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ONLY A FEW PEDIATRIC PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM PROGRESS TO OVERT DISEASE WITHIN 3 YEARS

Radetti G, Maselli M, Buzi F, Corrias A, Mussa A, Cambiaso P, Salerno M, Cappa M, Baiocchi M, Gastaldi R, Minerba L, Loche S. **The natural history of the normal/mild elevated TSH serum levels in children and adolescents with Hashimoto's thyroiditis and isolated hyperthyrotropinaemia: a three year follow-up.** Clin Endocrinol (Oxf). October 10, 2011. [Epub ahead of print]. doi: 10.1111/j.1365-2265.2011.04251.x.

SUMMARY

BACKGROUND

To treat or not to treat, that is the question. Should a pediatric patient with an isolated increase of serum thyrotropin (TSH) or with positive thyroid autoantibodies but with normal free thyroxine (T_4) and free triiodothyronine (T_3) levels be treated? Most endocrinologists agree that patients with a serum TSH above 10 mU/L would benefit from thyroxine treatment. In fact, in this situation, serum thyroid hormone levels are mostly at the lower limit of normal or are decreased. In patients, who present with a serum TSH below 10 mU/L with or without thyroid antibodies, there is still no clear agreement on how to proceed. In the present study, the authors followed the evolution of thyroid function over three years in a large cohort of children collected in seven pediatric endocrinology centers in Italy.

METHODS AND RESULTS

The study included 382 children, with a mean age at the entry of 10.5 years. The study lasted 3 years; the mean age at the end of the study was 13.8 years. The patients were separated into subgroups with either an isolated increase of serum TSH (59 children) or with thyroid autoantibodies (323). Ultrasound evaluation of thyroid morphology was done in all patients. Additional subgroups were formed depending on the degree of alterations of serum TSH and of thyroid antibodies (serum TSH: grade 0, normal; grade 1, <8 to 10 mU/L; grade 2, > 8 to 10 mU/L; antibody titer: grade 1,<10 times normal; grade 2, >10 times normal). The family histories revealed a strong prevalence of autoimmune diseases.

Patients with initial grade 2 serum TSH levels and/or grade 2 thyroid antibodies were excluded from the study. Among the patients with autoimmune thyroid

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antibodies, 236 had normal serum TSH, while 86 had a serum TSH level of grade 1; 72% of these patients remained stable. Only 13% moved from normal to grade 1 TSH levels and a similar percentage became hypothyroid (grade 2), 39% who initially had a moderate TSH increase (<8 to 10 mU/L) had their serum TSH spontaneously normalize, while 39% remained stable and another 14% progressed to overt disease.

The changes in thyroid antibody levels over time were not significant. The percentage of children with moderate or marked increases of thyroid antibodies did not change. In both groups (isolated TSH increase or Hashimoto's thyroiditis), progression toward hypothyroidism occurred in a similar percentage of cases (21% vs. 14%). In search of predictors indicating future hypothyroidism, only the association of celiac disease with thyroid antibodies was found to increase this risk—by a factor of 4. This association was not present in patients with only an increased serum TSH.

In most patients with an isolated TSH increase, the thyroid volume was normal and did not change. In patients with autoimmune antibodies, thyroid volume tended to be initially slightly increased, and this tendency persisted to a moderate degree during the observation period.

CONCLUSIONS

Pediatric patients with either increased serum TSH or thyroid autoantibodies need careful monitoring because no criteria exist to predict the development of frank hypothyroidism. It was only the association of celiac disease with thyroid autoantibodies that increased the risk of hypothyroidism by a factor of 4. It is reassuring that in a large proportion of patients, serum TSH or thyroid antibody levels returned to normal. Overt hypothyroidism developed in less than one fifth of patients with moderate TSH elevations or euthyroid Hashimoto's thyroiditis.

COMMENTARY

This study confirms the widely held opinion that patients with an isolated TSH increase or with thyroid autoantibodies need thorough and similar careful follow-up. The percentage of patients in whom hypothyroidism developed is not large and is quite similar in both groups. The findings of the present study may be compared with the results of the famous Whickham study, in which over a much longer observation period (20 years) approximately 30% of patients needed treatment (1). Both studies stress the point that hypothyroidism develops in only a minority of patients and, if the thyroid abnormalities persist, it is advisable to follow thyroid function at yearly intervals for the next 10 to 20 years.

The authors also raise the question of how to define tissue hypothyroidism, since elevated serum TSH is clearly a poorly sensitive indicator that points only to the need to recruit the remaining capacities of a failing thyroid. Thus, thyroid hormone levels remain within the normal range for a long time. There is, however, no doubt that in each affected individual there is a moderate decrease of thyroid hormone levels as compared with the disease-free state. Do peripheral tissues recognize these changes? At present, we have no unequivocal way to answer this question; therefore, some clinicians start treatment early and others do not. It needs to be stressed that serum TSH levels or thyroid hormone antibodies normalize in a considerable percentage of subjects over time In my view, this is a strong argument in favor of an initial follow-up of these patients without treatment.

— Albert G. Burger, MD

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MOLECULAR ANALYSIS FOR MUTATIONS IN THYROID FNA IMPROVES THE DIAGNOSIS OF MALIGNANCY FOR ALL CATEGORIES OF INDETERMINATE CYTOLOGY

Nikiforov YE, Ohori NP, Hodak SP, Carty SE, Lebeau SO, Ferris RL, Yip L, Seethala RR, Tublin ME, Stang MT, Coyne C, Johnson JT, Stewart AF, Nikiforova MN. **Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples.** J Clin Endocrinol Metab 2011;96:3390-7. Epub August 31 2011.

SUMMARY

BACKGROUND

Nodules classified as indeterminate make up about one-fourth of those tested by thyroid fine-needle aspiration biopsy (FNAB). In the Bethesda classification, these are further classified into one of three categories that have increasing likelihood of thyroid cancer: (1) follicular lesion of undetermined significance (FLUS), (2) follicular or oncocytic (Hürthle)-cell neoplasm or suspicious for follicular or oncocytic-cell neoplasm (FN), and (3) suspicious for malignant cells (SMC). Studies of oncogene mutations in thyroid FNAB have improved the diagnosis of thyroid cancer. The current report is a large prospective study that defines the diagnostic utility of analysis for oncogene mutations in patients with indeterminate cytology on FNAB.

METHODS

From April 2007 through April 2009, a total of 1056 consecutive FNA samples from thyroid nodules with indeterminate cytologic diagnoses were tested prospectively for mutations at the University of Pittsburgh Medical Center. Samples were from 762 patients, including 294 who contributed multiple FNAB samples from the same or different nodules. Each sample was considered independently.

The sample was placed into a preservative solution; the adequacy of the quantity and quality of DNA was assessed by polymerase-chain-reaction (PCR) amplification of RAS and BRAF genes and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) cDNA. The sample was considered satisfactory when the amplification cycle threshold was less than 35 cycles. The proportion of epithelial cells within the FNAB sample was assessed by performing PCR measurement of cytokeratin gene KRT7, which is found in thyroid epithelial cells, and comparing it to the housekeeping gene GAPDH. The difference in amplification between KRT7 and GAPDH had to be more than 3.5 cycles for an adequate sample.

BRAF V600E, NRAS codon 61, HRAS codon 61, and KRAS codons 12 and 13 point mutations were detected using real-time PCR and fluorescence melting curve analysis. RET/PTC1, RET/PTC3, and PAX8/PPARg rearrangements were detected by real-time reverse transcriptase–PCR.

RESULTS

Of 1056 consecutive FNAB samples with indeterminate cytology, 50 had an insufficient amount of isolated nucleic acids and another 39 had insufficient epithelial cells for mutational analysis. The remaining 967 samples collected from 729 patients were subjected to mutational analysis. Among these samples, a cytologic diagnosis of FLUS was established in 653, FN in 247, and SMC in 67. Molecular analysis revealed 87 mutations, including 19 BRAF V600E, 47NRAS, 12HRAS, and three KRAS, as well as one RET/ PTC1 and five PAX8/PPARg rearrangements. A total of 479 patients underwent thyroidectomy that provided histopathological diagnosis for 513 FNAB samples. The results of the mutational analysis were correlated with the pathological diagnosis.

In the group of 247 FLUS samples in patients who had surgery, mutations were found in 22 of 38 cancers; RAS was the most common mutation; 3 RAS mutations were found in follicular adenomas. The risk of cancer in nodules in the FLUS category that were negative for mutations was only 5.9%.

There were 247 surgical samples in the FN group; 33 of 58 cancers were found to have mutations in the FNAB sample. Of 34 FNABs positive for RAS

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mutations, 29 were in malignant nodules, mainly the follicular variant of papillary thyroid carcinoma, and 5 occurred in follicular adenomas.

Of the 52 FNABs classified as SMC for which surgical material was obtained, malignancy was found in 28 nodules, and 19 had mutations; 10 were BRAF, 7 RAS, 1 PAX8/PPARg, and1 RET/PTC1; 9 were negative for mutations.

For the three cytologic categories, FLUS, FN, and SMC, the cancer risk by cytology alone was 14%, 27%, and 52%, respectively; based on finding any mutation, this increased to 88%, 87%, and 95%. Correlation of mutation testing in surgical samples and FNAB showed that the FNAB study detected 95% of the mutations found in the surgical samples.

CONCLUSIONS

Molecular analysis for a panel of mutations has significant diagnostic value for all categories of indeterminate cytology.

COMMENTARY

This group has taken the leading role in diagnosis of thyroid cancer using oncogene biomarkers in FNAB material. The present paper validates an earlier study on a smaller number of samples (1). Using the molecular markers for the indeterminate group is probably the most cost-effective approach, even though the oncogene may be positive in some samples deemed to be inadequate for cytologic diagnosis or in some diagnosed as hyperplastic colloid goiters; however, this may be so uncommon that it is not justified economically.

The high frequency of RAS mutations in this study is probably related to the selection of samples in the indeterminate category. If samples that were positive for papillary thyroid carcinoma had been tested, then the BRAF mutation would have been more frequent than RAS. Although RAS mutations were found in follicular adenomas, the finding of a RAS mutation in an indeterminate sample increases the likelihood of thyroid cancer to 80%. This is certainly a justification for sending a patient for thyroidectomy. The authors propose that when the tested mutations are negative, patients should be recommended for lobectomy rather than total thyroidectomy because of the reduced possibility of cancer. The frequency of the three RAS mutations was not reported in this paper.

The follicular variant of papillary thyroid cancer (FV/PTC) made up 72% of the 93 cancers found in the FLUS and FN categories. Recently, Daniels wrote a scholarly analysis of FV/PTC proposing that it be subdivided into three categories based on histology and molecular markers: (1) papillary thyroid carcinoma with follicular architecture, (2) follicular thyroid carcinoma with nuclear atypia, and (3) follicular adenoma with nuclear atypia (2). A discussion of the consequences of this classification is beyond the scope of my commentary, but this new classification provides food for thought in this controversial area.

— Jerome M. Hershman, MD

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DOSIMETRIC CALCULATION OF ^{131}I DOSES MAY BE MORE EFFECTIVE THAN EMPIRIC DOSES FOR PATIENTS WITH LOCALLY ADVANCED DIFFERENTIATED THYROID CANCER

Klubo-Gwiezdzinska J, Van Nostrand D, Atkins F, Burman K, Jonklaas J, Mete M, Wartofsky L. **Efficacy of dosimetric versus empiric prescribed activity of ^{131}I for therapy of differentiated thyroid cancer.** J Clin Endocrinol Metab 2011;96:3217-25. Epub August 17, 2011.

SUMMARY

BACKGROUND

Radioiodine-131 (RAI) has been used for over 50 years for the treatment of metastatic or persistent differentiated thyroid cancer (DTC). It is usually administered in arbitrary or emipiric doses that are based on the extent of the metastases or residual disease. Some institutions use a method called "dosimetry." which involves measurements of blood activity after a small test dose, such as 1 or 2 mCi of ^{131}I, as well as measurements in the lesions at various time intervals. The purpose of the dosimetry is to achieve a balance between the maximum dose that can be given without depressing the bone marrow or causing radiation pneumonitis and restrictive lung disease and yet getting an effective dose into the lesions. The use of dosimetry often shows that much larger ^{131}I doses can be given than doses based on the empiric method; for example, in the empiric method, doses of 200 mCi are often given for metastatic disease, but this dose is seldom exceeded, whereas dosimetry may show that it is safe to give a larger dose; or conversely, the 200-mCi dose may produce serious side effects and dosimetry would have indicated that a lower dosage was more appropriate or safe. In theory, dosimetry is more scientific, but it has not become the standard of care because it is very time-consuming and the results to date had not shown that dosimetry was clearly better than using empiric doses of ^{131}I. The current study is a comparison of the results of dosimetric RAI dosage practiced at one institution and empiric dosage given at another institution in the Washington, DC, area in groups of matched patients.

METHODS

This was a retrospective study of patients with DTC monitored at two Washington area hospitals between 2006 and 2009. The inclusion criteria included evidence of distant metastases (DM) or locoregionally advanced disease based on pathological data, imaging studies, and documented RAI-avid disease, and at least one complete follow-up examination. One hospital used dosimetry (D-Rx) to determine RAI doses and the other used empiric doses (E-Rx). The dosimetric method is based on calculation of the maximum tolerated activity of ^{131}I that would deliver a radiation dose to the blood (as a surrogate for the bone marrow) of 200 rad (2 Gy) or less in order to decrease the likelihood of an adverse bone marrow effect and to ensure that whole-body retention at 48 hours does not exceed 120 mCi (4.44 GBq) with iodine-avid distant nonpulmonary disease or 80 mCi (2.96 GBq) with iodine-avid pulmonary disease.

Patients received 1 to 3 mCi ^{131}I as a tracer and blood samples were obtained at 2, 24, 48, 72, 96, and 144 hours to assess blood radiation doses; whole–body scans were performed at approximately the same time points to estimate the tumor radiation. The response to therapy was based on the Response Evaluation Criteria in Solid Tumors (RECIST) and secondarily on thyroglobulin measurements. Side effects monitored included leukopenia, thrombocytopenia, chronic dry mouth, and pulmonary fibrosis.

RESULTS

The 87 patients studied included 48 women and 39 men. There were 29 patients with DM in the D-Rx group and 14 in the E-Rx group. For those with DM, the first dose of RAI was significantly higher for the D-Rx group than for the E-Rx group (mean, 251 vs. 164 mCi; $P<0.05$). The total cumulative prescribed activity received by these patients during the follow-up period was not significantly higher in the D-Rx group (mean, 393 mCi vs. 348 mCi). The responses by the RECIST criteria were not significantly different between the two dosage regimens; the 5-year survival was about 60% in each group.

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There were 14 patients with locally advanced disease in the D-Rx group and 30 in the E-Rx group. For those with locally advanced disease, the first treatment was significantly higher for the D-Rx group as compared with the E-Rx group (303.5 mCi vs. 148.9 mCi; P<0.05]; the total cumulative prescribed activity was also significantly higher in the D-Rx group (362.9 mCi vs. 226.8 mCi; P<0.05). There was a significantly higher rate of complete remission in D-Rx group as compared with the E-Rx group (5 of 14 [35.7%] vs. 1 of 30 [3.3%]). There was a trend favoring progression-free survival in the D-Rx group.

The frequency of side effects did not differ between patients treated with D-Rx as compared with those treated with E-Rx.

CONCLUSIONS

The higher efficacy of dosimetric RAI therapy with a similar safety profile as compared with empiric RAI doses supports the rationale for using individually prescribed activity in high-risk patients with locally advanced DTC.

COMMENTARY

The few thyroid cancer specialists who use dosimetry to determine optimal RAI doses for advanced DTC have been outspoken advocates of this approach, but there has not been a previous comparison of the two dosage methods during a similar time period. The investigators are to be commended for performing this study, but for several reasons it must be considered a pilot study. The number of patients in each group was small, and the groups were not balanced with regard to the number of subjects with metastatic disease or locally advanced disease for each dosage regimen. Perhaps there was a referral bias by sending patients with metastatic disease to the institution that used the dosimetric approach. Not surprisingly, the doses calculated using the dosimetric approach were larger than those using the empiric method. The most impressive result is that a larger number of patients with locally advanced disease had complete remission, with the larger doses calculated by the dosimetric method being safe and effective. For those of us who are "stuck" with the empiric approach, perhaps we should use larger doses in patients with advanced local disease, such as 200 mCi rather than 100 or 150 mCi. However, earlier studies from this group as well as the Sloan-Kettering group indicated that such large empiric doses may constitute excessive radiation doses above 2 Gy, especially in the elderly and those with pulmonary metastases (1, 2). Surprisingly only about 10% of patients in each group had chronic dry mouth due to salivary-gland damage.

The current study indicates that a large randomized, multiinstitutional controlled study of these two methods is needed, preferably with randomization in the same institutions. This is needed because we are seeing many more patients with thyroid cancer. It is more likely that such a study will be done in Europe or Asia than in the United States because medical investigators in these areas seem to be able to plan and initiate these studies more easily than those of us in the United States, perhaps because they have more centralization of referral centers than we have here.

— Jerome M. Hershman, MD

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RISK OF MALIGNANCY MAY BE HIGHER IN CYTOLOGICALLY SUSPICIOUS THYROID NODULES THAT ARE SMALLER OR MULTIPLE

Castro MR, Espiritu RP, Bahn RS, Nery MR, Gharib H, Caraballo, PJ, Morris JC. **Predictors of malignancy in patients with cytologically suspicious thyroid nodules.** Thyroid 2011;21:1191-8. Epub October 18, 2011.

SUMMARY

BACKGROUND

Fine-needle aspiration biopsy (FNAB) has a high predictive value for benign and malignant thyroid nodules but has a lower predictive value for indeterminate or suspicious nodules. Clinical data was extracted from an electronic medical record from January 2004 through September 2008 of patients who had undergone FNAB and thyroid surgery for cytologically suspicious nodules.

METHODS AND RESULTS

This was a retrospective chart review study at a single referral center, the Mayo Clinic. Review of the electronic medical records revealed that 573 (8%) of 7039 FNAB samples had a suspicious cytologic diagnosis. Of these patients, 111 did not have surgery and did not return for reevaluation. The remaining 462 patients with a suspicious biopsy underwent thyroid surgery. The demographic and clinical characteristics of this group are as follows: 69% female; mean (±SD) age, 53.7±15.2 years; prior head and neck radiation, 5.4%; multiple nodules, 65%; mean nodule size, 2.8±1.7 cm; and thyroid hormone therapy, 19.5%. Of these patients, 326 had lesions suspicious for follicular neoplasm or Hürthle-cell neoplasm, 126 were suspicious for papillary thyroid carcinoma (PTC), and 10 were suspicious for other neoplasms (medullary thyroid carcinoma, lymphoma, atypia). The malignancy rate was 15% for cytology that was suspicious for follicular and Hürthle-cell lesions and 77% for those suspicious for PTC. Age, elevated levels of thyrotropin (TSH), and history of radiation exposure were not associated with increased malignancy risk. Although the authors state that smaller nodules measured by ultrasonography had a higher risk of malignancy (2.6±1.8 vs. 2.9±1.6 cm; P = 0.008), 34% of nodules >4 cm were malignant. Multiple nodules, as compared with a single nodule, had a higher risk of malignancy (41.1% vs. 26.4%; P = 0.014). In patients with cytology suspicious for follicular and Hürthle-cell neoplasm, malignancy risk was higher in those who were undergoing thyroid hormone therapy than in those who were not (37.7% vs. 16.5%; P = 0.0004; odds ratio, 3.0), but the TSH values did not differ significantly between the thyroxine users and nonusers.

CONCLUSIONS

The risk of malignancy is higher in patients with nodules that are cytologically suspicious for Hürthle-cell or follicular neoplasms or PTC when the index nodule is smaller or if the patient has multiple thyroid nodules. This study demonstrates an increased risk of malignancy in patients using thyroid hormone therapy but the reason for this is unknown.

COMMENTARY

This study has a number of difficulties, including its retrospective design and the incomplete information for the subjects. These data should not alter the belief that head and neck radiation exposure is a significant risk for thyroid cancer. First, only 5.4% of the cohort had radiation exposure and 55.6% denied radiation exposure. This means that 39% of the cohort were either not asked about radiation exposure or it was not documented in the medical record. I also question the clinical significance of the statement that smaller size (2.6±1.8 vs. 2.9±1.6 cm; P = 0.008) is a risk factor for thyroid cancer, since the means of the two groups are very similar and 34% of nodules >4 cm were malignant. Because of the large number of patients, there is a statistical difference, but it may

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not be clinically important. The increased risk of thyroid cancer in patients taking thyroid hormones is interesting based on the number of studies suggesting that the risk of thyroid malignancy is associated with higher TSH values, even within the normal range (1).

The take-home message is that this type of study is difficult even at an elite institution with excellent electronic medical records. This paper strengthens my opinion that clinical characteristics will not identify all patients who have cancer with a suspicious biopsy. The selection of patient with suspicious biopsies who should have surgery may rest with other characteristics of the nodule, including ultrasound characteristics (2, 3), mutational analysis, including BRAF (4, 5), gene expression (6), elastography (7), and 18fluorodeoxyglucose–positron-emission tomographic hypermetabolic activity (8). It is not yet clear which of these tests is the most cost-effective method to prevent unnecessary surgery in patients with a suspicious FNAB.

— Stephanie L. Lee, MD, PhD

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TALLER-THAN-WIDE SHAPED THYROID NODULES IN ANY PLANE HAVE AN INCREASED RISK OF THYROID CANCER

Moon HJ, Kwak JY, Kim EK, Kim MJ. **A Taller-than-wide shape in thyroid nodules in transverse and longitudinal ultrasonographic planes and the prediction of malignancy.** Thyroid 2011;21:1249-53. Epub August 30, 2011.

SUMMARY

BACKGROUND

A taller-than-wide shape of a thyroid nodule has been shown by several groups to be associated with differentiated thyroid cancer (1-6). Most of the prior studies have defined taller-than-wide as the ratio >1 of the anteroposterior measurement as compared with the transverse measurement in the transverse (anteroposterior) plane. This group looked at which ultrasound plane, transverse, longitudinal (sagittal), or either, a taller-than-wide shape was most predictive of thyroid malignancy.

METHODS AND RESULTS

This was a retrospective observational study at a single referral center. A total of 471 nodules in 435 patients were included in the study. There were 370 women (mean age, 50.4 years [range, 15 to 82]) and 65 men (mean age, 50.4 years [range, 15 to 82]). Each nodule was evaluated by ultrasound (US) and an ultrasound-guided fine-needle aspiration biopsy (FNAB). The cytology in 339 (72%) was benign, in 98 (20.8%) it was malignant for papillary thyroid carcinoma (PTC), in 20 (4.2%) it was suspicious for PTC, in 1 (0.21%) it was indeterminate, and in 12 (2.8%) results were nondiagnostic. Thyroid surgery was performed in 120 patients. There were 326 nodules in 315 patients in the study who did not have surgery after the FNAB. These patients were classified by the FNAB cytology result. The sensitivity, specificity, and negative predictor value of predicting malignancy for taller-than-wide nodules in the transverse plane were 58.4%, 83.5%, and 84.8%, respectively; in the longitudinal (sagittal) plane 44%, 94.5%, and 82.4%; and in either plane 68%, 82.1%, and 87.7%.

CONCLUSIONS

This study demonstrates that taller-than-wide shape in either the transverse or longitudinal plane was useful to predict thyroid malignancy.

COMMENTARY

The 2009 ATA thyroid nodule and cancer guidelines specifically indicate that a shape taller than the width measured in the transverse dimension is suspicious for malignancy. Some studies have suggested that this measurement should be in the transverse plane, the longitudinal plane, either plane, or the plane was not indicated. The results of this study have sensitivity, specificity, and negative predictive value similar to prior studies showing that taller-than wide shape predicts malignancy. The previous studies showed sensitivity, specificity, and negative predictive values of 32.7% to 83.6%, 60% to 92.5%, and 67.4% to 98%, respectively (1-6). This is the first study to show that a taller-than-wide thyroid nodule in either the transverse or longitudinal plane is useful to predict malignancy.

— Stephanie L. Lee, MD, PhD

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WELL-DIFFERENTIATED THYROID CANCERS SMALLER THAN 4 CM WITH NEGATIVE LYMPH NODES CAN BE EFFECTIVELY TREATED BY THYROID LOBECTOMY

Nixon IJ, Ganly I, Patel SG, Palmer FL, Whitcher MM, Tuttle RM, Shaha A, Shah JP. **Thyroid lobectomy for treatment of well differentiated intrathyroid malignancy.** Surgery. October 14, 2011 [Epub ahead of print].

SUMMARY

BACKGROUND

There is an increasing incidence of small papillary thyroid cancers worldwide. The current guidelines of the American Thyroid Association recommend total thyroidectomy for any cancer larger than 1 cm (1). This study is a review of the outcome of thyroid surgery at Memorial Sloan-Kettering Cancer Center from 1986 through 2005 comparing lobectomy with total thyroidectomy for well-differentiated thyroid cancer (WDTC).

METHODS

During this time period, 889 patients had thyroidectomy for T1 (<2 cm) or T2 (2 to 4 cm) lesions. Data collected included patient demographics, extent of thyroid surgery, presence of pathologic lymph nodes found at surgery, the presence of gross extrathyroid extension or residual disease after completion of surgery, tumor histology, and size. Based on clinical and pathological features, the patients were classified as being at low, intermediate, or high risk for death. Patients were followed for a median of 99 months to determine outcomes.

RESULTS

Thyroid lobectomy was performed in 382 patients, but 21 of them had immediate completion thyroidectomy, so that the eventual thyroid lobectomy group was 41%; total thyroidectomy was performed in 528 patients (59%). The proportion of patients in the various risk categories was similar in the two groups; 83% had T1 and 17% T2 lesions. The percentage of patients under 45 years of age (54%) was higher in the lobectomy group, but there were no other significant demographic differences or risk factors between the two groups. There was no evidence of residual neck disease or distant metastases. Only 8% had central neck dissection and no lymph nodes contained tumor.

The 10-year survival was 93% in the lobectomy and 91% in the total thyroidectomy group. Disease-specific survival was 98.5% in the lobectomy group and 100% in the total thyroidectomy group. The local recurrence rate was 0% in both groups, and regional recurrence was 0% in the lobectomy group and 0.8% in the total thyroidectomy group. The 10-year distant recurrence rate in patients treated with thyroid lobectomy was 0%, as compared with 3% in the total thyroidectomy group. None of the differences were statistically significant.

CONCLUSIONS

Patients with well-differentiated thyroid tumors smaller than 4 cm and negative lymph nodes can be safely treated by thyroid lobectomy alone.

COMMENTARY

This strong and apparently heretic conclusion requires interpretation. This is a retrospective study. Although there may have been selection of patients for lobectomy, the only apparent difference between risk factors for the two groups is that there were younger patients in the lobectomy group. Also, it is surprising that no pathologic lymph nodes were detected at surgery or in the few cases of central-node dissection. The very low recurrence rate is surprising. Currently, recurrence is usually found by measurement of serum thyroglobulin and ultrasonography. When one lobe remains, the thyroglobulin measurement is not useful for detection of early recurrence.

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An argument in favor of lobectomy is the significant reduction of vocal-cord palsy, a lower incidence of hypoparathyrodism, and a shorter length of hospitalization (2). It is pertinent that lobectomy, usually with nodal dissection, is commonly performed for well-differentiated thyroid cancer (WDTC) in Japan (3). Based on this paper and the fact that good outcomes are commonly found by other centers that perform only lobectomy for WDTC (2,3), it is reasonable to rethink the current practice of treating WDTC by total thyroidectomy, often with central-node dissection, in the absence of abnormal lymph nodes on ultrasonography and computed tomography. This retrospective study should also make us reconsider the practice of performing completion thyroidectomy when there is a follicular variant of papillary thyroid cancer found on lobectomy classified as T1 with no evidence of vascular invasion in a young patient. In the case of follicular thyroid cancer, I would recommend completion thyroidectomy because of the worse prognosis, the possibility of vascular spread, and the need to consider 131-iodine ablation. However, completion thyroidectomy may not be essential when the pathology of the lobectomy shows only minimally invasive follicular carcinoma with no lymphovascular invasion because this lesion has a good prognosis. In other words, one size does not fit all for small WDTC.

— Jerome M. Hershman, MD

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Clinical THYROIDOLOGY
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CAN THE MEASUREMENT OF MICRORNA LEVELS IN "INDETERMINATE" FINE-NEEDLE ASPIRATION (FNA) BIOPSIES HELP IN DIAGNOSING THYROID MALIGNANCY?

Vriens MR, Weng J, Suh I, Huynh N, Guerrero MA, Shen WT, Duh Q-Y, Clark OH, Kebebew E. **MicroRNA expression profiling is a potential diagnostic tool for thyroid cancer.** Cancer. October 17, 2011. [Epub ahead of print]. doi:10.1002/cncr.26587.

SUMMARY

BACKGROUND

Cytopathologists and clinicians alike feel disappointed when a thyroid fine-needle aspiration (FNA) biopsy, that seemed to have plenty of cells must be given an "indeterminate" reading. The discovery of microRNAs (miRNAs), which are transcribed from regions of DNA previously thought to be silent, has revealed a new level of complexity in genetic regulation. MicroRNAs are small (approximately 22 nucleotides long), noncoding single-stranded RNAs that constitute a novel class of gene regulators. Each miRNA regulates the expression of hundreds of different messenger RNAs (mRNAs) by blocking their translation and promoting their degradation, and in turn, each mRNA is targeted by multiple miRNAs. Several groups studying thyroid malignancy have measured the levels of many of the 1000-plus miRNAs, looking for miRNA patterns that would identify thyroid cancer in FNA biopsies by nonhistologic means. Although miR-121, -122, -146a&b have been reported in some studies to be over-expressed on average in thyroid cancers, it remains to be shown in large prospective studies whether they consistently establish that an indeterminate FNA is benign or malignant (1). If a specific pattern of miRNAs that discriminated between all thyroid cancers and all benign tissues on FNA biopsies were found consistently, it would be an excellent diagnostic tool.

METHODS

The authors compared the levels of about 850 miRNAs in two RNA pools, one containing total RNA from 56 "benign" thyroid tissues (7 normal glands 14 multinodular goiters, 15 follicular adenomas, and 12 Hürthle-cell adenomas) and the other pool from 48 "malignant" thyroid tissues (8 papillary thyroid carcinomas [PTCs], 12 follicular variant PTCs, and 12 follicular, 20 Hürthle–cell, and 4 anaplastic carcinomas). The miRNA probes were made of nucleic acid analogs whose sugar-ring structure was chemically locked to strengthen binding and reduce cross-hybridization. The levels of the five most overexpressed and the five most underexpressed miRNAs found on this screen were then measured in all the individual tissue samples making up the two pools, by reverse transcription using primers specific for each of the 10 miRNAs, followed by polymerase-chain-reaction amplification. Control miRNAs were also measured, and the most stable one was used to normalize the measurements. The levels of the 10 miRNAs were also measured in a series of 125 FNA biopsies that had been read as "indeterminate," and the miRNA levels were compared to the histopathology findings after surgery.

RESULTS

When the levels of the five most underexpressed miRNAs (0.06 to 0.20 times lower than in the benign pool), and the five most overexpressed (4 to 8 times higher than in the benign pool) were measured in the 94 tissue samples individually, only 4 of 10 were still significantly different, all being down-regulated (miR100, miR125b, miR138, and miR768-3p; $P<0.002$).

The level of miR138 gave a theoretical diagnostic accuracy of 79% in distinguishing all benign neoplasms from all malignant tissue samples. The level of miR768-3p apparently was lower in the 12 follicular variant of PTC samples than in all 56 benign samples. When the 125 indeterminate FNA samples were assayed for the levels of the 10 miRNAs, only the miR138 level was significantly different between the 37 malignant and the 78 benign FNA samples, with a theoretical accuracy rate of 75% and a negative predictive value of 81%.

CONCLUSIONS

If the level of an individual miRNA like miR138 or even a pattern of miRNAs were to consistently distinguish malignancy on indeterminate thyroid FNA biopsies, it would certainly deserve to be studied in prospective clinical trials.

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COMMENTARY

Trying to analyze the significance of differences in a study that has many variables—but only a small number of samples of each variable—can be tricky. In this paper, it was not always clear how many comparisons were made, whether significance levels were corrected for the total number of comparisons performed, or whether a "difference" observed was an increase or a decrease. There is also the ever-present concern about whether the small amount of tissue obtained by FNA is representative of disease present elsewhere in the thyroid. In thyroid cancer, the relative level of expression of different miRNAs differs not only from normal tissue, but also between malignant regions (2), presumably reflecting environmental differences such as hypoxia or inflammation, as well as genetic changes. Malignancy can alter the covalent modification and processing of miRNA precursors, thus altering the level of the mature miRNAs in the cytoplasm. Upon binding to one of the Argonaute proteins in the cytoplasm, an miRNA is not only protected from nuclease degradation, but can also then form complexes with the other proteins needed for it to attack its target mRNAs. However, free mature miRNA also can bind directly to target sequences found in long noncoding RNAs and transcribed pseudogenes, as well as in mRNAs. This nonspecific binding can "buffer" miRNA levels. Thus, the finding that an miRNA appears to be substantially down-regulated in indeterminate FNAs from diverse thyroid malignancies, but not in diverse benign samples, does suggest that the metabolism of some miRNAs is altered with some consistency in thyroid cancer. The true utility of specific miRNAs for diagnosis of thyroid cancer will require additional studies.

— Stephen W. Spaulding, MD

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AMERICAN THYROID ASSOCIATION
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Call for Proposals – American Thyroid Association (ATA) Research Grants -- Deadline: January 31, 2012

Electronic Submission: Proposals must be submitted electronically through the research grant application feature on the ATA website, www.thyroid.org.

The American Thyroid Association (ATA) is pleased to announce the availability of funds to support new investigator initiated research projects in the area of thyroid function and disease. Topics may include, but are not limited to, Thyroid Autoimmunity, Iodine Uptake and Metabolism, Thyroid Cancer, Medullary Thyroid Cancer, Clinical Disorders of Thyroid Function, Thyroid Hormone Action and Metabolism, Thyroid Imaging, Thyroid Nodules and Goiter, Thyroid Development and the Brain. Research awards are intended to assist new investigators in obtaining preliminary data for submission of a more substantial application (i.e., to the NIH). Research grants, up to $25,000 annually, will be awarded for two year terms based on receipt and review of a satisfactory progress report from funded investigators in the fourth quarter of the first year of funding.

Guidelines for All Research Grant Proposals: As mentioned above, research awards are targeted for funding of new investigators to obtain preliminary data for submission of a more substantial application (i.e., to the NIH). Interested investigators should submit a brief description of the proposed research by January 31, 2012.

Eligibility of Applicant and Use of Funds Guidelines:

a. New investigators are individuals who are less than 6 years from completion of their post-doctoral fellowship and have never been a PI on an NIH RO1 or equivalent grant (recipients of NIH R29, R21 and KO8 awards are eligible).
b. Faculty members (MD and PhD) are eligible; however, those investigators who have reached the rank of associate professor or higher are not eligible.
c. Postdoctoral fellows are eligible if their department provides written confirmation that at the time of the award the applicant will have a junior faculty position.
d. Students working towards an MD or a PhD are not eligible.
e. Investigators and individuals who have previously received ATA, ThyCa or THANC awards are not eligible.
f. Applications are limited to one per individual researcher.
g. The funds can be used for direct costs associated with the proposal, including technician's salary, supplies or equipment but not for PI's salary.
h. Recipients of ATA grants must be ATA members (submit application online if not already a member). For new members, membership dues for the first year will be waived.

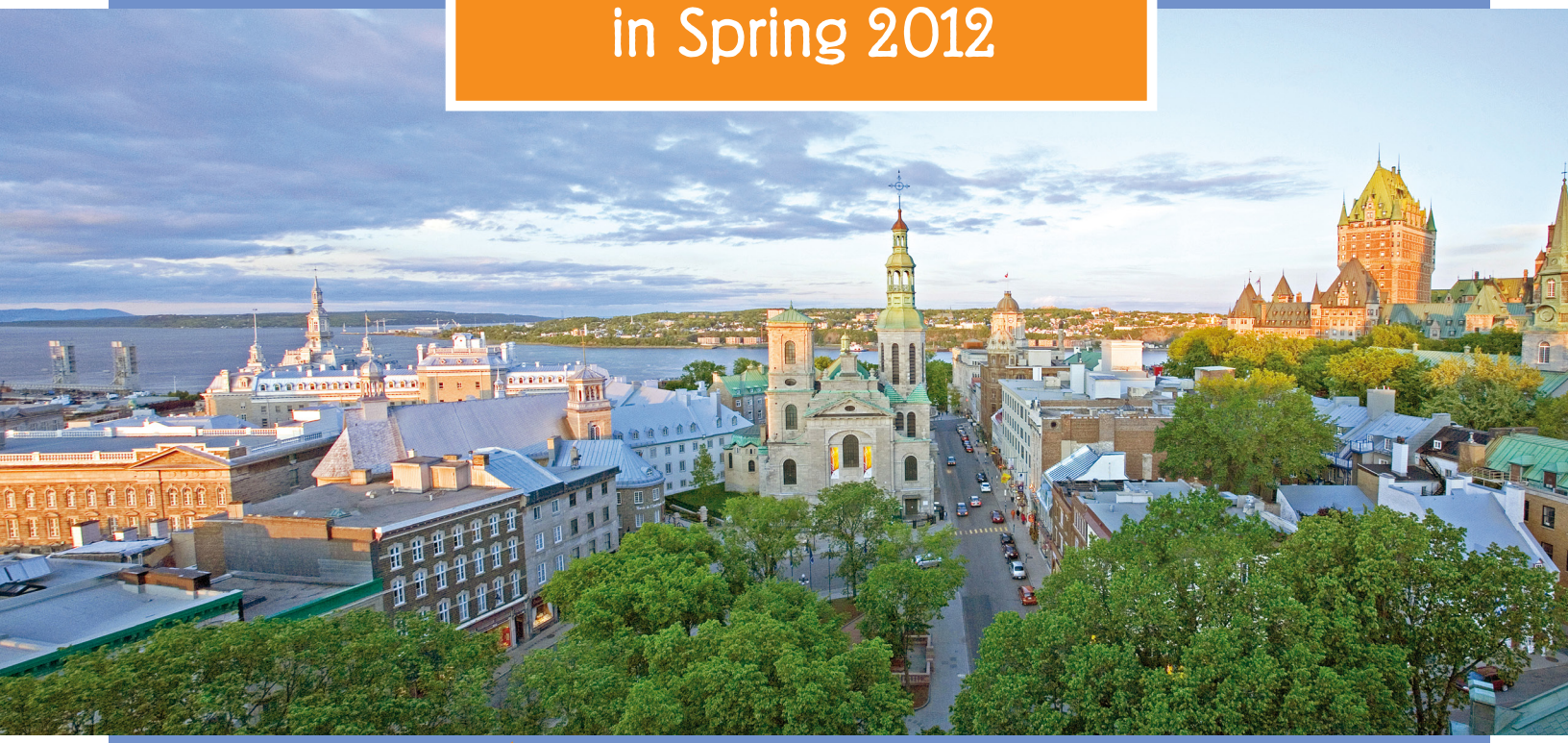
Proposal Requirements (please submit the following documents online):

1. Demographic information: Name /affiliation of applicant, complete work/home contact information – submitted into online system (do not include in grant proposal).
2. Grant Proposal (A **s**hort proposal that should be no longer than 900 words (including selected references) and no more than three double-spaced pages in 12 point type with 1" margins. These space requirements are absolute and nonconformance will preclude review. Do not include letterhead, name, address, institution, etc. This short proposal should include:
   - Title of proposed study
   - Background to the project
   - Hypothesis and/or outline of proposed studies
   - Outline of methodology
   - Anticipated results and implications
   - A short statement of how the grant will aid the applicant
   - Selected References (e.g. Uchino S, et al. World J Surg 2002;26:897-902)

   a. CV (NIH-style CV – up to 4 pages) - including evidence that the applicant is a new investigator with date of completion of postdoctoral training and current grant support (if any). In the case of postdoctoral fellows, written confirmation from the department chair must be provided that the applicant will have a junior faculty position at the time of the award. **Note: Without a suitable CV, applications will not be considered.**
3. Cover letter

Grant Review: The ATA Research Committee will rank proposals according to their scientific merit. Authors of selected proposals will be notified in March 2012 and invited to submit a complete grant application.

Registration Opening in Spring 2012



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The American Thyroid Association (ATA) is a nonprofit medical society composed of physicians and scientists who specialize in the research and treatment of thyroid diseases. Dedicated to improving the lives of the millions of Americans of all ages living with thyroid problems, we are strongly committed to serving as a resource for these patients and the public and to promoting the prevention, treatment, and cure of thyroid-related diseases.

With extensive online resources for thyroid patients, families, and the general public at *www.thyroid.org*, each year we reach thousands of people who have come to rely on us for health information they can trust.

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- Brochures on specific thyroid diseases;
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