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Iodine Supplementation in Euthyroid Pregnant Women Does Not Alter Maternal Free T₄ Levels

Elizabeth N. Pearce

bodies, thyroxine-binding globulin (TBG), and serum thyroglobulin were obtained at enrollment, week 22, week 33, and 3 months postpartum. Thyroid ultrasound was performed at baseline, at week 33, and at the postpartum visit. Comparisons between groups were performed using χ^2 and Fisher's exact tests for categorical data and Mann-Whitney testing for continuous data.

Results

A total of 86 of the 111 women were followed until delivery, and 36 were followed to 3 months postpartum. Ten women taking iodine-containing supplements and only one woman in the control group dropped out because of nausea and vomiting. Median urinary iodine excretion was similar in the treatment and control groups at baseline (111 µg/L vs. 103 µg/L), and 84% of

women in both groups reported using iodized salt. In the treatment group, urinary iodine increased to 161 µg/L by the third trimester, whereas in the controls the urinary iodine concentration decreased to 76 µg/L ($P<0.001$). Free T₄ decreased by 15% in treated women and 21.6% in the controls between the first and second trimesters ($P = 0.27$), and then remained stable in the third trimester. Total T₄, free T₄, free T₃, TSH, TBG, and thyroid volume did not differ between groups at any time point. Serum thyroglobulin was lower in the treated group than in controls at the second-trimester and postpartum visits ($P<0.01$).

Conclusions

Iodine supplementation in mildly iodine-deficient, antithyroid antibody-negative, euthyroid pregnant women did not alter maternal free T₄ levels.

ANALYSIS AND COMMENTARY ● ● ● ● ●

Serum free T₄ and free T₃ concentrations typically decrease after the first trimester of pregnancy. This is due, at least in part, to the fall in serum level of human chorionic gonadotropin (hCG), a stimulator of the thyroidal TSH receptor, after weeks 8 to 10 of gestation. In this study, an decrease of approximately 20% in free peripheral thyroid hormone levels was observed in both groups between the first and second trimesters, with no concomitant increase in TSH. The ratio of total T₄ to TBG followed the same pattern as free T₄, arguing against free T₄ assay artifact as a reason for the observed decline in free T₄. These data suggest that the free T₄ decline after the first trimester is physiologic, not pathologic, and is not the result of mild iodine deficiency. There is a need for trimester-specific, assay-specific reference ranges for free T₄ to guide clinical decision-making.

Strengths of the study include its randomized, prospective design and the fact that iodine supplementation was started relatively early in gestation. The supplementation dose of 150 µg of iodine daily is in agreement with ATA and Endocrine Society guide-

lines (3,4). However, results may not be generalizable to antithyroid antibody-positive women or to those with baseline hypothyroxinemia or TSH elevations, who might be more susceptible to the development or worsening of thyroid hypofunction in the setting of iodine deficiency. There was more gastrointestinal intolerance of iodine-containing prenatal multivitamins, leading to differential dropout, in the treatment group. It is important to note that effects of iodine supplementation on fetal and neonatal thyroid function and developmental outcomes were not assessed.

These data should not be interpreted as a reason to avoid iodine supplementation for iodine-deficient pregnant women. Even mild maternal iodine deficiency in pregnancy has been associated with deleterious effects on child cognition (5,6). In the present study, iodine supplementation prevented a rise in serum thyroglobulin levels, a marker for iodine deficiency, and normalized urinary iodine concentrations. Supplementation with 150 µg of iodine daily in mildly deficient regions has been demonstrated to be safe; supplementation should optimally be started before a woman conceives.

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Iodine Supplementation in Euthyroid Pregnant Women Does Not Alter Maternal Free T₄ Levels

Elizabeth N. Pearce

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Some Dental Materials Cause Hot Spots in the Oral Region When Whole Body ^{131}I Scans Are Done after Thyroidectomy

Stephen W. Spaulding

Savas H, Wong KK, Saglik B, Hubers D, Ackermann RJ, Avram AM. SPECT/CT characterization of oral activity on radioiodine scintigraphy. *J Clin Endocrinol Metab*. September 3, 2013 [E-published ahead of print]. doi:10.1210/jc.2013-2467.

SUMMARY • • • • • • • • • • • • • • • •

Background

When an ^{131}I total-body scan is performed after thyroidectomy to look for metastases, radioactivity is often detected in the mouth. This has previously been attributed to saliva or dental/periodontal disease. The authors noted many such foci of uptake in the oral region on planar scans, and they felt these foci were too common to be attributed to pooled saliva or to dental or periodontal inflammation.

Methods

The authors utilized single-photon-emission computed tomography (SPECT) combined with computed tomographic (CT) radiography to obtain a more precise three-dimensional localization of these radioactive foci than is possible on planar ^{131}I scanning. Between April 2007 and April 2011, a total of 216 consecutive patients with differentiated thyroid cancer had undergone both a preablation diagnostic ^{131}I planar scan and SPECT/CT imaging. None had reported symptoms of tooth pain or oral swelling. All had eaten a low-iodine diet for 2 weeks and then had either been deprived of L-T₄ for 4 to 6 weeks or had been deprived of L-T₃ for 2 weeks after having received it for 4 weeks. The investigators determined the location of any focal or diffuse oral uptake on SPECT/CT fusion images and classified it as being maxillary, mandibular, or within the oral cavity. The relationship to any region of high-density dental materials was noted. Dental phantoms containing amalgam or composite filling materials, gold partial

dentures, titanium abutments, porcelain fused to metal and all-ceramic crowns were soaked in 100 ml of distilled water containing 250 μCi ^{131}I for 24 hours, to simulate the amount of ^{131}I in the saliva of patients receiving a 1-mCi diagnostic scan. After air-drying for 2 hours and rinsing in water, the dental models underwent the same imaging procedures.

Results

Planar scans from 123 of 216 patients were judged to be positive or equivocal for oral cavity uptake: bilateral foci were present in 85%. Twelve patients were excluded because the scans did not include the complete oral cavity; in the remaining 111 patients, uptake that co-localized with high-density dental material was found in 86%. A total of 323 foci were observed (up to 12 foci in a single patient). Some regions with high-density dental material were not associated with ^{131}I uptake, possibly indicating that they were resin or amalgam fillings or ceramic crowns containing no metal. Scans from 16 patients showed uptake within the oral cavity: in 4 it appeared to be associated with dental material, while in 12 it was localized in the floor of the mouth, in the soft palate, or in teeth that did not contain dental materials. In all cases with focal uptake on the diagnostic scan, uptake was also observed on the therapeutic scans. The phantom tooth studies showed intense uptake in the porcelain fused-to-metal crown and the gold partial denture, less uptake in the titanium abutment, and no focal uptake in the all-ceramic crown or in the resin or amalgam fillings.

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Some Dental Materials Cause Hot Spots in the Oral Region When Whole Body ^{131}I Scans Are Done after Thyroidectomy

Stephen W. Spaulding

Conclusions

The authors postulate that the negatively charged ^{131}I ion can form a permanent or semipermanent bond with positively charged ions on dental materials

containing gold, silver, palladium, or mercury. The bond formed with titanium seems weaker. Most of the uptake detected in the mouth on postthyroidectomy scans appears to be due to this benign cause.

ANALYSIS AND COMMENTARY ● ● ● ● ●

The authors had no information about the actual dental materials that they found to be correlated with the SPECT/CT foci, and the patients did not undergo dental examination to look for evidence of subclinical gingivitis or dental abscess associated with the dental materials. The phantom model study showed clear-cut interactions of a tracer dose of ^{131}I with several virgin dental metals, but the results might have been somewhat different if saliva had been used to soak the dental phantoms instead of distilled water. (Saliva contains substantial amounts of nonradioactive iodide, and the iodine level does not differ

between euthyroid and hypothyroid subjects [1]). Interestingly, no uptake was found on the dental phantom containing a mercury/silver amalgam filling, although iodides of mercury and silver have been well characterized. A prospective study is now needed to correlate such oral foci of ^{131}I with the specific dental materials present in each patient, the length of time those materials have been in place, plus other clinical (and metallurgical) parameters. Nonetheless, previous clinical studies concerning the kinetics of radioiodine in the salivary glands, and on salivary-gland function in patients treated with ^{131}I may need to be reinterpreted.

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Differentiated Thyroid Cancers in the Wake of the Chernobyl Nuclear Accident May Be Efficiently Treated with I-131 Even in Patients with Disseminated Pulmonary Metastases

Albert G. Burger

Reiners C, Biko J, Haenscheid H, Hebestreit H, Kirinjuk S, Baranowski O, Marlowe RJ, Demidchik E, Drozd V, Demidchik Y. Twenty-five years after Chernobyl: outcome of radioiodine treatment in children and adolescents with very high-risk radiation-induced differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 2013;98:3039-48. Epub April 24, 2013.

SUMMARY • • • • • • • • • • • • • • • • • •

Background

Following the Chernobyl nuclear accident, the people living in the surrounding areas were exposed to high ^{131}I radiation and had no access to appropriate countermeasures. Children were at particularly high risk, since the milk they drank was contaminated (1). Among the population who was below 14 years of age in 1986, a total of 5127 cases of differentiated thyroid carcinomas (DTCs) were medically followed. DTC is a very rare pediatric tumor. In the United States, the incidence is 1 to 5 cases per million population per year. In the areas severely hit by the Chernobyl accident, this incidence increased to 40 per million per year. Because of the relatively short half-life of ^{131}I , the contamination did not persist for years. At present, the incidence of DTC in children below 10 years of age is not higher than in children from uncontaminated areas. In 2006 (2), the authors had published a report about the clinical course of 740 surgically treated children. In the present article, they report on the outcome after postsurgical radioiodine therapy (RIT).

Methods

The patients were chosen for ^{131}I treatment in Germany if there was local tumor invasion, and/or lymph-node or distant metastasis. In a typical case, the first cancer surgery took place in early adoles-

cence, approximately 10 years after exposure. The tumors were exclusively papillary cancers. At that stage, three quarters of the study cohort had local invasion. Practically all patients had lymph-node involvement. Following the initial scintigraphy, distant metastases could be visualized in approximately 50% of cases. If affected, the lungs showed a miliary spread or mixed tissue with focal uptake. Clearly defined lung nodules were rarely found. All patients had undergone radical surgery with total thyroidectomy and lymph-node dissection.

Before RIT, a classical workup was performed in Germany, including chest x-ray examination. Thyroxine treatment was stopped for 4 weeks. If a thyroid remnant was found, ablation with 100 MBq per kilogram of body weight (2.7 mCi/kg) was attempted. Follow-ups in Germany were performed 3 to 12 months after each RIT and, if necessary, repeat radioactive iodine treatment was applied. Since 1999 and 2004, intensive pulmonary surveillance by using CT and functional respiratory tests was introduced in order to identify patients with pulmonary fibrosis.

While patients were hypothyroid ($\text{TSH} >80 \text{ mU/L}$), complete remission was defined by undetectable serum thyroglobulin and a nearly complete remission was characterized by a detectable thyroglobulin of $<10 \mu\text{g/L}$ with negative scintigraphy. Partial remission

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Differentiated Thyroid Cancers in the Wake of the Chernobyl Nuclear Accident May Be Efficiently Treated with I-131 Even in Patients with Disseminated Pulmonary Metastases

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was considered in patients with thyroglobulin measurements >10 µg/L with a response of the tumor to treatment and a progressive decline of serum thyroglobulin values. The remaining patients were considered to be suffering from progressive disease.

Results

In 134 children without distant metastases the cumulative high ^{131}I doses varied between 1 and 25 GBq (27 and 675 mCi). Obviously, 100 patients with distance metastases received higher cumulative doses (4 to 63.6 GBq [100 to 1700 mCi]; median, 16.9 GBq [450 mCi]). Note that because of local circumstances, in some instances the interval between surgery and the first RIT treatment was as long as several years.

Complete remission was achieved in 64% of the 134 children, nearly complete remission in 30%, and partial remission in 4.8%; there was no relapse. The follow-up between the last ^{131}I therapy and the latest examination ranged from 7.4 to 13.9 years. Most importantly, there were no local or distant DTC recurrences in incomplete responders or any sign of disease progression in nearly complete responders. One patient died of advanced pulmonary fibrosis 19 years after diagnosis and 17 years after treatment. Two other patients died of causes unrelated to DTC. No patient died of DTC. As expected, complete remissions were more frequent in patients in whom the disease was discovered long after 1986 and in

those with low initial serum thyroglobulin levels. Pulmonary fibrosis was not limited to the one patient who died of it: seven other patients showed persistence or transient evidence of lung fibrosis. All these cases had diffuse pulmonary metastases with high initial TG levels (290 to 9760 µg/L).

Clinical follow-up indicates that reproductive function was impaired in males, since only 24% of the affected men have children while 51% of the women have children.

Conclusions

This cohort of patients with DTC with local invasion and/or distant metastases is a selected group of patients at increased risk. The follow-up, which now extends over 11 years after RIT, is very encouraging; none of the patients died of progressive thyroid cancer, the majority (64%) were in complete remission, and some (4.8%) had partial remission, with clinical follow-up indicating an improvement of their health status because thyroglobulin levels tended to decrease over years with suppressive doses of thyroxine alone. In some cases, the ^{131}I doses that had to be given were very high, but on the average dose of 141 MBq/kg (3.8 mCi/kg) was still acceptable. Lung fibrosis was seen in several cases, but only in patients initially presenting with pulmonary metastases. One of these patients died of pulmonary insufficiency.

ANALYSIS AND COMMENTARY ● ● ● ● ●

Among the 5127 young patients with papillary thyroid carcinoma in the Chernobyl area, no aggressive forms (e.g., tall-cell, insular, or columnar-cell carcinoma) were found; therefore, the prognosis of these tumors is essentially good, provided the children have access to adequate treatment (3). In control populations, the more aggressive forms are also extremely rare, so it is premature to conclude that aggressive forms do not

occur after incidents like that in Chernobyl. Although, the increased cancer risk was limited to children and adolescents below 14 years of age in 1986, the whole population continues to be surveyed.

The results of this study are highly encouraging. Some patients had very advanced disease with disseminated miliary pulmonary metastases. Following repeat treatments with radioactive iodine, the pulmonary

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Differentiated Thyroid Cancers in the Wake of the Chernobyl Nuclear Accident May Be Efficiently Treated with I-131 Even in Patients with Disseminated Pulmonary Metastases

Albert G. Burger

seeding disappeared or was markedly reduced. This experience certainly contrasts with the rare success rate in sporadic DTC with pulmonary involvement in adults.

The most difficult question is with regard to the balance between treatment and secondary effects of treatment, particularly pulmonary fibrosis. In this

context, it would be interesting to know the cumulative dose of ^{131}I in the patient who died of pulmonary fibrosis. Also, we do not know the incidence of secondary tumors that have been reported in the adult DTC population treated with ^{131}I . For the moment, however, there is no alternative way of treating these cancers.

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Patients with Differentiated Thyroid Cancer and Coexistent Hashimoto's Thyroiditis Have a Better Prognosis Than Those without Thyroiditis

Jerome M. Hershman

Dvorkin S, Robenshtok E, Hirsch D, Strenov Y, Shimon I, Benbassat CA. Differentiated thyroid cancer is associated with less aggressive disease and better outcome in patients with coexisting Hashimotos thyroiditis. *J Clin Endocrinol Metab* 2013;98:2409-14. Epub April 22, 2013.

SUMMARY • • • • • • • • • • • • • • • •

Background

There is a high prevalence of Hashimoto's thyroiditis (HT) in patients who undergo surgery for differentiated thyroid cancer (DTC). The purpose of this study was to determine whether patients with HT and DTC have a better prognosis than those with DTC without HT.

Methods

The study included 753 patients with DTC in a database of the Rabin Medical Center in Tel Aviv. All patients had been treated with total thyroidectomy and RAI ablation and had been followed for more than 1 year. The diagnosis of HT was made based on a history of hypothyroidism and positive antithyroid antibodies or diffuse lymphocytic infiltration in both lobes on the pathology specimen. Patients with peritumoral lymphocytic infiltration were excluded.

There were 646 patients in the control group without HT and 107 in the HT group. Various clinical variables were compared in the two groups. A multivariate analysis was performed with regard to lymph-node involvement, stage at diagnosis, and persistent disease at the end of follow-up. In addition, a subgroup analysis was carried out comparing 98 patients in the HT group with a similar number in the control group matched for age, sex, and disease severity.

Results

Hashimoto's thyroiditis was present in 14% of the 753 patients. In comparison with the control group, the HT group was predominantly female (93% vs. 77%, P<0.001), had a slightly smaller primary tumor (17.9 mm vs. 21.2 mm, P<0.01), had less lymph-node involvement (23% vs. 34%, P<0.02), and had less persistent disease at 1 year (13% vs. 26%, P<0.04).

The multivariate analysis showed that the presence of HT was an independent negative predictor of lymph-node involvement at presentation (odds ratio, 0.34; 95% confidence interval [CI], 0.17 to 0.66) and persistent disease at the end of follow-up (odds ratio, 0.48; 95% CI, 0.24 to 0.93). The subgroup analysis showed that patients with HT were less likely to receive additional treatments with radioiodine.

The disappearance of antithyroglobulin antibodies was tracked in 50 patients. The median time to disappearance from the initial treatment was 15 months (range, 2 to 78). Eight patients had persistent antibodies despite no evidence of recurrent disease.

Conclusions

The study shows that HT is associated with a less aggressive form of differentiated thyroid cancer and a better long-term outcome.

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Patients with Differentiated Thyroid Cancer and Coexistent Hashimoto's Thyroiditis Have a Better Prognosis Than Those without Thyroiditis

Jerome M. Hershman

ANALYSIS AND COMMENTARY ● ● ● ● ●

Patients with HT are not predisposed to the development of DTC (1). However, in patients with HT who also have DTC, the cancer is less aggressive and the prognosis is better than in those without DTC, as shown in this study. This conclusion is in agreement with some other studies (2-4), but other reports do not substantiate the beneficial effect of HT on the outcome of DTC (5-7). Based on their conclusion that DTC in the presence of HT follows a less aggressive course, the authors of the present report recommend that this concept should be included in tailoring therapy. In an effort to relieve the stress of

the disorder, it is reasonable to tell patients with DTC and Hashimoto's or focal lymphocytic infiltration that this is a favorable host response to the tumor.

One limitation of the study is that the authors do not clearly state how many patients with HT were diagnosed by clinical criteria and how many were diagnosed by histopathology or how many with clinical criteria did not have typical histopathology.

What is the possible mechanism whereby HT may ameliorate DTC? Infiltration by cytotoxic T cells may kill carcinoma cells.

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Is Long-Term Follow-up Necessary for Benign Thyroid Nodules?

Jerome M. Hershman

Lee S, Skelton TS, Zheng F, Schwartz KA, Perrier ND, Lee JE, Bassett RL, Ahmed S, Krishnamurthy S, Busaidy NL, Grubbs EG. The biopsy-proven benign thyroid nodule: is long-term follow-up necessary? J Am Coll Surg 2013;217:81-9. Epub May 6, 2013.

SUMMARY • • • • • • • • • • • • • • • •

Background

The vast majority of thyroid nodules that are biopsied are reported as benign. Recommendation 14 of the American Thyroid Association guideline states that “all benign thyroid nodules should be followed with serial ultrasound examinations 6–18 months after the initial FNA. If nodule size is stable (i.e., no more than a 50% change in volume or <20% increase in at least two nodule dimensions in solid nodules or in the solid portion of mixed cystic–solid nodules), the interval before the next follow-up clinical examination or ultrasound may be longer, e.g., every 3–5 years.” (1). The aim of the study reported in the current paper was to determine whether long-term follow-up of benign thyroid nodules was associated with a change in treatment or an improvement in diagnosing a missed malignancy as compared with short-term follow-up.

Methods

Results of thyroid FNA biopsies at the MD Anderson Cancer Center performed from 1998 to 2009 were reviewed, and patients with benign cytology were selected for further review of the clinical and ultrasound (US) findings. Patients who had follow-up were divided into two groups: those followed for <3 years and those followed for ≥ 3 years.

Results

Of the 848 patients with benign cytology, 92 underwent surgery. Of the remaining 646 patients, 280 had no further follow-up and 366 were followed; 226 had <3 years of follow-up and 140 had ≥3 years of follow-up. The median follow-up in the short-term group was 13 months and in the long-term group 57 months. The median nodule size for both groups was 2.3 cm. The long-term group had significantly more US performed ($P<0.01$) and significantly more repeat FNAs done (13% vs. 4%, $P<0.01$). Of the 26 nodules (previously biopsied as benign) on which FNA had been performed, 20 were again found to be benign, 3 were found to be follicular lesions, 2 were nondiagnostic, and 1 was found to be suspicious for papillary thyroid cancer (at surgery it was a follicular variant of PTC). The reasons for rebiopsy of the 26 lesions included increased growth in 12, continued suspicious features such as calcification and increased vascularity in 5, and no documented reason in 9. Two malignancies were found in those who underwent surgery after observation, both in the short-term group.

Conclusions

Long-term follow-up of patients with benign thyroid nodules is associated with increased repeat FNA and US without improvement in the detection rate of malignancy. After 3 years of follow-up, consideration should be given to stopping long-term routine follow-up.

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Is Long-Term Follow-up Necessary for Benign Thyroid Nodules?

Jerome M. Hershman

ANALYSIS AND COMMENTARY ● ● ● ● ●

This interesting study considers the problem of how frequently and how long to follow thyroid nodules that are benign. Although the ATA guideline that is described in the introduction is open-ended, it does not specify the absolute length of follow-up, but it does state that longer follow-up of nodules thought to be stable at earlier intervals should be carried out, perhaps at intervals of 3 to 5 years.

The current study has serious flaws. First it is retrospective. Second, perhaps because MD Anderson Cancer Center is a referral center, 43% (280 of 646) of patients did not undergo follow-up there, and no follow-up data are provided on these patients. The authors point out that there were no clear clinical differences in the remaining patients who underwent either short-term or long-term follow-up. On that basis, their conclusions may be considered valid. Of course, what is needed is a prospective study with nearly 100% follow-up to determine whether there is a significant yield of new findings suggestive of

malignancy in patients who are followed for longer than 3 years.

Continued growth of cytologically benign nodules may be worrisome and justify another FNA. Another concern is false negative FNA results. In the case of small nodules, it is possible that the sampling included mainly the benign tissue surrounding the nodule. In the case of larger nodules, the possibility of heterogeneity has been raised as a basis for false negative cytology, but a recent study from the Walter Reed National Military Medical Center showed that false negative cytology was not more common in nodules larger than 4 cm as compared with smaller nodules (2). Nevertheless, the rate of false negatives in that series was 7%.

For the above reasons, it seems reasonable to follow patients with benign thyroid nodules by ultrasound for 3 years and at much longer intervals after that. Additional studies will be needed to justify stopping follow-up at 3 years when there is no growth of the nodule in order to reduce costs of follow-up.

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Complete Cervical Sonography Is Essential for Operative Planning in Differentiated Thyroid Cancer

Cord Sturgeon

O'Connell K, Yen TW, Quiroz F, Evans DB, Wang TS. The utility of routine preoperative cervical ultrasonography in patients undergoing thyroidectomy for differentiated thyroid cancer. *Surgery*. September 5, 2013 [Epub ahead of print]. doi: 10.1016/j.surg.2013.06.040.

SUMMARY • • • • • • • • • • • • • • • •

Background

Lymph-node metastases are found in 30% to 80% of cases of papillary thyroid cancers (PTCs), are usually located in level VI (central compartment), and are a risk factor for disease recurrence. Cervical recurrence may be due to occult central neck metastases not detected or removed at the index operation. The ATA and the NCCN both recommend preoperative cervical ultrasound for all patients with biopsy proven differentiated thyroid cancer (DTC) (1,2). This study was designed to assess the impact of preoperative cervical ultrasound on the surgical approach during an index operation for thyroid cancer. The authors hypothesized that preoperative ultrasound of the neck would identify clinically occult metastatic lymphadenopathy that would alter the initial operative procedure in some patients with DTC.

Methods

This is a retrospective study of 70 patients with biopsy-proven DTC who underwent preoperative radiologist-performed ultrasound of the central and lateral nodal basins at a single high-volume institution in the midwestern United States. All patients underwent total thyroidectomy with appropriate lymph-node clearance. Data were collected on demo-

graphics, physical examination findings, preoperative sonographic findings, FNA results, extent of operation performed, number of lymph nodes retrieved, and final pathology.

Results

The authors found that 7% of their patients had results on physical examination that were consistent with palpable cervical adenopathy. In the remaining patients with no palpable lymphadenopathy, 22% had sonographic evidence of suspicious lymphadenopathy. Within this subgroup of patients with sonographically suspicious nodes, 92% were confirmed to have nodal metastases on final pathology. The sensitivity of ultrasound for lateral neck metastases was 93%. A preoperative ultrasound changed the operative management in 23% of patients with biopsy-proven DTC.

Conclusions

The results of this study underscore the importance of routine use of high resolution preoperative cervical ultrasound in patients with DTC. The sonographic findings changed the operative management in 23% (16 of 70) of patients. 13 of 16 patients had a more complete operation for pathologically confirmed, but clinically occult, lymph node metastases. 2 of 16 avoided an unnecessary modified radical neck dissection. 1 patient in 16 had false-positive US results.

ANALYSIS AND COMMENTARY • • • • •

Ultrasound is a key component of the preoperative workup and the postoperative surveillance for thyroid cancer. A preoperative cervical ultrasound including

the thyroid and both central and lateral compartments is recommended by the ATA and NCCN guidelines (1,2). Both guidelines also recommend preoperative FNA biopsy of suspicious lymph nodes. In their *continued on next page*

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longitudinal care algorithms, both the ATA and NCCN guidelines recommend periodic ultrasound (1,2). Physical examination is not sensitive for the presence of cervical-node metastases, and postoperative patients will be subjected to rigorous surveillance, including cervical ultrasound. Therefore, it behooves the surgeon to have knowledge of sonographically detectable metastases prior to the index operation for thyroid cancer, so that a complete resection, including appropriate lymph-node clearance, can be performed. Theoretically, this should lead to better locoregional control of disease, and may decrease recurrence (3), and possibly the need for radioiodine or reoperation.

In a prior study, a group from MD Anderson Cancer Center found that cervical ultrasound detected additional sites of metastatic disease not found on physical exam in 20% of patients undergoing an index operation for thyroid cancer, in 32% undergoing reoperation for persistent disease, and in 68% undergoing reoperation for recurrent disease (4). The operation performed was altered by the sonographic data in 39% of these patients. In a study from the University of Miami, surgeon-performed preoperative

ultrasound identified nonpalpable metastatic lymph nodes in 24% of patients (5). In a study from the Mayo Clinic of over 700 patients with PTC, preoperative ultrasound detected nonpalpable nodal metastases in 32.9% (6). Preoperative ultrasound findings altered the operation in 40.5% of index cases and in 42.9% of reoperative cases.

In this contribution by O'Connell et al., 23% of the total group had findings from the preoperative ultrasound that changed the operative management. These findings are similar to those of other researchers who have studied the subject and underscore the importance of preoperative high-resolution sonographic imaging for patients with thyroid cancer. Taken together, these studies indicate that preoperative ultrasound has a high sensitivity for nodal disease and will detect nonpalpable nodal metastases in roughly 20% to 40% of patients with DTC and will alter the index operation in a similar percentage of patients. For these reasons, complete cervical sonography is an essential component of the preoperative workup and operative planning for patients with thyroid cancer.

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BRAF Mutation Is Not an Independent Predictor of Central- Lymph- Node Metastases in the Classical Variant of Papillary Thyroid Cancer

Jerome M. Hershman

Li C, Aragon Han P, Lee KC, Lee LC, Fox AC, Beninato T, Thiess M, Dy BM, Sebo TJ, Thompson GB, Grant CS, Giordano TJ, Gauger PG, Doherty GM, Fahey TJ 3rd, Bishop J, Eshleman JR, Umbricht CB, Schneider EB, Zeiger MA. Does BRAF V600E mutation predict aggressive features in papillary thyroid cancer? Results from four endocrine surgery centers. *J Clin Endocrinol Metab* 2013;98:3702-12. Epub August 22, 2013.

SUMMARY • • • • • • • • • • • • • • • •

Background

The BRAF V600E mutation, found in a high proportion of papillary thyroid cancers (PTCs), results in constitutive activation of the mitogen-activated protein (MAP) kinase pathway and is generally believed to indicate that the tumor is aggressive (1). A controversial aspect of the surgical treatment of PTC is whether to perform routine prophylactic lymph-node dissection in the central compartment (level 6). The aim of this retrospective study was to determine the prognostic value of the BRAF mutation status as a predictor of lymph-node metastases. If the mutation status predicted lymph-node metastases to the central compartment, then mutation status could be used to justify prophylactic central-lymph-node dissection.

Methods

The study included 388 consecutive patients who underwent surgery for PTC between January 2009 and December 2011 at four tertiary endocrine surgery centers (Mayo Clinic, University of Michigan, Cornell, and Johns Hopkins). All patients had central-lymph-node dissections; in 76% of patients this was done on a prophylactic basis and in 24% there was preoperative evidence of central-lymph-node involvement.

The BRAF mutation was identified in DNA extracted from frozen or paraffin-embedded tissue samples by PCR amplification.

The patients were divided into three groups: classical variant PTC (315 patients), follicular variant PTC (41 patients), and aggressive variant PTC (32, of whom 31 had tall-cell variant).

Statistical analysis included a bivariate analysis of the association between BRAF mutation status and patient and disease features, including age, sex, tumor size, lymph-node metastases, extrathyroidal extension, multifocality, lymphovascular invasion, involvement of surgical margins, and AJCC stage. Multivariate logistic-regression analyses of these features were conducted to examine which preoperative variables were independently associated with central-lymph-node metastases.

Results

The BRAF mutation prevalence was found to be 80.3% in the classical variant, 39% in the follicular variant, and 87.5% in the aggressive variant PTC. The bivariate analysis of all PTC subtypes showed a significant positive association between the BRAF mutation status and lymph-node metastases ($P = 0.002$) and advanced AJCC stage ($P = 0.002$). Multivariate logistic-regression analysis of all patients with PTC found that BRAF mutation ($P = 0.001$), tumor size >2 cm ($P = 0.045$), and extrathyroidal extension ($P = 0.001$) were independent predictors of lymph-node metastases. Age >45 years was negatively associated with the presence of lymph-node metastases ($P = 0.001$).

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BRAF Mutation Is Not an Independent Predictor of Central-Lymph-Node Metastases in the Classical Variant of Papillary Thyroid Cancer

Jerome M. Hershman

When the bivariate analysis was performed for only the 315 classic variant PTCs, there was no significant association between BRAF mutation and lymph-node metastases or any of the other tumor variables. Multivariate logistic-regression analysis found that only age >45, tumor size >2 cm, and extrathyroidal extension were independent predictors of lymph-node metastases. There was no significant association between BRAF mutation status and lymph-node metastases in this group.

Conclusions

Although BRAF mutation was found to be an independent predictor of central-lymph-node metastases in the overall cohort of patients with PTC, this relationship lost significance when only classical variant PTC was included in the analysis. Prospective studies are needed before BRAF mutation can be considered a reliable factor to guide the treatment of patients with PTC with regard to performing prophylactic central-lymph-node dissection.

ANALYSIS AND COMMENTARY ● ● ● ● ●

This interesting study, concluding that BRAF mutation status is not a predictor of lymph-node metastasis for the classical variant of PTC, which occurred in 81% of the patients, is somewhat heretical with regard to the recent concern about the ominous prognostic value of this mutation. The finding that the BRAF mutation does not correlate with lymph-node metastasis is supported by a Japanese study of 613 patients with PTC of whom 38% had the BRAF mutation (2). In a meta-analysis of 32 studies including 6372 patients (written by some authors of the current study), BRAF mutation was associated with lymph-node metastases (3), but only 2 of the studies included prophylactic lymph-node dissection.

How can the contrary findings be reconciled? First, PTC has a very good prognosis in about 90% of patients, making it difficult to believe that the BRAF mutation indicates an ominous prognosis when it is currently found in such a high prevalence of PTC

patients. The finding that 80% of the classical variant PTCs had the mutation makes the statistical comparisons somewhat lopsided. If the large majority of patients with PTC have the BRAF mutation, then it becomes tough to prove that it predicts a poor outcome, including lymph-node metastases that correlates with more recurrence.

Second, the introduction of the current paper contains an excellent discussion about the controversial benefit of prophylactic central-lymph-node dissection, although it does not highlight the downside of the procedure, namely a higher incidence of surgical complications. It states that "most occult nodal micro-metastases, although they occur in 31% to 62% of patients with PTC, remain clinically insignificant." Perhaps the use of the BRAF mutation will be as a marker of more aggressive PTC that should be treated more aggressively in patients who have gross lymph-node macrometastases that have been detected pre-operatively. These patients are probably more likely to benefit from central-lymph-node dissection.

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THYROID CANCER TUMOR BOARD

Lymph Node Metastases Can Have a Significant Impact on Recurrence of Thyroid Cancer

Wendy Sacks and Pouyan Famini

CASE PRESENTATION • • • • • • • •

In April 2012, a 28-year-old woman at 5 weeks postpartum presented to her obstetrician because she felt a new lump in the right side of her neck. She was referred to an endocrinologist for further evaluation. Neck ultrasound demonstrated a 4.1-cm nodule in the right thyroid lobe; the nodule had irregular borders and microcalcifications. In addition, multiple enlarged, abnormal, cystic lymph nodes were visualized in the central and lateral neck at levels III, IV, and VI, ranging from 1.5 to 3.5 cm (Figures 1 and 2). Fine-needle aspiration (FNA) of the right thyroid nodule and a right level IV lymph node confirmed papillary thyroid cancer (PTC) with lymph-node metastasis.

In May 2012, the patient underwent subtotal thyroidectomy with central compartment and right modified neck dissection. Surgical pathology demonstrated multifocal classic variant PTC involving the entire right lobe, with the largest nodule in the isthmus measuring 2.4 cm. The tumor extended beyond the

thyroid and into the soft tissue and fibrous connective tissue of the neck. Eighteen of 18 central compartment lymph nodes and 8 of 12 level III/IV lymph nodes were involved, with extranodal extension (pT3, pN1b, pMX). In June, 2012, she received 155 mCi of ^{131}I following recombinant human TSH (rhTSH) stimulation. The 7-day posttreatment whole-body scan (WBS) demonstrated focal intensive activity in both sides of the thyroid bed, focally increased activity in the superior mediastinum, and low-grade, nonspecific uptake in the high posterior right neck. Further imaging with CT or MRI was recommended. Her thyroglobulin (Tg) was 6 ng/ml on thyroid hormone suppression prior to ^{131}I treatment.

In September 2012, with TSH <0.01 mU/L, her Tg was 5.4 ng/ml. Six months after RAI treatment, the patient underwent thyroid ultrasonography, which showed two oval, circumscribed, avascular nodules in the left thyroid bed and no irregular lateral neck lymph nodes; however, a neck MRI

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Figure 1. Transverse view of 4.1-cm right-lobe nodule with microcalcifications.

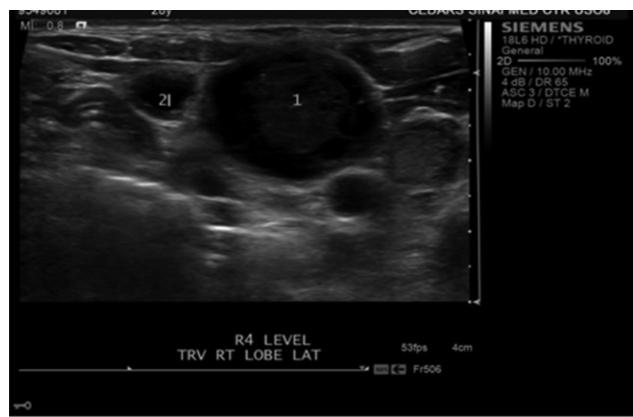


Figure 2. Two cystic level IV nodes. The larger node measures 3.5 by 2.0 cm.

THYROID CANCER TUMOR BOARD: Lymph Node Metastases Can Have a Significant Impact on Recurrence of Thyroid Cancer

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performed to evaluate right-salivary-gland enlargement showed a 2-cm mass in the right posterior triangle, level II, just posterior and medial to the tail of the parotid gland but deep to the sternocleidomastoid muscle. FNA of this right level II lymph node demonstrated metastatic PTC. A chest CT (without contrast material) demonstrated a 6-mm nodular area on each side of the trachea in the region of the thyroid bed, possibly corresponding to the focal intense uptake seen on the prior WBS. There was no evidence of pulmonary metastases. In April 2013, she underwent resection of this biopsy-proven metastatic lymph node as well as four adjacent benign lymph nodes. Current thyroglobulin remains elevated, at 4.2 ng/ml with TSH <0.01 mU/L, and the thyroid-bed ultrasound shows stability in size of the 0.6- and 0.8-cm left thyroid bed nodules, but now there are cystic changes and microcalcifications in these lesions (Figure 3).



Figure 3. Two left-thyroid-bed nodules with microcalcification and cystic change in the thyroid bed.

ANALYSIS AND COMMENTARY ● ● ● ● ●

Despite the extensive locoregional tumor involvement with extrathyroidal extension, lateral lymph-node metastases, and extranodal extension, most would agree that this patient's overall disease-specific survival is still excellent as prognosticated by various staging systems: Stage I by AJCC/UICC, MACIS score <6 ("low risk"), and low risk by AGES. What is the prognostic impact and the risk for recurrence of overt lymph-node metastases?

There are several prognostic factors for persistent or recurrent PTC with cervical lymph-node metastases. These include a high number of lymph nodes with metastatic disease at presentation (more than 10), number of lymph nodes with extracapsular invasion (more than 3), and elevated Tg at 6 to 12 months after levothyroxine withdrawal. Furthermore, the impact of nodal metastases depends on age, with a negative impact on outcome seen mainly in older patients.

In addition, the number of nodes, their location and size, and the presence of extracapsular extension are important prognostic factors for patients with PTC (1-3). At postoperative follow-up, patients who achieve undetectable serum Tg levels can expect a high rate of disease-free survival with a low risk for recurrent disease up to 10 years after initial treatment. However, patients with elevated serum Tg levels and a higher number of metastatic lymph nodes at presentation are at greater risk for recurrence or persistent disease. This latter group of patients should therefore be more closely monitored (1).

A recent review of prospectively maintained surgical databases at the University of Sydney and University of Wisconsin endocrine surgical units between 2000 and 2010 identified 121 patients with PTC and lateral neck nodal metastases who underwent concurrent total thyroidectomy and central and lateral compartment neck dissections (4). Ninety-eight percent also

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received postoperative RAI ablation. At a median follow-up of 31 months (2.6 years; range, 12 to 140 months), 66% had disease-free survival ($N = 76$). Approximately one third of the patients had recurrence of lymph-node metastases (4). In 2010, Tuttle et al. (5) published the Memorial Sloan-Kettering risk-adapted approach for estimating the risk of recurrence in patients risk-stratified by ATA criteria (6). Focusing on the intermediate-risk patients, as in our case, persistent structural disease or recurrence was identified in 21%. If the Tg was <1 ng/ml without structural evidence of disease within 2 years after initial treatment, the recurrence risk dropped to 2%. However, with an incomplete response to initial therapy (suppressed Tg >1 ng/ml and structural disease identification within the first 2 years of follow-up), the likelihood of persistent structural disease or recurrence was 41%. Our patient falls in the latter category, with high risk for additional treatments including repeat surgery, radioiodine treatment, or both. Occasionally, external-beam radiation is used, particularly in older patients for locoregional control. Because morbidity is high for these procedures, the

completeness of initial surgical resection is crucial. In hindsight, perhaps our patient's initial surgery should have included a level II dissection. At least one study has demonstrated that patients with lateral neck lymph-node metastases in levels III and IV have occult disease in level II almost 20% of the time (7).

Conclusions

The patient's clinical data were reviewed by our multidisciplinary institutional Thyroid Cancer Tumor Board. Questions posed to the group included whether the patient would benefit from a second dose of ^{131}I versus continued monitoring with tumor markers and neck ultrasound. Consideration was also given to repeat left central neck dissection if the lesions in the left thyroid bed are confirmed to be cancer; however, the risk of surgical complications is high for a second surgery in this location. While there are no data to suggest that another dose of RAI will improve her overall survival, perhaps it may decrease her risk for further recurrence. The majority of the group recommended a second dose of ^{131}I for ablation. To date, the patient has refused further treatment.

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