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The Thyroglobulin: A Technically Challenging Assay for a Marker of Choice During the Follow-Up of Differentiated Thyroid Cancer

Anne Charrié

Lyon University, INSERM U1060, CarMeN laboratory and CENS, Univ Lyon-1
Laboratory of Nuclear Technics and Biophysic, Hospices Civils de Lyon
France

1. Introduction

The thyroglobulin (Tg) is a normal secretory product of the thyroid gland. Tg is stored in the follicular light of the thyroid where it constitutes the majority of colloid proteins. It is the place of synthesis and storage of thyroid hormones.

This glycoprotein of high molecular weight (660 kDa) is constituted by two identical sub-units bound by disulphide-bridges. Each sub-unit contains 2 749 amino acids (Malthiery & Lissitzky, 1987 and Van de Graf et al., 1997). Its gene is situated on the chromosome 8 and different isoforms of Tg are secreted by alternative splicing. This molecule is heterogeneous by its degree of iodination (0.2 to 1.0%), of glycosylation, and by its contents in oses and in sialic acid (8 to 10%). The epitopic map of Tg revealed approximately about forty antigenic determinants, twelve epitopes grouped together in six domains (Piechaczyck et al., 1985). The central region of the Tg molecule is in majority immunoreactive (Henry et al, 1990).

Tg is not confined in the follicle, some molecules are co-secreted with thyroid hormones by a complex process which can modify it. Any conformational change entails a different antigenicity because some epitopes can be masked or on the contrary be exposed. Molecular forms of Tg found in the serum of patients with differentiated thyroid cancer correspond to dimeric Tg. It is little iodized and presents a change of the glycosylation (Sinadinovic et al., 1992 and Druetta et al., 1998). The heterogeneousness of Tg in the thyroid gland is increased in the cancer (Persani et al., 1998) and the changes of its conformation modifies its immunoreactivity (Kohno et al., 1985). All these structural characteristics are very important to know and can give some explanations about differences between Tg assays. It is not surprising to notice differences between Tg assays which use monoclonal antibodies by definition very specific. The follow-up of the differentiated thyroid cancers is the essential indication of the dosage of the serum Tg. Tg signs the presence of normal or pathological thyroid tissue. It is not possible to differentiate the normal tissue of the cancerous tissue thanks to serum Tg value. One reference point is mentioned in the laboratory medicine practice guidelines (Baloch et al., 2003): one gram of normal thyroid releases about 1µg/L Tg into the circulation when the serum thyroid stimulating hormone (TSH) is normal and 0.5 µg/L if the TSH value is suppressed below 0.1 mUI/L. Since its concentration is correlated

with the size rather than with the nature of nodule of the thyroid gland, Tg is not used for the diagnosis of the thyroid cancer. Routine preoperative measurement of serum Tg for initial evaluation of thyroid nodules is not recommended (Cooper et al., 2006).

2. Thyroglobulin assay in serum

Serum Tg measurement is a technically challenging assay for a marker of choice during the follow-up of differentiated thyroid cancer. The use of the Tg assays requires a good knowledge of the technical difficulties. The quality of current Tg assay methods varies and influences the clinical utility of this test. All techniques are today immunometric assays with isotopic signal or not. Several methodological problems must be taken into account: standardization, functional sensitivity, precision, hook effects, interference by heterophile antibodies and interference by Tg antibodies (TgAb) (Spencer et al., 1996). Precision and hook effects are two parameters which are usual in biology when markers are used in the follow-up of cancer. Every laboratory scientist knows that it is sometimes better to measure stored serum samples from the patient in the same run as the current specimen to better appreciate the variability of the marker during the time. As regards the hook effect it is careful either to use a technique in 2 steps or to dilute systematically the serum suspected of very high values of Tg. Heterophile antibodies may cause falsely elevated serum Tg levels as in al immunometric assays. It is possible to reduce this interference by using heterophile blocking tubes when these antibodies are suspected (Preissner et al., 2003). Even if some solutions were studied for the other problems (standardisation, functional sensitivity and interference by TgAb) all persist always for more than fifteen years and guidelines have been published (Baloch et al., 2003; Pacini et al., 2006; Borson-Chazot et al., 2008).

2.1 Standardisation

Different guidelines and consensus (Baloch et al., 2003; Pacini et al., 2006; Borson-Chazot et al., 2008) recommended the use of the European human reference material CRM 457 (Feldt-Rasmussen U et al., 1996). Even if the use of this standard doesn't resolve all problems between different techniques it will be a minimal consensus that manufacturers would follow to get a homogenous basis of standardisation. The CRM 457 is produced from normal thyroid tissue. Now we know that tissular Tg is not strictly the one which circulates in the blood (Schulz et al., 1989). The ideal standard would be a preparation of thyroglobulin extracted from the blood. Because of a too small quantity of circulating Tg the manufacturing of such a reference was not possible. The actual recommendation is to use 1:1 CRM 457 standardisation. The configuration of the Tg molecule is not enough taken into account in the various Tg methods.

2.2 Functional sensitivity

Since Tg measurements have to detect very small amount of thyroid tissue, it is absolutely necessary to determine the sensitivity of the Tg assays. The definition of the functional sensitivity was established by Spencer for the TSH (Spencer et al., 1996 a). The same concept can be applied to Tg (Spencer et al, 1996 b): it is the Tg value that can be measured with 20% between-run coefficient of variation (CV), using a 1:1 CRM 457 standardisation. The proposed protocol is similar for Tg with the establishment of a profile of precision

measuring human pool sera over 6 to 12 months (compatible deadline with the follow-up of the patients) with at least 2 batchs of reagents and 2 instrument calibrations (Baloch et al., 2003). The pools of serum used for this profile have to be TgAb negative. It must be repeated to the scientists how to verify the functional sensitivity of a Tg assay and not to take that given by the manufacturer. Analogous to TSH, Tg assay functional sensitivity permits a generational classification of Tg assays. Most current assays are actually first generation with a functional sensitivity about 0.5 to 1.0μg/L. The functional sensitivity is of a big importance to determine the «detectable Tg < institutional cut-off » mentioned in the European Consensus (Pacini et al., 2006) specially in the flow chart for the follow-up after initial treatment (6 to 12 months) and recombinant human thyrotropin (rhTSH). For example some authors (Kloos & Mazzaferri, 2005) considered a thyroglobulin cutoff level of 2.0μg/L highly sensitive for identifying persistent tumor after rhTSH stimulation in patients who had TSH-suppressed thyroglobulin undetectable with an assay functional sensitivity value of 1μg/L. This cut-off is also mentioned in the recommendations of the American Thyroid Association (Cooper et al., 2006).

In the European consensus, supersensitive Tg assays which have a higher sensitivity but at the expense of a much lower specificity are not currently recommended for routine use. Nevertheless some current assays are second generation with a ten-fold better functional sensitivity. An insufficient functional sensitivity is at the origin of most of false-negative results corresponding to an authentic recurrence of the disease with a value of Tg given undetectable. With a more sensitive second generation assay it would be possible to detect responses that will be undetectable with a first generation assay. At present this very low functional sensitivity for certain cases of dosages could allow to replace rhTSH stimulated Tg testing for the patients at low risk by a simple dosage of second generation Tg. Low risk patients are those with well-differentiated papillary or follicular thyroid cancer, patient age <45 years, thyroid tumor size ranging from 1 cm to <4 cm in diameter, no extension of the tumor beyond the thyroid capsule, no lymph-node involvement and no distant metastases (Schlumberger et al., 2007; Smallridge et al., 2007; Schlumberger et al., 2011).

2.3 Interference by TgAb

This type of analytical problem is completely characteristic of Tg assays and exists in no other immunoassay. It is connected to the fact that Tg is a major auto-antigen. All the actually methods are prone to interference by TgAb (Mariotti et al., 1995). The combined use of judiciously selected monoclonal antibodies directed against antigenic domains of Tg not recognized by most TgAb allowed to develop a Tg assay with minimal interference from TgAb (Marquet et al., 1996). In every case the presence of TgAb that mask certain epitopes can lead to underestimation of the Tg concentrations with the actuals immunometric methods.

We are however unable to evaluate the true interference of these TgAb: it is known that in some patients few Tgab can induce a major interference while in some others a lot of TgAb induce only a smooth interference. Everything depends on the affinity of these antibodies which we do not estimate. The various consensus recommend to measure antibodies by a enough sensitive method in a systematic way with any dosage of Tg. At first it had been suggested realizing a test of recovery to estimate the importance of the interference but this one was abandoned because of a bad standardization of the protocol

(Spencer et al, 1996c). When there is presence of TgAb and if Tg is found undetectable, its value is not interpretable. When the value of Tg is dosable with presence of antibodies, the returned value is then a "minimal" value knowing that she could be more raised in the absence of antibody. After thyroidectomy, TgAb will decrease and disappear in patients with remission but these antibodies may persist during 2-3 years after disappearance of Tg (Chiovato et al., 2003). During the follow-up of some patients persistence or reappearance of circulating TgAb may be regarded as an indicator of disease. More recently Spencer even concluded that TgAb trends can be used as a surrogate tumor marker in differentiated thyroid cancer in preference to Tg measurement, provided that the same method is used.

3. Thyroglobulin in fine needle aspiration biopsy

After surgery for differentiated thyroid cancer, cervical ultrasound is recommended to evaluate the thyroid bed and central and lateral cervical nodal compartments should be performed at 6 and 12 months and then annually for at least 3-5 years, depending on the patients' risk for recurrent disease and thyroglobulin status (Cooper et al., 2006). At present numerous studies describe the utility to look for thyroglobulin measurements in fine-needle aspiration biopsies (FNA-Tg) of lymph node (LN) during the follow-up of differentiated thyroid carcinoma. Although most patients have a long term survival rate, 5 to 20% of them will develop recurrence during follow-up, primarily in the cervical lymph nodes. An accurate distinction between metastatic and reactive benign lymph nodes (BLN) is essential in the management of thyroid cancer prior to surgery; it is necessary to specify the extent of surgery and identify early cervical relapse.

Cytological examination of fine-needle aspiration cytology (FNA-C) the reference method for the diagnosis of thyroid nodules has also been, until recently, the best method to diagnose a cervical LN in subjects with suspicion of thyroid cancer or patients followed for thyroid neoplasia. However, sensitivity of FNA-C is far from excellent, varying from 75 to 85% and altered by a high rate of non-diagnostic samples. Pacini was the first author who showed in 1992 high concentrations of thyroglobulin in metastatic LN of thyroid carcinoma. Although the performance of FNA-Tg is now well established, some methodological factors may influence the results and threshold value remains controversial. The first step is how to obtain the material from the fine needle aspiration. Ultrasound-guided fine-needle aspiration biopsy is carried out by a trained operator with a fine needle, preferably 25 to 27 gauges. After aspiration, the needle is rinsed.

3.1 The middle

The middle used to rinse the needle is variable according to the teams; it can be either physiological saline solution or a liquid supplied by the laboratory (assay buffer or Tg-free serum). Two studies show that some parasite effects are present in the dosage: some "noise" in the Tg assay was described by Baskin et al. (2004). Snozek et al. (2007) demonstrate with a recovery test (after an overload of exogenous Tg) that the values of Tg are 25% higher with the saline solution than with a serous matrix with his Tg assay. The nature of the buffer may have an influence on the conformation of proteins and affect antibody binding. The most important matrix effect is that due to the matrix used to prepare the calibration curve and

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the matrix to measure samples (Wild, 2005). We think that it is much better to use the Tg-free medium of the test kit to avoid bias in the determination of thyroglobulin in FNA wash samples (Bournaud et al., 2010). But for practical use the saline solution is often used and so it is recommended in the French good practice guide for cervical ultrasound scan and echo-guided techniques (Leenhardt et al., 2011) to check for the absence of matrix effect in the usual assay method. It is possible to validate the use of saline solution by comparing the results of Tg immunoreactivity obtained with Tg-free solution, saline solution and saline solution supplemented with serum albumin (Borel et al., 2008).

3.2 The volume

The quantity of the liquid used to rinse the needle varies between 0.5 to 1.0mL but is in general 1.0mL. All content of the needle is carefully removed by washing with from one to three pumping depending of the operator. Borel et al. (2008) shows that a triple pumping action of the 1 mL liquid through the needle was sufficient to wash out 97% of Tg out of the needle. If the needle has to be inserted several times into the same lymph node, the needle rinse can be poured into the same tube (Leenhardt et al., 2011).

3.3 The Tg method

The Tg method is the same used for the Tg serum assay. The problem of the interference by TgAb is however different. The presence of TgAb in fine needle aspiration biopsy washout can result of blood contamination when they are present or of active lymph node synthesis (Boi et al., 2006). But this interference seams to have small effect on the result of FNA-Tg. An explanation of this could be that the excessive high concentration of Tg is able to saturate TgAb binding sites. So it is not recommended to assay TgAb in the rinsing liquid (Leenhardt et al., 2011).

Another interference could be also evoked: the contamination with serum Tg. It seems that FNA-Tg is not affected by the circulating serum levels. In 2008 Borel et al calculate that the maximal contamination of FNA-Tg by serum Tg varied from 0.003 to 0.012% what is not significant. He measured also albumin in the LN washout to evaluate the contamination by plasma proteins. He concluded that serum Tg did not interfere in results of FNA-Tg and specially in negative controls (not thyroidectomized) who had undetectable FNA-Tg values.

3.4 The results and interpretation

The expression of the results varies according to studies. Some authors (Baskin, 2004; Boi et al, 2006; Kim et al, 2009) use the unit µg/L (or ng/ml), others (Pacini et al., 1992; Cignarelli et al., 2003; Borel et al., 2008; Bournaud et al., 2010) use µg/FNA. It is more suitable to use this type of result which reflects only the quantity of Tg present in the needle after rinsing and not a concentration of Tg in the LN.

We find here again the problem of functional sensitivity of the Tg method which directly affect the cut-off value. In the first study (Pacini et al., 1992), the cut-off value was 21.7µg/L but the functional sensitivity was only 3µg/L. This cut-off value was established as equal to the mean plus two standard deviations of the FNA-Tg values in patients with negative cytology. Other authors used the same type of cut-off (Cignarelli et al., 2003; Baskin, 2004;

Boi et al., 2006). In other studies of the literature threshold are sometimes the functional sensitivity (Cunha et al., 2007; Snozek et al., 2007) or study of sensitivity and specificity and choice of the better cut-off with a Receiver Operating Characteristic Curve (ROC) (Bournaud et al., 2010; Giovanella et al., 2011). For others again the FNA-Tg is compared with serum Tg: when the FNA-Tg value is greater than serum Tg value the LN is considered as metastasis (Uruno et al., 2005; Sigstad et al., 2007). However there is no correlation between serous Tg and FNA-Tg (Frasoldati et al., 1999). Kim et al. (2009) tested different threshold and propose a combination: the threshold values for FNA-Tg levels should be >10ng/ml if the serum Tg level or the mean plus two standard deviation in node-negative patients is not available for reference. Finally the French consensus (Leenhardt et al., 2011) recommends: Tg <1ng/FNA: normal result, Tg between 1 and 10 ng/FNA: to be compared with the results from cytology and Tg> 10 ng/FNA: suggest the presence of tumoral tissue.

FNA-Tg levels are significantly lower in subjects with metastatic poorly differentiated thyroid carcinoma than in subjects with differentiated thyroid cancer (Cignarelli et al., 2003) and may be nil (Boi et al., 2006), causing "false negatives" values.

Conversely FNA-Tg is particularly usefull for the diagnosis of LN metastasis when these LN have cystic changes (Cignarelli et al., 2003; Baloch et al., 2008). FNA-Tg is more sensitive for detecting metastasis when compared with FNA cytology (FNA-C) alone and allows the accurate diagnosis for samples with non conclusive cytology (Giovanella et al., 2011). For patients who received therapy with ^{131}I the delay between the treatment and FNA has to be enough long (more than 3 months) to allow definitive destruction of the metastatic LN because FNA-Tg value can be false-positive. Sensitivity of FNA-Tg in the different studies are comprise between 84% (Frasoldati et al., 1999) and 100% (Pacini et al., 1992; Snozek et al., 2007; Cunha et al., 2007; Sigstad et al., 2007). When FNA-Tg is combined with FNA-C 100% sensitivity and 100% specificity can be obtained (Bournaud et al., 2010; Giovanella et al., 2011). So FNA-C should remain combined with FNA-Tg (Leenhardt et al., 2011).

4. Conclusion

It seems that we can again progress in the evolution of the dosage of Tg in terms of quality. We underlined here the importance of analytical quality for a highly strategic parameter in the decision tree of the follow-up of differentiated thyroid cancer: the thyroglobulin. During these periods of great changes in laboratories with automation we have to remember ourselves another guideline: "choose a method Tg on the basis of its characteristics of performance not the costs". The biologist has to know all the difficulties of Tg assays to argue the choice of his method, to guarantee the quality of the dosage and to avoid serious medical errors especially in the follow-up of differentiated thyroid carcinoma. A good laboratory-physician dialogue is more than ever of great importance.

5. References

Baloch, Z.; Carayon, P.; Conte-Devolx, B.; Demers, L.M.; Feldt-Rasmussen, U.; Henry, J.F.; LiVosli, V.A.; Niccoli-Sire, P.; John, R.; Ruf, J.; Smyth, P.P.; Spencer, C.A.; Stockigt, J.R. & Guidelines Committee, National Academy of Clinical Biochemistry.(2003).

Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid,* Vol. 13, pp.3-126.

Baloch, ZW.; Barroeta, JE.; Walsh, J.; Gupta, PK.; Livolsi, VA.; Langer, JE & Mandel, SJ. (2008). Utility of thyroglobulin measurement in fine needle aspiration biopsy specimens of lymph nodes in the diagnosis of recurrent thyroid carcinoma. *Cytojournal* Vol.5, pp.1-5.

Baskin, HJ. (2004).Detection of recurrent papillary thyroid carcinoma by thyroglobulin assessment in the needle washout after fine-needle aspiration of suspicious lymph nodes. *Thyroid,* Vol. 14, pp.959-63.

Boi, F.; Baghino, G.; Atzeni, F.; Lai, ML.; Faa, G. & Mariotti, S. (2006). The diagnostic value for differentieted thyroid carcinoma metastases of thyroglobulin (Tg) measurement in washout fluid from fine-needle aspiration biopsy of neck lymph nodes is maintained in the presence of circulating anti-Tg antibodies. *J Clin Endocrinol Metab,* Vol.91, N0.4, pp.1364-9.

Borel, AL.; Boizel, R.; Faure, P.; Barbe, G.; Boutonnat, J.; Sturm, N.; Seigneurin, D.; Bricault, I.; Caravel, JP.; Chaffanjon, P. & Chabre, O. (2008). Significance of low levels of thyroglobulin in fine needle aspirates from cervocal lymph nodes of patients with a history of differentiated thyroid cancer. *Eur J Endocrinol,* Vol. 158, pp.691-8.

Borson-Chazot, F.; Bardet, S.; Bournaud, C.; Conte-Devolx, B.; Corone, C.; D'Herbomez, M.; Henry, JF.; Leenhardt, L.; Peix, JL.; Schlumberger, M.; Wemeau, JL.; Baudin, E.; Berger, N.; Bernard, MH.; Calzada-Nocaudie, M.; Caron, P.; Catargi, B.; Chabrier, G.; Charrié, A.; Franc, B.; Hartl, D.; Helal, B.; Kerlan, V.; Kraimps, JL.; Leboulleux, S.; Le Clech, G.; Menegaux, F.; Orgiazzi, J.; Perie, S.; Raingeard, I.; Rodien, P.; Rohmer, V.; Sadoul, JL.; Schwartz, C.; Tenenbaum, F.; Toubert, ME.; Tramalloni, J.; Travagli, JP. & Vaudrey, C. (2008). Guidelines for the management of differentiated thyroid carcinoma of vesicular origin. *Ann Endocrinol (Paris)* Vol. 69, pp.472-86.

Bournaud, C; Charrié, A.; Nozières, C.; Chikh, K.; Lapras, V.; Denier, ML.; Paulin, C.; Decaussin-Petrucci, M.; Peix, JL.; Lifante, JC.; Cornu, C.; Giraud, C.; Orgiazzi, J. & Borson-chazot, F. (2010). Thyroglobulin measurement in fine-needle aspirates of lymph nodes in patients with differentiated thyroid cancer: a simple definition of the threshold value, with emphasis on potential pitfalls of the method. *Clin Chem Lab Med*, Vol.48, N0.8, pp.1171-7.

Chiovato, I.; Iatrofa, F.; Braverman, LE. ; Pacini, F.; Capezzone, M.; Masserini, I.; Grasso, L. & Pinchera, A. (2003). A disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. *Ann Intern Med* Vol.139, pp.346-51.

Cignarelli, M.; Ambrosi, A.; Marino, A.; Lamacchia, O.; Campo, M.; Picca, G. & Giorgino, F. (2003). Diagnostic utility of thyroglobulin detection in fine-needle aspiration of cervical cystic metastatic lymph nodes from papillary thyroid cancer with negative cytology. *Thyroid* Vol.13, N012, pp.1163-7.

Cooper,DS.; Doherty, GM.; Haugen, BR.; Kloos, RT.; Lee, SL.; Mandel, SJ.; Mazzaferri, EL.; McIver, B.; Sherman, SI. & Tuttle, RM. (2006). Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* Vol.16, No.2, pp.109-42

Cunha, N.; Rodrigues, F.; Curado, F.; Ilheu, O.; Cruz, C.; Naidenov, P.; Rascao, MJ.; Ganho, J.; Gomes, I.; Pereira, H. Real, O.; Figueiredo, P.; Campos, B. & Valido, F. (2007). Thyroglobulin detection in fine-needle aspirates of cervical lymph nodes: a

technique for the diagnosis of metastatic differentiated thyroid cancer. *Eur J Endocrinol* Vol.157, pp.101-7.

Druetta, L.; Croizet, K.; Bornet, H. & Rousset, B. (1998). Analyses of the molecular forms of serum thyroglobulin from patients with Graves' disease, subacute thyroiditis or differentiated thyroid cancer by velocity sedimentation on sucrose gradient and Western blot. *Eur J Endocrinol*. Vol.139, pp.498-507.

Feldt-Rasmussen, U.; Profilis, C.; Colinet, E.; Black, E.; Bornet, H.; Bourdoux, P.; Carayon, P.; Ericsson, UB.; Koutras, DA.; Lamas de Leon, L.; DeNayer, P.; Pacini, F.; Palumbo, G.; Santos, A.; Schlumberger, M.; Seidel, C.; Van

Herle, AJ. & De Vijlder, JJ. (1996) (a). Human thyroglobulin reference material (CRM 457). 1st Part: Assessment of homogeneity, stability and immunoreactivity. *Ann Biol Clin (Paris)* Vol.54, pp.337-42. (b) a human thyroglobulin reference material (CRM 457). 2nd Part: Physicochemical characterization and certification. *Ann Biol Clin (Paris)* Vol.54, pp.343-8.

Frasoldati, A.; Toschi, E.; Zini, M.; Flora, M.; Caroggio, A.; Dotti, C. & Valcavi, R. (1999). Role of thyroglobulin measurement in fine-needle aspiartion biopsies of cervical lymph nodes in patients with differantiated thyroid cancer. *Thyroid*. Vol.9, pp.105-11.

Henry, M.; Malthiery, Y.; Zanelli, E. & Charvet, B. (1990). Epitope mapping of human thyroglobulin Heterogeneous Recognition by thyroid pathologic sera. *J Immunol* Vol.145, pp.3692-8.

Kim, MJ.; Kim, EK.; Kim, BM.; Kwak, JY.; Lee, EJ.; Park, CS.; Cheong, WY. & Nam, KH. (2009). Thyroglobulin measurement in fine-needle aspirate washouts: the criteria for node dissection for patients with thyroid cancer. *Clin Endocrinol* Vol.70, pp.145-51.

Kloos, RT. & Mazzaferri, EL. (2005). A single recombinant human thyrotropin-stimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. *J Clin Endocrinol Metab*. Vol.90, pp.5047-57.

Kohno, Y.; Tarutani, O.; Sakata, S. & Nakajima, H. (1985).Monoclonal antibodies to thyroglobulin elucidate differences in protein structure of thyroglobulin in healthy individuals and those with papillary adenocarcinoma. *J Clin Endocrinol Metab* Vol.61, pp.343-50.

Leenhardt, L.; Borson-Chazot, F.; Calzada, M.; Carnaille, B.; Charrié, A.; Cochand-Priolet, B.; Cao, CD.; Leboulleux, S.; Le CLech, G.; Mansour, G.; Menegaux, F.; Monpeyssen, H.; Orgiazzi, J.; Rouxel, A.; Sadoul, JL.; Schlumberger, M.; Tramalloni, J.; Tranquart, F.; Wemeau, JL.; (2011).Good practice guide for cervical ultrasound scan and echo- guided techniques in treating differentiated thyroid cancer of vesicular origin. *Ann Endocrinol* Vol. 72, pp.173-97.

Malthiery, Y. & Lissitzky, S. (1987). Primary structure of human thyroglobulin deduced from the sequence of its 8448-base complementary DNA *Eur J Biochem* Vol.165, pp.491-8.

Mariotti, S.; Barbesino, G.; Caturegli, P.; Marino, M.; Manetti, L.; Pacini, F.; Centoni, R. & Pinchera, A. (1995). Assay of thyroglobulin in serum with Tg antibodies: un obtainable goal? *J Clin Endocrinol Metab* Vol.90, pp.5566-75.

Pacini, F.; Fugazzola, I.; Lippi, F.; Ceccarelli, C.; Centoni, R. & Miccoli, P. (1992). Detection of thyroglobulin in fine needle aspirates of nonthyroidal neck masses: a clue to

diagnosis of metastasis differentiated thyroid cancer. *J Clin Endocrinol Metab* Vol.74, pp.1401-4.

Pacini, F. Schlumberger, M.; Dralle, H.; Elisei, R.; Smit, JWA.; Wiersinga, W.& the European Thyroid Cancer Taskforce (2006). European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *Eur J Endocrinol* Vol.154, pp.787-803.

Persani, L.; Ferrari, M.; Borgato, S.; Bestagno, M.; Faglia, G. & Beck Peccoz, P. (1998). Concanavalin A affinity chromatography can distinguish serum thyroglobulin (Tg) from normal subjects or patients with differentiated thyroid cancer. *J Endocrinol Invest* Vol.21 No.Suppl 4, pp.4.

Piechaczyck, M.; Chardès, T.; Cot, C.; Pau, B. & Bastide, JM. (1985). Production and characterisation of monoclonal antibodies against human thyroglobulin *Hybridoma* Vol.4, pp.361-7.

Preissner, CM.; O'Kane, DJ.; Singh, RJ.; Morris, JC. & Grebe, SK. (2003). Phantoms in the assay tube: heterophile antibody interferences in serum thyroglobulin assays. *J Clin Endocrinol Metab* Vol.88, pp.3069-74.

Schlumberger, M.; Hitzel, A.; Toubert, ME.; Corone, C.; Troalen, F.; Schlageter, MH.; Claustrat, F.; Koscielny, S.; Taieb, D.; Toubeau, M.; Bonichon, F.; Borson-Chazot, F.; Leenhardt, L.; Schwartz, C.; Dejax, C.; Brenot-Rossi, I.; Torlontano, M.; Tenenbaum, F.; Bardet, S.; Bussière, F.; Girard, JJ.; Morel, O.; Schneegans, O.; Schlienger, JL.; Prost, A.; So, D.; Archambaud, F.; Ricard, M. & Benhamou, E. (2007). Comparison of seven serum thyroglobulin assays in the follow-up of papillary and follicular thyroid cancer. *J Clin Endocrinol Metab* Vol.92, pp.2487-95.

Schlumberger, M.; Borget, I.; Nascimento, C.; Brassard, M. & Leboulleux S (2001). Treatment and follow-up of low-risk patients with thyroid cancer. *Nat Rev Endocrinol* Vol7, pp.625-8.

Schultz, R.; Bethauser, H.; Stempka, L.; Heilig, B.; Moll, A. & Hufner, M. (1989). Evidence for immunological differences between circulating and tissue-derived thyroglobulin in men. *Eur J Clin Invest* Vol.19, pp.459-63.

Sigstad, E.; Heilo, A.; Paus, E.; Holgersen, K.; Groholt, KK.; Jorgensen, LH.; Bogsrud, TV.; Berner, A. & Bjoro, T. (2007). The usefulness of detecting thyroglobulin in fine-needle aspirates from patients with neck lesions using a sensitive thyroglobulin assay. *Diagn Cytopathol* Vol.35, pp.761-7.

Sinadinovic, J.; Cvejic, D.; Savin, S.; Jancic-Zuguricas, M. & Micic, JV. (1992). Altered terminal glycosylation of thyroglobulin in papillary thyroid carcinoma. *Exp Clin Endocrinol.* Vol.100, pp.124-8.

Smallridge, RC.; Meek, SE.; Morgan, MA.; Gates, GS.; Fox, TP.; Grebe, S. & Fatourechi, V. (2007). Monitoring thyrogloulin in a sensitive immunoassay has comparable sensitivity to recombinant human TSH stimulated thyroglobulin in follow-up of thyroid cancer patients. *J Clin Endocrinol Metab* Vol.92, pp.82-7.

Snozek, CL.; Chambers, EP.; Reading, CC. ; Sebo, TJ.; Sistrunk, JW. ; Singh, RJ. & Grebe, SK. (2007). Serum thyroglobulin, high resolution ultrasound and lymph node thyroglobulin in diagnosis of differentiated thyroide carcinoma nodal metastases. *J Clin Endocrinol Metab*, Vol. 92, pp. 4278-81.

Spencer, C.; Takeuchi, M. & Kazarosyan, M. (1996), (a) Current status and performance goals for serum thyrotropin (TSH) assays. *Clin Chem* Vol42, pp.140-45 (b) Current

status and performance goals for serum thyroglobulin assays. *Clin Chem* Vol.42, pp.164-73 (c) Recoveries cannot be used to authenticate thyroglobulin (Tg) when sera contain Tg autoantibodies. *Clin Chem* Vol.42, pp.661-3.

Uruno, T.; Miyauchi, A.; Shimizu, K.; Tomoda, C.; Takamura, Y.; Ito, Y.; Miya, A.; Kobayashi, K.; Matsuzukz, F.; amino, N. & Kuma, K. (2005). Usefulness of thyroglobulin measurement in fine-needle aspiration biopsy specimens for diagnosing cervical lymph node metastasis in patients with papillary thyroid cancer. *World J Surg* Vol.29, pp.483-5.

Van de Graf, SA.; Pauws, E.; de Vijlder, JJ. & Ris-Stalpers, C. (1997). The revised 8307 base pair coding sequence of human thyroglobulin transiently expressed in eukaryotic cells. *Eur J Endocrinol* Vol.136, pp.508-15.

Wild, D. (Ed). (2005). *The immunoassay handbook*, Third edition, Elsevier Ltd Publisher, ISBN-10: 0080445268, London
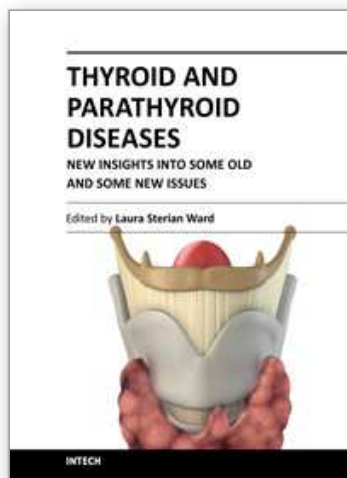
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This book was designed to meet the requirements of all who wish to acquire profound knowledge of basic, clinical, psychiatric and laboratory concepts as well as surgical techniques regarding thyroid and parathyroid glands. It was divided into three main sections: 1. Evaluating the Thyroid Gland and its Diseases includes basic and clinical information on the most novel and quivering issues in the area. 2. Psychiatric Disturbances Associated to Thyroid Diseases addresses common psychiatric disturbances commonly encountered in the clinical practice. 3. Treatment of Thyroid and Parathyroid Diseases discusses the management of thyroid and parathyroid diseases including new technologies.

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