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A Gene-Expression Classifier on FNA Biopsy of a Thyroid Nodule May Be Helpful to Determine Whether an Indeterminate Nodule Is Benign

Alexander EK, Kennedy GC, Baloch ZW, Cibas ES, Chudova D, Diggans J, Friedman L, Kloos RT, Livolsi VA, Mandel SJ, Raab SS, Rosai J, Steward DL, Walsh PS, Wilde JI, Zeiger MA, Lanman RB, Haugen BR. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. N Engl J Med. June 25, 2012 [Epub ahead of print].

SUMMARY

Background

Fine-needle aspiration biopsies of thyroid nodules yield "indeterminate" cytologic diagnosis in 15 to 30% of biopsies. According to the Bethesda classification, the indeterminate category is further subdivided into three categories: (1) atypia of undetermined significance or follicular lesion of undetermined significance, (2) follicular neoplasm or suspicious for a follicular neoplasm, and (3) suspicious for malignancy, with estimated risks of malignancy of 5 to 15%, 15 to 30%, and 60 to 75%, respectively (1). Various molecular diagnostic procedures have been reported to clarify the diagnosis of malignant or benign in the indeterminate category in order to determine whether surgical thyroidectomy is appropriate therapy. The authors report a multicenter study that evaluates a commercial method that classifies indeterminate FNA biopsies into either a benign or a suspicious category.

Methods

Samples. The Veracyte company collected 4812 nodule aspirates from 3789 patients at 49 clinical sites in the United States; 577 were classified as indeterminate (12%). For 413 of the 577 samples, surgical resection of the nodule was performed. Based on quality-control procedures, 328 samples were processed to yield valid "classifier" results, but pathologic diagnosis was available for only 312 samples. Forty-seven samples were excluded for various reasons, leaving 265 samples for primary analysis; 129 were in the atypia category, 81 in the follicular neoplasm category, and 55 in the suspicious for malignancy category. In addition to the indeterminate samples, 47 cytologically benign and 55 cytologically malignant surgical samples were evaluated by the classifier.

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A Gene-Expression Classifier on FNA Biopsy of a Thyroid Nodule May Be Helpful to Determine Whether an Indeterminate Nodule Is Benign

Gene-expression classifier. The method is a microarray assay to determine the expression of 167 genes. The assay includes 142 genes in the main classifier to determine benign versus malignant, and 25 genes in cassettes that are labeled parathyroid, medullary cancer, Hürthle, renal carcinoma, breast carcinoma, and melanoma. "A linear modeling approach was used for feature selection, and a support-vector machine was used for classification." To obtain sufficient RNA for the microarray, two needle insertions were performed after one needle insertion in the first part of the study was apparently unsatisfactory for producing sufficient cellular material. The data on 367 samples is available on the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus website.

Results

In the atypia category, 31 of 129 samples (24%) were malignant by pathology; 28 of 31 were classified as suspicious by the gene-expression classifier (GEC). Ninety-eight of the 129 in the atypia category were benign, but the GEC result was suspicious in 46 of them and benign in 52.

In the follicular neoplasm category, 20 of 81 samples (25%) were malignant by pathology, and the GEC was suspicious in 18 of 20 but benign in two. Sixty-one of the 81 were benign, but 31 of them were classified as suspicious by GEC.

In the suspicious for malignancy category, 34 of 55 samples (62%) were malignant by pathology, and the GEC classified 32 of them as suspicious; of the 21 that were benign, the GEC classified only 11 as benign and the other 10 as suspicious.

Of the seven false benign results, one was a Hürthle-cell carcinoma and the others were papillary thyroid cancers. The results were attributed to the low content of follicular cells in the samples used for microarray gene analysis.

All of the additional 55 pathologically malignant samples were categorized as suspicious. Of the 47 additional samples considered benign cytologically, 3 were malignant and 44 were benign by pathology; of these 44, the GEC considered 13 as suspicious.

Conclusions

The gene-expression classifier may be used to identify a subpopulation of patients with a low likelihood of thyroid cancer who might otherwise have been treated by thyroidectomy.

ANALYSIS AND COMMENTARY

This is an interesting report of a validation study that has long been awaited for a commercial method that has been recommended for patients who had a previous indeterminate FNA biopsy. A benign GEC would spare the patient from unnecessary surgery. The authors are outstanding authorities in the area of diagnosis and management of thyroid nodules, thyroid cancer, and thyroid pathology. However, there are weaknesses in the paper, the study, and the interpretation of results.

Most clinicians would recommend surgery for patients in the suspicious for malignancy category. The GEC missed 2 of 34 malignancies (6%) in patients who would otherwise have surgery. It categorized as suspicious 10 of 21 benign lesions in this category, so it was incorrect in 48% of these cases.

In the follicular neoplasm cytology category, the GEC again identified only about half of the benign nodules and missed 10% (2 of 20) that were malignant. In the atypia of undetermined significance category, the GEC misclassified almost 10% (3 of 31) of the malignant

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lesions and was correct for only 52% (52 of 98) that were benign.

In the atypia category, I use clinical parameters, such as size and ultrasound characteristics, for making the decision about surgery, rather than recommending surgery for all such patients. I am not convinced that the current GEC adds much to this approach. Experience suggests that about 90% of the samples in this category are likely to be benign (1); the GEC found that 57% (74 of 129) were suspicious. In this series the proportion of the atypia category that were malignant, 24%, is higher than expected; the GEC misclassified about 10% of the malignant nodules (3 of 31).

It should be noted that about 30% of the benign nodules in the additional group were classified as suspicious by GEC. Because of this, the authors recommend that the test not be used for nodules that are cytologically benign, as the suspicious categorization may be tantamount to a recommendation for surgery.

My additional concern is the method itself. The relative weight given to the expression of each of the 142 genes in the classifier is not described in the appendix; only the approach to validation is described. Apparently the details of the GEC are proprietary. My browsing of the National Center for Biotechnology Information website and a cursory examination of the data on several benign samples convinced me that analysis of this gene-expression data is exceedingly complicated. As with any test, the physician must accept the data based on faith in the veracity and integrity of the laboratory that produced it.

Currently the Veracyte Affirma GEC method "retails" for $3,350 plus $300 for cytopathology. I regard this as a substantial cost for its possible contribution to avoiding diagnostic surgery, in part because it also misclassifies lesions as suspicious about half the time. However, another interpretation is that the method can be used only to classify a nodule as benign and that the "suspicious" category by GEC should not be used.

The other approach to molecular diagnosis of thyroid cancer is the measurement of oncogenes, such as BRAF, on FNA to make a positive diagnosis of thyroid cancer in cytologically indeterminate FNA biopsies (2). This approach is being marketed by several laboratories and was reviewed in the December 2011 issue of Clinical Thyroidology. The oncogene molecular method misses cancers that do not express the oncogenes tested, but has the advantage of having a much lower rate of false positives as compared with the GEC method, assuming that "suspicious" is positive. In a world where there are unlimited financial resources, both the oncogene and the GEC methods could be applied to all indeterminate nodules, but this approach is not practical currently.

— Jerome M. Hershman, MD

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Clinical THYROIDOLOGY
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Chronic Renal Disease is a Clinical indication for Thyroid Replacement Therapy in Subclinical Hypothyroidism

Shin DH, Lee MJ, Kim SJ, Oh HJ, Kim HR, Han JH, Koo HM, Doh FM, Park JT, Han SH, Yoo T-H, Kang S-W. Preservation of renal function by thyroid hormone replacement therapy in chronic kidney disease patients with subclinical hypothyroidism. J Clin Endocrinol Metab. June 20, 2012 [Epub ahead of print].

SUMMARY

Background

Subclinical hypothyroidism is not a rare condition, but the use of thyroid hormones to treat subclinical hypothyroidism is an issue of debate. This study was undertaken to investigate the impact of thyroid hormone therapy on the changes in estimated glomerular filtration rate (eGFR) in patients with subclinical hypothyroidism who also have stage 2 to 4 chronic kidney disease.

Methods

A total of 309 patients were included in the final analysis. The changes in eGFR over time were compared between patients with and without thyroid hormone–replacement therapy using a linear mixed model. Kaplan–Meier curves were constructed to determine the effect of thyroid hormone on renal outcome, a reduction of eGFR by 50%, or end-stage renal disease. The independent prognostic value of subclinical hypothyroidism treatment for renal outcome was ascertained by multivariate Cox regression analysis.

Results

Among the 309 patients, 180 (58.3%) took thyroid hormone (treatment group), whereas 129 (41.7%) did not (nontreatment group). During the mean follow-up of 34.8 ± 24.3 months, the overall rate of decline in eGFR was significantly greater in the nontreatment group as compared with the treatment group (–5.93±1.65 vs. –2.11±1.12 ml/min/yr/1.73 m2; P = 0.04). Moreover, a linear mixed model revealed that there was a significant difference in the rates of eGFR decline over time between the two groups (P<0.01). Kaplan–Meier analysis also showed that renal event-free survival was significantly lower in the nontreatment group (P<0.01). In multivariate Cox regression analysis, thyroid hormone–replacement therapy was found to be an independent predictor of renal outcome (hazard ratio, 0.28; 95% CI, 0.12 to 0.68; P = 0.01).

Conclusions

Thyroid hormone–replacement therapy not only preserved renal function better, but it was also an independent predictor of renal outcome in patients with chronic kidney disease who had subclinical hypothyroidism, suggesting that thyroid hormone replacement should be considered in these patients.

ANALYSIS AND COMMENTARY

With the exception of women planning a pregnancy or who are pregnant, the use of thyroid hormone–replacement therapy in subclinical hypothyroidism is controversial, unless the serum TSH value is over 10 mIU/L (1,2). Thyroid hypofunction in patients with renal disease is not uncommon; in the third National Health and Nutrition Examination Survey (NHANES III) (3), the prevalence of hypothyroidism was reported as 10.9 to 23.1% in patients with stage 2 to 5 chronic kidney disease (CKD), 56% of these cases were considered subclinical. In another report, the prevalence of subclinical hypothyroidism was 17.9%

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in patients with stage 3 to 5 CKD, independent of age, sex, and fasting plasma glucose, total cholesterol, and triglyceride concentrations (4). It has been postulated that the beneficial effect of thyroid hormone replacement on cardiac dysfunction, dyslipidemia, and blood pressure could be explained by preservation of renal function in treated hypothyroidism (5,6). For this study, Shin et al. excluded patients <18 or >75 years of age; those with nephrotic syndrome, terminal malignancy, or pregnancy; those undergoing thyroid replacement therapy, and those followed for less than 12 months. To exclude the possibility of transient elevation of serum TSH concentration, measurement of serum TSH level was repeated within 3 months before starting thyroid hormone–replacement therapy in order to confirm the diagnosis. The initial dose was usually 25 µg/day, adjusted as needed. Because it was a retrospective medical record–based study, the authors recognize that the possibility of selection bias could not be completely ruled out, such as selecting those patients with higher cardiovascular risk factors or positive TPOAb for thyroid therapy.

This preliminary study needs to be confirmed, but in the meantime it appears very reasonable to normalize thyroid-function tests in patients with subclinical hypothyroidism who have any degree of renal insufficiency, starting with a low levothyroxine dose and adjusting it at regular intervals to avoid levothyroxine toxicity. If further studies support the conclusions of Shin et al., renal insufficiency should be added to the selective group of women who have subclinical hypothyroidism in their reproductive years that could benefit from thyroid replacement therapy (7).

— Jorge H. Mestman, MD

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Using Age-Specific Upper Limits for Normal TSH Slightly Reduces the Incidence of Subclinical Hypothyroidism in the Elderly

Kahapola-Arachchige KM, Hadlow N, Wardrop R, Lim EM, Walsh JP. Age-specific TSH reference ranges have minimal impact on the diagnosis of thyroid dysfunction. Clin Endocrinol (Oxf). June 15, 2012 [E-pub ahead of print]. doi:10.1111/j.1365-2265.2012.04463.x

SUMMARY

Background

It is fairly common to find that a patient's TSH level is above normal (but below 10), yet the thyroid hormone levels are normal. What is more, TSH levels increase with age—even in elderly patients without thyroid disease—whereas FT_4 levels do not change (1). This raises the question of when (or whether) a high TSH should be treated in elderly patients, particularly in view of recent reports that longevity is associated with higher TSH levels in several groups of individuals, which raises the possibility that a mildly elevated TSH could somehow be beneficial in certain elderly patients. The authors of this paper determined age-specific reference ranges for the TSH assay used in their region, permitting them to estimate how raising the upper limit of normal for TSH in apparently euthyroid elderly patients would affect the number of patients given the diagnosis of subclinical hypothyroidism.

Methods

Over 220,000 consecutive TSH screening assays were performed in 2010 in a statewide reference lab in Western Australia that uses the Siemens ADVIA Centaur assay. The majority of samples came from general practitioners' offices. Dietary iodine is sufficient in this area, where the population is predominantly of European descent. Based on information provided on pathology request forms, sera from patients with known or suspected thyroid disease were excluded, as were samples from any patients on whom FT_4, FT_3, or antithyroid antibodies had been requested. They also eliminated samples from infants and from patients who were pregnant or taking lithium, amiodarone, or anticonvulsants. Also eliminated were samples obtained after 6 p.m. or before 7 a.m. This left about 150,000 TSH determinations from unique patients for analysis. The TSH data were sorted by patient age in 5-year intervals. The authors also performed a separate study that compared the consistency of TSH determinations obtained using the Centaur assay with results from three other commonly used third-generation assays (Architect [Abbott], Modular Analytics [Roche] and Immulite [Siemens]) using 120 samples with TSH values between 0 and 10 mU/L.

Results

For patients up to 55 years of age, the 97.5th percentile for TSH values was less than 4.0 mU/L. Above that age, the upper value for the 97.5th percentile gradually rose, reaching about 4.75 mU/L in the 11,000 patients who were between 75 and 85 years of age, and reaching 5.0 mU/L for the 2500 patients between 85 and 90.

The comparison of the four third-generation TSH assays revealed that their variability on samples with TSH values under 2 mU/L was not as striking as on samples with values above 4.0 mU/L, where the assay results could differ by more than 1 mU/L.

Conclusions

Using age-specific reference ranges for TSH does reduce the fraction of elderly patients who would be given a diagnosis of subacute hypothyroidism, but only by 2% for patients over age 75, and by 5% for those over age 90. In addition, some third-generation TSH assays seem to have steeper TSH dose–response slopes than others, which makes it more difficult to compare TSH values between studies that have used different assays. A TSH reported as being slightly elevated on one assay could be reported to be normal on another assay.

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ANALYSIS AND COMMENTARY

A recent reanalysis of the NHANES III data, using age-, sex- and ethnicity-specific TSH reference limits, eliminated 144 of 13,344 subjects in the "Reference Population" because they had a TSH >10 or <0.1 mU/L, leaving 4671 whites for analysis (2). The 97.5th percentile for TSH values in whites 70 to 79 years old was 5.6 mU/L, and for those over age 80 it was 6.6 mU/L. The reference population was known not to be overtly hyperthyroid or hypothyroid, was not taking medications known to affect thyroid-function tests, and was specifically known to have no detectable antithyroid antibodies, and thus is closest to the Western Australian population studied, with the exception that anyone who had had antithyroid antibodies ordered was excluded from the Australian study. In the 14,347 Australian subjects who were 70 to 79 years old, the 97.5th percentile for TSH was 4.5 mU/L; for the 8417 subjects over age 80, it was 5.0 mU/L. Thus, the increase in TSH with increasing age in Australia was not as great as that found in the reanalysis of the NHANES III data. One major difference between the two studies is the much greater sample size in the Australian study, but the differences between the TSH assays used, in geography, and in ethnic backgrounds also need consideration.

Until recently, manufacturers of TSH assays indicated that values between 0.4 to 4.0 mU/L were normal, although it is now clear that the TSH level in a healthy individual does not vary by that much. Some of the genes that contribute to the TSH set point have been identified, but as an individual ages, there could be changes in 1) TSH bioactivity, 2) thyroidal TSH responsiveness, 3) factors regulating thyroid hormone uptake and metabolism, 4) thyroid hormone receptors, and/or 5) cofactors that modulate the T_3-responsiveness of a given gene in a given tissue. A recent study of patients over 65 years of age who were able to function normally in a community and were not taking thyroid hormone indicates that subclinical hypothyroidism commonly persists for at least 4 years, but if a patient's TSH is below 7 mU/L (as determined by Elecsys 2010 analyzer, Roche) and the anti-TPO titer is normal, the TSH is more likely to normalize within 2 years (3). Undoubtedly, administering L-T_4 to elderly patients with mild subclinical hypothyroidism can alter physiological and biochemical parameters. (For example, Dr. Mestman discusses such a report in this issue of Clinical Thyroidology on patients under age 75 with subclinical hypothyroidism plus chronic kidney disease, in which giving L-T_4 reduced the rate of decline in renal function [4]). In general, replacement of T_4 in elderly patients with subclinical hypothyroidism should be gradual and monitored closely, to avoid overreplacement. Evidence that such therapy improves mortality remains meager, however, particularly in those over age 65 (5).

— Stephen W. Spaulding, MD

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TSH Expression by Fibrocytes Provides New Insights into the Pathophysiology of Thyroid-Associated ophthalmopathy

Gillespie EF, Papageorgiou KI, Fernando R, Raychaudhuri N, Cockerham KP, Charara LK, Goncalves ACP, Zhao S-X, Ginter A, Lu Y, Smith TJ, Douglas RS. Increased expression of TSH receptor by fibrocytes in thyroid-associated ophthalmopathy leads to chemokine production. J Clin Endocrinol Metab 2012;97:E740-E746. Epub March 7, 2012.

SUMMARY

Background

A fundamental insight into the pathophysiology of thyroid-associated ophthalmopathy (TAO) is still lacking, although it is widely accepted that an autoimmune process involving fibroblasts plays a crucial role. There is considerable evidence that TSH receptor antibodies, or a subset of them, are crucial factors in the pathogenic process (1). Indeed, orbital–fibroblast-TSH receptors have unequivocally been identified and are likely to be a dominant autoimmune target. These cells may modulate immune responses by producing cytokines in response to TSHR activation.

Fibrocytes are bone marrow–derived pluripotent cells that can migrate to sites of tissue inflammation and remodeling (2). In healthy subjects, they represent a subset of only 0.5% of the circulating monocytes, but in patients with Graves' disease, their abundance is increased (3). Here, the authors identified and quantified TSHR-positive fibrocytes in peripheral blood in patients with TAO and controls.

Methods and Results

The authors recruited 31 patients with TAO and 19 healthy subjects. Patients with Graves' disease without TAO were excluded. The fibrocytes of interest were identified by flow cytometry. Monocytes expressing CD45 and CD34 were selected. Furthermore, these fibrocytes were stimulated with TSH or with the monoclonal TSHR antibody M22, and their response was compared with Interleukin-1b (IL-1β) stimulation. One known responding marker, IL-8 mRNA was measured by quantitative real-time PCR.

The results showed that, in TSHR, levels of positive fibrocytes were at least 5 to 6 times higher in peripheral blood than in orbital fibroblasts. As expected, the expression of TSH receptors in normal fibrocytes was very low—approximately 2%. The receptor could be clearly identified in approximately 18% of circulating fibrocytes from patients with TAO. Stimulation of the cells by TSH or M22 induced production of several proinflammatory cytokines that could also be induced with IL-1β.

Conclusions

The authors elegantly demonstrate that peripheral fibrocytes, known to migrate to inflammatory sites, are increased in number in patients with TAO and that they express TSH receptors more frequently than fibrocytes from normal subjects. The density of these TSH receptors on circulating fibrocytes exceeded the density in orbital fibroblasts, which are thought to be critical for the autoimmune process in TAO. When standardized to the number of circulating monocytes, TSHR-positive cells were more frequent in patients with TAO than in controls, even though a small number of control cells also expressed some TSH receptors. In order to test the functional relevance of these receptors, the fibrocytes were stimulated with TSH or M22 to study the production of many different cytokines. The panel of responses varied slightly between TSH and M22, with the responses to M22 being stronger. These findings strongly support an important role of fibrocytes in the pathogenesis of TAO.

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ANALYSIS AND COMMENTARY

Treatment of TAO is still frustrating for many patients and often patience is the most important advice the physician can give. Indeed, in the majority of cases, eye symptoms will ameliorate within years ,and eventually the outcome is satisfactory, even though it is rare for all symptoms to resolve completely. There is hope for some therapeutic innovations, since basic research is steadily progressing. The presence of TSH receptors or a truncated form of them was discovered in the orbital cavity at least 20 years ago. We know that these receptors are expressed in fibroblasts in the process of being transformed into fat cells. Closely related fibrocytes can be identified in a subset of monocytes in the peripheral blood. They are more frequent in cases of Graves' disease and a high percentage of these cells express the TSH receptor. The most recent data from this group indicate that the very same cells also contain thyroglobulin, another crucial antigen in the orbital cavity (4). Normal circulating fibrocytes migrate to sites of injury and provoke an antigen-specific T-cell stimulation. It is therefore highly likely that the family of fibroblasts and fibrocytes expressing TSH receptors are implicated in the inflammatory process in the orbit that, because of its rigid structure, has little possibility for expansion. The authors mention that recently Neumann et al. suggested that a small molecule antagonist binding to TSH receptor could offer a new possibility of treating TAO, allowing interruption of the autoimmune process (5). Such molecules might help to treat hyperthyroidism and TAO at the same time and would certainly represent a major breakthrough.

— Albert G. Burger, MD

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Fluorodeoxyglucose PET/CT Scans Are More Sensitive than High-Dose I-131 Scans for Detecting Recurrent Thyroid Cancer in Patients with Elevated Serum Thyroglobulin

Leboulleux S, El Bez I, Borget I, Elleuch M, Deandreis D, Al Ghuzlan A, Chougnet CN, Bidault F, Mirghani H, Lumbroso J, Hartl DM, Baudin E, Schlumberger M. Post-radioiodine treatment whole body scan in the era of fluorodesoxyglucose positron emission tomography for differentiated thyroid carcinoma with elevated serum thyroglobulin levels. Thyroid. June 5, 2012 [Epub ahead of print].

SUMMARY

Background

Some patients with differentiated thyroid cancer (DTC) who have had successful radioiodine ablation after surgery have elevated serum thyroglobulin (Tg) levels as they are followed. When the source of the increased Tg cannot be found by neck ultrasound or various scans, some experts have recommended that the patient be given an empiric treatment dose of I-131 and then undergo a posttreatment scan to treat and detect the metastatic thyroid tissue because the scan after the large therapeutic dose can be much more sensitive than a diagnostic radioiodine scan. However, one recent study did not confirm this concept (1). The current retrospective study compared the sensitivity of a scan after an empiric dose of 100 mCi of ^{131}I with that of an FDG PET/CT scan in this clinical context.

Methods

Inclusion criteria for patients were DTC treated with total thyroidectomy and postoperative I-131 ablation; a normal postablation whole-body scan, defined by the absence of abnormal iodine uptake outside the thyroid bed; increasing or persistently elevated serum Tg levels; empiric I-131 administration given in the absence of iodine contamination; and FDG PET/CT performed within 4 months of empiric I-131 treatment. Patients received 100 mCi of I-131 for empiric therapy based on an elevated serum Tg and had a whole-body scan (WBS) 3 or 4 days later.

Results

Thirty-four patients met the criteria; 32 were papillary and 2 were follicular cancer; 8 were aggressive subtypes. The median time between postoperative ablation and empiric I-131 treatment for an elevated serum Tg was 33 months (range, 6 to 208). The median Tg level after thyroid hormone withdrawal was 47 ng/ml (range, 4 to 3230). FDG PET/CT was performed before empiric radioiodine was administered in 25 cases, usually within 5 days.

In 23 patients (68%), WBS or FDG PET/CT localized at least one lesion; the findings were concordant in 16 patients; both were normal in 11 patients and abnormal in 5. FDG PET/CT was abnormal in 17 patients with normal WBS and normal in 1 patient with an abnormal WBS. The sensitivity of FDG PET/CT for disease localization was 65%, whereas the sensitivity of WBS was only 18%.

A total of 75 lesions were detected—30 in the neck, 28 in the lungs, 11 in the mediastinum, and 6 in the bones. FDG PET/CT detected 66 lesions, 7 of which had I-131 uptake. The WBS detected 12 lesions, among which 5 did not disclose any FDG uptake. The WBS detected 12 lesions, 5 of which had no FDG uptake. Ultrasound detected 18 of the 30 lesions in the neck.

Conclusions

In patients with suspicious recurrence of DTC based on an elevated Tg level after apparently successful I-131 ablation, FDG PET/CT is more sensitive for localizing lesions than a WBS after a 100-mCi dose of I-131. Empiric I-131 administration should be reserved for those who do not have significant FDG uptake.

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ANALYSIS AND COMMENTARY

Measurement of serum Tg has become a mainstay in the management of DTC. When patients with a previously successful ablation and undetectable Tg have a subsequent Tg that is elevated beyond some arbitrary threshold, often 1 or 2 ng/ml in the TSH-suppressed state or 4 or 5 ng/ml in the TSH-stimulated condition, there is concern about recurrence. Many of these patients have only nodal disease in the neck that can be found by ultrasonography (US), as was the case here, so this is a good first step. When US is negative, other scans are performed, usually diagnostic I-131 scans with a dose of 2 to 5 mCi, but that was not done in this study. Nevertheless, the study clearly shows that FDG PET/CT is more sensitive for finding metastatic thyroid cancer than is a high-dose I-131 scan.

Another limitation of the study is that nearly one-fourth of the patients had aggressive subtypes of DTC that are less likely to concentrate I-131. Wang and colleagues showed that, in patients with metastatic DTC, the lesions that were PET-positive did not concentrate I-131 (2). Despite these caveats, the current study by Leboulleux and colleagues is a valuable contribution to the evidence indicating that "blind" large doses of I-131 are not as useful as PET/CT for localizing metastatic disease in patients with elevated serum Tg after previously successful ablation.

— Jerome M. Hershman, MD

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Clinical THYROIDOLOGY
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One Month Is Sufficient for Urinary Iodine to Return to its Baseline Value after the Use of Water-Soluble Iodinated Contrast Agents in Patients Who Have Undergone Thyroidectomy

Padovani R, Kasamatsu TS, Nakabashi CC, Camacho CP, Andreoni DM, Malouf EZ, Marone MM, Maciel RM, Biscolla RP. One month is sufficient for urinary iodine to return to its baseline value after the use of water soluble iodinated contrast agents in post-thyroidectomy patients requiring radioiodine therapy. Thyroid. July 24, 2012 [Epub ahead of print].

SUMMARY

Background

After exposure to an iodinated contrast agent, the plasma concentration of free iodide remains elevated for a long period because the iodine stores are expanded in interstitial fluids and in the colloid within the thyroid. The large iodine load of intravenous contrast studies, such as CT, can interfere with the uptake of radioiodine by thyroid tissue. There is a paucity of data on how long it takes for the iodine to be cleared from the body after this load, especially in patients who have undergone thyroidectomy and who are candidates for radioiodine therapy. The current study measures urinary iodine after a contrast load in patients who have undergone thyroidectomy for differentiated thyroid cancer.

Methods

Twenty-five patients with papillary thyroid carcinoma (PTC) treated with total thyroidectomy and radioiodine therapy were advised to receive chest and neck CT with intravenous contrast material to investigate the possibility of metastasis during their follow-up. The patients received 1 ml/kg of body weight of iobitridol (300 mg of iodine/ml), a water-soluble, low-osmolarity contrast agent, intravenously for the CT, equivalent to an iodine load of 15,000 to 30,000 mg. The patients collected 24-hour urine and spot urine samples before the CT and 1 week, 1 month, 2 months and 3 months afterward. Values were expressed in micrograms per deciliter. To be included in the study, the patients had to have a baseline urine iodine level of <100 µg/dl.

Results

The median 24-hour urine iodine at baseline, 1 week, and 1, 2, and 3 months after the CT were 21.8, 800, 19, 17.5, and 19.2 µg/dl. The median values on the spot urine samples were almost identical. The data show that by 1 month, the urine iodine was back to baseline and no individual values exceeded 57 µg/dl.

Conclusions

Only 1 month is required for urinary iodine to return to its baseline value after the use of water-soluble iodinated contrast agents used for CT in patients who have had thyroidectomy and radioiodine ablation.

ANALYSIS AND COMMENTARY

The authors have provided valuable data for follow-up of patients with recurrent thyroid cancer. My PubMed search yielded no papers that provided similar data. The authors are appropriately careful to qualify that their data are applicable only to patients without thyroid glands because uptake of some of the iodide from the large iodine load (after deiodination of the contrast agent) could provide a reservoir of iodine that could last much longer than 1 month. Although I have heard that it is safe to do radioiodine scans in the follow-up of patients with differentiated thyroid cancer as early as 1 month after the procedure,

continued on next page

many "authorities" recommend waiting 2 or even 3 months (1). The current data show that 1 month is sufficient to excrete the iodine load and, by inference, to perform radioiodine studies. In addition, the data show that iodine measurement in spot urine samples correlates tightly with 24-hour urine iodine.

— Jerome M. Hershman, MD

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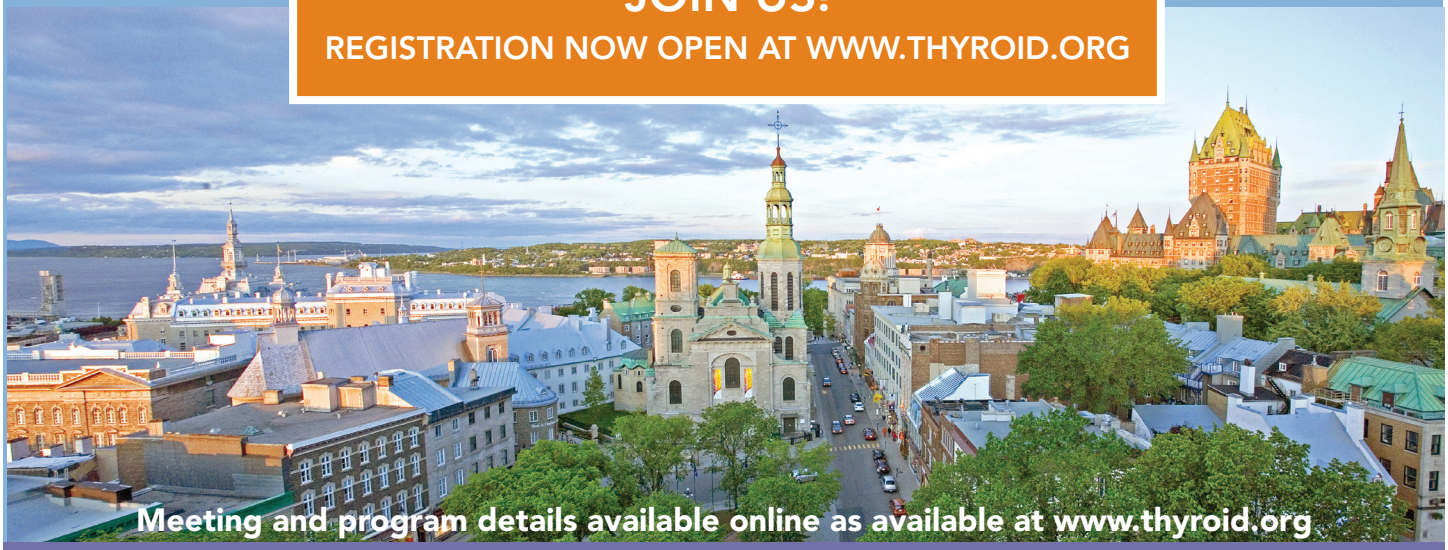

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