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A Consensus Report of the Role of Serum Thyroglobulin as a Monitoring Method for Low-Risk Patients with Papillary Thyroid Carcinoma

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Recent studies have provided new information regarding the optimal surveillance protocols for low-risk patients with differentiated thyroid cancer (DTC). This article summarizes the main issues brought out in a consensus conference of thyroid cancer specialists who analyzed and discussed this new data.

There is growing recognition of the value of serum thyroglobulin (Tg) as part of routine surveillance. An undetectable serum Tg measured during thyroid hormone suppression of TSH (THST) is often misleading. 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 (rhTSH), a rise in serum Tg to more than 2 μg/liter. When this happened, 36% of the patients were found to have metastases (36% at distant sites) that were identified in 91% by an rhTSH-stimulated Tg above 2 μg/liter. Diagnostic whole body scanning, after either rhTSH or thyroid hormone withdrawal, identified only 19% of the cases of metastases. Ten studies comprising 1599 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. On the basis of the foregoing, we propose a surveillance guideline using TSH-stimulated Tg levels for patients who have undergone total or near-total thyroidectomy and ^{131}I ablation for DTC and have no clinical evidence of residual tumor with a serum Tg below 1 μg/liter during THST. (*J Clin Endocrinol Metab* 88: 1433–1441, 2003)

THE INITIAL MANAGEMENT of papillary and follicular thyroid carcinoma, often termed differentiated thyroid carcinoma (DTC), has evolved substantially over the past several decades (1). Patients with DTC have 10-yr cancer-specific mortality rates of less than 10% (2), which represents a significant improvement in survival rates over the past four decades (3), due in part to early diagnosis and effective initial therapy. In the 1960s, most patients were treated with lobectomy alone without adjunctive medical therapy (4), whereas now most undergo total or near-total thyroidectomy followed by ^{131}I remnant ablation and thyroid hormone suppression of TSH (THST; Refs. 5–12). Although the current trends in initial management are widely accepted in the United States and Europe, some still challenge the validity of this approach (13, 14).

Debate concerning management of DTC has been fueled by its low incidence, prolonged clinical course, and the paucity of prospective randomized trials. It has been estimated, for example, that a randomized study to detect a 10% reduction in thyroid cancer mortality rates 25 yr after ^{131}I therapy would require 4000 patients in each arm of the study and would take 10 yr or more to enroll, making results available after 35 yr (15). At present, the core information about the efficacy of initial therapy accordingly derives from large retrospective cohort studies of patients observed for decades. This is the basis for the clinical management guidelines offered by a number of organizations, including the American Association of Clinical Endocrinologists (16), the American Association of Endocrine Surgeons (16), the American Thyroid Association (17), the British Thyroid Association (18), and the National Cancer Center Network (NCCN; Ref. 8).

Abbreviations: DTC, Differentiated thyroid carcinoma; DxWBS, diagnostic whole body scanning; IMA, immunometric assay; rhTSH, recombinant human TSH; RxWBS, posttherapy whole body scanning; Tg, thyroglobulin; TgAb, anti-Tg antibodies; THST, thyroid hormone suppression of TSH; THW, thyroid hormone withdrawal.

Defining the most effective follow-up paradigm has been more elusive. Few large studies have focused on optimal surveillance strategies, resulting in less explicit follow-up guidelines that do not clearly separate the roles for various tests (8, 17, 18). The NCCN 2001 guidelines, for example, advise that patients with papillary thyroid carcinoma undergo physical examination every 3–6 months for 2 yr, then annually if disease-free. For patients who have undergone total thyroidectomy with ^{131}I ablation, the guidelines advise thyroglobulin (Tg) measurement at 6 and 12 months, on or off THST, and a TSH-stimulated radioiodine diagnostic whole body scan (DxWBS) every 12 months, until one or two are negative. Serum Tg determinations and DxWBS are less accurate in patients with a large thyroid remnant, because both require high serum TSH levels, usually above 25 mIU/ml, for optimal sensitivity (8, 17, 18).

A number of recently published studies using recombinant human TSH (rhTSH) with sensitive Tg measurements and newer imaging techniques provide fresh insight into optimal long-term surveillance strategies of patients who appear to be free of disease. This is especially important because the prevalence of DTC is so high, affecting more than 200,000 patients in the United States alone (3). New explicit follow-up paradigms thus would likely have an important and beneficial impact on the management of many of these patients. Sparked by these issues, a group of thyroid cancer experts met on June 18, 2002, in San Francisco, California, in an attempt to seek a consensus concerning follow-up management. Although all authors did not agree on every point, this article represents the consensus of the 15 attendees of that meeting.

The Questions Addressed

The goal of the meeting was to formulate from the current literature a cost-efficient postoperative surveillance paradigm for DTC patients who clinically appear to have no evidence of disease after having undergone total or near-total thyroidectomy and ^{131}I thyroid remnant ablation. Seven key points were addressed. The conference attendees reached a consensus on a follow-up paradigm, which is shown in an algorithm (Fig. 1). What follows is the rationale for this recommendation.

1) What are the characteristics of the patients for whom we should address follow-up paradigms?

The consensus is that this follow-up paradigm should only be applied to those who are at low risk for persistent or recurrent disease or cancer death. The guideline is intended for patients who have undergone total or near-total thyroidectomy and ^{131}I ablation for DTC, who have no clinical evidence of tumor, and who have undetectable serum Tg levels (<1 μg/liter) during THST (Fig. 1). The majority will have had tumors smaller than 4 cm (pT3), not of a virulent subtype, which were completely resected with or without nodal metastases, but without distant metastases. These are low-risk patients in the Age-Metastasis-Extent-Size scoring system (19), or they usually have Metastasis-Age-Completeness scores of less than 6 (20), or they are American Joint Commission/International Union Against Cancer (AJCC/UICC) stage I if younger than 45 yr or stage I or II if 45 yr of age or older (21).

2) What is the minimal acceptable performance standard of Tg assays used in the detection of residual thyroid cancer?

The consensus is that the physician using this paradigm must have a good working knowledge of the serum Tg assay that is being used, which should meet the minimum performance standards outlined by the U.S. National Academy of Clinical Biochemistry (NACB). Accuracy of the serum Tg measurement, which is the keystone of the algorithm shown in Fig. 1, is essential (22). A reliable serum Tg measurement can identify patients with residual tumor, preventing unnecessary additional testing in those who are cured (23, 24). Several things may interfere with the accurate measurement of Tg, which is discussed in detail by the NACB (22).

In general, 1 g of normal thyroid tissue results in a serum Tg of approximately 1 μg/liter when the TSH is in the normal range and about 0.5 μg/liter when TSH is suppressed (22). Serum Tg levels rise with TSH stimulation, but the duration of stimulation is generally longer in the hypothyroid state, resulting in higher serum Tg levels than occur 72 h after the last of two 0.9-mg doses of rhTSH in the euthyroid state (22).

The accurate measurement of Tg is technically challenging (25, 26). The most popular commercial assays are immunometric (IMA), but the results are influenced by: 1) the use of the CRM-457 international standard, 2) assay functional sensitivity low enough to detect small amounts of thyroid tissue when TSH is suppressed, 3) interassay precision across monitoring intervals up to 12 months, 4) hook effects[1] that can falsely lower Tg results, and 5) anti-Tg antibodies (TgAb) that also can falsely lower IMA Tg results (25, 26). It is thus strongly recommended that serial Tg measurements in a patient be made in the same laboratory using the same assay method because Tg values are not interchangeable among laboratories, even when using the international Tg standard. The assay should have a functional sensitivity of at least 1 μg/liter (22), with a normal lower Tg limit of 3 μg/liter, and the results should be standardized to the CRM-457 standard, which reduces but does not eliminate biases between Tg methods (26).

According to NACB guidelines, Tg should be measured in sera free of TgAb, which must be determined in the same serum sample in which Tg is measured (25, 26). The presence of TgAb usually invalidates the serum Tg result (23, 27). There is some controversy, however, over the use of recovery assays used by some thyroid cancer experts that measure serum Tg levels in serum samples containing TgAb, which the NACB disapproves of (7, 25, 26, 28). Sera should be analyzed for TgAb with a sensitive immunoassay rather than hemagglutination tests, which are too insensitive to detect low TgAb levels (1–10 IU/ml) that may interfere with Tg measurement (25, 26). Using sensitive detection methods,

[1] Inappropriately normal or even low serum Tg values may occur in sera with very high serum Tg concentrations, which require dilution. Laboratories that use IMA methods should run every serum specimen at two dilutions, undiluted and 1:10, or use methods to detect a hook effect before reporting the serum Tg level.

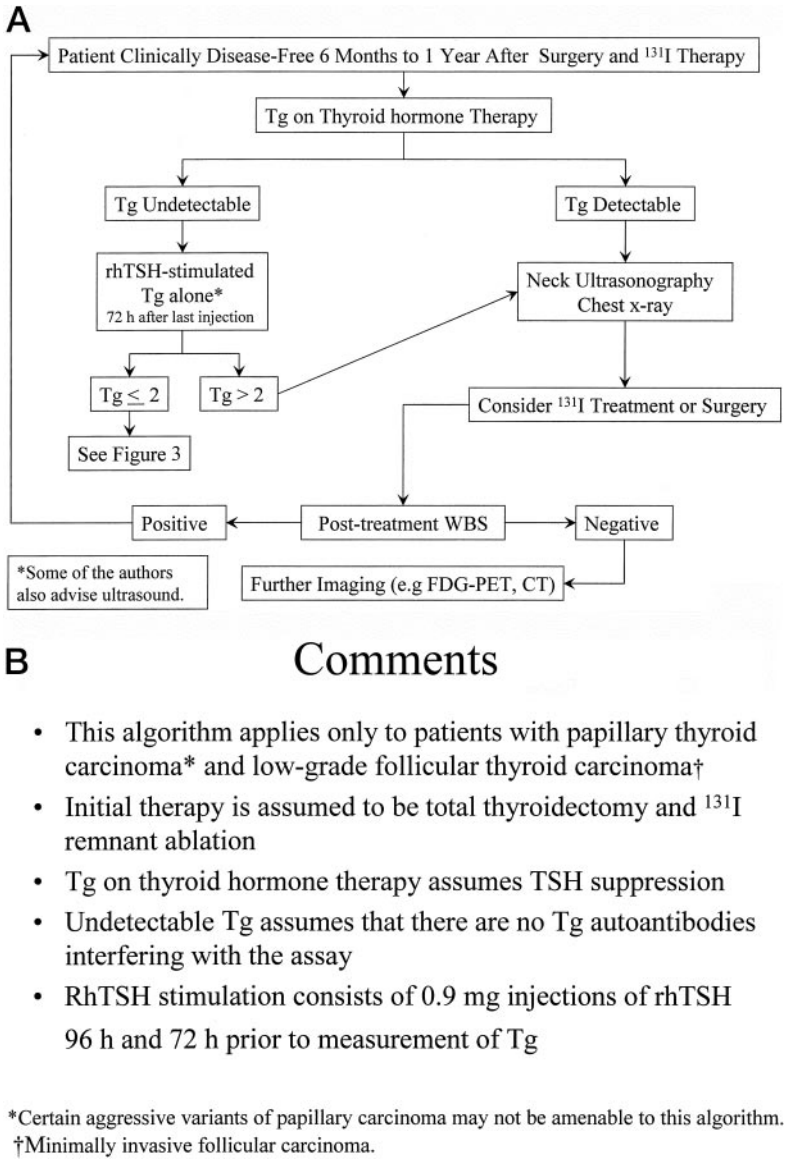

FIG. 1. A, Algorithm for follow-up. An experienced endocrinologist or radiologist should perform neck ultrasonography. Negative RxWBS implies that the tumor does not concentrate ^{131}I or is too small to be imaged on RxWBS and that further studies are necessary. B, Important features of the recommendations made in the algorithm.

TgAb is found in 25%[2] of patients with DTC compared with 10% in the general population (23). With TgAb in sera, there is a significant discordance between serum Tg results measured simultaneously by RIA and IMA, the former measuring higher Tg values than the latter. Although this effect is more severe with high serum TgAb concentrations, it is unpredictable, occurring with TgAb levels as low as 1–2 IU/ml, whereas sometimes not occurring with TgAb values higher than 1000 IU/ml (23).

3) Is an undetectable serum THST-Tg level sufficiently sensitive to consistently identify patients who are free of residual tumor?

The consensus is that an undetectable serum Tg measured during thyroid hormone suppression is misleading in a large proportion of patients with residual DTC. An undetectable serum Tg during THST is usually achieved only by total or near-total thyroidectomy and ^{131}I ablation. For example, one study (29) of 180 patients with DTC found that THST-Tg levels were often above 10 μg/liter after partial thyroidectomy, with or without ^{131}I ablation. Even after near-total or total thyroidectomy and ^{131}I ablation, Tg levels were higher than 10 μg/liter in almost 2% of patients during THST (29).

On the other hand, among patients displaying a low or undetectable serum Tg level during THST, the Tg often rises to above 2 μg/liter after TSH stimulation. In the Phase III rhTSH study (30), for example, a serum Tg lower than 2 μg/liter measured during THST failed to identify 23% of evaluable patients with metastatic disease, yet a TSH-stimulated Tg above 2 μg/liter (rhTSH or THW) identified all patients with metastases (Table 1 and Fig. 2).

In eight studies (28, 30–36) comprising a total of 1028 low-risk patients thought to be clinically free of disease, the Tg level was less than 1 μg/liter during THST in 76% (784 of 1028 patients), rising above 2 μg/liter in 21% of 784 pa-

[2] Percentages are rounded to the nearest integer in the text, but not in the tables.

TABLE 1. Studies in eight patients with metastatic disease on posttreatment whole-body ^{131}I scans and baseline THST serum Tg < 2 ng/ml during THST[a]

Patient ID	Serum Tg (ng/ml)			DxWBS results[b]		RxWBS results
	Baseline on LT4	After rhTSH	After LT4 withdrawal	After rhTSH	After LT4 withdrawal	
201	1.5	16.5	9.0	1	2B	2B
202	0.9	5.2	22.0	1	1	2B
207	1.5	22.2	32.8	1	1	3B
310	0.5	6.9	11.8	4A	4A	4A
311	0.5	2.0	16.5	1	1	2B
1407	0.5	6.6	7.9	2A	1	2A
1426	0.5	5.4	25.3	0	0	2B
1713	1.6	8.7	45.4	0	3A	3A

LT4, Thyroxine.

[a] Data from Haugen *et al.* (30).

[b] Thyroid scans classified as: 0, no uptake; 1, thyroid bed uptake; 2, uptake limited to the neck (outside the thyroid bed; A, solitary focus; B, multiple foci); 3, uptake in chest (A, mediastinum; B, nodular lung metastases); 4, uptake outside chest (A, solitary skeletal focus).

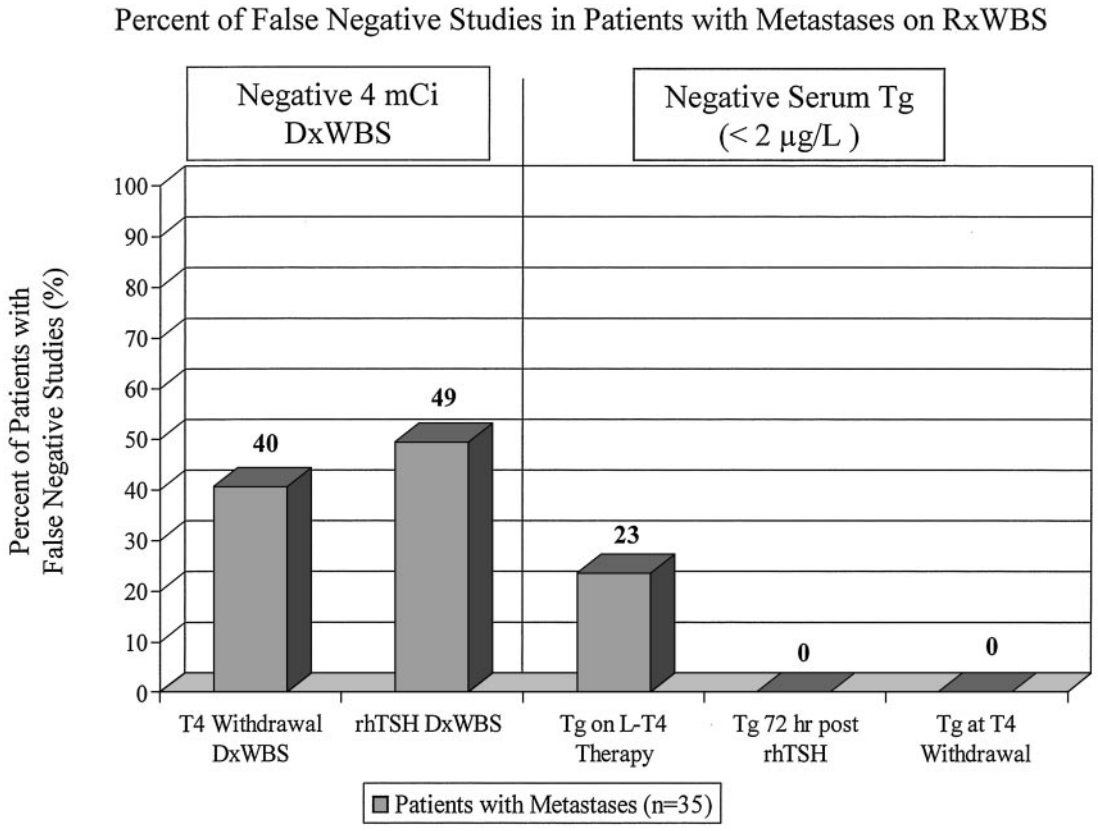

FIG. 2. False negative rate of studies in patients with metastases seen on RxWBS. This includes all 35 patients with complete Tg data and metastatic disease confirmed by RxWBS. [Reproduced with permission from B. R. Haugen *et al.*: *J Clin Endocrinol Metab* 84:3877–3885, 1999 (30). ©The Endocrine Society.]

tients in response to rhTSH (Table 2). When this occurred, almost 36% had metastases, of which over 36% were at distant sites.

4) Is an endogenous TSH-stimulated (hypothyroid) serum Tg level produced by THW more sensitive than measuring an rhTSH-stimulated Tg?

The consensus is that hypothyroid and euthyroid rhTSH-stimulated serum Tg levels (measured 72 h after the last dose of rhTSH) are comparable in detecting metastases when a cutoff of 2 μg/liter is used. Considerable evidence supports the notion that the two methods used to stimulate Tg, THW-induced hypothyroidism and euthyroid rhTSH stimulation, are equally effective in detecting metastatic thyroid cancer. In the large Phase III rhTSH study (30), the median serum Tg values were 0.5 μg/liter during THST, 1.1 μg/liter 72 h after the last of two 0.9-mg doses of rhTSH, and 1.8 μg/liter during THW; however, using a Tg cutoff of 2 μg/liter, all metastases were identified with either an rhTSH- or THW-stimulated Tg test. Robbins *et al.* (37) were unable to demonstrate a difference in the diagnostic accuracy of serum Tg concentrations in the detection of metastases among patients prepared by either THW (161 patients) or

TABLE 2. Serum Tg and DxWBS studies, after THW and rhTSH stimulation

First author (Ref. no.)	Total patients (n)	No. of patients with metastases[a] (%[b] [n])	THST Tg ≤ μg/liter (% [n])	rhTSH studies in patients with THST Tg ≤ 1 μg/liter			Metastatic sites (n = 58) among 728 patients with complete Tg data and follow-up
				rhTSH Tg > 2 (% [n])	Yield of rhTSH testing (% [no. with metastases/no. with Tg > 2])	Metastatic disease on DxWBS[k] (% [n])	
Haugen (30)	220	4[c] 8/220	55 121/220	38[g] 46/121	17 8/46	4 4/121	Locoregional 5/8 and distant metastases 3/8
David (31)	33	6[c] 2/33	88 29/33	7 2/29	100 2/2	0 0/29	Lung 2/2
Vitale (32)	104	3[d] 3/104	44 46/104	17[h] 8/46	38 3/8	0 0/46	Locoregional 1/3[h] and distant metastases 2/3
Haugen (34)	83	8[c] 7/83	88 73/83	34[g] 25/73	28 7/25	0 0/73	Lymph node neck 3/7 and chest 4/7
Mazzaferri (33)	107	10[d] 11/107	100 107/107	19 20/107	55 11/20	0 0/107	Lymph node neck 5/11, lung 4/11, and uncertain site 2/11
Pacini (35)	72	15[e] 11/72	100 72/72	43[i] 31/72	35 11/31	ND	Lymph node neck 7/11 and lung 4/11
Robbins (28)	109	15[f] 16/109	63 69/109	14 10/69	68.8 11/16[f]	10.1 7/69[f]	Lymph nodes neck 13/16[f,h], mediastinum/cervical nodes 2/16[f], and lung 2/16[l]
Wartofsky (36)	300	3[c] 9/300	89 267/300	10[e] 26/267	ND[j]	ND[j]	ND[j]
Total (%) of all patients in column	100 [1028]	6.5[f] 67/1028	76.3 784/1028	21.4 168/784	35.8 53/148[f]	2.3 11/485[f]	Distant metastases 21/58[l] 36.2%, locoregional 35/58 60.3%, and uncertain 2/58 3.4%

ND, Not determined.

[a] Metastases found in low-risk patients as the result of rhTSH-stimulated studies or a DxWBS showing uptake outside the thyroid bed.

[b] Percentages rounded to the nearest integer in all but last row.

[c] Patients with baseline THST-Tg <2 μg/liter.

[d] Patients with a baseline THST-Tg ≤1 μg/liter.

[e] Patients with a baseline THST-Tg <1 μg/liter.

[f] Patients (n = 4) with baseline TSHT-Tg ≤ 2 μg/liter. Seven patients had metastases seen on DxWBS, yet 5 had rhTSH-stimulated Tg < 2 (false-negative rhTSH-stimulated Tg levels), and 9 of 16 patients with rhTSH Tg > 2 μg/liter had metastatic disease with a negative DxWBS. One patient had both neck nodes and mediastinal uptake.

[g] Patients with rhTSH-stimulated Tg ≥ 2 μg/liter.

[h] Personal communication with the authors.

[i] Patients with rhTSH-stimulated Tg > 1 μg/liter.

[j] Only limited follow-up data were reported in the Wartofsky study, and these data thus have been omitted from the table.

[k] Positive, uptake in metastases on DxWBS (not thyroid bed).

[l] DxWBS negative and Tg ≥ 2 μg/liter.

rhTSH (128 patients). Pacini *et al.* (35), comparing peak rhTSH- and THW-stimulated serum Tg concentrations in the same patients, found that none of those with a TSH-stimulated Tg less than 1 μg/liter had metastases, whereas an elevated TSH-stimulated Tg identified 100% of the patients with local or distant metastases, regardless of whether the TSH stimulation was by rhTSH or THW. In eight recent studies (28, 30–36), an rhTSH-stimulated Tg above 2 μg/liter identified 91% of the 58 patients with metastases (Table 2).

5) Is TSH-stimulated serum Tg measurement sufficiently sensitive to be used alone in the follow-up of patients with DTC?

The consensus is that a TSH-stimulated Tg alone is sufficient for follow-up of low-risk patients with no clinical evidence of disease and suppressed serum Tg levels during THST. Although serum Tg and DxWBS have been considered complementary in identifying residual tumor (38), an undetectable TSH-stimulated Tg alone, whether by THW or rhTSH, is usually sufficient to do this (Table 2 and Fig. 3). Little information is added by performing a DxWBS in the evaluation of patients at low-risk of having persistent disease. Tumor is rarely found when the serum Tg value is less than 2 μg/liter after rhTSH stimulation (28, 30–36) or THW (7, 39). Two THW studies show that TSH-stimulated serum Tg measurement consistently identifies patients with residual tumor (7, 39). Eight other studies (28, 30–36) show that metastatic tumor is almost always identified by an rhTSH-stimulated serum Tg above 2 μg/liter. Six of the eight studies (28, 31–35) show the extent to which unsuspected tumor is detected by rhTSH-Tg and DxWBS. When 784 patients underwent testing, 36% of those with an rhTSH-Tg above 2 μg/liter were found to have unsuspected metastases that were usually not detected by DxWBS (Table 2). Almost all (91%) of the patients with metastases were identified by an rhTSH-stimulated Tg above 2 μg/liter, whereas only 19% were identified by a positive rhTSH-stimulated or hypothyroid THW DxWBS (Table 2). Thus, 10 studies (7, 28, 30–36, 39) comprising 1599 patients demonstrate that TSH-stimulated Tg testing (either rhTSH or THW) is sufficiently sensitive to be used alone in the follow-up management of low-risk patients with DTC.

6) During long-term follow-up, are there any circumstances in which THST-Tg measurements are sufficiently sensitive to forgo or reduce the frequency of further testing?

The consensus is that serum Tg measurements during thyroid hormone suppression are sufficiently sensitive to forgo further testing in a low-risk patient who is clinically free of disease and has had an undetectable (< 1 μg/liter) serum Tg level during THST and after rhTSH or THW. A Tg that remains undetectable after either THW or rhTSH stimulation is strong evidence of complete tumor ablation (7, 28, 30, 32–36, 39). Such patients usually require nothing more than annual physical examination and serum Tg measurement during THST, unless

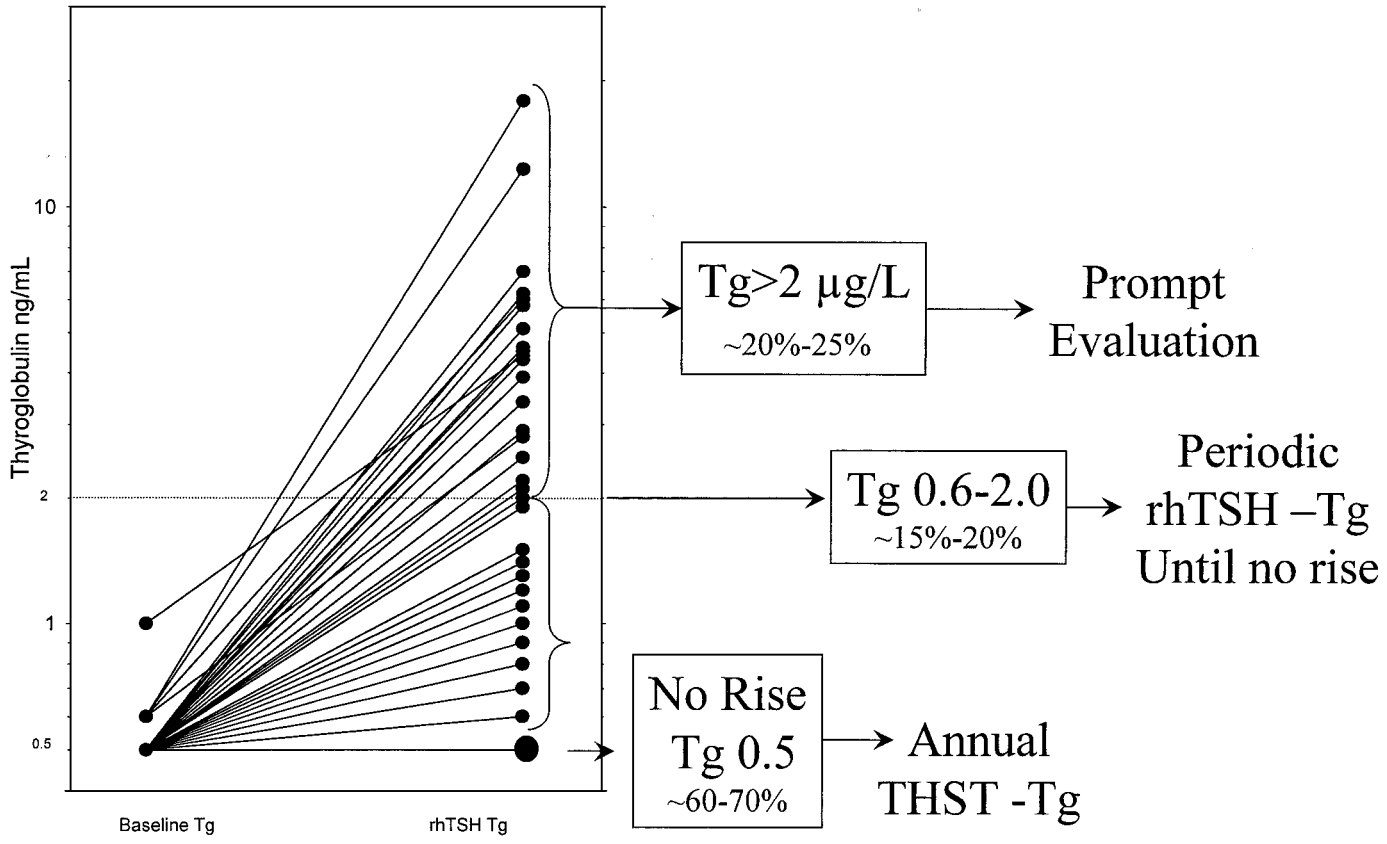

FIG. 3. Suggested frequency and intensity of follow-up. [Adapted with permission with example data from Mazzaferri and Kloos: *J Clin Endocrinol Metab* 87:1490–1498, 2002 (33). ©The Endocrine Society.]

there is clinical evidence of tumor or other compelling reasons for performing TSH-stimulated testing.

7) Can any recommendations be made concerning the frequency and type of long-term follow-up testing?

The consensus is that many patients do not require annual TSH-stimulated serum Tg measurement. Information garnered from the prior Tg response to rhTSH stimulation can form the basis of recommendations for further testing (Fig. 3). Among patients with an undetectable THST-Tg who undergo rhTSH stimulation, there are three possible scenarios using a Tg cutoff of 2 μg/liter:

a) Tg remains undetectable: Up to 65% of low-risk patients who have undergone near-total thyroidectomy and ^{131}I ablation have no rise in serum Tg concentrations after rhTSH. Annual TSH-stimulated serum Tg measurement does not need to be done in this group, but thereafter how often or whether it should be done at all is uncertain.

b) Tg rises no higher than 2 μg/liter: This occurs in about 20% of low-risk patients (Figs. 1A and 3) and may not call for immediate evaluation but usually warrants periodic rhTSH stimulation studies, perhaps as often as once yearly. Neck ultrasonography plays an important diagnostic role in this group. In some patients, the high TSH-stimulated serum Tg level will spontaneously decline over one or more years, and in others it will steadily rise, and metastases will become apparent (7, 29, 40).

c) Tg rises above 2 μg/liter: This occurs in about 20% of low-risk patients after rhTSH stimulation (Table 2) and usually indicates a substantial thyroid remnant or residual cancer. Patients with this pattern usually require further testing to localize the source of the Tg (Fig. 1 and Tables 1 and 2).

Discussion

The surveillance of patients whose tumors appear to have been completely removed by surgery and a single ^{131}I treatment, which represents the majority with DTC, is the main focus of our recommendations. Ten studies (7, 28, 30–36, 39) of nearly 1600 patients demonstrate that TSH-stimulated Tg testing (either rhTSH or THW) is sensitive enough to be used alone in the follow-up of low-risk patients, and that a DxWBS adds little, if any, information in most of them.

The algorithm we propose does not require a patient to become hypothyroid at the 1-yr follow-up evaluation, instead recommending preparation by rhTSH. Two large studies (30, 37) have now confirmed that the sensitivity of the rhTSH-stimulated Tg is similar to the hypothyroid-stimulated Tg for the detection of metastatic disease, despite the greater elevation of Tg that prolonged hypothyroidism may produce (35). Ultrasonography performed by expert endocrinologists or radiologists is particularly useful in patients with high Tg levels.

Early detection of tumor affects thyroid cancer mortality (1). The outcome of patients with metastatic disease is highly dependent on the size and extent of neoplastic foci when detected, with survival dramatically decreasing if foci remain unidentified until they become large and/or widespread (41). When serum Tg rises above 2 μg/liter after rhTSH, our algorithm suggests further evaluation and possibly ^{131}I therapy if the THW-Tg rises above some arbitrary limit, without performing a DxWBS, relying on the posttherapy whole body scan (RxWBS) for localizing the tumor and confirming its uptake of ^{131}I.

The choice of a 2 μg/liter cutoff to identify tumor is supported by studies that show a substantial likelihood of residual disease in patients with TSH-stimulated serum Tg levels above 2 μg/liter, whether induced by rhTSH or by endogenous TSH (7, 39). Eight studies (28, 30–36) comprising 1028 patients showed that almost 90% of those with metastases were identified using an rhTSH-Tg cutoff of 2 μg/liter. However, because different Tg assays return different Tg levels from the same serum specimen, the choice of the optimum cutoff may vary depending on the unique characteristics of individual Tg assays as outlined earlier in this report.

An elevated serum Tg may be the only indication of metastases ultimately found on the RxWBS after administering ^{131}I therapy. The Tg cutoff for empiric ^{131}I therapy, albeit arbitrary, is about 10 μg/liter after THW in many centers (8, 42, 43). The frequency of lung metastases in patients empirically treated with ^{131}I for a high serum Tg and negative DxWBS ranges from nearly 6% in one study (44) to 9% in another (1), and from 35–55% of selected patients in two other studies (45, 46). Schlumberger (41) reported 100% 10-yr survival after empiric ^{131}I treatment of lung metastases found by an elevated serum Tg level and negative DxWBS, but positive RxWBS. In contrast, 10-yr survival was 91% with a normal chest x-ray and a positive DxWBS and RxWBS, and it was considerably worse with a positive chest x-ray, *i.e.* 63% with micronodules and 11% with macronodules. Pineda *et al.* (46), after treating 17 Tg-positive and DxWBS-negative patients, found that the serum Tg decreased in 81% after the first ^{131}I treatment, 90% after the second treatment, and 100% after the third treatment. These studies show that empiric ^{131}I therapy may be useful for diffuse lung uptake, especially in young and middle-aged patients with negative chest x-rays and DxWBS. It is, however, of little benefit in patients with macronodular lung metastases, especially when they do not concentrate ^{131}I or when they are visualized on FDG-PET (47, 48). Pacini *et al.* (40) emphasize that once tumor ^{131}I uptake cannot be demonstrated on RxWBS, further ^{131}I treatment is not indicated. Treating patients with large cumulative doses of ^{131}I for tumors that do not concentrate the isotope has a potential for harm that outweighs any minor benefit it might have. Pacini *et al.* (49) also recommend that repeat ^{131}I treatments should not be given for trivial thyroid bed uptake, whereas if lung metastases concentrate ^{131}I on the first RxWBS after empiric treatment, ^{131}I therapy should be continued until remission. Optimal therapy for lymph node metastases is often surgery (8).

Omitting follow-up DxWBS studies in low-risk patients after initial surgery and ^{131}I ablation has important cost implications. The price for a DxWBS varies by region and ranges from $1022 to $1844 (Table 3). The cost for rhTSH is approximately $900, but this varies among providers. The cost of performing rhTSH-stimulated serum Tg measurements without DxWBS thus would be about the same as performing THW-stimulated serum Tg measurements and DxWBS. The least costly approach insofar as direct medical costs are concerned is to simply withdraw thyroid hormone

TABLE 3. Cost of performing whole-body scans (by region)

	Northeast	Midwest	West Coast	South
Whole body scan	$971–$1844	$640	$1037	$883
^{131}I	Bundled–$200	$382	$658	$154
Professional fee	Bundled–$166	N/A	N/A	Bundled

All costs shown are what actual facilities charge for these procedures; one or two price examples per region were obtained. Bundled means that cost is included in cost of WBS scan. N/A, Not available.

and proceed with the algorithm shown in Fig. 1; however, this requires the patient to become hypothyroid, with its attendant problems, including indirect costs of hypothyroidism such as lost work and productivity. Although we have not performed a detailed pharmacoeconomic analysis, we believe the proposed paradigm using rhTSH-stimulated serum Tg measurements alone is a cost-effective and sensitive means of detecting early metastases in patients who clinically appear to be free of disease and who have undetectable serum Tg concentrations while taking TSH-suppressive doses of thyroid hormone. Follow-up paradigms are likely to be substantially different in patients who have not undergone total or near-total thyroidectomy and ^{131}I ablation who have a thyroid remnant.

Establishing optimal follow-up paradigms for patients with DTC remains challenging. Yet it is important, because even modest increments in detecting occult tumor that is amenable to treatment will benefit many patients. Some prominent thyroidologists and surgeons disagree with routine thyroid remnant ablation, and this consensus statement is for the benefit of those who perform this therapeutic maneuver. In this conference, we have reviewed recently published data and proposed guidelines for the routine follow-up of low-risk patients with DTC. For each individual patient, however, the physician must rely on clinical judgment and consider the presentation of the disease and the patient's wishes before deciding on the management strategy.

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