

REVIEW

Follow-up of low-risk patients with differentiated thyroid carcinoma: a European perspective

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Abstract

Objective: Because differentiated (follicular and papillary) thyroid cancer (DTC) may recur years after initial treatment, the follow-up of patients with DTC is long term. However, this population has changed, with more individuals being discovered at an earlier stage of the disease, so that previous follow-up protocols based mostly on data from high-risk patients no longer apply. We sought to develop an improved protocol for the follow-up of low-risk patients with DTC based on the findings of recent studies.

Methods: We analysed recent literature on the follow-up of DTC.

Results: Recent large studies have produced three important findings: (i) in patients with low-risk DTC with no evidence of disease up to the 6- to 12-month follow-up, diagnostic whole-body scan adds no information when serum thyroglobulin (Tg) is undetectable and interference from anti-Tg antibodies is absent; (ii) use of recombinant human thyroid-stimulating hormone to aid Tg measurement is effective and provides greater safety, quality-of-life and work productivity than does levothyroxine withdrawal with its attendant hypothyroidism; and (iii) ultrasonography performed by an experienced operator is the most sensitive means of detecting neck recurrences of DTC.

Conclusions: We present a revised follow-up protocol for low-risk patients taking into account the above findings. This protocol should help clinicians enter a new era of monitoring characterized by greater safety, simplicity, convenience and cost savings.

European Journal of Endocrinology 150 105–112

Introduction

Differentiated (papillary and follicular) thyroid carcinoma (DTC) is generally characterized by an indolent course with low morbidity and mortality and is among the most curable cancers (1). In most cases, initial treatment for DTC is total or near-total thyroidectomy, with or without lymph node dissection. Depending on the completeness of surgery and prognostic classification, the surgery may be followed by administration of large activities of ¹³¹I while the patient is hypothyroid to ablate remnant tissue and any residual disease. Patients are then placed on levothyroxine (L-thyroxine; LT4) treatment to decrease serum thyroid-stimulating hormone (TSH) to a level that minimizes the risk of stimulating growth of any cancerous thyroid cells while avoiding deleterious effects of LT4 overdosage on the heart or bone.

Because DTC may recur at any time for years after the initial treatment, and LT4 therapy is lifelong, long-term follow-up is necessary. Since the estimated European population of DTC patients and survivors is 200 000 (2, 3), any follow-up protocol will affect the safety and quality-of-life of a large population and exert an important impact on health economics.

In recent years, the spectrum of patients with DTC has changed. In part due to incidental findings on neck ultrasonography (US) for non-thyroid indications, a larger number of thyroid tumours, mainly papillary, are being discovered at an earlier stage, accounting for the increased incidence of the disease (2, 4, 5). Because of this change in the composition of the patient population, follow-up protocols mainly based on data from high-risk patients no longer apply. In fact, the majority of patients are at low risk of recurrence. In these patients, follow-up should be guided by a protocol

with a high negative predictive value, to exclude from unnecessary investigations those with a non-significant risk of recurrence and to identify the few individuals who have a previously unrecognized risk of recurrence and therefore merit a closer follow-up.

Indeed, patients with distant metastases, extensive neck disease (pT4), poorly differentiated histotypes or incomplete thyroid surgery should be treated and followed-up according to specific protocols, and will not be considered in this article.

A group of European thyroid cancer specialists gathered at the Institut Gustave Roussy, Villejuif, France on 24 March 2003 to assess the implications of pertinent recent studies on the follow-up of DTC, and to issue recommendations for a revised follow-up protocol (Fig. 1). The revised protocol includes three important elements addressing recent findings. First, in patients with no clinically obvious residual disease, the protocol bases the type of subsequent monitoring and, if needed, treatment that the patient receives on the presence or absence of evidence of disease between the time of ablation and the 6- to 12-month evaluation, rather than on prognostic indicators at the time of initial treatment. In the balance of this paper, the term 'ablation' refers to the final intervention that reduces the thyroid remnant to a size below the institutional threshold for re-ablation in patients without clinically obvious disease.

Secondly, the protocol uses rhTSH as the 'gold standard' to obtain TSH stimulation for diagnostic follow-up. Thirdly, the protocol virtually obviates diagnostic radioiodine WBS (dxWBS) and highlights the importance of neck US in the follow-up of low-risk patients with no evidence of disease up to the 6- to 12-month follow-up. The balance of this paper presents the entire protocol in greater detail, and discusses its rationale, particularly for these three elements.

Objectives and stages of follow-up

After initial treatment, the follow-up of patients with DTC has two objectives: (i) to discover at the earliest possible time persistent or recurrent disease, allowing for treatment that may extend survival (1, 6) and (ii) to ensure that the patient receives the lowest effective LT4 dose, i.e. one that provides no more TSH suppression than necessary (7).

Monitoring patients with DTC comprises four stages: (i) evaluation at the time of radioiodine ablation of thyroid remnant; (ii) ~3-month follow-up while the patient is on LT4 treatment; (iii) 6- to 12-month follow-up, while the patient is on LT4 treatment and after TSH stimulation; and (iv) subsequent follow-up.

Early follow-up and patient classification

Evaluation at the time of ablation consists of serum Tg measurement while the patient is hypothyroid,

'post-therapy' WBS 3–7 days after administration of the ablative activity of ^{131}I and physical examination. Neck US performed at this time may be useful in detecting previously undiagnosed lymph node metastases although, in a few cases, images may be difficult to interpret or uninformative due to recent surgery.

In making such comparisons, one must, of course factor in whether serum Tg is measured on the day when the first ablative activity of ^{131}I is administered to provide early identification of residual tissue or tumour and an early value for comparison with subsequent measurements. In making such comparisons, it must, of course, be borne in mind to factor in whether and which kind (i.e. LT4 withdrawal or rhTSH administration) of TSH stimulation was present for each measurement.

A low or undetectable serum Tg at the time of ablation generally indicates a favourable outcome. Elevated values have indeterminate prognostic significance and may be related to persistent disease or to lingering leakage from post-surgical thyroid residues.

WBS, which should include spot imaging of the neck, should be performed using a large field of view gamma camera with thick crystals and high-energy collimators. Whole-body images should be taken for at least 30 min or with at least 140 000 counts, and single spot images for at least 10 min or with at least 60 000 counts (8, 9). An accurate anatomical view of any neck uptake is important to differentiate whether the uptake is present in normal thyroid remnant (or along the thyrogloss tractus) or lymph node metastases, as well as to guide any necessary surgical excision. The risk of artifacts should be minimized by having the patient drink lemon juice and large amounts of liquid, chew gum, and shower and change clothes before scanning. Iodine contamination should be avoided by the patient's following a low iodine diet for some days or a few weeks before radioiodine treatment. Testing of urinary iodine concentration may be helpful in ruling out excessive iodine levels and should be considered as a routine practice before radioiodine administration.

Tg measurement should always employ a modern immunometric assay with a functional sensitivity of <1 ng/ml, and should be performed by a laboratory experienced in Tg testing. Because of the difficulty in comparing Tg determinations by different assays and laboratories, the same method and laboratory should be used for serial measurements in each patient. To aid in the interpretation of Tg results and identify the ~20% of cases with anti-Tg antibodies (TgAb) (10), Tg testing should be accompanied by a TgAb assay, or by recovery testing.

In cases of interference with Tg measurements by TgAb, patients should be monitored according to a modified protocol. In such cases, follow-up cannot rely on a serum Tg determination and should comprise clinical examination, neck US and ^{131}I WBS. Of note, a detectable serum Tg level in the presence of TgAb

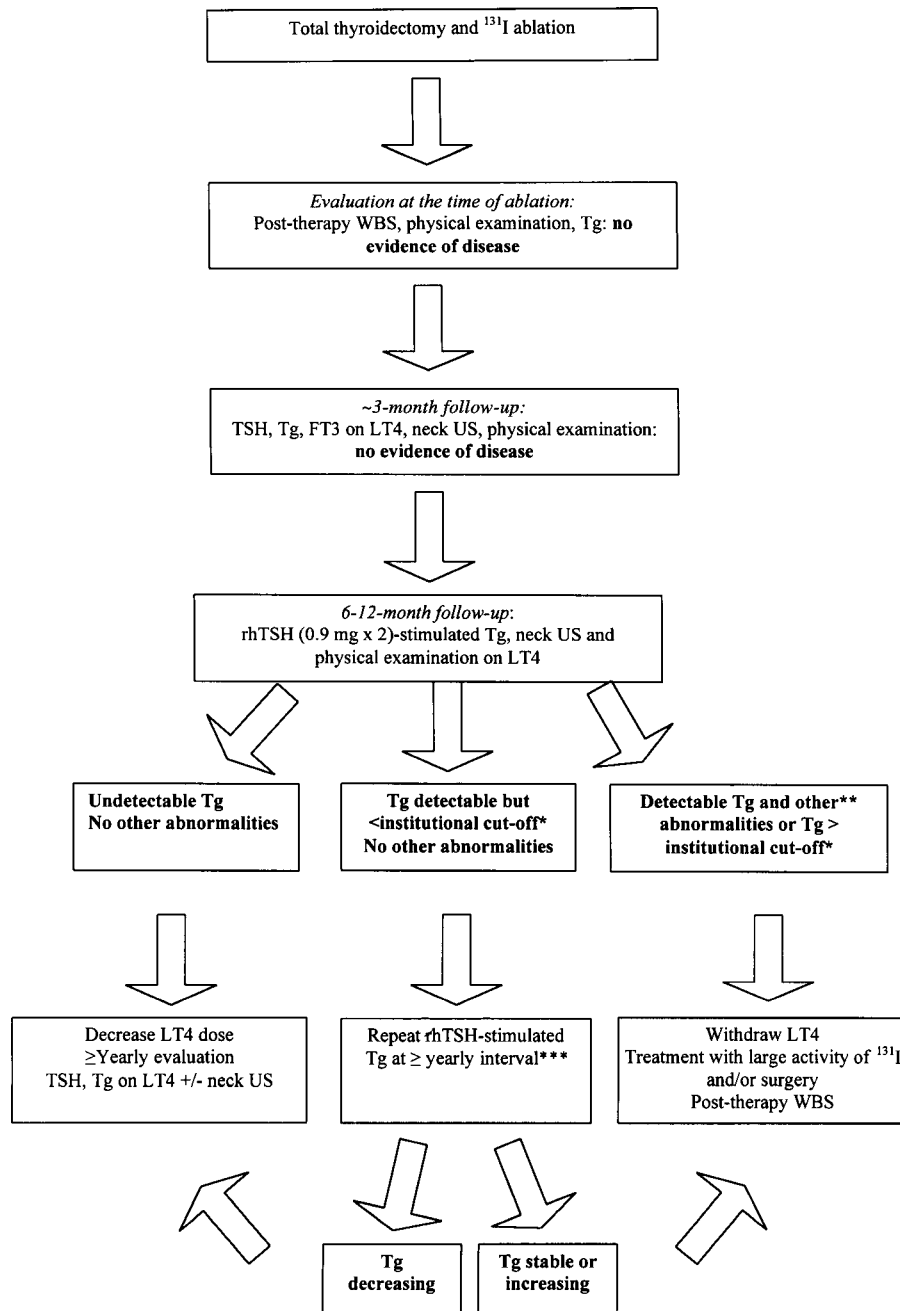


Figure 1 Recommended protocol for follow-up of differentiated thyroid carcinoma in low-risk patients who have received thyroidectomy and radioiodine ablation. Patients with distant metastases, extensive neck disease (pT4), poorly differentiated histotypes or incomplete thyroid surgery, or with anti-thyroglobulin (Tg) antibodies should be followed up according to other specific protocols. FT3, free triiodothyronine; rhTSH, recombinant human TSH; WBS, whole-body scan; + / - , with or without. *The Tg threshold should be determined after rhTSH stimulation for each assay method. **Any suspicious finding on neck US warrants fine-needle aspiration (FNA) with cytological evaluation and measurement of Tg concentration in the aspirate. ***This interval depends on exact Tg level and on the clinical context.

is generally observed in patients with persistent or recurrent disease. Also of note, in the absence of disease, TgAb will progressively decrease and disappear within the first 2 years of follow-up (10, 11).

The ~3-month follow-up consists of TSH, FT3 (12) and, optionally, free T4 determinations while the

patient is on LT4 treatment. Serum Tg is also measured and neck US and physical examination are performed. TSH testing is not conducted until ~3 months after ablation because elevated TSH levels may persist until that point and may lead to over-treatment with LT4. At this stage of follow-up, a TSH concentration

$\leq 0.1 \mu\text{U/ml}$, normal FT3 levels, and normal or high-normal free T4 levels denote an appropriate dose of LT4.

The results of the post-ablation and ~ 3 -month follow-ups should be used to distinguish two groups of patients: those (i) with or (ii) without evidence of disease. Justifying this categorization, various large studies have shown that patients without evidence of disease in early follow-up, more than 80% of the DTC population, comprise a homogeneous group in terms of outcome (13–15).

Patients should be classified as showing no evidence of disease if they have complete tumour resection according to the surgeon's report, no uptake outside the thyroid bed on post-ablative ^{131}I WBS, undetectable serum Tg levels ($< 1 \text{ ng/ml}$ during LT4 treatment), and no abnormality on any neck US that has been performed 3 or more months post-surgery.

Patients meeting these criteria but with evidence of a large thyroid remnant, following partial thyroidectomy or shown by a thyroid uptake, e.g. $> 5\text{--}15\%$, should be considered for additional surgery and/or treatment with large activities of radioiodine. Re-operation is generally preferable for the largest remnants (e.g. those with $\geq 10\%$ uptake) and the availability of radioiodine treatment should not foster complacency about poor technique in the initial thyroid surgery. A volume of thyroid remnants above an institutional threshold, e.g. $> 2 \text{ ml}$ in total and $> 1 \text{ ml}$ on each side of the thyroid bed, on US may be a helpful additional criterion for consideration of further treatment. The decision on whether to administer additional ablative treatment may also be deferred until 6–12 months after the first ablative intervention since, in some cases, even large thyroid residues may disappear during that period in a delayed response to the first intervention.

In patients with large thyroid remnants treated with radioiodine, immediate post-ablation WBS may be poorly sensitive for detecting uptake outside the thyroid bed and a subsequent dxWBS, e.g. at 6–12 months, may be indicated. Whenever rhTSH is used to provide TSH elevation for dxWBS, an activity of at least 148 MBq (4 mCi) of ^{131}I should be administered 1 day after the last injection of rhTSH. To avoid stunning, use of 123-iodine may be considered for dxWBS (16).

Patients with evidence of disease also should be referred for treatment with radioiodine and/or any other indicated modalities. However, patients whose evidence of disease comprises only detectable but low Tg at the time of ablation and/or at any subsequent follow-up should be followed with rhTSH-stimulated Tg measurement 1 year or more later depending on the Tg level and clinical context (see below).

Six- to twelve-month follow-up

For patients without evidence of disease at the 3-month follow-up, the 6- to 12-month follow-up should consist

of Tg testing during LT4 treatment before and 3–5 days after rhTSH stimulation, and of neck US and physical examination. rhTSH should be administered in two consecutive daily intramuscular injections of 0.9 mg and blood should be drawn for Tg measurement 2 or 3 days later.

The rationale for the use of TSH stimulation is the well-documented appreciable percentage of patients having false-negative Tg measurements during LT4 treatment when no TSH stimulation is employed: $\sim 20\%$ of patients with lymph node metastases and 5% of patients with distant metastases but normal plain radiographs (1). However, it should be noted that only a small minority of patients with no clinically obvious disease will have persistent disease at follow-up examination; therefore, the percentage of patients for whom any testing with rhTSH will permit the discovery of disease will be relatively low. In our view, rhTSH-stimulated serum Tg determination is still warranted because it will obviate other testing and provide reassurance for the majority of these patients and, in the others, will indicate further testing and/or treatment.

The rationale for using rhTSH instead of LT4 withdrawal for TSH stimulation is threefold. First, the sensitivity of rhTSH-stimulated serum Tg measurement has been amply demonstrated (15, 17–25). Secondly, rhTSH stimulation avoids the discomfort and quality-of-life impairment and decreases the safety risks associated with the hypothyroidism that is secondary to LT4 withdrawal (18, 26–30). Thirdly, use of rhTSH stimulation largely avoids the negative economic and professional consequences of that hypothyroidism. In patients working outside the home, a non-randomized French multicentre study found a mean 0.7 days of missed work per follow-up with rhTSH, versus 13.7 days with LT4 withdrawal (J Leclère, Satellite Symposium Presentation at the European Association of Nuclear Medicine Congress, Paris, France, 3 September 2000). The corresponding data from a German tertiary referral center were 2 days missed with rhTSH, versus a median 11 days missed with LT4 withdrawal (M Luster, R Felbinger, M Dietlein & C Reiners, unpublished observation).

The rationale for using neck US in combination with Tg testing and avoiding dxWBS in the 6- to 12-month follow-up of patients with no evidence of disease up to that time is also threefold. First, six recent studies totaling almost 750 consecutive patients given LT4 withdrawal (13, 14), rhTSH (15, 17, 21) or a combination of these methods (31) have shown that dxWBS adds no information to that obtained by Tg testing (Table 1). In these studies, no patient who was Tg negative, defined as having a value below the institutional cut-off or limits of detectability, was WBS positive, defined as having uptake outside the thyroid bed. Moreover, no more than a fraction of Tg-positive patients were also WBS positive. A seventh recent study (24) shows a small percentage of Tg-negative, WBS-positive patients.

Table 1 Diagnostic relevance of dxWBS: data from recent studies.

Study patient population	TSH stimulation method	Follow-up point	Patients Tg- /dxWBS ⁺	Patients Tg + dxWBS ⁺
Robbins <i>et al.</i> 2002 (24); 366 consecutive patients	rhTSH	Not given	24/175 (13.7%)	145/191 (76%)
Pacini <i>et al.</i> 2002 (14); 315 consecutive patients who were Tg - under withdrawal at previous evaluation	LT4 withdrawal	6-12 months	0/315	No Tg ⁺ patients
Cailleux <i>et al.</i> 2000 (13); 256 consecutive patients	LT4 withdrawal	6-12 months	0/210	0/46
Mazzaferrri & Kloos 2002 (21); 107 consecutive patients	rhTSH	10 months-35 years	0/68	0/39
Torlontano <i>et al.</i> 2003 (15); 99 consecutive patients	rhTSH	6-12 months	0/78	0/21
Pacini <i>et al.</i> 2001 (31); 72 consecutive patients	rhTSH for Tg, withdrawal for dxWBS	Not given	0/41	11/31
David <i>et al.</i> 2001 (17); 33 patients	rhTSH	6-24 months	0/29	2/4

+ , positive; - , negative. Tg - is defined as below the standard institutional cut-off or in studies 21 and 31, below the limit of detectability. WBS⁺ is defined as a scan showing uptake outside the thyroid bed.

However, this study appears to include some patients who received further therapy after initial treatment and presumably had evidence of disease at the post-ablation or 6- to 12-month follow-up: not the population in which our protocol suggests avoidance of dxWBS. By contrast, only a handful of patients in one (21) of the aforementioned six studies appear to have received additional therapy after the initial treatment.

Secondly, obviation of dxWBS prevents possible impairment of uptake of any necessary therapeutic activity of radioiodine due to stunning from a diagnostic activity (32-35).

The third rationale for using neck US and avoiding dxWBS in patients with no evidence of disease before the 6- to 12-month follow-up is the efficacy of neck US in detecting neck recurrences, documented by three recent large studies (15, 23, 36). This contrasts with the low sensitivity of neck palpation (15, 23, 36). One of the studies (36) involved 494 patients followed for ~5.5 years, of whom 51 developed recurrences in the lateral or central neck compartments. Neck US had a 94% sensitivity in detecting the recurrences, versus 57% and 45% sensitivities for withdrawal-aided Tg testing and dxWBS respectively. Another of the studies (23) involved 340 consecutive patients with DTC who had received near-total thyroidectomy and radioiodine remnant ablation, and were scheduled for routine diagnostic follow-up. The investigators found that rhTSH-aided Tg testing and neck US had a sensitivity of 96.3% and a negative predictive value of 99.5% for detecting active disease, versus 92.7% and 99.0% respectively with rhTSH-stimulated Tg testing and dxWBS.

In patients with DTC, and especially those with the papillary variant, neck lymph nodes are the most frequent site of recurrence, and almost the only site in patients with undetectable Tg during LT4 treatment

(1, 13, 15, 23); this argues the desirability of employing the most sensitive modality in addition to Tg testing to detect neck recurrences. US abnormalities are suspicious when they are hypoechogenic, lack an echogenic central line, have a round shape, contain microcalcifications or a cystic component, and/or have a hypervascularised appearance on colour doppler. Neck US can detect lymph node metastases as small as 2-3 mm in diameter. In these patients with a small tumour mass, serum Tg may remain undetectable even following TSH stimulation and WBS may be negative. Indeed, it is estimated (37, 38) that 1 g neoplastic tissue will increase serum Tg obtained during LT4 treatment by about 0.5-1 ng/ml, and that TSH stimulation will increase serum Tg values by about tenfold over baseline levels.

It is essential that neck US be performed by an operator with day-to-day experience in evaluating patients with thyroid cancer, not just thyroid disease in general. Likewise, US-guided FNA should only be performed by an operator experienced in that procedure. Neck US should employ a probe containing a linear transducer of at least 7.5 MHz. In addition, the US report should list all three dimensions of any lesions detected and results should be shown on a diagram.

All suspicious lesions that are accessible to puncture should be subjected to FNA with cytological evaluation. Measurement of Tg concentrations in the aspirate is frequently useful because of the challenging nature and sometimes uncertain reliability of cytology of some specimens (39). Tg RT-PCR may serve as an alternative to such measurement (40).

Subsequent follow-up and management

In patients with an undetectable rhTSH-stimulated Tg concentration and normal findings on neck US at

the 6- to 12-month follow-up, the risk of subsequent recurrence is less than 0.5% (13, 23, 41). These patients can be reassured and the dose of LT4 may be safely decreased to allow a TSH concentration of 0.1–0.5 μ U/ml. These patients should be followed yearly with TSH and Tg and eventually neck US. Tg testing may be conducted during LT4 therapy without rhTSH stimulation; whether such stimulation is justified by providing added data needs to be ascertained.

In patients with detectable rhTSH-stimulated Tg concentrations at the 6- to 12-month follow-up, subsequent management depends on the Tg levels and the presence or absence of abnormalities on neck US and any other evaluation methods that may have been performed. In evaluating Tg measurement results, it often is preferable to assess the slope between consecutive values, factoring in their TSH-stimulation status, rather than to rely on a single value in isolation. An increasing Tg slope has been shown to have substantially greater positive predictive value than the 6- to 12-month Tg concentration alone (41, 42). This is because detectable serum Tg may be produced for some months after initial treatment by irradiated cancer cells that will eventually disappear, or by neoplastic foci that will progress. The slope between the 6- to 12-month and subsequent Tg values can differentiate between these two sources of elevated Tg.

Patients with a Tg concentration that is detectable but below an institutional cut-off (determined under rhTSH stimulation for each particular assay employed) and no other abnormalities should be followed with rhTSH-stimulated Tg measurement 1 year or more later depending on the Tg level and the clinical context. If serum Tg shows a decrease between the 6- to 12-month follow-up and the subsequent testing point, monitoring should be conducted in the same manner as in patients without any evidence of disease up to the 6- to 12-month follow-up. In individuals who show a stable or increasing Tg concentration between the 6- to 12-month follow-up and the subsequent testing point, persistent or recurrent disease should be carefully sought, starting with the administration of a large activity of 131 I. Patients who at the 6- to 12-month follow-up have detectable rhTSH-stimulated Tg levels and abnormalities on other evaluation methods or rhTSH-stimulated Tg above the institutional cut-off also should receive such management. If the post-therapy WBS does not show any uptake, other imaging modalities may be employed: spiral computed tomography of the neck and chest, bone scintigraphy and [18 F]fluorodeoxyglucose positron emission tomography (FDG-PET) (33). FDG-PET may be more sensitive when performed following rhTSH stimulation (43).

Conclusion

With the introduction of serum Tg measurement into everyday practice, the follow-up of patients with DTC

entered a second era. The elimination of routine chest X-rays and diminution in the frequency of dxWBS decreased radiation exposure of the patient, inconvenience to the patient and family, risk of interference with uptake of therapeutic activities of radioiodine, and cost to the patient and third-party payer. The monitoring of patients with DTC is on the threshold of a third era of still greater safety, simplicity, convenience and cost savings with the recent documentation of (i) the lack of sensitivity of dxWBS in identifying individuals suspicious for disease among patients without evidence of DTC up to the 6- to 12-month follow-up who are also receiving TSH-stimulated Tg testing, (ii) the efficacy of rhTSH stimulation and its safety and preservation of patients' work productivity relative to LT4 withdrawal and concomitant hypothyroidism and (iii) the superior efficacy of neck US in detecting neck recurrences. Along with findings of a recent, primarily North American consensus meeting (44), our recommended protocol gives the clinician a guide for entering this new era.

Acknowledgements

Editorial assistance in the preparation of this manuscript was supported by an unrestricted educational grant from Genzyme Europe BV, Naarden, The Netherlands.

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Received 21 October 2003

Accepted 6 November 2003