Thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma in children

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FOLLOW-UP TREATMENT of children who have undergone an operation for differentiated thyroid carcinoma (DTC) has involved generally the use of 131-I whole-body scans (WBS) and measurement of serum thyroglobulin (Tg) levels once thyroid hormone suppressive therapy with levo-thyroxine (L-T4) was withdrawn.[1] It is now possible, however, to give the patient recombinant human thyroid stimulating hormone (rhTSH) so as to maintain the patient on L-T4 suppressive therapy. In fact, many studies have confirmed the efficacy of rhTSH in stimulating the uptake of radioactive iodine as well as the release of Tg by any remaining thyroid tissue, as well as a recurrence or distant metastasis from DTC.[2-5]

Neck ultrasonography[6] has proven to be effective in the diagnosis of neck lymph node metastases and local recurrences in adult patients who underwent total thyroidectomy for DTC. Recently, Pacini et al[7] found that use of the rhTSH-stimulated Tg test in combination with neck ultrasonography has the highest diagnostic accuracy in detecting persistent disease during the follow-up of adults who have undergone operation for DTC. Other studies have assessed rhTSH in the follow-up of children who had undergone operation for DTC in the United States,[8] but its use in children is not approved in several countries such as Italy, where the measurement of serum Tg after withdrawal of thyroid hormone is used routinely in this class of patients.

In addition, in a previous article, we have shown[9] that, in children with DTC, neck ultrasonography can detect and locate the anatomic site of lymph node metastases in the neck that had not been detected by palpation, WBS, or serum Tg determination.

This study aims to compare the diagnostic accuracy of endogenous TSH-stimulated WBS, serum Tg measurements and neck ultrasonography, alone or in combination, in a large retrospective study of children who had undergone operation for DTC.

MATERIALS AND METHODS

Ninety-two consecutive children (71 females, 21 males) with DTC (88 papillary, 4 follicular) were retrospectively studied. All patients had undergone a near total thyroidectomy and post-operative 131-I thyroid ablation and had been scheduled for routine diagnostic whole-body scanning (WBS) and measurement of serum Tg levels. Mean age at diagnosis was 11 ± 4 years (range, 5 to 18 years). The De Groot classification[10] was used to determine the stratification of the disease: class 1, tumor confined to the thyroid gland; class 2, metastases in the neck lymph nodes; class 3, tumor invading the thyroid gland; and class 4, distant metastases. At the time of diagnosis, 52% of patients were class 1, 40% were class 2, and 8% were class 3.

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The reason for testing was: (1) to check for thyroid ablation after operation and radioiodine treatment (34% of the patients); (2) a second control after a negative test (15% of the patients); and (3) to check for disease remission in those patients who, at a previous evaluation, had been taken off L-T4 treatment, had evidence of residual or metastatic tissue (51% of the patients) (local or distant metastases were evident in 19 of 92 patients [21%]; there was persistence of thyroid bed uptake in 28 of 92 patients [30%]). At study start and when receiving L-T4 suppressive therapy, 79% of the patients had undetectable (<1 ng/ml) serum Tg levels and were negative for anti-Tg autoantibodies (TgAb), 7% (6 patients) were positive for TgAb, and 14% (13 patients) had detectable serum Tg levels and were negative for TgAb. The mean interval between initial radioactive iodine ablation treatment and entry to the study was 11.5 months (range, 9 to 87). All parents gave their informed consent to the treatment and study.

The study design involved serum Tg measurements and WBS with endogenous TSH stimulation after L-T4 withdrawal. Serum samples for measurement of TSH and Tg levels were collected before the 131-I injection. All patients underwent neck ultrasonography. Suspicious neck masses or lymph nodes were investigated by fine-needle aspiration cytology (FNAC). Additional imaging procedures (such as post-therapy 131-I WBS, computed tomography [CT], and magnetic resonance imaging) were scheduled only when indicated. In the absence of a gold-standard method for defining metastatic disease, the final evaluation of diagnostic accuracy accounts for the results of these tests, the results of neck ultrasonography plus FNAC, and the previous patient history.

Diagnostic WBS was carried out 3 days after the oral administration of a test dose of 131-I of 3 to 4 MBq (0.08 to 0.1 mCi)/kg body weight. The patients followed a strict low-iodine diet 10 days before administration of the radioiodine tracer, for the period of imaging and after treatment. The levels of urinary iodine excretion were evaluated in all patients before the WBS and was less than 200 μg/24 hours for all patients. Thyroid hormone therapy with L-T4 was withdrawn at least 45 days before administration of radioiodine, and to avoid prolonged hypothyroidism the patients were maintained on triiodothyronine (T3) until 2 weeks before the therapeutic dose (to obtain a serum TSH concentration higher than >30 μU/ml).

Post-therapy WBS was carried out 3 to 10 days after the administration of a therapeutic dose of 131-I of 37 MBq (1 mCi)/kg body weight for residual functioning thyroid tissue and 74 MBq (2 mCi)/kg for thyroid metastases.

Whole-body images (20 min/meter, matrix 512 × 128), and anterior and lateral planar images of the neck and the thorax (matrix 128 × 128 without zoom factor) were obtained with a LFOV gamma camera (StarCam 3000XC, General Electric Co., Milwaukee, Wis) equipped with a high-energy parallel-hole collimator with a 20% window centered on the 364-KeV photopeak. Planar images of the neck with 100,000 counts or 30-minute acquisition times were obtained in combination with adequate anatomic markers to distinguish between residual thyroid tissue, salivary gland uptake, and lymph node metastases. All scans were reviewed randomly by 2 nuclear medicine physicians blinded to the patient's history, clinical data, and ultrasonography findings.

Neck ultrasonography was always carried out by the same operator who was unaware of the WBS and Tg results, using a probe (Esaote AU5, Florence, Italy) with a sectorial 7.5 MHz transducer. Neck ultrasonography was carried out in all patients immediately before administration of the tracer dose of 131-I. The following criteria were used to define sonographic indications of lymph node metastasis[6,9]: (1) diameter greater than or equal to 1 cm; (2) clear hypo-echoic pattern or non-homogeneous pattern, with alternating hypo- and hyper-echoic areas; (3) irregular cystic appearance; (4) presence of internal calcifications; (5) a rounded or bulging shape, with increased antero-posterior diameter; and (6) ratio of shorter/longer diameter greater than 0.7. Any hypo-echoic mass detected in the post-operative thyroid bed, which appears normally as an area of highly reflective echoes, was considered evidence of cancer recurrence.

Serum Tg and TSH levels were measured in the same assay. Serum Tg levels were measured using a commercial immunometric assay (Diagnostic Products, Los Angeles, Calif) with a lower detection limit of 0.2 ng/ml and a functional sensitivity of 0.9 ng/ml. The assay is standardized against the certified reference material for human Tg (CRM 457) of the Community Bureau of Reference of the European Commission.[7] In our laboratory, the intra- and inter-assay coefficients of variation of the method were 4.3% and 7.0%, respectively. Based on the functional sensitivity of the assay (0.9 ng/ml), we selected 1 ng/ml as the cut-off value to distinguish undetectable from detectable Tg levels. TgAb levels were measured in all serum samples using an immuno-radiometric assay method (ICN Pharmaceuticals, Inc., Beerse, Belgium). A TgAb

concentration less than 5 U/ml was considered negative. Serum TSH levels were measured using an ultra-sensitive commercial immunometric assay (Diagnostic Products).

RESULTS

Forty-seven patients were found to be negative for neck lymph node metastases according to neck ultrasonography, diagnostic WBS, and clinical examinations. Of these 47 patients, 8 (17%) had detectable levels of serum Tg, whereas the others had Tg levels less than 1 ng/ml. Of the 8 patients with detectable levels of Tg (ranging from 9 to 153 ng/ml), 6 had lung or mediastinic lymph node metastases, whereas post-therapy WBS identified neck lateral lymph node metastases in 2 patients who had been negative at diagnostic WBS.

Twenty-five patients tested positive for lymph node metastases both by neck ultrasonography and WBS. Of these, 18 (72%) had detectable serum Tg levels (from 3 to 731 ng/ml) (3 also had lung or mediastinic lymph node metastases), whereas the other 7 had Tg levels less than 1 ng/ml (4 had detectable TgAb levels greater than 5 U/ml). In 5 patients of this group, WBS showed the presence of other metastatic lymph nodes that were not detected by neck ultrasonography on the same or the opposite side of the neck.

Eleven patients tested positive for lymph node metastases with WBS but not with neck ultrasonography. All had detectable serum Tg levels (2 to 73 ng/ml), 7 also had lung metastases. In this group, although neck ultrasonography did detect the lymph nodes, this test could not distinguish between inflammatory and metastatic involvement because of a normal hypo-echoic pattern, with internal echoic line coursing through the mid substance.

Nine patients tested positive for lymph node metastases with neck ultrasonography but not with WBS. Of these, 6 had detectable serum Tg levels (13 to 173 ng/ml), 4 had lung metastases, and 2 had detectable TgAb levels (>5 U/ml). In 8 patients, post-therapy WBS and neck ultrasonography tests indicated lateral lymph node metastases on the same side of the neck. One patient had suspected neck lymph nodes that were not detected by diagnostic or post-therapy WBS, but were confirmed by FNAC and FNAC-Tg; in this patient, the presence of lung metastases was confirmed by high levels of serum Tg (69 ng/ml) and by CT.

Neck ultrasonography images of 34 patients indicated the presence of lymph node metastases, which were confirmed by diagnostic or post-therapy WBS or FNA. In 16 patients, lymph nodes had a rounded or bulging shape and a uniformly hypo-echoic texture and were well separated from the surrounding, relatively hyper-echoic tissues (Fig 1); only 5 patients presented with lymph nodes with echogenic lines running through the mid-substance. A non-homogeneous echo pattern of metastatic lymph nodes was observed in 7 patients. In a further 5 patients, this non-homogeneous appearance was associated with the presence of internal calcification (Fig 2), and in 3 cases with internal hyper-echoic spots. Three patients had a large (2 cm) lymph node with cystic appearance (Fig 3). In 9 of 34 patients (26%), the lymph nodes were located in

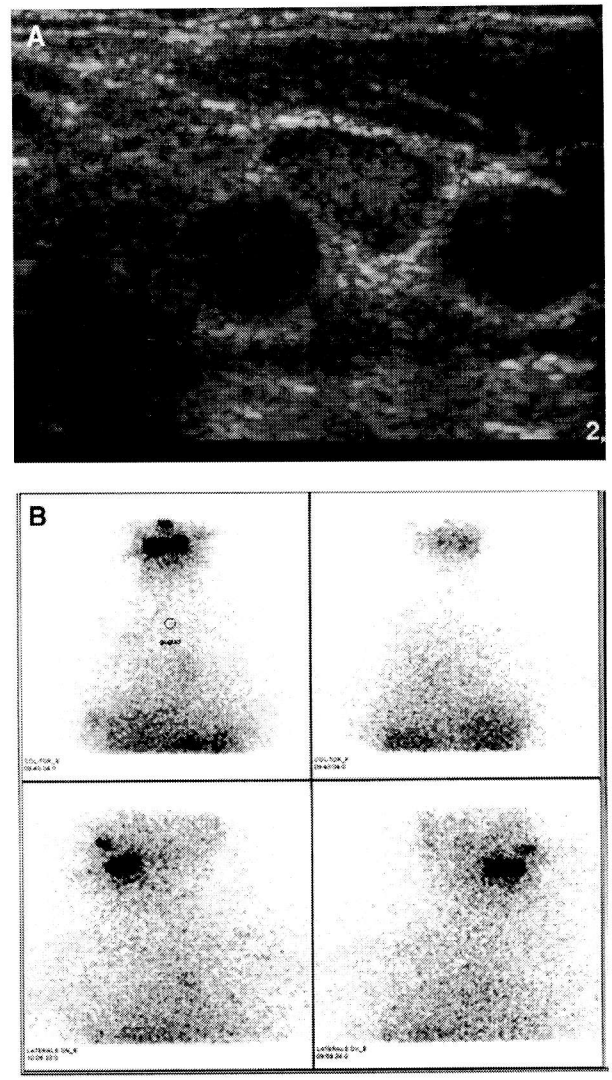

Fig 1. A, Metastatic lymph node with a rounded or bulging shape and a uniformly hypo-echoic texture, well separated from the surrounding, relatively hyper-echoic tissues and located between the carotid and jugular veins. **B,** Diagnostic WBS of the same patient.

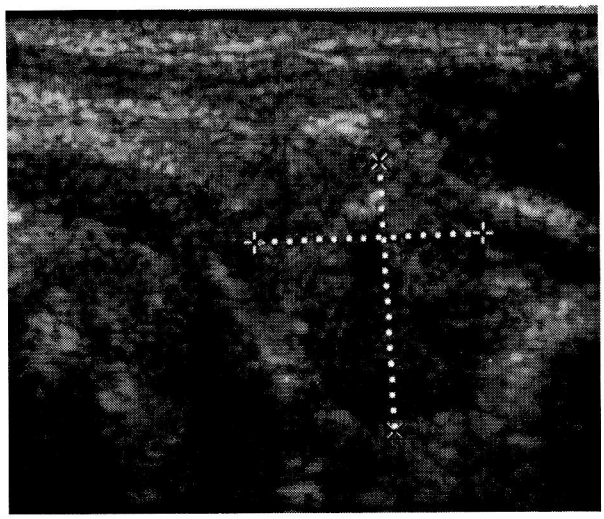

Fig 2. Metastatic lymph node with non-homogeneous appearance associated with the presence of internal calcification and located near to the carotid.

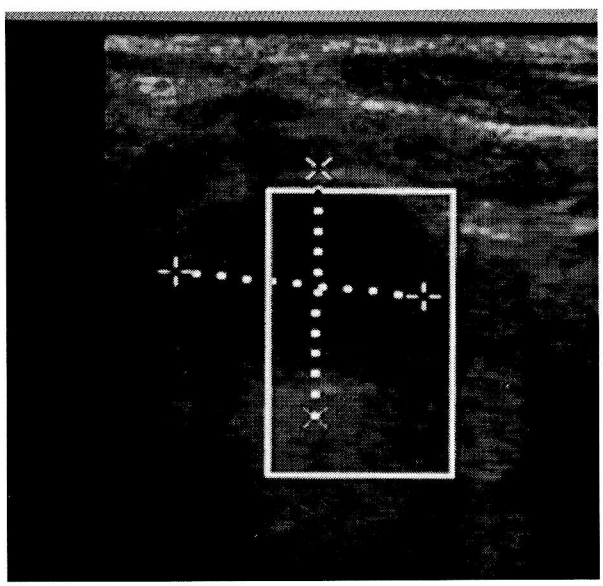

Fig 3. Metastatic lymph node with a cystic appearance.

the internal jugular chain, whereas in the other patients they were located higher up in the neck.

All children had palpable angulo-mandibular or laterocervical lymph nodes. Of 34 patients who had neck ultrasonography suspect images confirmed by diagnostic or post-therapy WBS or FNAC, the metastatic lymph nodes of 13 were palpable during physical examination (38%). Of all patients with metastatic lymph nodes, they were detectable at the neck palpation in 48% of the cases.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of neck ultrasonography, diagnostic WBS, measuring Tg, or a combination of these analyses are shown in Tables I and II.

The initial De Groot classification had no effect on the PPV and NPV.

In all cases, neck ultrasonography identified the precise anatomic location of lymph node metastases in the neck, and in particular their location with respect to the trachea, carotid artery, and jugular vein. This proved to be particularly important for lymph nodes that were not palpable or that were located behind the carotid or the jugular veins when these patients underwent operation. Data on 35 children have been published previously in another study.[9]

DISCUSSION

The main tools to identify DTC metastases or early recurrence of DTC are 131-I WBS and serum Tg measurements. Several studies have shown the latter to be markedly more sensitive and reliable,[11,12] and suggest the use of serum Tg measurements alone instead of WBS. Furthermore, administration of rhTSH allowed the patient to continue on L-T4 therapy while undergoing WBS and during Tg serum measurements,[2,3] thus improving the performance status, which is particularly important in children.

Neck ultrasonography has been shown to be an accurate and sensitive technique for the detection of a recurrence of thyroid cancer in the thyroid bed and of lymph node metastases.[6,13] We have recently systematically assessed neck ultrasonography for the detection of new cases of local recurrence and lymph node metastases in patients for whom WBS or Tg serum measurement tests were negative.[6] That study showed that a combination of neck ultrasonography and FNAC can detect cases of lymph node metastasis and local recurrence of DTC that are not detected by WBS or serum Tg measurements. These results have been confirmed recently by other studies suggesting that the combined use of serum Tg measurement, neck ultrasonography and WBS gives the best results in the follow-up of patients after operation for DTC.[14] However, this might be a more questionable approach for treating thyroid cancer in children. In children who undergo operations for thyroid cancer, the prevalence of lymph node metastases is higher than in adults.[15-17] In addition, the presence of large inflammatory lymph nodes in the neck, which are more common in children than in adults,

Table I. Accuracy of serum thyroglobulin after L-T4 withdrawal,* neck ultrasonography, and diagnostic WBS

	Tumor positive	*Tumor negative*	*Total*	
Serum thyroglobulin				
Test positive	43	0	43	PPV 100%
Test negative	10	39	49	NPV 80%
Total	53	39	92	
	Sensitivity	Specificity		
	81%	100%		
Neck ultrasonography				
Test positive	34	0	34	PPV 100%
Test negative	19	39	58	NPV 67%
Total	53	39	92	
	Sensitivity	Specificity		
	64%	100%		
Diagnostic WBS				
Test positive	42	0	42	PPV 100%
Test negative	11	39	50	NPV 78%
Total	53	39	92	
	Sensitivity	Specificity		
	79%	100%		

NPV, negative predictive value; *PPV*, positive predictive value; *WBS*, whole-body scans.
*Positive test Tg >1 ng/ml.

Table II. Accuracy of combinations of tests*

	Tumor positive	*Tumor negative*	*Total*	
Neck ultrasonography and serum thyroglobulin†				
Test positive	53	0	53	PPV 100%
Test negative	0	39	39	NPV 100%
Total	53	39	92	
	Sensitivity	Specificity		
	100%	100%		
Diagnostic WBS and serum thyroglobulin‡				
Test positive	50	0	50	PPV 100%
Test negative	3	39	42	NPV 93%
Total	53	39	92	
	Sensitivity	Specificity		
	94%	100%		
Neck ultrasonography and diagnostic WBS§				
Test positive	51	0	51	PPV 100%
Test negative	2	39	41	NPV 95%
Total	53	39	92	
	Sensitivity	Specificity		
	96%	100%		

NPV, negative predictive value; *PPV*, positive predictive value; *WBS*, whole-body scans.
*A combination of tests was considered positive if either of the tests were positive.
†Combination of neck ultrasonography and serum thyroglobulin after L-T4 withdrawal.
‡Combination of diagnostic WBS and serum thyroglobulin after L-T4 withdrawal.
§Combination of neck ultrasonography and diagnostic WBS.

makes the differential diagnosis more difficult. One recent study[9] indicated that neck ultrasonography may be useful in detecting lymph node metastases in children even when WBS is negative (shown for 3 of 45 patients; 7%) or serum Tg is undetectable (for 5 of 45 patient; 11%). In both children and adults,[18] the presence of lymph node metastases has been associated with a high rate of local recurrence,[19-21] and when there are signs of dedifferentiation, such as

absence of 131-I uptake or Tg production, this prognostic factor becomes even more significant.[19]

A retrospective study[7] in adults to assess the diagnostic accuracy of rhTSH-stimulated serum Tg and 131-I WBS showed that measurement of rhTSH-stimulated serum Tg alone is highly effective in predicting the presence of recurrent or metastatic disease. It also indicates the low sensitivity of WBS and the importance of neck ultrasonography for detecting neck lymph node metastases or local recurrences that were not detected by Tg and WBS evaluation. In the present study, most patients with undetectable basal and rhTSH-stimulated serum Tg levels were apparently disease-free. The association of neck ultrasound and serum Tg measurement increased the diagnostic sensitivity from 85% (stimulated Tg alone) to 100%. However, the diagnostic sensitivity of WBS was as low as 20.5%, which was similar to that reported when the test is carried out on hypothyroid patients.[7]

The results of our study are in agreement with previous studies. In fact the simple WBS test failed to detect metastases in 11 of 53 metastatic patients. Many of these cases were detected after the patient had undergone a therapeutic WBS, which is in agreement with studies demonstrating the superiority of this technique over diagnostic WBS.[22,23] In our study, the combination of WBS and the Tg test had a sensitivity of 94%, which was higher than that of the Tg test alone (81%). It is important to note however that combining the Tg test and neck ultrasonography gave sensitivity levels as high as 100%.

In a recent study,[24] WBS carried out on patients who had been withdrawn from L-T4 therapy or taking rhTSH, failed to detect 17% and 29% of the metastases, respectively.

By contrast, other studies[5] have shown that the rhTSH Tg test failed to identify 13% of the metastatic patients; it should be noted that the authors adopted a cut-off of 2 ng/ml.

Our study indicates that most children with a well-differentiated thyroid carcinoma do not need to undergo WBS at their first follow-up after operation, and indeed that this may also apply to adults.[7] We advocate that in children the endogenous TSH-stimulated Tg test should be combined with neck ultrasonography, because avoiding unnecessary radiation exposure in children is even more important than in adults when considering the possible dangerous effects of radiation, in particular in young males.[25]

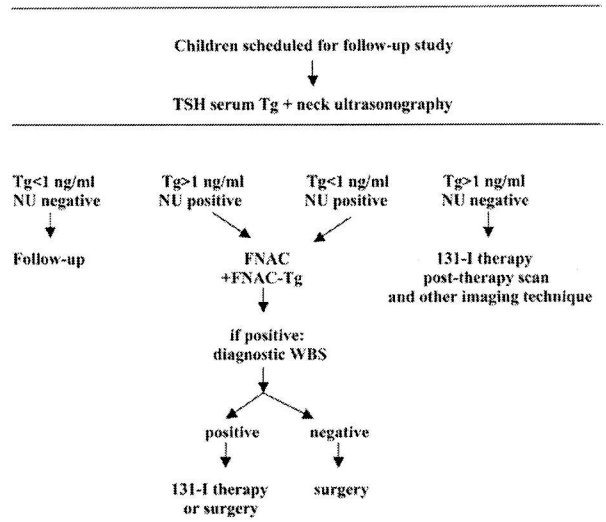

Fig 4. Schematic flow chart for the follow-up of children with differentiated thyroid carcinoma in the absence of circulating TgAb.

In conclusion, an increase in serum Tg levels above the cut-off identified in each center (1 ng/ml in our laboratory) or identification of a neck mass by echography showing the characteristic pattern of a lymph node metastasis should indicate the patient should undergo a more thorough evaluation and relative treatment. In children who are more prone to develop lateral neck node metastases, if FNAC confirms a malignant lesion and WBS is negative the operation should be repeated; this should also be considered when WBS is positive. The sequence of screening tests that may be proposed according to our results is schematically shown in Fig 4. Further studies are needed to verify the combination of rhTSH and ultrasound in children with DTC.

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DISCUSSION

Dr Quan Yang Duh (San Francisco, Calif): I just want to clarify something. Was the study done with thyroid hormone withdrawal, which is one way to increase TSH, or was it done with recombinant human TSH injection, or did you do both?

Dr Paolo Miccoli (Pisa, Italy): None of these patients underwent thyroglobulin serum measurement using human recombinant thyrotropin; all of them were off levothyroxine when they underwent thyroglobulin serum measurement

Dr Quan Yang Duh: As a follow-up question, is there any theoretical concern for using recombinant TSH on children? Toxicity, other problems?

Dr Paolo Miccoli: No. Up to date there is no agreement of using recombinant human thyrotropin in children, and, at least in Italy, we are not allowed to use it in this class of patients. I presume that once it will be allowed, we are going to use it also in children extensively.

Dr Irving B. Rosen (Toronto, Ontario, Canada): Thank you for the presentation of your article. I just wish to ask you 2 questions. What maneuvers did you carry out at the time of the thyroidectomy surgery to assess whether there was nodal positivity? And in the ultrasonic graphic (?) presumptive positive nodes, was that verified by fine needle aspiration biopsy?

Dr Paolo Miccoli: Yes. In terms of the second question, even in presence of the most clear patterns of positive metastatic lymph nodes, we always carried out fine needle aspiration cytology and thyroglobulin wash-out evaluation.

Dr Irving B. Rosen: What maneuvers did you carry out at the time of surgery to see whether there was positive nodal involvement?

Dr Paolo Miccoli: All these patients had undergone preoperative ultrasonography. And our policy is to carry out basically a lymphadenectomy only when there is a previous evidence of metastatic disease in the neck. In the presence of a clear macroscopic pattern of node metastases we certainly carry out a clearance: we have no experience of intra-operative ultrasonography.

Dr Ashok R. Shaha (New York, NY): Very nice presentation and clearly you have contributed to the Society immensely. I have just 2 important points.

The first point is that we have been using recombinant TSH in children without any major toxicity problems and it has been very helpful. I just want to make sure we appreciate when we make these children hypothyroid by thyroxine withdrawal that the disease in the neck or neck nodes grow and may become apparent. I think that needs to be kept in mind. And if we are going to use more and more radioiodine, I think we need to avoid thyroxine withdrawal. That may be of some help.

The second point is, I think this is a more generic point when it comes to nodal metastasis and well differentiated thyroid cancer. We know from our previous experience 50% to 60% of the patients have microscopic disease. And when we operated 20 years back, 30 years back, we did not bother with them. We left that disease. They lived happily ever after. We examined them every year and there was no clinical abnormality. Now we have the technology to find the disease and we are going after the disease, which is clinically probably not significant. Maybe it is significant in some patients, but not in every patient. In trying to chase this microscopic disease we need to dampen our enthusiasm and weigh it against complications, we may be hurting more people and helping a few. I think we need to keep this in mind.

Dr Paolo Miccoli: I am in complete agreement about the poor clinical importance of this microscopic metastases. But the paper mainly deals with the possibility of reducing the incidence of invasive diagnostic investigations. Because I think that when there will be total agreement about the use of recombinant thyrotropin hormone, these children might take advantage really from less and less invasive diagnostic procedures. Most of these patients, all the low-risk patients and this is probably true also for others, will have few investigations in the future and they can mainly rely on thyroglobulin serum measurement and ultrasonography in the neck, which certainly are the less invasive diagnostic tools we can use.

Dr Bruno Carnaille (Lille Cedex, France). Your presentation reflects the French experience and recommendation for management of differentiated thyroid cancer. I have one question. You show in your management slides that you used FNA Tg and you did not give us any more explanation concerning this. How is it used? We had the same experience. And we use it a lot mainly for the cystic lymph nodes where it is histologically negative usually.

Dr Paolo Miccoli: FNA Tg means fine needle aspiration cytology with a thyroglobulin measure in the wash out. Of course, in the cystic lymph nodes you just measure thyroglobulin rather than looking for neoplastic cells. But I think that the pattern of the lymph nodes as I showed is probably very, very predictive of malignancy, also independently from other investigations.