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Molecular technology and the recombinant TSH have changed diagnostics of thyroid carcinoma with positive I-131 whole body scan but low serum thyroglobulin

Liliana Montella[1,4], Michele Caraglia[2,4], Alberto Abbruzzese[2], Andrea Soricelli[3], Salvatore Del Prete[1], Giovanni Squame[3] and Marco Salvatore[3]

[1]Operative Unit of Medical Oncology
"S. Giovanni di Dio" Hospital, Frattamaggiore, Italy
[2]Department of Biochemistry and Biophysics
Second University of Naples, Italy
[3]Diagnostic Imaging and Radiotherapy
Department, "Federico II" University, Naples, Italy
[4]Corresponding author: Tel/Fax, 39-081-8991233;
E-mail, limontel@libero.it; michele.caraglia@unina2.it

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Abbreviations: DTC, differentiated thyroid carcinoma; Tg, thyroglobulin; TSH, thyroid stimulating hormone; WBS, whole body scan

Abstract

The early detection of recurrent differentiated thyroid carcinoma (DTC) cells in the post surgery DTC patients relies on the sensitivity of measuring both the level of thyroglobulin (Tg) and 131-Iodine distribution by Whole Body Scan (WBS). Undetectable level of Tg associated with negative WBS or elevated levels of Tg associated with positive WBS ("concordant") is ordinarily indicative of either absence or presence of disease. At times, elevated level of Tg with negative WBS or low levels of Tg with positive WBS ("discordant") could also occur. In the present study, we retrospectively reviewed series of 573 patients with DTC followed in the Diagnostic Imaging and Radiotherapy of the University "Federico II" of Naples between 1993 and 1997. We focused on 9 out of 573 patients (1.56%) who had a discordant pattern with low level of Tg/positive WBS in the post-surgical follow-up. Four patients were metastatic at presentation while 5 patients with metastasis during follow-up still remained in persistently low levels of Tg (<5 ng/mL). This result does point to some flaw in the evaluation of "discordant" cases. Reviewing data previously described series by resetting cut-off values of Tg <1 ng/ml as undetectable changed the apparent "discordant" subgroup of patients into "concordant". Recent introduction of recombinant human TSH (rhTSH) to enhance the expression level of Tg brought significant increase in the sensitivity of diagnostic evaluation of thyroid cancer patients. The role of burdensome WBS in the follow up evaluation of DTC patients is significantly reduced over time especially in low-risk patients while the relevance of Tg assay is steadily increased. Sensitive Tg assays, significantly improved our ability to assess disease status in follow-up of DTC. Given the possibility of late disease relapses, the need for long-term follow-up, and reduced delay in treatment of persistent disease, there is still need for greater sensitive diagnostic tools for DTC.

Keywords: differentiated thyroid carcinoma; follow-up; thyroglobulin; whole body scan

Introduction

The aim of the post-surgical follow-up in patients with differentiated thyroid carcinoma is the early discovery of persistent or recurrent disease. Sensitive monitoring for thyroid cancer recurrence includes ^{131}I whole body scan (WBS) and measurement of serum thyroglobulin (Tg) after withdrawal of thyroid hormone (Ronga *et al.,* 1990; Pacini *et al.,* 1995) and, more recently, after exogenous administration of rhTSH, which avoids the need for discontinuing thyroid hormone. Recently, large clinical studies have demonstrated the safety and efficacy of rhTSH in stimulating the uptake of diagnostic doses of radioiodine as well as the release of Tg by thyroid remnants and metastatic lesions of well differentiated thyroid carcinoma (Ladenson *et al.,* 1997; Mazzaferri, Kloos 2002).

Regarding the results of Tg and WBS, different subgroups of patients can be identified. Undetectable serum Tg levels are found in the large majority of disease-free patients, while elevated concentrations of serum Tg are associated with the presence of residual or metastatic thyroid tissue. Patients who are

thyroglobulin-positive but radioiodine-negative ("discordant" results) are a clinical challenge. Moreover, previous series also described DTC patients showing low Tg and positive WBS ("discordant results"). Patients with elevated Tg levels, but negative ^{131}I WBS, are usually not treated with high- dose ^{131}I. In fact, the therapeutic benefit of a "blind" radioiodine treatment is not clear (van Tol *et al.,* 2003). The detection of neoplastic foci not seen with diagnostic doses of ^{131}I by other imaging techniques may identify patients candidate to treatment. Recently, positron emission tomography (PET) with 18-fluoro-2- deoxy-glucose (FDG) has been introduced to detect metastatic lesions in patients with DTC who present with elevated hTG and negative ^{131}I WBS (Hung *et al.,* 2003; Wu *et al.,* 2003). Tc-99m Tetrofosmin Single Photon Emission Computed Tomography is a useful additional tool to detect metastatic lesions in DTC (expecially papillary) with elevated hTg but negative ^{131}I WBS. However, smaller lymph nodes and miliary lung metastases may be missed (Wu *et al.,* 2003). However, many economic and practical problems are associated with a wide use of these imaging techniques.

The percentage of patients with low levels of Tg and positive WBS usually described in the different patient series is low (Ashcraft, Herle 1981; Arning *et al.,* 1987; Black *et al.,* 1987).

Pacini *et al.* have recently suggested that the presence of undetectable levels of serum Tg off L-T4 at the time of the first control with WBS after initial treatment, is highly predictive of complete and persistent remission. With the exception of detecting persistent thyroid bed uptake in a minority of cases, the control WBS has never given information that could influence the following therapeutic strategies. On this basis, it is proposed that the diagnostic ^{131}I WBS may be avoided in patients with undetectable levels of Tg off L-T4 (Pacini *et al.,* 2002). Before the introduction of recombinant TSH and modern biochemical assays diagnostic ^{131}I WBS was routinely performed in the follow-up of these patients.

In this paper we have retrospectively reviewed the files of all patients treated with ^{131}I prior to the introduction of recombinant TSH at the Nuclear Medicine Therapy Unit of the University “Federico II” of Naples and identify the subgroup of patients with low levels of Tg and positive WBS. This revision led us to review papers published on DTC surveillance prior and after the introduction of recombinant TSH in clinical practice. The variety of data published in the pre-recombinant TSH era may comprehensively be interpreted as a result of different cut-off levels of Tg used. Nowadays the available sensitive Tg assays have redefined surveillance guidelines.

Subjects and Methods

We reviewed the data of 573 patients with DTC treated with ^{131}I between 1993 and 1997. We have revised the records of 451 (79%) females and 122 (21%) males, ranging in age from 13 to 82 yr (mean age: 47.5 years). Four-hundred-twenty-five (74.2%) patients had papillary carcinoma, 128 (22.3%) had follicular carcinoma and 20 (3.5%) had Hurtle carcinoma.

After surgery, all patients underwent residual thyroid ablation with radioiodine. Post-therapy WBSs were performed 2-10 days later and patients were given suppressive therapy with L-Thyroxine. After ablation, patients underwent periodical clinical controls, including detection of Tg and anti-thyroglobulin antibodies (TgAbs) during treatment and after the suspension of therapy with L-Thyroxine and diagnostic WBSs.

To select patients with low Tg/positive WBS a serum Tg levels $<$ 5 ng/ml was considered as “low”, during and after suspension of therapy. Serum Tg $>$ 5 ng/ml was considered as “high”. All patients characterized in this subgroup had levels of TgAbs lower than 30 U/ml.

WBSs were performed after withdrawal of L-Thyroxine (T4) therapy. T4 was withdrawn for 45 days and substituted for triiodothyronine that was withdrawn 15-20 days before WBS. WBS was performed 2 days after the administration of 110-185 MBq ^{131}I.

Results

In our series 9 out of 573 patients (1.56%) showed persistent low levels of Tg and positive WBS. All patients but two underwent previous total thyroidectomy. The characteristics of this subgroup of patients were the following: age range 20-75 years (mean: 47 years), 8 females/1 male, 5 papillary carcinomas/4 follicular carcinomas.

The WBS performed after ablation showed the presence of thyroid bed uptake in all patients. Post-ablation WBS visualized lung and bone metastases in 2 and 1 patients, respectively. The other patients developed metastases during follow-up with an interval ranging from 1 to 3 years from diagnosis. Relapse occurred exclusively in the neck in one patient, in the lungs in 3 patients and in lymph nodes in two patients. One patient presented concomitant lymph node and bone metastases and two patients showed lymph node and lung involvement by disease. In most cases diagnostic WBS overlapped therapeutic WBS. In 3 cases therapeutic WBS was able to show additional sites of metastases not visualized by diagnostic scans. Different imaging techniques (computed

Table 1. Clinical and scintigraphic data of patients with low Tg/positive WBS.

No	Sex/ Age	Histology	Thyroidectomy	^{131}I	post-ablation WBS	Range hTg (ng/mL)	WBS
1	F/20	Pap.	total thy.	2590 MBq (Jan '93) 1110 MBq (Nov '96)	+ neck, med.	1.8-3.0	dWBS (Dec '93): N dWBS (Nov '96): Lym Met tWBS (Nov '96): Lym Met, Lung Met
2	F/68	Pap.	total thy.	2960 MBq (July '93)	N	0.1-5.0	dWBS (May '97): Med Met
3	F/51	Foll.	total thy.	4662 MBq (Sep '93) 7400 MBq (Oct '94)	Res.	2.0-4.0	dWBS (June '94) : + thyroid reg. tWBS (Oct '94) :+ thyroid reg.
4	F/38	Pap.	total thy	1850 MBq (March '96) 1110 MBq (March '97)	Res.	1.0-5.0	dWBS (March '97) :Lym. Met.
5	F/62	Pap.	total thy.	7400 MBq (March '96) 7400 MBq (April '96) 7400 MBq (Sep '97)	Res, Lung Met	1.0-3.0	tWBS (March '97): Lung Met tWBS (Sep '97) :N
6	F/75	Foll.	total thy	7400 MBq (June '96) 5550 MBq (Dec '96) 7400 MBq (April '97)	Bone Met	1.0-5.0	tWBS (Dec '96): Bone Met tWBS (April '97) : Lym Met, Bone Met

tomography, magnetic resonance, bone scintigraphy) were performed to confirm the metastases according to the location. In all patients but one (patient n.8) the sites of ^{131}I trapping resulted to be metastases. In fact in patient n.8 the uptake in the right hypocondrium showed by therapeutic WBS did not correspond to any abnormality in the other imaging techniques. All patients with confirmed metastases were treated with repeated doses of radioiodine. In 2 cases therapeutic WBS was able to show additional sites of metastases not visualized by diagnostic scans.

All patients presented persistent low levels of Tg, as defined by chosen cut-off, with a maximum of 5 ng/mL in 3 patients. However, with a lower cut-off to define Tg as low ($<$1 ng/mL) the apparent discordant pattern of this subgroup of patients changes into a concordant one, and the described subgroup results to have concordant findings.

Discussion

Although in most patients there is concordance between the results of WBS and Tg, there is the possibility of disagreement between the two most important diagnostic tools in the follow-up of treated DTC. In our study we selected patients presenting persistent low levels of Tg ($<$5 ng/ml) and WBS images showing iodine uptake at periodic follow-up evaluations.

Metastatic spread detected only by WBS associated with lacking rises of Tg levels can be explained by several reasons such as the small size of tumor, unable to release detectable amounts of Tg (Muller-Gartner, Schneider 1988), or loss of the ability of secreting Tg with preserved capability of ^{131}I trapping (Ashcraft, Herle 1981; Ronga *et al.,* 1990; Franceschi 1996). Moreover, in the presence of residual and/or recurrent thyroid disease and/or local neck metastases, usually Tg values do not significantly arise, while diagnostic WBS shows ^{131}I uptake in these regions. In these cases diagnostic WBS can give more clinical information than serum Tg measurements (Müller-Gärtner, Schneider 1988; Aiello, Manni 1990; Pacini *et al.,* 1995; Franceschi 1996). Another explanation of low levels of Tg in patients with persistent disease identified by scintigraphy can be found in structural changes of Tg which can occur as integral part of malignant transformation (Ashcraft, Herle 1981; Black *et al.,* 1981; Franceschi *et al.,* 1996). The alterations of Tg structure can be based on reduced iodine content (Schneider *et al.,* 1983; Kohno *et al.,* 1987), and different amounts of several amino acids and monosaccharides as demonstrated by Kohno et al. who found that Tg in papillary adenocarcinomas differs from normal Tg (Kohno *et al.,* 1987).

Low levels of Tg can be artificially induced by circulating anti-Tg antibodies (Ashcraft, Herle 1981), which can favour the metabolic clearance of Tg and cause apparently reduced Tg values. Patients who underwent near total thyroidectomy or total thyroidectomy followed by ^{131}I ablation can also show a progressive decrease of Tg as demonstrated by a 18 year follow-up study (Ozata *et al.,* 1994). ^{131}I ablation

and T4-suppressive therapy may play a role in determining gradual atrophy or death of residual cells able to produce Tg (Ozata *et al.,* 1994). Therefore, the possibility of changes in biology and clinical appearance of disease has to be kept into account during long-term follow-up.

As Tg can be low in patients with metastases, it is critical to define which serum Tg value must be considered in order to distinguish between presence or absence of disease. In presence of normal thyroid tissue, such as in patients with a partial thyroidectomy with or without ablation, the diagnostic value of Tg measure is obviously poor (Ozata *et al.,* 1994). Different cut-off Tg values have been used in order to detect patients with active disease from those without known cancer. Using a cut-off Tg value of 10 ng/ml, Tg and WBS were considered both necessary in the follow-up of treated DTC (Schneider *et al.,* 1981; Blahd 1990). Colacchio *et al.* (Colacchio *et al.,* 1982) reached the same conclusions using a cut-off of 15 ng/ml. In their study 3/34 (8.8%) patients having low Tg presented recurrences.

Black *et al.* (Black *et al.,* 1987), using a cut-off Tg level of 5 ng/ml, found a positive correlation between low serum Tg and absence of disease of 95.9%. They reported a percentage of 1.7% cases with abnormal WBS and low Tg, which was considered "an acceptable false negative figure". They concluded that Tg can be routinely used because it is sensitive, specific and less expensive than WBS, which might be performed only if Tg was elevated or if clinical examination detected signs of disease. With the same cut-off, Tg was undetectable during off-suppression therapy in 15/55 patients with metastases (15/359 overall patients, 4.2%) in the study performed by Franceschi *et al.* (Franceschi *et al.,* 1996). Ozata *et al.* (Ozata *et al.,* 1994) reported that a Tg level less than 5 ng/ml during on-therapy correlated with the absence of tumour in 95% of patients. In this study no patient who underwent near total thyroidectomy or total thyroidectomy and ^{131}I ablation with Tg values <2 ng/ml on- or <3 ng/ml during off-therapy showed recurrences or persistent disease. At the time of recurrence 20% of patients had Tg values <5 ng/ml, but such measurements had been obtained during suppressive therapy. These authors concluded that Tg and WBS are both necessary in the follow-up study of patients with DTC and a Tg level as defined above was "highly indicative of a cancer-free state".

In a series of 53 patients, Ashcraft and Van Herle (Ashcraft, Herle 1981) found no metastases in patients whose Tg was below 1 ng/ml during on-suppressive therapy or less than 10 ng/ml during off-T4. These authors considered WBS unnecessary if Tg value is less than 1 ng/ml during T4 or less than 10 ng/ml during off-T4. They analyzed data of 1323 reported cases of DTC comparing Tg and WBS. Among 284 cases with documented metastases, 12 had undetectable Tg levels by the investigators' criteria.

Sixteen out of 374 patients (4.3%) with undetectable Tg (lower detection limit of the assay: 3 ng/ml) were found by Müller-Gärtner and Schneider (Muller-Gartner, Schneider 1988).

They found that so called "false negative Tg determinations" were associated with papillary histologic characteristics, manifestation in lymph nodes of the neck or mediastinum, and small size. In our series of thyroid cancer patients, using a cut-off of 5 ng/ml, we identified 9 patients (9/573, 1.56%) with low Tg levels and positive scans. However, no patient with low/undetectable Tg and positive WBS should be identified if a cut-off of 1 ng/ml is selected. The previous described studies reporting different percentages of patients with low Tg/positive WBS were conditioned by the Tg assays used and the cut-off adopted. With advent of more modern biochemical assays, the value of diagnostic WBS decreases (Pacini *et al.,* 2002).

The ability to obtain stimulated Tg-values under recombinant human TSH (Ladenson *et al.,* 1997; Ramirez *et al.,* 1997) further reduced the need for WBS. The recent cloning of human TSH-beta gene has allowed the production of rhTSH by recombinant DNA technology in mammalian cells (Chinese hamster ovary cells) (Cole *et al.,* 1993). In details, stable transfectants which expressed high levels of rhTSH were selected, and subsequently cultured on microcarrier beads. The rhTSH-containing media, produced under serum-free conditions, were clarified and purified by a combination of ion exchange, dye and gel filtration chromatographies in order to obtain highly purified rhTSH. The use of rhTSH avoids the debilitating effects of hypothyroidism and its use successfully promotes iodine uptake and increases the sensitivity of serum Tg testing. Eight studies show that 21% of 784 patients who had no clinical evidence of tumor with baseline serum Tg levels usually below 1 μg/liter during THST had, in response to recombinant human TSH, a rise in serum Tg to more than 2 μg/liter (Mazzaferri *et al.,* 2003). Ten studies comprising 1,599 patients demonstrate that a TSH-stimulated Tg test using a Tg cutoff of 2 μg/liter (either after thyroid hormone withdrawal or 72 h after rhTSH) is sufficiently sensitive to be used as the principal test in the follow-up management of low-risk patients with DTC and that the routine use of diagnostic whole body scanning in follow-up should be discouraged (Mazzaferri *et al.,* 2003). Thyroglobulin auto-antibodies remain a significant obstacle to thyroglobulin measurement. Tg mRNA measurement from peripheral blood has been tested as an alternative to

serum Tg determination in these instances. Although the measurement of Tg mRNA hold great promise, recent results are disappointing (Elisei *et al.,* 2004). Unlike anti-Tg autoantibody interferences, heterophile antibody (HAB) immunoassay interferences are not well recognized by laboratorians or clinicians as a Tg assay problem. When HAB interferences occur, they usually result in false positive test results (Preissner *et al.,* 2003). With the current trend to treat some thyroid cancer patients with radioiodine on the basis of an elevated serum Tg result alone, this has the potential to result in unwarranted therapy. The immunoradiometric assay (IRMA) is currently considered the gold standard for Tg measurement. However, in a recent study a comparison among the results obtained by seven types of assays were widely dispersed and the classification of thyroid cancer patients according to Tg appeared to be strongly dependent on the assay used (Ferrari *et al.,* 2003). We can highlight once again the limited value of patient classification used in the past. Despite the significant advancements, Tg measurement is still today affected by a relevant degree of analytic inaccuracy. New types of assays seem promising especially to detect low Tg concentration (Morgenthaler *et al.,* 2002; Zophel *et al.,* 2003). However, the interpretation of any given thyroglobulin value always requires the careful synthesis of all clinical and laboratory data available to the clinician.

In conclusion, the experimental advances in molecular medicine based on recombinant protein engineering and on the improvement of serum protein detection assays have changed the diagnostic algorithm of DTC and increased the sensitivity of determination of patients with advanced DTC.

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