

# Possible Explanations for Patients with Discordant Findings of Serum Thyroglobulin and $^{131}\text{I}$ Whole-Body Scanning\*

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The long-term monitoring of patients with differentiated thyroid carcinoma (DTC) is essential throughout the patient's life after total or near-total thyroidectomy followed by  $^{131}\text{I}$  remnant ablation and thyroid hormone suppression of thyroid-stimulating hormone (TSH). Sensitive surveillance for DTC recurrence and metastases includes radioiodine diagnostic whole-body scanning (DWBS) and measurement of serum thyroglobulin (Tg) after endogenous or exogenous TSH stimulation. Serum Tg levels during thyroid hormone withdrawal (Tg-off) are usually well correlated with the results of DWBS. In general, undetectable Tg levels with negative DWBS (DWBS<sup>-</sup>) suggest complete remission, whereas detectable or elevated Tg concentrations are suggestive of the presence of  $^{131}\text{I}$  uptake in local or distant metastases. However, DTC patients with discordant results of Tg measurement and  $^{131}\text{I}$  WBS have been observed in the follow-up study. Negative  $^{131}\text{I}$  DWBS and a positive Tg test (DWBS<sup>-</sup> Tg<sup>+</sup>) are found in most of these cases. Positive  $^{131}\text{I}$  DWBS and a negative Tg test (DWBS<sup>+</sup> Tg<sup>-</sup>), though of uncommon occurrence, has also been demonstrated in a small but significant number of cases. With this scenario, one should first attempt to uncover a cause for possibly false-negative or false-positive  $^{131}\text{I}$  WBS or serum Tg. Explanations for the discordance are speculative but should be scrutinized when confronted with discrepant data in a given patient.

**Key Words:** differentiated thyroid carcinoma; thyroglobulin;  $^{131}\text{I}$ ; whole-body scanning

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**T**he predominant method for treatment of differentiated thyroid carcinoma (DTC) is total or near-total thyroidectomy followed by  $^{131}\text{I}$  remnant ablation and thyroid hormone suppression of thyroid-stimulating hormone (TSH). The prognosis of DTC is generally considered favorable

with an 80%~95% overall survival rate at 10 y for middle-age adults (1). Local recurrences and distant metastases are not seen frequently, particularly during the first years of follow-up, but sometimes occur many years later, with the overall survival decline to 40% when distant metastases are present (2). Therefore, long-term monitoring of DTC recurrence and metastases is essential throughout the patient's life. Generally, 2 “markers” of thyroglobulin (Tg) and  $^{131}\text{I}$  whole-body scanning (WBS), when used at the same time, offer the best possibilities in the follow-up of patients with DTC. Serum Tg levels during thyroid hormone withdrawal (Tg-off) are usually correlated with the results of diagnostic WBS (DWBS). Undetectable Tg levels with negative DWBS (DWBS<sup>-</sup>) suggest complete remission, whereas detectable or elevated Tg concentrations are associated with the presence of  $^{131}\text{I}$  uptake in local or distant metastases (3). However, discordant results of Tg measurement and  $^{131}\text{I}$  WBS have been reported. Negative  $^{131}\text{I}$  DWBS and a positive Tg test (DWBS<sup>-</sup> Tg<sup>+</sup>) were found in most of these cases (4–6). The uncommon occurrence of positive  $^{131}\text{I}$  DWBS and a negative Tg test (DWBS<sup>+</sup> Tg<sup>-</sup>) has also been demonstrated in a small but significant number of cases (7,8). With this scenario, one should first attempt to uncover a cause for possibly false-negative or false-positive  $^{131}\text{I}$  WBS or serum Tg.

In this article, we will review the available literature to uncover the possible causes of the discordance between Tg and  $^{131}\text{I}$  WBS.

## FALSE-POSITIVE Tg

Tg is produced only by thyroid follicular cells. Therefore, if all normal and malignant thyroid tissue is successfully ablated, any Tg that is detected subsequently in a patient with DTC can only be the product of recurrent malignancy. This concept led to the initial studies that indicated the usefulness of isolated and serial serum Tg determinations as a marker for DTC and as an indicator of the effectiveness of surgery and  $^{131}\text{I}$  therapy (9). In patients with DTC, the Tg level depends on the capacity of the tumor to respond to endogenous or exogenous TSH stimulation, the ability of

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the tumor to synthesize and release immunologically active Tg, the amount of thyroid tissue remnant, and the tumor size (10).

At present, immunoassays available to measure serum Tg include single- and double-antibody radioimmunoassays (RIAs), immunoradiometric assays (IMAs), and the enzyme-linked immunosorbent assay. The most popular commercial assays are IMAs. The accurate measurement of Tg is technically challenging. The presence of anti-Tg antibodies (Tg Ab) usually invalidates the serum Tg result because any change in the concentration or affinity of Tg Ab has the potential to alter the measured Tg value (11). For patients with positive Tg Ab, Tg circulates as both free and complexed with Ab. As a result, measurement of Tg offers little reliable information. No method of Tg measurement seems to be unaffected by Tg Ab interference. The magnitude and direction of Tg Ab interference with serum Tg measurements is determined by the characteristics of the Tg methods used (12). IMA methodology cannot quantify Tg moieties complexed with Tg Ab. This results in an underestimation of the total Tg concentration of the specimens (11). Some RIA methods that incorporate specific separation systems against heterologous antibodies and quantify both the free and Tg Ab-complexed Tg molecules in the specimens can result in falsely elevated levels and overestimation of serum Tg. These technical differences may explain the discordance seen between the Tg values of Tg Ab-positive specimens when measured by both RIA and IMA, with the Tg RIA result typically  $\leq 2.8$  ng/mL and the IMA result undetectable (10,12).

Ways can be found to minimize the interference of Tg Ab. According to the new Academy of Clinical Biochemistry (ACB) guidelines, Tg should be measured in serum free of Tg Ab, which must be also measured in the same serum sample (11). Tg Ab concentrations should be determined by a sensitive, quantitative immunoassay method (not a qualitative insensitive agglutination test) (9,10,13), not only because Tg Ab concentrations below the sensitivity limit of agglutination tests may well interfere with serum Tg measurement (13,14) but also because Tg Ab immunoassays are standardized and reported in IU/mL, whereas qualitative agglutination is reported as a titer (1:100; 1:400, etc.) (12). Therefore, physicians should know the Tg methods used by the units of measurement. They should also quantitatively analyze Tg Ab on each specimen because the Tg Ab status of patients can change from positive to negative, and vice versa.

Serial serum Tg Ab per se can be detected as an independent surrogate tumor marker test (15). Specifically, Tg Ab-positive patients who are rendered athyreotic by their initial treatment typically display progressively declining postoperative serum Tg Ab concentrations (on L-3,5,3',5'-tetraiodothyronine [ $T_4$ ] therapy) often to undetectable levels by the third postoperative year (12). In contrast, patients with persistent or recurrent disease usually display stable or rising Tg Ab levels. Thus, serial measure-

ment of Tg Ab may itself be of prognostic value. However, as many as 10% patients may have stable or increasing Tg Ab concentrations because of the existence of undetectable and stable microscopic disease or lymphocytic memory cells capable of producing antibodies for extended periods of time (10).

Recombinant human thyrotropin (rhTSH) stimulation is not an answer—not only because rhTSH-stimulated serum Tg responses are often blunted or absent in Tg Ab-positive patients but also because the clearance of free and Tg Ab-complexed Tg is different, which most likely underlies many paradoxical rhTSH stimulation test results.

Serum thyroid peroxidase (TPO) polypeptide-specific antigen has been proposed as a potential alternative tumor marker (16). Recently, several groups have evaluated reverse transcription polymerase chain reaction of thyroid-specific Tg and TSH receptor messenger RNA (mRNA) in peripheral blood as a tumor marker (17). Although considerable overlap in absolute values has been observed between patients with thyroid remnants and those with recurrence or metastases, these techniques may be valuable in serial follow-up of Tg Ab-positive patients. However, Eszlinger et al. (18) have shown recently that the detection and quantification of Tg mRNA in the peripheral blood is unlikely to be a suitable alternative for the follow-up of patients with DTC because of high false-positive rates. Thus, the efficacy of Tg mRNA measurement for Tg Ab patients remains uncertain.

Apart from the interference of Tg Ab, benign lesions (possibly containing thyroiditis) of the persistent residual thyroid tissue or nonthyroidal tissue producing Tg may also result in false-positive Tg in DTC patients (10).

## FALSE-NEGATIVE Tg

DWBS<sup>+</sup> Tg<sup>-</sup> has been documented in a small but significant number of cases (7,8,19). Muller-Gartner et al. (19) reported that false-negative serum Tg test results occurred in patients with small papillary carcinoma with cervical or mediastinal lymph node metastases and suggested that the small tumor mass might account for undetectable Tg production. Mertens et al. (8) presented the case of a 54-y-old woman with metastatic follicular thyroid cancer and false-negative Tg. Many years after the patient had a subtotal thyroidectomy, metastatic bone disease was found. When the bone metastases were detected, serum Tg values remained undetectable, whereas <sup>131</sup>I WBS demonstrated abundant uptake in the metastases during the follow-up period. This case indicates that the combination of <sup>131</sup>I scintigraphy and serum Tg values is superior to the measurement of serum Tg alone in detecting DTC. The reliability of very low serum Tg-off levels (<3 ng/mL) was evaluated in 224 patients without Tg Ab—who had undergone total thyroidectomy (125 patients) or thyroidectomy followed by 1 or more courses of <sup>131</sup>I therapy (99 patients)—by performing WBS after a therapeutic dose of <sup>131</sup>I with Tg measurement

at the same time. DWBS<sup>+</sup> Tg<sup>-</sup> was found in 79 patients (35%). In 60 patients, the <sup>131</sup>I uptake was limited to the thyroid bed, but in 19 patients (8.5%), metastases were demonstrated (7). This study indicates that even serum Tg-off is not a completely reliable method for follow-up of DTC patients.

The possible causes of false-negative Tg are as follows:

- The functional sensitivity of Tg methods is low enough to detect small amounts of thyroid tissue when TSH is suppressed.
- The presence of Tg Ab has been mentioned earlier.
- Hook effects arise when an excessive amount of Tg in the specimen overwhelms the antibody test reagent and produces a paradoxically low signal response.
- Immunologically inactive Tg evades detection in a given Tg RIA. Tg produced by the tumor contains unique epitopes and altered biochemical features may obscure recognition by the antibodies used in the assay (10), which result in falsely low Tg values.

The dedifferentiated DTC cells can still concentrate iodine but are unable to synthesize or release Tg. It was observed that the least differentiated metastases are prone to be associated with lower Tg levels. This could be explained by a decrease in the synthesis or release of a normal Tg and by the synthesis of an immunologically inert Tg unrecognized by antibodies used in routine assays or there is a more rapid clearance of Tg from the plasma (7).

Several observations on Tg measurement in DTC patients are worthy of noting:

- Tg acts as a tumor marker only after near-total or total thyroidectomy.
- Circulating Tg Ab may cause false-negative or false-positive results. One should be aware that underestimation, typical of Tg Ab interference with Tg IMA methodology, is clinically the most problematic direction of interference because underestimation has the potential to mask the detection of metastatic disease (12). A sensitive Tg Ab assay should be adopted to minimize the possibility of antibody interference.
- No current Tg or Tg Ab method is perfect. There can be a 4-fold between-method variability that precludes the use of different Tg methods for serial monitoring of DTC patients (9). Thus, in the clinical management of DTC patients, physicians should understand the technical limitations of these tests and meticulously select Tg and Tg Ab methods of quality that are available in the laboratory. New ACB guidelines require laboratories to consult their physician-users before changing their Tg method and before changing baseline patient values if the bias between methods exceeds 10% (14). The practice optimizes the best possible assessment of any change.
- The clinician's response to a particular Tg level should be individualized. It is necessary that clinicians inter-

pret serum Tg values with respect to the patient-specific factors (20), the biologic behavior of the tumor (15), the physiologic factors that control Tg secretion, and the technical limitations of the Tg methods used. The histologic degree of differentiation of tumor tissue may not always correlate with the production of Tg. High levels of serum Tg have been observed in poorly or moderately differentiated DTC, whereas low serum levels have been observed in highly differentiated DTC.

- Tg synthesis and radioiodine uptake reflect different functions of thyroid tissues. The serum Tg level does not predict radioiodine uptake, nor does radioiodine uptake predict the Tg level (21). Hürthle cell carcinomas may be able to synthesize Tg but have poor radioiodine uptake capability (22).
- Clinicians should be aware that "undetectable" does not always mean <1 ng/mL and relies on the sensitivity of the given Tg method. Moreover, low or even undetectable "Tg-on" offers no guarantee for the absence of recurrent or metastatic disease (7). It is suggested that the follow-up of DTC should depend not only on the Tg test but also on periodic DWBS (7).

High levels of serum Tg have been found more often in patients with follicular thyroid cancer than in patients with papillary thyroid cancer (10).

## NEGATIVE <sup>131</sup>I WBS

Iodine uptake is a prerequisite for <sup>131</sup>I WBS diagnosis. Loss of iodine uptake provides a reason for the DWBS<sup>-</sup> that is observed frequently in metastasized DTC. As many as 15% of DTC patients with an elevated Tg level but a DWBS<sup>-</sup> are found on further evaluation to have persistent, recurrent, or metastatic disease (23). The possible causes have been mentioned.

## Defective Iodine-Trapping Mechanism

Thyroid hormone synthesis starts with the active uptake of iodine from the circulation via the sodium/iodine symporter (NIS). This process, known as iodine trapping, is stimulated directly by TSH and more circuitously by iodine deficiency. Other proteins, including TPO and pendrin, also play an important role in the thyroid metabolism of iodine. Trapped iodine appears to be transported by pendrin to a site in or near the follicular lumen, where it is converted to a reactive organified species under the influence of TPO (24). Any defect in the iodine-trapping mechanism can lead to a change of the amount of radioiodine that is taken up by the DTC and the change of the kinetics of iodine release from those cells contributing to the false DWBS<sup>-</sup> (25).

Recent structural analyses of the members of the Na<sup>+</sup>/glucose cotransporter family suggest the involvement of membrane proteins composed of 13 putative transmembrane domains (25). The human NIS (hNIS) gene encodes a protein of 643 amino acid residues that is 84% homologous to the rat NIS gene. Transfection of the hNIS gene into



malignant rat thyroid cells that did not concentrate iodine resulted in a 60-fold increase in cell accumulation of  $^{125}\text{I}$  in vitro (26). TPO is the key enzyme in the synthesis of thyroid hormones and is involved in 2 important reactions in the biosynthesis of thyroid hormone: the iodination of tyrosine residues on Tg and the intramolecular coupling reaction of iodinated tyrosines. Thus, a balance between NIS-mediated iodine influx and TPO-inhibited efflux determines the intracellular concentration of iodine in thyroid tissue. Any defect in NIS or TPO can cause a loss of iodine-trapping capacity.

The loss of radioiodine uptake ability observed in some patients with DTC may be ascribed to the reduced expression of an acquired mutation of NIS or TPO gene (25). Immunohistochemistry has confirmed the much lower expression and the heterogeneous expression of NIS protein in DTC tissues. NIS mRNA expression was 10- to 1,200-fold lower and TPO mRNA was 5- to 500-fold lower in neoplastic thyroid tissues than in normal tissues (27). Conversely, an increase in hNIS expression at the mRNA and protein levels was found in the majority of papillary carcinomas (28). These observations suggest that both the expression and the functional integrity of hNIS are critical for iodine transport and accumulation. This is of paramount importance in DTC patients in whom radioiodine is used to both detect and eradicate neoplastic tissue. Previously identified biochemical and molecular defects of TPO may also hamper  $^{131}\text{I}$  concentration and account for its absence in some DTC metastases. The lower tumor  $^{131}\text{I}$  concentration in patients with DTC compared with the normal Tg synthesizing capability suggests the loss of the organification activity because of an acquired mutation or a lower level expression of TPO gene. Therefore, the discordance between Tg and  $^{131}\text{I}$  WBS that is observed frequently in clinical practice indicates variation in the expression of NIS and TPO genes.

It was also observed that intrathyroidal iodine metabolism is profoundly altered in thyroid cancer tissues. The limited degree of iodination of Tg was found in DTC not only because of defects in the iodine-trapping ability and in the iodination process through low TPO biochemical activity but also because of the low expression of apical pendrin. Pendrin, a highly hydrophobic transmembrane protein—composed of 780 amino acid residues—is localized by immunohistochemistry at the apical pole of the thyrocyte and has been shown in vitro to act as a transporter of chloride and iodine, thereby emphasizing a potential critical role for this protein in thyroid physiology. In thyroid carcinomas, pendrin expression is dramatically decreased, and pendrin immunostaining is low and positive only in rare tumor cells. In addition, an alteration in iodine organification is confirmed by a positive perchlorate discharge test and the presence of Tg molecules displaying a normal monomer size but a low hormone content and iodine content as the result of an intrinsic defect in thyroid iodine organification that is attributed to an inactivation mutation of the pendrin (29). It remains to be established whether, and to

what extent, pendrin expression constitutes a critical alteration in DTC.

Taken together, iodine uptake is an indicator of differentiated behavior, as is the expression of NIS, TPO, Tg, and TSH receptor. Any defect in them will contribute to false-negative  $^{131}\text{I}$  WBS.

### Loss of Differentiation

Loss of differentiation is observed in up to one third of DTC patients, paralleled by an increase in tumor grading and loss of thyroid-specific functions (30). Aldinger et al. (31) reported 18 (1.9%) cases of anaplastic transformation in a series of 960 patients with DTC. These 18 cases account for slightly more than 20% of the total patient population with undifferentiated cancer of the thyroid in that institute. Ito et al. (32) found evidence of undifferentiated transformation in 8 of 14 patients who died of papillary cancer and proposed that such transformations may indicate an end stage for DTC.

There is histopathologic evidence that the undifferentiated thyroid carcinomas are derived from differentiated carcinomas. Moreover, it is postulated that some genetic agents might be involved with such changes (32,33). The study of mutations in p53 was performed by direct sequencing analysis after polymerase-chain-reaction amplification of exons 5–8 in paraffin-embedded primary tumors and cultured cells. No mutations in exons 5–8 were detected in 10 differentiated papillary adenocarcinomas, whereas 6 of 7 anaplastic carcinomas were found to carry base substitution mutations. The results put a high premium on p53 mutations in human thyroid glands in the progression of DTC to undifferentiated carcinomas (33).

Thus, limitations in the detection of recurrent or metastatic lesions occur when progressive dedifferentiation of DTC cells leads to a loss of iodine-concentrating ability, but retaining the Tg synthesizing capability, thereby becoming more difficult to monitor and less responsive to traditional therapeutic modalities (31). It is possible that recovery of p53 function in undifferentiated thyroid carcinoma cells with an altered p53 gene is able to modify cell tumorigenic properties (30).

### Dispersed Microscopic Metastases

Dispersed microscopic metastases are too small to be visualized. In this situation, the choice of diagnostic equipment affects the ability to display small metastatic foci. Most emission CT (ECT) scanners now available in most laboratories have relatively thin crystals designed for lower-energy radionuclides than  $^{131}\text{I}$ . The efficiency of ECT for  $^{131}\text{I}$  depends on both the thickness of the crystal and the collimator. If a lesion of DTC is smaller than the full width at half maximum of ECT, the target-to-background ratio will be much lower. At depth in the attenuating medium, the effect of point spread is magnified and may result in more loss of resolution. With these concerns in mind, efforts should be made to optimize whatever is available in a given laboratory (34).

Different administered activities of  $^{131}\text{I}$  make a difference in providing diagnostic information. With higher activities, more lesions can be shown. A 4-fold increase in sensitivity in detecting functioning thyroid tissue with a 370-MBq dose relative to a 74-MBq dose has been reported (35). However, the higher the dose of  $^{131}\text{I}$  used for diagnostic information, the greater the potential reduction in subsequent therapeutic effect. Therefore, the usefulness of these larger doses is abrogated because of thyroid “stunning” (36).

#### Improper Patient Preparation Before $^{131}\text{I}$ WBS

Improper patient preparation before  $^{131}\text{I}$  WBS should be kept in mind in suspected DWBS<sup>-</sup>. When it is determined that an elevation of Tg is valid, if DWBS is negative, causes of a false-negative scan—such as stable iodine contamination and inadequate TSH elevation—must be excluded. It should be noted that iodine is found in many radiographic contrast media and in certain antiseptic soaps. Hurley et al. (37) recommended minimum times between exposure to these agents and the initiation of diagnostic radioiodine studies. In cases with a suggestion of abnormality, serum and urinary iodine should be measured and WBS should be repeated 4–6 wk after an iodine-depletion regimen is considered (7). A combination of low-iodine diet ( $\leq 50$   $\mu\text{g}$  iodine per day) (38) and a modified diuretic program increases the radioiodine uptake and retention in tumor tissue. In our laboratory, we meticulously avoid the high-iodine sources noted and institute our low-iodine diet at least 4 wk before DWBS.

TSH stimulation of thyroid cells is required for optimal imaging with  $^{131}\text{I}$ .  $^{131}\text{I}$  WBS will be not feasible unless circulating TSH levels are high enough to stimulate maximum radioiodine uptake into thyroid cells. Even normal thyroid tissue incorporates very little  $^{131}\text{I}$  if serum TSH levels are suppressed. During prolonged exogenous levothyroxine therapy in some patients, recovery of the ability of the pituitary gland to secrete TSH can be delayed and may persist for several months (10). Consequently, DWBS<sup>-</sup> Tg<sup>+</sup> can occur when endogenous TSH levels are adequate to induce Tg synthesis but inadequate to promote  $^{131}\text{I}$  uptake. It is suggested that serum TSH levels should be obtained and verified as being elevated to at least 30 mIU/L before concluding that DWBS<sup>-</sup> is meaningful. Serum TSH  $> 30$  mIU/L seems adequate to stimulate radioiodine uptake in metastatic lesions that are capable of concentrating it. This can be achieved either by withdrawal of thyroxine or by rhTSH administration. In some patients who are unable to secrete pituitary TSH on levothyroxine withdrawal, rhTSH is the only acceptable method to prepare them for  $^{131}\text{I}$  WBS or Tg measurement. More meaningfully, the administration of rhTSH allows patients to be examined without having to render them hypothyroid (39).

A summary of appropriate patient preparation for  $^{131}\text{I}$  DWBS in the hypothyroid state is presented in Table 1. In our laboratory, patients are required to be off thyroxine for 1–2 wk with a following 1-wk administration of metoclo-

**TABLE 1**

Summary of Appropriate Patient Preparation for  $^{131}\text{I}$  DWBS

Appropriate patient preparation
Withdrawal of $\text{T}_4$ for 4–6 wk or of $\text{T}_3$ for 2 wk.
A strict low-iodine diet ( $\leq 50$ $\mu\text{g}$ iodine per day) followed for 7–14 d before $^{131}\text{I}$ DWBS and continuing throughout period of imaging.
Avoidance of iodine-containing medications (e.g., iodinated contrast medium, amiodarone, betadine), iodine-rich foods (e.g., kelp), and possible additives of iodine in vitamin and electrolyte supplements.
TSH $\geq 30$ mIU/L.
A mild laxative sometimes administered on the evening before $^{131}\text{I}$ DWBS to simplify image interpretation.
Information relating to patient's compliance with low-iodine diet, TSH level, history of thyroid hormone withdrawal, measurement of Tg, history of prior administration of contrast medium or iodine-containing drugs (e.g., amiodarone), menstrual history/pregnancy test, nursing/lactation history, etc.
Measurement of urinary iodine in doubtful cases to rule out iodine contamination; repeated WBS 4–6 wk after iodine-depletion regimen such as diuretic program.
Rule out women with pregnancy and breast feeding.
 T <sub>3</sub> = triiodothyronine.

pramide (a blocker of dopamine receptor with resultant effective elevation of TSH) to shorten the period of hypothyroidism and relieve gastric symptoms caused by high-dose  $^{131}\text{I}$ .

#### FALSE-POSITIVE $^{131}\text{I}$ WBS

Many DTCs retain the unique ability to concentrate, organify, and store  $^{131}\text{I}$ . Thus, foci of uptake on postthyroidectomy  $^{131}\text{I}$  WBS are considered highly specific for thyroid tissue—be it residual remnant, normal, or neoplastic tissue in the neck or elsewhere in metastatic deposits. Unfortunately, uptake in other tissues that can trap  $^{131}\text{I}$  but do not retain it in organic form can blur this specificity. False-positive WBS occurs for a wide range of reasons, including external contamination through saliva and sweat, internal contamination through nasopharyngeal secretion, as well as physiologic uptake in nonthyroidal tissue such as choroid plexus, salivary glands, gastric mucosa, and urinary tract. Shapiro et al. (40) provide a logical classification and pathophysiologic interpretation of the disparate literature of the host of artifacts, anatomic and physiologic variants, and nonthyroidal diseases that are responsible for false-positive  $^{131}\text{I}$  WBS, such as ectopic foci of normal thyroid tissue; nonthyroidal physiologic sites; contamination by physiologic secretions; ectopic gastric mucosa; other gastrointestinal abnormalities; urinary tract abnormalities; mammary abnormalities; serous cavities and cysts; inflammation and infection; nonthyroidal neoplasms; and currently unexplained causes. These cases of nonspecific  $^{131}\text{I}$  accumulation make more acute the urgency to be familiar with unusual

but possible causes that may mimic uptake by DTC metastases.

### OTHER IMAGING MODALITIES FOR DTC PATIENTS WITH POSITIVE Tg AND NEGATIVE $^{131}\text{I}$ WBS

Elevated serum Tg levels or the presence of Tg Ab with DWBS<sup>-</sup> have resulted in a diagnostic and a therapeutic dilemma in the management of DTC. In the clinical setting, there is an urgent need for noninvasive modalities to localize recurrent or metastatic lesions in DTC patients with DWBS<sup>-</sup> Tg<sup>+</sup> to follow the recommendation of surgery or external radiotherapy of the lesions when appropriate. Non-iodine imaging agents—such as  $^{201}\text{Tl}$ ,  $^{99\text{m}}\text{Tc}$ -sestamibi,  $^{99\text{m}}\text{Tc}$ -tetrofosmin,  $^{111}\text{In}$ -octreotide,  $^{18}\text{F}$ -FDG, and  $^{123}\text{I}$ —are primarily useful in the DWBS<sup>-</sup> Tg<sup>+</sup> setting. The major advantage of noniodine isotopes is that without withdrawal of levothyroxine therapy, patients can avoid the occurrence of long-time hypothyroidism. In addition, some of the agents used, such as  $^{99\text{m}}\text{Tc}$  and  $^{201}\text{Tl}$ , have physical imaging characteristics superior to those of  $^{131}\text{I}$ .

The primary value of  $^{201}\text{Tl}$  is in imaging regional nodal disease and is less reliable in visualizing bony and pulmonary metastases.  $^{99\text{m}}\text{Tc}$ -Sestamibi and  $^{99\text{m}}\text{Tc}$ -tetrofosmin are most sensitive in detecting lymph node metastases and are less sensitive for lung or bone disease (41).

Somatostatin receptor imaging (SRI) has a great potential for the visualization of somatostatin receptor-positive tumors. Although papillary, follicular, and anaplastic thyroid cancers, and also Hürthle cell carcinomas, do not belong to the group of classic neuroendocrine tumors, most of them show uptake of radiolabeled octreotide during SRI. Metastasized DTCs that do not take up radioactive iodine may show radiolabeled octreotide accumulation. SRI with  $^{111}\text{In}$ -octreotide has been used successfully in imaging DWBS<sup>-</sup> tumors (42).

Currently,  $^{18}\text{F}$ -FDG PET has established its diagnostic value in DTC patients with DWBS<sup>-</sup> Tg<sup>+</sup>. Interestingly, an inverse relationship was found between uptake of  $^{18}\text{F}$ -FDG and  $^{131}\text{I}$  in most DTC metastases, a phenomenon termed “flip-flop”—namely, functional tumor differentiation is associated with low  $^{18}\text{F}$ -FDG uptake and retaining  $^{131}\text{I}$  uptake, whereas dedifferentiation is associated with the loss of iodine-accumulating ability and an increase in metabolism from progressive growth. Because of the alteration in  $^{18}\text{F}$ -FDG and  $^{131}\text{I}$  uptake in recurrent or metastatic DTC, DWBS<sup>-</sup> tumor masses might be identified by  $^{18}\text{F}$ -FDG PET. Therefore, the selection of patients with DWBS<sup>-</sup> metastases will lead to more favorable evaluation by this modality. Using  $^{18}\text{F}$ -FDG PET in patients with DWBS<sup>-</sup> Tg<sup>+</sup>, Muros et al. (43) found 6 recurrent lesions in 10 patients, including 4 cases with isolated nodal relapse. Alnafisi et al. (44) studied 37 patients and found that PET changed the clinical management in 19 patients (51%). A large and homogeneous population study indicated that  $^{18}\text{F}$ -FDG PET may well be a choice in the follow-up of DTC patients with

DWBS<sup>-</sup> Tg<sup>+</sup> as it appears superior to other WBS imaging techniques because of a better spatial resolution and the difference in the tracer uptake mechanism. However, false-positive  $^{18}\text{F}$ -FDG PET scans have been found mainly in the acute or chronic local inflammatory state, especially if previous surgery has been performed. In addition,  $^{18}\text{F}$ -FDG can be trapped not only in malignant tissue but also in granulomatous disease in the presence of osteomyelitis and abdominal abscesses (45).

$^{123}\text{I}$ , mainly a  $\gamma$ -emitter, with a high counting rate compared with  $^{131}\text{I}$ , provides a higher tumor-to-background signal, thereby improving sensitivity. The better imaging quality of  $^{123}\text{I}$  versus that with  $^{131}\text{I}$  for WBS has been acknowledged by many researchers (46,47). Moreover, with the same administered activity,  $^{123}\text{I}$  delivers an absorbed radiation dose that is approximately one-fifth that of  $^{131}\text{I}$  to thyroid tissue, thereby lessening the likelihood of stunning from imaging (46). A recent study by Siddiqi et al. (46) indicated that 185 MBq  $^{123}\text{I}$  WBS can provide greater sensitivity than comparable doses of  $^{131}\text{I}$ . Gerard and Cavalieri (47) found that 111–185 MBq  $^{123}\text{I}$  WBS performed at 48 h can enhance sensitivity for detecting weakly avid sites of thyroid tissue or DTC compared with that obtained when imaging at 6 or 24 h. Therefore, the superior image quality of  $^{123}\text{I}$  WBS and the presumed avoidance of the risk for stunning justify its utility for DTC patients. A potential disadvantage of  $^{123}\text{I}$  with earlier imaging is higher background noise. However, a high counting rate for  $^{123}\text{I}$  means that the tumor signal and thereby tumor-to-background ratios remain high and tumor detectability is not compromised. The earlier imaging also makes  $^{123}\text{I}$  theoretically less sensitive for lesions with delayed uptake kinetics. Another disadvantage of  $^{123}\text{I}$  is the cost, which makes it expensive to use in higher activities. However, given the high sensitivity of the  $^{123}\text{I}$  studies and very low false-negative rate, savings on therapy may be made. Hopefully,  $^{123}\text{I}$  WBS may replace  $^{131}\text{I}$  in the follow-up study of DTC patients in the future.

**TABLE 2**  
Summary of Reasons for  $^{131}\text{I}$  DWBS<sup>-</sup> Tg<sup>+</sup>

Reasons for $^{131}\text{I}$ DWBS <sup>-</sup> Tg <sup>+</sup>
False-positive Tg and true-negative $^{131}\text{I}$ DWBS
Interference of circulating Tg Ab.
Benign lesions (possibly containing thyroiditis) of persistent residual thyroid tissue or nonthyroidal tissue producing Tg.
True-positive Tg and false-negative $^{131}\text{I}$ DWBS
Defective iodine-trapping mechanism such as acquired inactivation mutation of NIS, TPO gene, and pendrin.
Dedifferentiation of tumor such that it can still produce Tg but has lost its iodine-trapping ability.
Dispersed microscopic metastases too small to be visualized.
Improper patient preparation before $^{131}\text{I}$ DWBS such as stable iodine contamination and inadequate TSH elevation.



However, no imaging is perfect. The modalities for DTC follow-up will be arbitrary until more information becomes available and requires tailoring to fit one's laboratory and the patient's comfort level with the risk and benefit odds (48).

## CONCLUSION

Many possibilities can produce the discordance between serum Tg and  $^{131}\text{I}$  WBS in the follow-up of patients with DTC, which puzzles the subsequent management. Necessarily, one should first attempt to unmask a cause for possibly false-negative or false-positive  $^{131}\text{I}$  WBS or serum Tg. Fortunately, DWBS<sup>+</sup> Tg<sup>-</sup> is of rare occurrence, compared with DWBS<sup>-</sup> Tg<sup>+</sup>. A summary of the reasons for  $^{131}\text{I}$  DWBS<sup>-</sup> Tg<sup>+</sup> is shown in Table 2. Other radioisotopes and additional diagnostic options have the potential to play an important role in the ascertainment of patients with recurrent or metastatic DTC in the not-too-distant future.

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## Possible Explanations for Patients with Discordant Findings of Serum Thyroglobulin and $^{131}\text{I}$ Whole-Body Scanning

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