear Medicine, Ankara University Medical School, Ankara, Turkey. okucuk@medicine.ankara.edu.tr

AIMS: (1) To investigate whether elevated serum anti-thyroglobulin antibody (ATG) reflects the recurrence of cancer in patients with differentiated thyroid carcinoma (DTC) in whom thyroglobulin was undetectable after radioiodine ablation. (2) To assess the sensitivity of disease detection for (99m)Tc-MIBI whole-body scans (WBSs) in these patients and investigate the correlation between MIBI WBS results and high serum ATG levels. MATERIALS AND METHODS: In this retrospective study, we evaluated 14 patients (13 women and 1 man; mean age 44 +/- 19 years) with DTC who underwent total or near-total

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thyroidectomy followed by an ablative dose of I at various time intervals. According to histopathological findings, 10 patients (71.4%) who were diagnosed as having papillary carcinoma and four patients (28.6%) as having follicular cell carcinoma, had high serum ATG concentrations ( $> 40 \text{ IU x ml}^{-1}$ ); range, 62-2000  $\text{IU x ml}^{-1}$ ), but low serum thyroglobulin concentrations ( $< 1.6 \text{ ng x ml}$ ). Post-therapeutic and diagnostic (131I) WBSs and (99m)Tc-MIBI WBSs were performed. Scans were visually evaluated for detecting recurrence. If necessary, bone scans, chest X-rays, computerized tomography, ultrasonography and histopathological evaluation were performed. RESULTS: Recurrent and/or persistent disease was found in 12 of the patients. This was confirmed pathologically in four patients and by using other imaging methods in eight (bone scans, computerized tomography, ultrasonography). The sensitivity and specificity of disease detection for MIBI WBSs was 66.7% and 100%, respectively. For (131I) WBSs, the sensitivity of disease detection was 55.6%. Among these 12 patients, 10 responded to treatment (three underwent surgery, seven received radioiodine therapy, and two had surgery + radioiodine therapy). ATG levels decreased in eight of the 10 patients, but remained persistently elevated in two despite treatment. CONCLUSIONS: (1) Persistently elevated ATG levels appear to serve as a useful marker for recurrent or persistent DTC in patients with undetectable serum thyroglobulin levels. Thus, the routine measurement of ATG antibody in such patients is of great value. (2) In these patients, (99m)Tc-MIBI has a relatively high sensitivity in the diagnosis of a recurrence of thyroid cancer or metastases. So, in patients with elevated ATG but undetectable serum thyroglobulin levels, (99m)Tc-MIBI can be used to determine whether there is a recurrence of DTC or metastases.

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Thyroid. 2006 Nov;16(11):1145-9.

### **Positive predictive value of detectable stimulated tg during the first year after therapy of thyroid cancer and the value of comparison with Tg-ablation and Tg measured after 24 months.**

**Valadão MM, Rosário PW, Borges MA, Costa GB, Rezende LL, Padrão EL, Barroso AL, Purisch S.**

Department of Thyroid, Endocrinology Service, Santa Casa de Belo Horizonte, Minas Gerais, Brazil.

This study evaluated the positive predictive value (PPV) of detectable stimulated thyroglobulin during the first year after treatment of thyroid carcinoma (Tg-1) and the value of comparison with Tg-ablation and measured after 24 months (Tg-2). Forty-two consecutive patients undergoing total thyroidectomy and ablation with detectable Tg-1 ( $>1 \text{ ng/mL}$ ) were selected. The patients had well-differentiated tumors, which were completely resected, and there was no ectopic uptake on whole body scan after 3.7-5.5GBq I(131). Imaging methods during follow-up revealed metastases in 10 patients (24%) (15% if Tg-1  $\leq 10 \text{ ng/mL}$  and 55% if Tg-1  $>10 \text{ ng/mL}$ ). Tg-ablation (cutoff of 10  $\text{ng/mL}$ ) presented a negative predictive value (NPV) of 91% and PPV of 42%. Comparing Tg-ablation with Tg-1, the PPV of an increase was 100%, whereas the NPV of a decrease was 88%. Thirty-six patients presented negative imaging results upon first assessment and Tg-1 was compared to Tg-2. Metastases were detected in all patients who presented an increase in Tg ( $n=4$ ), whereas patients without variation ( $n=4$ ) or with a decrease ( $n=28$ ) showed no apparent disease. Among disease-free patients ( $n=32$ ), 50% presented undetectable Tg and 40% showed a  $>50\%$  decrease after 2 years. In conclusion, most patients with detectable stimulated Tg during the first year after therapy had no metastases, and evaluation of the slope of Tg helped discriminate cases with apparent disease

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Exp Clin Endocrinol Diabetes. 2006 Oct;114(9):485-9.

### **Evaluation of the diagnostic value of the first thyroglobulin determination in detecting metastases after differentiated thyroid carcinoma surgery.**

**Makarewicz J, Adamczewski Z, Knapska-Kucharska M, Lewiński A.**

Department of Endocrinology and Metabolic Diseases, Unit of Nuclear Medicine and Oncological Endocrinology, Medical University of Lodz, Poland.

AIM: Evaluation of the diagnostic value of the first thyroglobulin (Tg) level measurement, performed after thyroidectomy, before another treatment, as an early marker of either metastases or local recurrence of differentiated thyroid carcinoma (DTC). MATERIALS AND METHODS: Data of 178 patients (160 women, 18 men, 14-79 years) with DTC and without known interference in Tg assay were evaluated retrospectively. In all patients, neck radioiodine uptake (Tup (24)), thyroid remnants volume (V), TSH and Tg were measured. The Tg/V and Tg/Tup (24) ratios were calculated to correct Tg concentration with regard to V and Tup (24). Six months after initial evaluation and routine therapy all patients underwent control examinations under endogenous TSH stimulation. RESULTS: During follow-up metastases or local recurrence were found in 32 patients. The groups of patients with no diagnosed metastases (M0) and with detected metastases (M1), did not differ with regard to V, serum TSH or Tup (24); difference between the two groups was found in Tg concentration (4.3  $\text{ng/ml}$  VS 97.4  $\text{ng/ml}$ ;  $p=0.000001$ ). The ratios of Tg/Tup (24) ( $p=0.000000$ ) and Tg/V ( $p=0.004$ ) were lower in the group M0 than M1. The areas under receiver operating characteristic curves (ROC) for Tg concentrations, Tg/Tup (24), and Tg/V ratios were 0.773 (95% CI - 0.655-0.892), 0.817 (0.709-0.925) and 0.712 (0.541-0.884), respectively. CONCLUSIONS: Both the absolute Tg concentration and Tg/V and Tg/Tup (24) ratios, determined after thyroidectomy but before another treatment in patients with metastases of DTC, diagnosed within 6 months after (131I) administration, are higher than those in patients without such metastases. This indicates that the mentioned parameters may be applied as early markers of either local recurrence or metastases of DTC. The highest discriminative value demonstrates Tg/Tup (24) ratio, Tg concentration has a lower value and Tg/V ratio has the lowest one.

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## Thyroid Cancer – Diagnosis, Therapy & Follow Up

Br J Radiol. 2006 Sep;79(945):e84-7

### **Unusual case of well-differentiated papillary thyroid carcinoma lacking thyroglobulin expression while still concentrating radioiodine.**

**Singh B, Bollmann R, Ahmadzadehfar H, Biersack HJ, Ezziddin S.**

Department of Nuclear Medicine, PGIMER, Chandigarh-160012, India.

We present an unusual case of a well-differentiated papillary thyroid carcinoma with bilateral lung metastases. Despite undetectable serum thyroglobulin (Tg) on thyroid stimulating hormone (TSH) stimulation and no immunohistochemical evidence of Tg expression in the primary tumour, the patient showed significant uptake of radioiodine in both lungs. After five cycles of high dose radioiodine therapy, the patient went into complete remission and therefore had an excellent response to radioiodine treatment. This case is a rare exception to the rule of Tg production as a prerequisite for differentiated thyroid cancers to concentrate radioiodine.

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J Pediatr Endocrinol Metab. 2006 Sep;19(9):1175-8

### **Importance of thyroglobulin levels for diagnosis and monitoring of follicular thyroid carcinoma in an adolescent with severe iodine deficiency.**

**Siklar Z, Ocal G, Berberoğlu M, Adiyaman P, Ergür AT, Evliyaoğlu O, Sak SD.**

Department of Pediatric Endocrinology, Ankara University Medical School, Ankara, Turkey. zeynepskl@hotmail.com

Optimal management of differentiated thyroid cancer in childhood is undetermined. During monitoring of thyroid carcinoma, serum thyroglobulin (hTG) levels provide valuable information. hTG levels not only increase in differentiated thyroid cancers but also in iodine deficiency because of compensation by the thyroid gland. A 14.6 year-old girl was diagnosed with nodular goiter, subclinical hypothyroidism and severe iodine deficiency. She had a very high hTG level. Despite benign fine-needle aspiration biopsy (FNAB), because the hTG level was still very high after treatment with LT4, thyroidectomy was undergone. Cytopathological examination showed minimally invasive follicular thyroid carcinoma. During follow-up, to exclude the presence of persistent/recurrent disease, the hTG level rose to an undesirably high level after withdrawal of TSH suppressive therapy, and radioiodine ablation therapy was applied. This report shows that even if there is an explanation for nodular goiter and high hTG levels, such as iodine deficiency, malignancy cannot be ruled out without thyroidectomy. FNAB is not reliable especially in iodine deficient areas. Serum hTG measurement is a valuable tool for both diagnosis and follow-up of differentiated thyroid carcinoma in children.

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Immunology. 2007 Jul;121(3):370-6. Epub 2007 Mar 22.

### **Variable influences of iodine on the T-cell recognition of a single thyroglobulin epitope.**

**Jiang HY, Li HS, Carayanniotis K, Carayanniotis G.**

Division of Endocrinology, Faculty of Medicine, Memorial University of Newfoundland, St John's, NL, Canada.

We have previously shown that iodotyrosyl formation within certain innocuous thyroglobulin (Tg) peptides confers on them immunopathogenic properties. In this report, we generated a panel of T-cell hybridoma clones specific for the immunogenic 16 mer Tg peptide p179 (amino acids 179-94) or its iodinated analogue (I-p179), with a view to examining the effects of a single iodine atom at the Y192 amino acid residue on T-cell recognition. We found that the peptide p179 was subdominant, and its binding to both A(k) and E(k) molecules was not significantly influenced by iodine. T-cell receptor (TCR) engagement was unaffected by the bulky iodine atom in two clones that responded to both analogues but it was sterically hindered in two other clones that recognized only p179. One clone was reactive only to I-p179, suggesting that the iodine atom is an integral part of its TCR ligand. Truncation analysis localized the determinant seen by all clones within the 11 mer peptide p184 (amino acids 184-194), suggesting that the cross-reactive clones were not activated by a minimal epitope lacking Y192 and that the negative influence of iodine was not the result of a flanking residue effect. These results demonstrate, at the clonal level, variable influences of a single iodine atom on the recognition of a single Tg peptide. Iodination of tyrosyl-containing, immunopathogenic Tg peptides may have unpredictable effects at the polyclonal level, depending on the extent of iodination at the particular site, and the relative number or effector function of autoreactive T-cell clones that are switched on or off by the neoantigenic determinant.

Clin Chem Lab Med. 2007 Jun 20;

### **Biological variation of thyroid autoantibodies and thyroglobulin.**

**Jensen E, Petersen PH, Blaabjerg O, Hegedüs L.**

1Department of Clinical Biochemistry, Odense University Hospital, Odense, Denmark.

Background: It has been shown that the level of serum thyroid antibodies affects serum thyrotropin (TSH) concentrations in men and women, and that these autoantibodies in combination with serum TSH are predictive of future thyroid disease. As the biological variation of these autoantibodies is unknown, we investigated this in fertile women during one complete regular menstrual cycle. Methods: A total of 24 healthy women (23-46 years) were investigated twice a week between 07:30 and 11:00 h. Antibodies against thyroid peroxidase (TPOAb), thyroglobulin (TgAb), and thyrotropin receptor (TRAb) were measured in serum, as well as thyroglobulin (Tg). TPOAb, TgAb and Tg were determined on an AutoDELFIA system (Perkin Elmer/Wallac) and TRAb by a radioreceptor assay from Brahms Diagnostica. Results: All 24 women had measurable levels of TPOAb and TgAb in all samples, and nine women had antibodies above the upper reference limit of the laboratory (6 had TPOAb >10 kIU/L, 6 had TgAb >20 kIU/L and 1 had TRAb >0.75 IU/L). Eight women had Tg below the lower reference limit, five of whom had elevated TgAb. Variations in the thyroid antibodies were random and not related to the menstrual cycle. For TPOAb (2.5-258 kIU/L), the CV biological was 11.3%, while the CV analytical was 10.6%. For TgAb (5.6 to 148 kIU/L) CV biological was 8.5% and CV analytical was 9.0%. The woman with TRAb had a CV biological of 4.8%, while the analytical variation in duplicates was 3.9% at a level of 2.8 IU/L. Conclusions: It is possible to measure TPOAb and TgAb in all samples with the AutoDELFIA. There is no systematic variation in autoantibodies during the menstrual cycle. The biological coefficient of variation for TPOAb and TgAb was 11.3% and 8.5%, respectively. Clin Chem Lab Med 2007;45.

J Clin Endocrinol Metab. 2007 Jun 5

### **Association between A C/T Polymorphism in Exon 33 of the Thyroglobulin Gene Is Associated with Relapse of Graves' Hyperthyroidism after Antithyroid Withdrawal in Taiwanese.**

**Hsiao JY, Hsieh MC, Tien KJ, Hsu SC, Shin SJ, Lin SR.**

Division of Endocrinology and Metabolism, Department of Internal Medicine, Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung, Taiwan; Graduate institute of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; Graduate institute of Medical Genetics, Kaohsiung Medical University, Kaohsiung, Taiwan.

Context: Graves' disease (GD) is an autoimmune disorder with genetic predisposition. The thyroglobulin (Tg) is a major autoantigen for GD. The human Tg gene polymorphism has specific features that make it important in GD. Objective: This study investigated whether Tg SNPs relates to GD development in a Taiwanese population. Design/Setting: This was a case control association study. Patients/Outcome Measures: We enrolled 215 Taiwanese patients with GD and 141 controls from the Endocrine Clinic of Kaohsiung Medical University Chung-Ho Memorial Hospital. This study investigated the association between gene polymorphism and relapse of hyperthyroidism after medication was discontinued in three GD patient groups and a control group, compare clinical and laboratory data obtained with patients with the three different genotypes with the three different Tg SNPs (E10SNP158, E12SNP, E33SNP). Results: We found a significant increase in the T/T genotype of E33SNP compared with the control group (P <0.001). We also found the E33SNP C/C genotype of the Tg gene were strongly associated with a subgroup of GD patients who were also characterized as having a higher relapse rate, significantly higher levels of persisting TSH-receptor antibody at the end of treatment, a higher frequency in smoking and a higher incidence of ophthalmopathy (P <0.05). Conclusions: This study showed that Taiwanese patients with the C/C genotype of E33SNP, smoking, ophthalmopathy and positive TSH-receptor antibodies at the end of the treatment were more likely to have a relapse of Graves' hyperthyroidism after antithyroid medication is withdrawn.

Endocrinology. 2007 Jun;148(6):2886-93. Epub 2007 Mar 1

### **A plasminogen-like protease in thyroid rough microsomes degrades thyroperoxidase and thyroglobulin.**

**Giraud A, Lejeune PJ, Barbaria J, Mallet B.**

INSERM/UMR 476, Laboratoire de Biochimie, Faculté de Médecine, 27 Boulevard Jean Moulin, 13385 Marseille Cedex 5, France.

Proteasome activity takes place in the cytosolic compartment and acts to degrade several proteins translated and unfolded. In transfected CHO cells expressing thyroid peroxidase (TPO), just-translated TPO undergoes proteasome activity, and then a second proteolytic system degrades more mature forms of TPO. A plasminogen-like (PI-like) protease is found in microsomal liver membranes and in the thyroid. In the thyroid, this PI-like protease is localized in the follicular lumen and efficiently degrades thyroglobulin (Tg) in vitro. Here we checked for the presence, in purified endoplasmic reticulum (ER) membranes of transfected CHO and in rough microsomes purified from thyroid tissue, of a second proteolytic system, different from the proteasome, and active against the two major proteins of the thyroid gland, TPO and Tg. We first confirmed that this proteolytic system was able to degrade folded endogenous TPO. We showed also that externally added TPO (folded form) was degraded by opened vesicles of ER in the same system. For thyroid tissue, we showed that added TPO, as well as purified Tg, was degraded by some unknown membrane-associated protease(s) in human and porcine thyroid rough microsomes, whereas BSA and IgG were not. These results indicated that major thyroid glycoproteins are preferential substrates of such protease(s). Immunoblot and zymography experiments identified the unknown membrane-associated protease in rough microsomes from thyroid tissues as being a PI-like protease. These results highly suggest that this system acts as a nonproteasomal degradation enzyme at the ER level, and we hypothesize that it contributes in regulating the level of major thyroid glycoproteins.

J Autoimmun. 2007 Jun;28(4):171-6. Epub 2007 Feb 26

### **Modifying effects of iodine on the immunogenicity of thyroglobulin peptides.**

**Li HS, Jiang HY, Carayanniotis G.**

Divisions of Endocrinology and Basic Sciences, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL A1B 3V6, Canada.

We have previously shown that iodotyrosyl formation within thyroglobulin (Tg) generates neoantigenic determinants that are immunopathogenic. In the current study, we have examined iodination effects on three tyrosyl-containing Tg peptides that are immunogenic in their non-iodinated form. We found that iodotyrosyl formation can enhance (p179, a.a. 179-194), suppress (p2540, a.a. 2540-2554), or not alter (p2529, a.a. 2529-2545) the immunogenic profiles of these peptides at the T-cell level. On the other hand, iodination did not alter the MHC-restriction profile of p2529 and p2540 (A(k)-binders) or p179 (A(k)- and E(k)-binder) and did not significantly influence the pathogenicity of these determinants. At the B-cell level, addition of an iodine atom on Y192 in p179 generated a neoantigenic determinant, but analogous effects were not discernible in p2529 or p2540. Our results demonstrate that iodotyrosyl formation can exert variable effects on the immunogenic behavior of Tg epitopes which may not always result in enhanced pathology. These findings also suggest that variations in the iodine content of Tg may significantly alter the hierarchy of antigenic determinants, to which the immune system may or may not be tolerant.

Clin Endocrinol (Oxf). 2007 May 28

### **Congenital hypothyroidism with goitre caused by new mutations in the thyroglobulin gene.**

**Caputo M, Rivolta CM, Esperante SA, Gruñeiro-Papendieck L, Chiesa A, Pellizas CG, González-Sarmiento R, Targovnik HM.**

Laboratorio de Biología Molecular, Cátedra de Genética y Biología Molecular, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Buenos Aires, Argentina.

Context Thyroid dyshormonogenesis is associated with mutations in the thyroglobulin (TG) gene and characterized by normal organification of iodide and low serum TG. These mutations give rise to congenital goitrous hypothyroidism, transmitted in an autosomal recessive mode. Objectives The aim of this study was to identify new mutations in the TG gene in an attempt to increase the understanding of the molecular basis of this disorder. Three unrelated patients with marked impairment of TG synthesis were studied. Methods The promoter and the complete coding regions of the TG gene, along with the flanking intronic regions, were analysed by direct DNA sequencing. Results Four different inactivating TG mutations, three novel mutations (c.548G>A, p.C164Y; c.759-760insA, p.L234fsX237; c.6701C>A, p.A2215D) and one previously identified mutation (c.886C>T, p.R277X) were identified. Multiple sequence alignment study revealed that the wild-type cysteine residue at position 164 is strictly conserved in the TG of all the species analysed, whereas the wild-type alanine residue at position 2215 is well conserved in the TG and acetylcholinesterase (AChE) of all the species analysed except in rabbit AChE, in which it is substituted by glutamic acid. Conclusions We report three patients with congenital hypothyroidism with goitre caused by two compound heterozygous mutations, p.C164Y/p.L234fsX237 and p.R277X/p.A2215D, and one homozygous mutation, p.R277X, in the TG gene. To our knowledge this is the first report of the presence of a nucleotide insertion mutation in the TG gene.

Endocr J. 2007 Apr 20

**Endemic Goiter due to Thyroglobulin Gene Abnormality and Social Ostracism.**

Fukata S, Hishinuma A, Kuma K, Miyauchi A, Sugawara M.

Kuma Hospital.

J Clin Endocrinol Metab. 2007 Apr;92(4):1451-7

**Thyroglobulin gene mutations producing defective intracellular transport of thyroglobulin are associated with increased thyroïdal type 2 iodothyronine deiodinase activity.**

Kanou Y, Hishinuma A, Tsunekawa K, Seki K, Mizuno Y, Fujisawa H, Imai T, Miura Y, Nagasaka T, Yamada C, Ieiri T, Murakami M, Murata Y.

Department of Genetics, Research Institute of Environmental Medicine, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan.

CONTEXT: Most patients with defective synthesis and/or secretion of thyroglobulin (Tg) present relatively high serum free T3 (FT3) concentrations with disproportionately low free T4 (FT4) resulting in a high FT3/FT4 ratio. The mechanism of this change in FT3/FT4 ratio remains unknown. OBJECTIVE: We hypothesize that increased type 2 iodothyronine deiodinase (D2) activity in the thyroid gland may explain the higher FT3/FT4 ratio that is frequently observed in patients with abnormal Tg synthesis. DESIGN: We recently identified a compound heterozygous patient (patient A) with a Tg G2356R mutation and one previously described (C1245R) that is known to cause a defect in intracellular transport of Tg. In the current study, after determining the abnormality caused by G2356R, we measured D2 activity as well as its mRNA level in the thyroid gland. We also measured the thyroïdal D2 activity in three patients with Tg transport defect and in normal thyroid tissue. RESULTS: Morphological and biochemical analysis of the thyroid gland from patient A, complemented by a pulse-chase experiment, revealed that G2356R produces a defect in intracellular Tg transport. D2 activity but not type 1 deiodinase in thyroid glands of patients with abnormal Tg transport was significantly higher than in normal thyroid glands, whereas D2 mRNA level in patient A was comparable with that in normal thyroid glands. Furthermore, there was a positive correlation between D2 activity and FT3/FT4 ratios. CONCLUSION: Increased thyroïdal D2 activity in the thyroid gland is responsible for the higher FT3/FT4 ratios in patients with defective intracellular Tg transport.

J Autoimmun. 2007 Mar-May;28(2-3):85-98

**The CD40, CTLA-4, thyroglobulin, TSH receptor, and PTPN22 gene quintet and its contribution to thyroid autoimmunity: back to the future.**

Jacobson EM, Tomer Y.

Division of Endocrinology, University of Cincinnati, The Vontz Center for Molecular Studies, 3125 Eden Avenue, Cincinnati, OH 45267, USA. eric.jacobson@uc.edu

Autoimmune thyroid diseases (AITD) are common autoimmune diseases, affecting up to 5% of the general population. Thyroid-directed autoimmunity is manifested in two classical autoimmune conditions, Hashimoto's thyroiditis, resulting in hypothyroidism and Graves' disease resulting in hyperthyroidism. Autoimmune thyroid diseases arise due to an interplay between environmental and genetic factors. In the past decade significant progress has been made in our understanding of the genetic contribution to the etiology of AITD. Indeed, several AITD susceptibility genes have been identified. Some of these susceptibility genes are specific to either Graves' disease or Hashimoto's thyroiditis, while others confer susceptibility to both conditions. Both immunoregulatory genes and thyroid specific genes contribute to the pathogenesis of AITD. The time is now ripe to examine the mechanistic basis for the contribution of genetic factors to the etiology of AITD. In this review, we will focus on the contribution of non-MHC II genes.

J Pediatr. 2007 Mar;150(3):315-7, 317.e2.

**Transient neonatal hypothyroidism is associated with elevated serum anti-thyroglobulin antibody levels in newborns and their mothers.**

Ordookhani A, Mirmiran P, Walfish PG, Azizi F.

Endocrine Research Center, Shaheed Beheshti University of Medical Sciences, Tehran, Iran. arash\_ordookhani@yahoo.com

Transient congenital hypothyroidism (TCH) was detected in 6 of 35,067 newborns (1:5845 births) screened in Iran. Antithyroglobulin antibodies positivity was present in 4 of 6 (66.7%) of those with TCH and in 6 of 106 (5.7%) of those with "transient hyperthyrotropinemia and normal" diagnoses (P = .0005), but positivity was similar in newborns with transient hyperthyrotropinemia versus normal neonates (P = .397).

Clin Exp Immunol. 2007 Feb;147(2):287-95.

### **Production of interleukin (IL)-5 and IL-10 accompanies T helper cell type 1 (Th1) cytokine responses to a major thyroid self-antigen, thyroglobulin, in health and autoimmune thyroid disease.**

Nielsen CH, Hegedüs L, Rieneck K, Moeller AC, Leslie RG, Bendtzen K.

Institute for Inflammation Research, Copenhagen University Hospital, Copenhagen, Denmark. C.H.Nielsen@rh.dk

Tumour necrosis factor (TNF)-alpha and interferon (IFN)-gamma exert detrimental effects in organ-specific autoimmune disease, while both destructive and protective roles have been demonstrated for interleukin (IL)-10, IL-4 and IL-5. We examined the production of these cytokines by peripheral blood mononuclear cells (PBMC) from patients with Hashimoto's thyroiditis (HT), Graves' disease (GD) and healthy controls, upon exposure to a thyroid self-antigen, human thyroglobulin (Tg), in the presence of autologous serum. Initially, TNF-alpha and IL-2 were produced in all three groups, accompanied by IL-10. Release of IFN-gamma, IL-4 and, notably, IL-5 ensued. Both patient groups exhibited increased TNF-alpha, IL-2, IFN-gamma and IL-10 responses, and PBMC from HT patients secreted lower amounts of IL-5 than male, but not female, controls. Enhanced TNF-alpha production by HT cells also occurred in the presence of pooled normal sera, indicating a dependency on intrinsic cellular factors. Conversely, higher production of TNF-alpha and IL-5 occurred in the presence of autologous sera than in the presence of pooled normal sera in both patient groups, indicating a dependency on serum constituents. Complement appeared to promote the production of IL-2 and particularly IL-5, the levels of which were reduced by neutralization of complement by heat- or zymosan treatment. The production of IFN-gamma and IL-2 of the three groups together correlated directly with the serum anti-Tg activity. Moreover, TNF-alpha, IFN-gamma, IL-5 and IL-10 responses were markedly inhibited by partial denaturation of Tg by boiling. We hypothesize that autoantibodies and complement may promote mixed Th1/Th2 cell cytokine responses by enhancing the uptake of autoantigens by antigen-presenting cells.

Life Sci. 2007 Jan 16;80(6):538-45.

### **Presence of beta-linked GalNAc residues on N-glycans of human thyroglobulin.**

Takeya A, Hosomi O, Nishijima H, Ohe Y, Sugahara K, Sagi M, Yamazaki K, Hayakawa H, Takeshita H, Sasaki C, Kogure T, Mukai T.

Department of Legal Medicine, St. Marianna University School of Medicine, 1-16-2 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan. a2takeya@marianna-u.ac.jp

Hepatic asialoglycoprotein receptor, which may mediate the clearance of circulating thyroglobulin, is known to have a high affinity for GalNAc. Recently, the receptor has been reported to be present also in the thyroid, implicating interaction with thyroglobulin. Here, mammalian thyroglobulins were analyzed for GalNAc termini by Western blotting with GalNAc-recognizing lectins labeled with peroxidase or (125)I. Wistaria floribunda lectin was found to bind human thyroglobulin and, to some extent, bovine, but not porcine thyroglobulin. After desialylation, the lectin bound all of the thyroglobulins tested. The binding was inhibited by competitive inhibitor GalNAc. Peptide N-glycanase treatment of human desialylated thyroglobulin resulted in the complete loss of reactivity with W. floribunda lectin, indicating that the binding sites are exclusively on N-glycans. The binding sites on human desialylated thyroglobulin were partly sensitive to beta-galactosidase, and the remainder was essentially sensitive to beta-N-acetylhexosaminidase. On the other hand, the binding sites of bovine and porcine desialylated thyroglobulins were totally sensitive to beta-galactosidase. Thus the lectin binds beta-Gal termini, as well as beta-GalNAc. GalNAc-specific Dolichos biflorus lectin also bound human thyroglobulin weakly. In contrast to W. floribunda lectin, desialylation diminished binding, suggesting that these two lectins recognize different GalNAc-terminated structures. Again, the binding was inhibited by GalNAc and by treatment with peptide N-glycanase. These results strongly indicate the presence of distinct GalNAc termini of N-glycans on human thyroglobulin.

Clin Exp Immunol. 2007 Jan;147(1):120-7.

### **Spreading of antibody reactivity to non-thyroid antigens during experimental immunization with human thyroglobulin.**

Thrasylouides A, Liakata E, Lymberi P.

Laboratory of Immunology, Department of Biochemistry, Hellenic Pasteur Institute, Athens, Greece.

Intermolecular spreading of antibody reactivity has been implicated in the evolution of autoimmune disease. In this study, spreading of antibody reactivity to non-thyroid autoantigens after experimental immunization with thyroglobulin (Tg) was investigated. For this purpose, two rabbits were injected with human Tg six times (stages 1-6) every 3 weeks. Animals were also bled before priming. Antisera were tested by enzyme-linked immunosorbent assay (ELISA) for reactivity to several non-thyroid antigens: bovine serum albumin (BSA), native DNA (nDNA), human myosin, human globular (G) and filamentous (F) actin and porcine tubulin. Tg-immunized animals developed the following serological reactivity pattern: (a) high reactivity to myosin from stage 2 onward, (b) significant reactivity to F-actin, remaining high up to stage 6, (c) reactivity to BSA with a peak at stage 3, (d) a small increase of reactivity to G-actin at stage 3 and (e) no increase of reactivity to nDNA and tubulin. The study of affinity-purified anti-Tg antibodies and the use of competitive assays revealed that reactivity to F-actin was not due to cross-reaction with Tg. On the contrary, reactivity to myosin during the first stages of immunization was due to cross-reaction with Tg, while at stage 6 it became myosin-specific. Reactivity to BSA at stage 3 was also due to cross-reaction with Tg. We conclude that at least part of the induced anti-Tg antibodies may result from the expansion of B cell clones producing

polyreactive natural autoantibodies, and polyreactivity of anti-Tg antibodies during the first stages of Tg-immunization may be responsible for the intermolecular spreading of antibody response.

Clin Chim Acta. 2006 Dec;374(1-2):8-24.

### **Molecular advances in thyroglobulin disorders.**

**Rivolta CM, Targovnik HM.**

Laboratorio de Biología Molecular, Cátedra de Genética y Biología Molecular, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, 1113 - Buenos Aires, Argentina.

Synthesis of tri-iodothyronine (T<sub>3</sub>) and thyroxine (T<sub>4</sub>) follows a metabolic pathway that depends on the integrity of the thyroglobulin structure. This large glycoprotein is a homodimer of 660 kDa synthesized and secreted by the thyroid cells into the lumen of thyroid follicle. In humans it is coded by a single copy gene, 270 kb long, that maps on chromosome 8q24 and contains an 8.5 kb coding sequence divided into 48 exons. The preprotein monomer is composed of a 19-amino acid signal peptide followed by a 2749-amino acid polypeptide. In the last decade, several mutations in the thyroglobulin gene were reported. In animals, four of them have been observed in Afrikaner cattle (p.R697X), Dutch goats (p.Y296X), cog/cog mouse (p.L2263P) and rdw rats (p.G2300R). Mutations in the human thyroglobulin gene are associated with congenital goiter or endemic and nonendemic simple goiter. Thirty-five inactivating mutations have been identified and characterized in the human thyroglobulin gene: 20 missense mutations (p.C175G, p.Q310P, p.Q851H, p.S971I, p.R989C, p.P993L, p.C1058R, p.C1245R, p.S1447N, p.C1588F, p.C1878Y, p.I1912V, p.C1977S, p.C1987Y, p.C2135Y, p.R2223H, p.G2300D, p.R2317Q, p.G2355V, p.G2356R), 8 splice site mutations (g.IVS3-3C>G, g.IVS5+1G>A, g.IVS10-1G>A, g.IVS24+1G>C, g.IVS30+1G>T, g.IVS30+1G>A, g.IVS34-1G>C, g.IVS45+2T>A) 5 nonsense mutations (p.R277X, p.Q692X, p.W1418X, p.R1511X, p.Q2638X) and 2 single nucleotide deletions (p.G362fsX382, p.D1494fsX1547). The thyroglobulin gene has been also identified as the major susceptibility gene for familial autoimmune thyroid diseases (AITD) by linkage analysis using highly informative polymorphic markers. In conclusion the identification of mutations in the thyroglobulin gene has provided important insights into structure-function relationships.

Autoimmunity. 2006 Sep;39(6):497-503.

### **Thyroid peroxidase and thyroglobulin auto-antibodies in patients with newly diagnosed overt hypothyroidism.**

**Carlé A, Laurberg P, Knudsen N, Perrild H, Ovesen L, Rasmussen LB, Jorgensen T, Pedersen IB.**

Department of Endocrinology & Medicine, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark.  
carle@dadlnet.dk

**OBJECTIVES:** Thyroid autoimmunity is a major cause for hypothyroidism. We describe thyroid auto-antibodies in patients with various nosological subtypes of hypothyroidism identified in a population study. **DESIGN:** Population-based follow-up study identifying all new cases of hypothyroidism in an open cohort. **METHODS:** We established a monitoring system, and identified all new cases with primary overt hypothyroidism (n = 685) in a 4 year period in a well-defined population cohort (2,027,208 person-years of observation). Patients were sub-classified into: spontaneous hypothyroidism, presumably of autoimmune origin (n = 578); non-spontaneous hypothyroidism (associated with medication, delivery, neck-irradiation or subacute thyroiditis, n = 97); and congenital hypothyroidism (n = 10). A total of 186 adult patients (61% of those invited) underwent thyroid ultrasonography and measurements of antibodies against thyroid peroxidase (TPOAb) and thyroglobulin (TgAb). **RESULTS:** In spontaneously hypothyroid patients: >99% were antibody-positive (TPOAb or TgAb), TPOAb were more often measurable than TgAb (95.9 vs. 80.7%, p < 0.001). A statistically significant but modest correlation was observed between the two antibodies (Pearson's r<sub>2</sub> = 0.11, p < 0.001). In a multivariate regression model both TPOAb and TgAb were positively associated with thyroid enlargement (p < 0.001), whereas no association was found with sex, age, iodine deficiency level or serum TSH level. We found no differences in patient characteristics between those who mainly developed TPOAb vs. those who preferentially harboured TgAb. **CONCLUSIONS:** Autoimmunity played a dominant role in practically all patients classified as spontaneously hypothyroid. Thyroid enlargement was associated with high levels of TPOAb and TgAb. We found no clue to why some spontaneously hypothyroid patients predominantly developed TPOAb whereas others mainly generated TgAb.

## Diagnosics

J Clin Endocrinol Metab. 2007 Jul;92(7):2487-95. Epub 2007 Apr 10.

### **Comparison of seven serum thyroglobulin assays in the follow-up of papillary and follicular thyroid cancer patients.**

**Schlumberger M, Hitzel A, Toubert ME, Corone C, Troalen F, Schlageter MH, Claustrat F, Koscielny S, Taieb D, Toubreau M, Bonichon F, Borson-Chazot F, Leenhardt L, Schwartz C, Dejax C, Brenot-Rossi I, Torlontano M, Tenenbaum F, Bardet S, Bussi re F, Girard JJ, Morel O, Schneegans O, Schlienger JL, Prost A, So D, Archambeaud F, Ricard M, Benhamou E.**

Institut Gustave Roussy, Rue Camille Desmoulins, 94805 Villejuif C dex, France. schlumbg@igr.fr.

Background: Serum thyroglobulin (Tg) is the marker of differentiated thyroid cancer after initial treatment and TSH stimulation increases its sensitivity for the diagnosis of recurrent disease. Aim: The goal of the study is to compare the diagnostic values of seven methods for serum Tg measurement for detecting recurrent disease both during L-T(4) treatment and after TSH stimulation. Methods: Thyroid cancer patients who had no evidence of persistent disease after initial treatment (total thyroidectomy and radioiodine ablation) were studied at 3 months on L-T(4) treatment (Tg1) and then at 9-12 months after withdrawal or recombinant human TSH stimulation (Tg2). Sera with anti-Tg antibodies or with an abnormal recovery test result were excluded from Tg analysis with the corresponding assay. The results of serum Tg determination were compared to the clinical status of the patient at the end of follow-up. Results: Thirty recurrences were detected among 944 patients. A control (131)I total body scan had a low sensitivity, a low specificity, and a low clinical impact. Assuming a common cutoff for all Tg assays at 0.9 ng/ml, sensitivity ranged from 19-40% and 68-76% and specificity ranged from 92-97% and 81-91% for Tg 1 and Tg2, respectively. Using assays with a functional sensitivity at 0.2-0.3 ng/ml, sensitivity was 54-63% and specificity was 89% for Tg1. Using the two methods with a lowest functional sensitivity at 0.02 and 0.11 ng/ml resulted in a higher sensitivity for Tg1 (81% and 78%), but at the expense of a loss of specificity (42% and 63%); finally, for these two methods, using an optimized functional sensitivity according to receiver operating characteristic curves at 0.22 and 0.27 ng/ml resulted in a sensitivity at 65% and specificity at 85-87% for Tg1. Conclusion: Using an assay with a lower functional sensitivity may give an earlier indication of the presence of Tg in the serum on L-T(4) treatment and may be used to study the trend in serum Tg without performing any TSH stimulation. Serum Tg determination obtained after TSH stimulation still permits a more reliable assessment of cure and patient's reassurance.

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Clin Endocrinol (Oxf). 2007 Jun 6

### **Will highly sensitive thyroglobulin assays change the management of thyroid cancer?**

**Mazzaferrri EL.**

Department of Medicine, University of Florida, Gainesville, FL, USA and Department of Internal Medicine, Ohio State University, Columbus, OH, USA.

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### **Clinical relevance of highly sensitive Tg assay in monitoring patients treated for differentiated thyroid cancer.**

**Iervasi A, Iervasi G, Ferdeghini M, Solimeo C, Bottoni A, Rossi L, Colato C, Zucchelli GC.**

Institute of Clinical Physiology, National Council of Research, Pisa, Italy.

Objective Serum thyroglobulin (Tg) represents a highly specific biomarker for detecting residual thyroid tissue/recurrence/metastases after treatment for differentiated thyroid cancer (DTC). We evaluated the clinical impact of a highly sensitive Tg assay during routine follow-up of DTC patients. Design Tg values were measured by a highly sensitive Tg assay during L-T4 suppressive therapy and after recombinant human thyrotropin (rh-TSH) stimulation and were compared with those obtained by using a routinely employed Tg assay. Patients One hundred and sixty consecutive DTC-treated patients (papillary carcinoma n = 124, follicular carcinoma n = 36) were studied. Measurements Measured variables included neck ultrasonography, (131)I whole body scanning, and Tg assayed by Immulite (Diagnostic Products Corporation, Los Angeles, CA) and by the highly sensitive Access assay (Beckman Coulter, Brea, CA). Results During L-T4 therapy, measurable Tg was found in only two patients (1% of total) by Immulite and in 23 patients (14% of total) by Access assay. Using the institutional cut-off of 2 microg/l after rh-TSH, a negative response was associated with undetectable Immulite Tg during L-T4 therapy in all patients (negative predictive value, NPV, 100%) and in 137 out of 152 patients with Access assay (NPV 90%). Measurable Tg during L-T4 therapy was found in 17% of positive patients with Immulite and in 100% of patients with Access, respectively. Conclusions The use of a highly sensitive Tg assay may represent a useful diagnostic tool for improving the interpretation of Tg results during monitoring of DTC-treated patients for the early detection of recurrence and for optimizing the use of the more expensive rh-TSH test.

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## Diagnostocs

Clin Biochem. 2007 Jun;40(9-10):735-8. Epub 2007 Mar 28

### **Mutual interference between serum thyroglobulin and antithyroglobulin antibody in an automated chemiluminescent immunoassay.**

**Gao Y, Yuan Z, Yu Y, Lu H.**

The Immunoassay Laboratory, Department of Nuclear Medicine, Shanghai Sixth People's Hospital, Shanghai Jiao Tong University, 600 Yishan Road, Shanghai 200233, China. gaokok@163.com

**OBJECTIVES:** To investigate the analytical interference between serum Tg and TgAb. **DESIGN AND METHODS:** Tg and TgAb were measured on an automated chemiluminescent immunoassay system in mixed sera from DTC patients and individual samples spiked with exogenous Tg. **RESULTS:** Tg and TgAb recoveries in mixed patient samples were inversely correlated with expected TgAb or Tg concentrations, respectively. Impaired TgAb recoveries were also found in 50% (10/20) samples with high Tg in the exogenous recovery tests. **CONCLUSIONS:** Mutual but not equal analytical interference between Tg and TgAb is present and concentration-dependent with interpatient variability.

Rinsho Byori. 2007 May;55(5):428-33.

### **Discrimination of thyroglobulin from thyroid carcinoma tissue and that from benign thyroid tissues with use of competitive assay between lectin and anti-thyroglobulin antibody.**

**Shimizu K, Nakamura K, Kobatake S, Satomura S, Maruyama M, Tajiri J, Kato R.**

Diagnostocs Research Laboratories Wako Pure Chemical Industries, Ltd., Amagasaki 661-0963.

Thyroglobulin is produced only by thyroid follicular cells, and has a molecular weight of 660,000 and carbohydrate content of approximately 10%. The composition of carbohydrate chains on thyroglobulin from thyroid carcinoma has been reported to differ from that in normal thyroid tissue. In this study, heterogeneities of carbohydrate chains on thyroglobulin obtained from thyroid tissues were investigated by competitive reaction between lectin and anti-thyroglobulin monoclonal antibody. Concanavalin A, Lens culinaris agglutinin, Ricinus communis agglutinin-120 and Datura stramonium agglutinin were compared. The ratio of Lens culinaris agglutinin-reactive thyroglobulin to thyroglobulin was significantly lower in thyroid carcinoma than in normal thyroid tissue, Graves' disease and benign thyroid tumor. However, no differences between malignant and benign tissues were observed with the other lectins tested. Differences in carbohydrate chain on thyroglobulin were observed between malignant and benign thyroid tissues.

Clin Chim Acta. 2007 Feb;376(1-2):88-95.

### **Performance characteristics of 5 automated thyroglobulin autoantibody and thyroid peroxidase autoantibody assays.**

**La'ulu SL, Slev PR, Roberts WL.**

ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, UT, United States.

**BACKGROUND:** Measurement of thyroid peroxidase autoantibodies (TPOAb) is useful in diagnosing patients with autoimmune thyroid disease. Measurement of thyroglobulin autoantibodies (TgAb) is used to detect potential interferences with thyroglobulin immunoassays and in limited situations for the diagnosis of autoimmune thyroid disease. **METHODS:** The limit of detection, imprecision, reference interval, method comparison and diagnostic concordance for the ADVIA Centaur, ARCHITECT i2000, AxSYM, Immulite 2000, Modular E170 (TPOAb only), and UniCel DxI 800 (TgAb only) methods were evaluated. The Advantage was used as the comparison method. **RESULTS:** Total imprecision ranged from 2.6% to 14.9% for TgAb and 2.1% to 15.8% for TPOAb. Passing-Bablok slopes ranged from 0.51 to 10.4 (TgAb) and 1.05 to 7.12 (TPOAb) with correlation coefficients of 0.48 to 0.82 (TgAb) and 0.66 to 0.78 (TPOAb). Assay cutoffs were adjusted using a common set of reference interval samples. Concordance with the Advantage assay using the new cutoffs was found to be improved and ranged from 68.5% to 84.7% (TgAb) and 77.5% to 84.7% (TPOAb). **CONCLUSIONS:** Although all assays generally performed well, assay concordance for a negative or positive result ranged from 54.2 to 84.7%. Quantitative agreement between methods was generally poor and methods could not be used interchangeably. Additional standardization efforts are required to improve inter-method agreement.

Clin Chem Lab Med. 2007;45(2):263

### **Is simultaneous measurement of anti-thyroid peroxidase and anti-thyroglobulin antibodies clinically useful in patients with thyroid dysfunction?**

**Giovanella L.**

## Diagnosics

J Clin Endocrinol Metab. 2007 Jan;92(1):82-7

### **Monitoring thyroglobulin in a sensitive immunoassay has comparable sensitivity to recombinant human tsh-stimulated thyroglobulin in follow-up of thyroid cancer patients.**

Smallridge RC, Meek SE, Morgan MA, Gates GS, Fox TP, Grebe S, Fatourehchi V.

Division of Endocrinology and Metabolism, Mayo Clinic College of Medicine, Jacksonville, Florida 32224, USA.  
smallridge.robert@mayo.edu

CONTEXT: Most thyroglobulin (Tg) assays have a sensitivity of 0.5-1 ng/ml. A minority of patients with undetectable T4-suppressed Tg levels have a recombinant human TSH (rhTSH)-stimulated Tg above 2 ng/ml and identifiable residual disease. OBJECTIVE: The objective was to determine whether a Tg assay with improved sensitivity could eliminate the need for rhTSH stimulation when baseline Tg is below 0.1 ng/ml. DESIGN: A retrospective study of two academic endocrine practices was conducted. POPULATION: A total of 194 patients undergoing rhTSH stimulation participated in the study. RESULTS: Of the 80 patients with Tg below 0.1 ng/ml, two (2.5%) had rhTSH-stimulated Tg above 2 ng/ml. One other patient with stimulation to 0.3 ng/ml and negative 123I scan had an ultrasound-detected malignant lymph node resected. None had 131I/123I imaging after rhTSH stimulation suggestive of local recurrence or distant metastasis. If T4-suppressed Tg was 0.1-0.5 or 0.6-2.0 ng/ml, rhTSH Tg was above 2 ng/ml in 24.2 and 82.4%, respectively. CONCLUSIONS: Patients with differentiated thyroid carcinoma and a T4-suppressed serum Tg below 0.1 ng/ml rarely have a rhTSH-stimulated Tg above 2 ng/ml, and none of these patients had 131I or 123I imaging after rhTSH stimulation suggestive of local recurrence or distant metastasis. We recommend monitoring such patients with a T4-suppressed Tg level and periodic neck ultrasonography. An increase in T4-suppressed serum Tg to a detectable level or the appearance of abnormal lymph nodes by physical or ultrasound exam should prompt further investigation.

J Clin Lab Anal. 2007;21(3):147-53

### **Comparison of immunoradiometric assays for determination of thyroglobulin: a validation study.**

Tortajada-Genaro LA, Cózar MP, Frigols JL, de Avila CR.

Departamento Química, Universidad Politécnica de Valencia, Valencia, Spain. luitorge@qim.upv.es

In this study we compared and validated commercial immunoradiometric assays (IRMA) to determine thyroglobulin (Tg) levels in serum. From a set of 440 samples, 68 were selected to calculate the validation parameters and the clinical performance of the assays. The commercial kits evaluated were the Tg-CTK (DiaSorin), IRMAZenco Tg (ZenTech), and SELco-Tg (Medipan). We found that 21% of the collected samples were in the critical range of concentration. Detection limits were calculated as being below 3 microg/L. Intra- and inter-reproducibility were lower than 3.1% and 9.2%, respectively. Dilution and recovery studies provided quantitative determinations. Correlation regression coefficients from the results of the methods were obtained. The determined concentrations were compared with the clinical evidence of disease. Variation in the 125-iodine-labeled antibody concentration and control charts showed the robustness of the methods. Analysis time and the simplicity of the methods were also evaluated. Reliable Tg determination is important for monitoring patients with differentiated thyroid cancer (DTC), controlling other thyroid diseases, and assessing the quality of imaging techniques. A strategy for verification and comparison based on analytical parameters and clinical performance is proposed. (c) 2007 Wiley-Liss, Inc.

J Clin Endocrinol Metab. 2006 Dec;91(12):4881-7.

### **Assessment of iodine status using dried blood spot thyroglobulin: development of reference material and establishment of an international reference range in iodine-sufficient children.**

Zimmermann MB, de Benoist B, Corigliano S, Jooste PL, Molinari L, Moosa K, Pretell EA, Al-Dallal ZS, Wei Y, Zu-Pei C, Torresani T.

Laboratory for Human Nutrition, Swiss Federal Institute of Technology, LFV E19, Schmelzbergstrasse 7, CH-8092 Zürich, Switzerland. michael.zimmermann@ilw.agrl.ethz.ch

CONTEXT: Thyroglobulin (Tg) may be a valuable indicator of improving thyroid function in children after salt iodization. A recently developed Tg assay for use on dried whole blood spots (DBS) makes sampling practical, even in remote areas. OBJECTIVE: The study aim was to develop a reference standard for DBS-Tg, establish an international reference range for DBS-Tg in iodine-sufficient children, and test the standardized DBS-Tg assay in an intervention trial. DESIGN, PARTICIPANTS, AND INTERVENTIONS: Serum Tg reference material of the European Community Bureau of Reference (CRM-457) was adapted for DBS and its stability tested over 1 yr. DBS-Tg was determined in an international sample of 5- to 14-yr-old children (n = 700) who were euthyroid, anti-Tg antibody negative, and residing in areas of long-term iodine sufficiency. In a 10-month trial in iodine-deficient children, DBS-Tg and other indicators of iodine status were measured before and after introduction of iodized salt. RESULTS: Stability of the CRM-457 Tg reference standard on DBS over 1 yr of storage at -20 and -50 C was acceptable. In the international sample of children, the third and 97th percentiles of DBS-Tg were 4 and 40 microg/liter, respectively. In the intervention, before introduction of iodized salt, median DBS-Tg was 49 microg/liter, and more than two thirds of children had DBS-Tg values greater than 40 microg/liter. After 5 and 10 months of iodized salt use, median DBS-Tg decreased to 13 and 8 microg/liter, respectively, and only 7 and 3% of children, respectively, had values greater than 40 microg/liter. DBS-Tg correlated well at baseline and 5 months with urinary iodine and thyroid volume. CONCLUSIONS: The availability of reference material and an international reference range facilitates the use of DBS-Tg for monitoring of iodine nutrition in school-age children.

## Diagnosics

Biomed Pharmacother. 2006 Sep;60(8):414-24

### **Serum thyroglobulin measurement: clinical background and main methodological aspects with clinical impact.**

**Iervasi A, Iervasi G, Carpi A, Zucchelli GC.**

National Council of Research, Institute of Clinical Physiology, Via Moruzzi, Pisa, Italy. [annalisa@ifc.cnr.it](mailto:annalisa@ifc.cnr.it)

It is worldwide recognized that circulating thyroglobulin (Tg) measurement represents a fundamental tool in the follow-up of patients affected by differentiated thyroid cancer (DTC). In the last American and European Consensus Conferences, a surveillance guideline has been extended to the use of thyrotropin (TSH)-stimulated Tg levels for thyroidectomized patients without clinical evidence of residual tumor with Tg below 1 microg/l during TSH suppression. Therefore, sensitivity of the methods is critical to detect small amounts of Tg and/or to observe minimal changes in Tg concentration in the management of DTC patients. It has been proposed that only methods providing the greatest distinction between the lower limit of euthyroid reference range (approximately 3.0 microg/l) and the functional sensitivity limit (at least 1 microg/l) of the assay may offer a suitable clinical sensitivity for detecting small amounts of functioning thyroid tissue in TSH-suppressed state (1 g of normal thyroid tissue results in a serum Tg of approximately 1 microg/l when TSH is normal and about 0.5 microg/l when TSH is suppressed). In the last 30 years sensitivity of Tg measurements has been greatly improved, nowadays methods can achieve very good analytical and functional sensitivity to give reliable results also in the very low concentration range (between 0.1 and 1 microg/l). In addition, with the introduction of fully automated assays, results can be readily available to the clinician while patients are still in the ambulatory area. However, despite the large clinical use of Tg measurement, wide differences (by threefold) still remain between results produced in different laboratories due to poor standardization, heterogeneity of circulating Tg, interference from auto-antibodies, differences in the epitope recognition by antibodies used in the assays.

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## Miscellaneous

J Endocrinol Invest. 2006 Nov;29(10):876-84.

### **Effects of percutaneous laser ablation treatment in benign solitary thyroid nodules on nodule volume, thyroglobulin and anti-thyroglobulin levels, and cytopathology of nodule in 1 yr follow-up.**

**Cakir B, Topaloglu O, Gul K, Agac T, Aydin C, Dirikoc A, Gumus M, Yazicioglu K, Ersoy RU, Ugras S.**

Ankara Ataturk Education and Research Hospital, Endocrinology and Metabolism Department, TR-, Bilkent, Ankara, Turkey. drcakir@yahoo.com

**OBJECTIVE:** To investigate the effects of ultrasound (US)-guided percutaneous laser ablation (PLA) in the treatment of benign solid hypoactive thyroid nodules on nodule volume, thyroid functions, nodule cytology and patients' complaints. **MATERIAL AND METHOD:** Criteria for enrollment in the study were as follows: patients with euthyroid, benign, hypofunctional nodule who had compressive symptoms or cosmetic complaints, but considered inoperable, or who rejected surgical treatment. PLA procedure at 3-5 watts (W) was applied to 15 thyroid nodules of 12 patients (4 male and 8 female; age range 20-78 yr, mean age 47.42 $\pm$ 17.05 yr), and patients were followed up for 12 months. Thyroid functions and nodule volumes (ultrasonographically) were evaluated. US-guided fine needle aspiration biopsy (FNAB) was performed before and after the procedure, and biopsy specimens were cytologically evaluated. **RESULTS:** The mean nodule volume before the procedure was 11.97 ml (min-max 0.95-26.30 ml). However, 12 months after the procedure the mean nodule volume was 2.21 $\pm$ 2.32 ml (min-max 0.10-7.65 ml). The mean reduction in nodule volumes was 82%. Thyroglobulin levels reached peak values at 1 month after the procedure, and anti-thyroglobulin levels at 3 months after the procedure. FNAB performed at 12th month showed neutrophil polymorphs, macrophages, abundant cell debris, colloid, multinucleated giant cells, and small fragments of fibrous stroma which indicated that PLA procedure led to degenerative changes in nodules. **CONCLUSION:** US-guided PLA is a new, successful treatment method which is reliable in the long term in benign solid thyroid nodules for selected patients who are inoperable or do not prefer surgery.

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Am J Forensic Med Pathol. 2006 Sep;27(3):280-2.

### **High thyroglobulin (Tg) concentrations in fatal traumatic brain injuries.**

**Dressler J, Mueller E.**

Department of Legal Medicine, Technical University, Medical School, Dresden, Germany. Jan.Dressler@tu-dresden.de

It is well known that under physiological conditions, the Tg molecule is the substrate for the hormones triiodothyronine and thyroxine. Its function outside the thyroid gland is unknown. Under certain pathologic conditions, an increase in Tg concentrations in the blood can occur, a phenomenon that is used in the clinical diagnosis of certain thyroid disorders. However, fatal traumatic brain injuries (TBI) can also produce a raised Tg concentration in blood. In such cases, mean (n=151) Tg concentrations of 405.8 $\pm$ 353.3 ng/mL have been observed, with the values in 57% of these cases exceeding 200 ng/mL. Since it was possible to rule out specifically any thyroid disorders in these cases, the raised values may be explained by the effect of TSH in the spectrum of the "hypothalamic-pituitary-thyroid axis." This assumption has been substantiated by immunohistochemical tests for TSH and Tg. Compared with the controls (sudden unnatural deaths: Tg 23.3 $\pm$ 27.6 ng/mL), the raised Tg values in the TBI cases were usually accompanied by a reduction in the intensity of immunohistochemical reactions relating to TSH and Tg. The hypophysis showed evidence of significant damage with morphologic changes such as edema, hemorrhages, and focal necrosis in association with reduced TSH levels.

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