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Is Robotic Thyroidectomy Too Expensive for Routine Use in the US?

Cord Sturgeon

Cabot JC, Lee CR, Brunaud L, Kleiman DA, Chung WY, Fahey TJ III, Zarnegar R. Robotic and endoscopic transaxillary thyroidectomies may be cost prohibitive when compared to standard cervical thyroidectomy. Surgery 2012;152:1016-24.

SUMMARY

Background

This study was designed to compare the costs of standard cervical (SC) thyroidectomy, transaxillary endoscopic (TAE) thyroidectomy, and transaxillary robotic (TAR) thyroidectomy in the context of the flat reimbursement schedule for surgical procedures in the United States.

Methods

This was a retrospective review of the costs unique to each of the three procedures. A cost model was created based on data from 140 patients who underwent surgery at either the Yonsei University College of Medicine in Seoul (n = 90) or Weill Cornell Medical Center in New York (n = 50). At Yonsei, 30 patients underwent SC, 30 patients TAE, and 30 patients TAR. All patients had papillary thyroid cancer (PTC). In each of these groups, there were 15 total thyroidectomies and 15 hemithyroidectomies. At Cornell, all 50 patients underwent SC, and 88% had PTC. Cost analysis was performed from the perspective of reimbursement in the United States. Sensitivity analysis was used to evaluate the effects of uncertainty in the model.

Results

Mean total costs for the SC, TAE, and TAR approaches were $9,028, $12,505, and $13,670, respectively. Higher costs of consumables (e.g., robotic instruments, which cost $2,200 each, must be replaced after 10 uses) and longer operating times are the main contributors to the higher costs in the TAE and TAR groups. One-way sensitivity analysis was used to determine the threshold operating time required for cost equivalence. The operating time for TAE would have to

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decrease from 185 to 111 minutes, and the operative time for TAR would have to fall from 166 to 68 minutes to reach cost equivalence with the SC group.

Conclusions

TAE and TAR thyroidectomy were more expensive than SC thyroidectomy, chiefly because of the higher equipment depreciation costs and substantially longer operating times. The flat reimbursement schedule in the United States is a disincentive to implementing the TAE or TAR approaches. It is unlikely that TAE and TAR thyroidectomy will become common in the United States, but they may survive as niche operations.

ANALYSIS AND COMMENTARY

Until recently, there was considerable enthusiasm for robot-assisted remote-access thyroidectomy. Many centers across the United States developed programs for remote-access thyroidectomy and attempted to reproduce the Korean experience with this new technique. However, enthusiasm began to wane in October 2011 when Intuitive Surgical, the manufacturer of the da Vinci surgical robot, indicated that it would stop supporting robotic thyroid surgery. In addition, controversy exists in the literature as to which of the remote-access approaches is superior, and even whether remote-access thyroidectomy is superior to conventional thyroidectomy. Lee and colleagues from Yonsei University have published that the TAR approach is superior to the TAE approach in terms of shorter operating time, greater lymph-node retrieval, and a shorter learning curve (1). In contrast, other authors from Korea have found the TAR approach to be longer, more costly, and associated with more drainage than the TAE approach (2). Another remote-access technique, the robotic facelift thyroidectomy, has also been compared with the TAR and was found to have a shorter operating time and was associated with a greater chance of being managed in the outpatient setting (3).

Few studies, however, have compared robotic with conventional techniques for thyroidectomy. In this model developed by Cabot and colleagues, the remote-access approaches were found to be considerably more costly than the conventional approach. This is not surprising, considering the costs of robotic and laparoscopic devices, consumables unique to the remote-access techniques, and increased operating time. Broome and colleagues came to the same conclusion in a similar study comparing the costs of conventional and robotic thyroidectomy; they found the latter to be approximately twice as costly (4). Considering the fact that hospitals and physicians in the United States are not reimbursed at a higher rate by third-party payers for these procedures, those increased costs of the operation could substantially burden the health care delivery environment in which they are performed. In addition to these cost concerns, other researchers in the United States have identified issues with remote-access thyroidectomy that have led them to abandon the procedure. Landry and colleagues from the MD Anderson Cancer Center found TAR to be associated with a longer operating time, a potential for brachial plexus injury, numbness in the anterior chest wall, and greater blood loss. They called for a prospective study to evaluate cost, quality of life, and patient-reported satisfaction (5). In addition, the senior author of that manuscript has recently publicly declared that they have abandoned robot-assisted transaxillary surgery (6). In her opinion, the cosmetic benefit of robotic transaxillary thyroidectomy does not offset the risks and liability of performing an operation that takes greater resources, might have some additional complications, and is not supported by the robotic equipment manufacturer.

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In Korea, where much of the robotic thyroidectomy literature and enthusiasm originates, reimbursement is apparently twice the standard amount for endoscopic thyroidectomy and four times the standard amount for robotic thyroidectomy (7). In contrast, in the United States there are no such incentives for TAE or TAR; reimbursement is equal for thyroidectomy regardless of surgical approach. The higher cost of the procedure is therefore borne by the health care facility instead of the third-party payer. Furthermore, because of declining reimbursements and shrinking health care budgets, there is currently much interest in the United States and abroad in comparative-effectiveness studies. Increased costs should be associated with a substantial improvement in outcome as compared with the standard approach in order for these remote-access approaches to be considered cost-effective. This study and others appropriately question whether the increased costs of remote-access surgery are warranted, and suggest that these approaches might be cost-prohibitive.

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Could Measuring Single-Nucleotide Polymorphisms (SNPs) Become Useful for Predicting a Relapse of Graves' Disease After Antithyroid Drugs Are Discontinued?

Stephen W. Spaulding

Wang P-W, Chen I-Y, Juo SH, Hsi E, Liu RT, Hsieh CJ. Genotype and phenotype predictors of relapse of Graves' disease after antithyroid drug withdrawal. Eur Thyroid J 2012;1:251-8.

SUMMARY

Background

When antithyroid drug treatment is discontinued, Graves' disease commonly recurs. The risk of relapse may be increased if a patient still has a goiter, has a persistently positive TSH receptor (TSH-R) antibody, and/or is an active smoker. Cytotoxic T-lymphocyte antigen 4 (CTLA4) is a highly polymorphic gene implicated in many autoimmune disorders. Several of its many single-nucleotide polymorphisms (SNPs) have been associated with increased risk for Graves' disease. The authors of the current paper have previously published data on some very similar patients, which indicate that having G/G alleles at rs231775 in CTLA4 is associated with an increased risk of relapse after antithyroid drugs are discontinued. They now have addressed SNPs in some other autoimmune-related genes as well, plus clinical and lab factors thought to have predictive value, to see whether they improved the accuracy of predicting relapse.

Methods

From 2001 to 2007, a total of 262 patients with Graves' disease were treated with antithyroid drugs alone. At diagnosis, all had a high serum T_4 and/or T_3 plus a suppressed TSH, diffuse uptake of 99mTcO4 or ^{131}I, and either a positive TBII assay ("TR-AB" CISbio, which measures whether a patient's IgG will block the binding of 125I-labeled porcine TSH to solubilized porcine TSH receptors bound on plastic tubes) or positive antimicrosomal antibodies. The initial daily dose of MMI (140 patients, generally given 30 mg) or PTU (79 patients, generally given 300 mg) was reduced as serum T_4 and T_3 normalized, generally reaching a low maintenance dose by 4 months. An additional group of 43 patients was given "block-and-replace" treatment with MMI (5 to 10 mg) plus 50 µg of L-T_4 to maintain euthyroidism. Patients who became euthyroid smoothly usually stopped antithyroid drugs by 12 months. (An unknown number whose antithyroid drug dose could not be reduced or who had persistently large goiters received antithyroid drugs for 2 to 3 years). After drugs were stopped, patients were followed every 3 months for the first year and every 6 months thereafter. The patients were divided into three groups. Those who had a relapse within 9 months, deemed "early relapses," had been treated for a mean of 30 months. Those who had a relapse between 10 and 36 months, deemed "late relapses," had been treated for a mean of 21 months. Those who had not had a relapse, deemed "long-term remissions," also had been treated for a mean of 21 months (some subsequently did have a relapse). At the end of follow-up, SNPs (three in CTLA-4, eight in CD28, six in ICOS and six in CD40) were assessed; current smoking (38 of 39 smokers were men), goiter size, serum T_4, T_3, and TBII levels, antithyroid regimen, and duration were also analyzed. Continuous data were analyzed by one-way ANOVA, categorical data by chi-square or Fisher's exact test, and the strength of associations by Cox proportional-hazards analysis; the P value was adjusted for multiple comparisons.

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Results

Only four SNPs were significantly associated with an increased risk of relapse at both 9 and 36 months (G/G in CTLA-4, plus three SNPs in CD40). Adding up the number of the risk alleles improved the prediction of relapse, although the combined risk alleles didn't reach the adjusted odds ratio of 2.2 or 3.1 the authors reported when using only G/G at rs231775 in their previous studies. Multivariate analysis showed that the hazard ratio (HR) for relapse was increased by a persistently high TRAb at the end of treatment (HR,1.64; 95% confidence interval (CI),1.15 to 2.35 based on only 216 of the 262 patients), by smoking (HR, 1.60; 95% CI 1.05 to 2.42), and by persistence of a large goiter (HR, 1.30; 95% CI,1.05 to 1.61 based on only 248 patients), whereas the genotyping, based on the total number of risk alleles, had an HR of 1.30 (95% CI, 1.09 to 1.56). Furthermore, 5 of the 10 patients who had no risk alleles still had a relapse. In patients 40 years of age or older, the only independent predictor was persistent goiter (HR, 1.56; 95% CI, 1.09 to 2.22), whereas in those younger than 40, a persistently high TRAb (HR, 1.93; 95% CI, 1.22 to 3.06) and the number of risk alleles (HR, 1.24; 95% CI, 1.01 to 1.53) were the only independent risk factors.

Conclusions

The best predictor of relapse after stopping antithyroid drug treatment was a persistently positive TRAb, followed in order by current smoking, a persistent goiter, and the number of risk SNPs in CLTA4 and CD40. However—perhaps because the number of patients was too small—for those younger than 40 years of age, a persistent TRAb and/or the number of risk SNPs were the only independent predictors, whereas for those 40 or older, a persistent goiter was the only independent predictor.

ANALYSIS AND COMMENTARY

If an individual has G/G at rs231775 in CTLA4, an increased risk of Graves' disease has now been confirmed in a variety of populations. Interestingly, G/G is three times more common in Asians in general, as compared with Caucasians. It will take years to sort out how SNPs present in hundreds of genes involved in immunity interact in different autoimmune conditions. Just considering CTLA4, the relative importance of different SNPs in susceptibility to Graves' disease varies substantially by geographic region (1). G/G alleles at rs231775 were first reported to be more common in Japanese patients with Graves' disease whose TSHR stimulating and/or blocking activities did not disappear within 5 years of treatment, as compared with patients in whom those activities had disappeared (2). However, this observation was not associated with risk of relapse (2). Some have reported that G/G at rs231775 is not useful for predicting remission versus relapse within 1 year after discontinuing antithyroid drugs (3). The definition of "relapse," the specific details of antithyroid drug therapies used, and the duration of follow-up doubtless influence the relative importance of a candidate SNP for predicting relapse (indeed, the authors themselves disregarded SNPs that only predicted a relapse within 9 months or within 3 years).

The current study included "block-and-replace" (methimazole + levothyroxine treated) patients. This approach may be useful for patients in whom the balance of blocking versus stimulating TSHR antibody activity is shifting. It therefore would have been interesting to know the results of a TSHR antibody assay that only detected stimulating activity, in addition to the "TS-AB" assay used in the current paper, which measured both TSHR blocking and stimulating antibodies.

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Although the importance of a given SNP can vary substantially based on the region and the genetic makeup of a given population, SNPs surely will be found that either consistently increase the risk of relapse, or else actually protect a patient from relapse. Eventually, such testing may be available to doctors before they need to decide for or against starting a course of antithyroid drugs, but it does not seem likely that a few magic SNPs will turn out to be the most important predictors of risk.

Meanwhile, for the practicing thyroidologist, the most interesting idea raised by this paper is a possible therapeutic intervention. Getting a patient to stop smoking is clearly important for reducing the risk of orbitopathy; maybe it reduces the risk of relapse after stopping antithyroid drugs as well.

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Are Anti-CD20 Antibodies Useful in the Management of Severe Graves' Orbitopathy?

Albert G. Burger

Mitchell AL, Gan EH, Morris M, Johnson K, Neoh C, Dickinson AJ, Perros P, Pearce SH. 2013. The effect of B cell depletion therapy on anti-TSH receptor antibodies and clinical outcome in glucocorticoid refractory Graves' orbitopathy. Clin Endocrinol. January 16, 2013 [Epub ahead of print].

SUMMARY

Background

Mild orbitopathy is seen in 25% to 50% of patients with Graves' disease; the orbitopathy mostly evolves favorably over a 2-year period. One rare but severe complication is optic-nerve involvement (dysthyroid optic neuropathy). In this situation, emergency interventions are necessary. The first choice is large doses of steroids, preferably intravenous methylprednisolone. This procedure induces a marked reduction of the lymphocyte population, particularly B lymphocytes. An even more efficient reduction of B lymphocytes may be achieved by specific B-cell antibodies. Rituximab (RTX) is an antibody against the cell-surface antigen CD20 and is capable of inducing a complete depletion of B lymphocytes. This treatment was first tested in Graves' orbitopathy in 2006, but the results were equivocal (1, 2). Several studies followed, since RTX could conceivably represent a valuable alternative to the orbital decompression that may be necessary in some cases after failure of intravenous methylprednisolone. The results provided positive results concerning the clinical activity score (CAS) (3), but none of the studies included an adequate control group.

Methods

Nine patients (one man, eight women; age range, 37 to 87 years) were treated. Four patients had sight-threatening optic-nerve involvement (No SPECS score, 6) (4), and the others had moderate to severe disease but did not respond to methylprednisolone treatment. Hyperthyroidism was under control at the time of treatment; the patients were either euthyroid or had hypothyroidism. The patients had received IV methylprednisolone at a high cumulative dose of 3 to 5 g over a median period of three months before treatment with RTX.

RTX treatment was given in combination with 500 mg of IV methylprednisolone and 10 mg of chlorpheniramine plus aspirin. This treatment was repeated at 2-week intervals. The cumulative doses of RTX were 1 g (2 x 0.5 g) in six cases and 2 g (2 x 1 g) in three cases. B-cell depletion, defined as <1 per 10,000 total lymphocytes, was achieved in all except one patient.

Results

No severe adverse effects were reported. Nine months after treatment, the number of B lymphocytes had returned to normal. The treatment had no effect on thyroid function or on peripheral thyroid hormone parameters. During the 8 months following treatment, the level of TSH-receptor binding inhibitory immunoglobulin (TBII) was markedly reduced in all cases, but the improvement of the CAS did not parallel the TBII pattern. Nevertheless, the CAS improved in all patients. The authors do not give detailed information as to the effect on orbital neuropathy. In one patient emergency orbital decompression was necessary.

Conclusions

RTX following methylprednisolone treatment was most successful in decreasing the TBII titer significantly in all patients. The CAS improved moderately, but the effects on optic neuropathy are not specified. Thyroid function was not affected by the treatment.

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ANALYSIS AND COMMENTARY

The present study differs from earlier ones, since RTX was given together with methylprednisolone. The positive findings of the study are the reduction in the CAS score and the good tolerance of RTX treatment. We know, however, how variable the evolution of Graves' orbitopathy can be and agree with the authors that only prospective multicenter studies can definitely prove the effectiveness of the proposed treatment.

The striking decrease in TBII is remarkable and compatible with the depletion of B lymphocytes. The article does not describe in detail the thyroid status of the patients; for example, we are not informed whether they underwent thyroidectomy or had received radioactive iodine, which would explain the absence of any change of thyroid function following RTX treatment There is also no information on anti-TPO and antithyroglobulin antibodies.

It is therefore too early to recommend the described treatment protocol routinely in severe Graves' orbitopathy. Rather, it should be further evaluated in specialized centers and in a prospective way. Thyroidologists are advised to collaborate with eye surgeons experienced in the field of Graves' disease. In some cases, surgical decompression may be the only means to bring relief to the optic nerve.

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Lower Cord Blood Total T_4 is Associated With Higher Child Neurodevelopmental Scores at Age 5.5 Years

Elizabeth N. Pearce

Williams FL, Watson J, Ogston SA, Visser TJ, Hume R, Willatts P. Maternal and Umbilical Cord Levels of T_4, FT_4, TSH, TPOAb, and TgAb in Term Infants and Neurodevelopmental Outcome at 5.5 Years. J Clin Endocrinol Metab 2013;98:829-38. Epub January 15, 2013.

SUMMARY

Background

Most (1-3), but not all (4) previous observational studies have noted associations between mild maternal thyroid hypofunction and decreased child intelligence. The goal of this study was to determine associations between maternal and cord-blood thyroid function and associations between maternal and neonatal thyroid function and the neurodevelopment of offspring.

Methods

This was a prospective observational cohort study that included 97 women and their full-term infants. Subjects were drawn from the larger Millennium Study, which enrolled 666 preterm and 135 full-term Scottish infants between 1998 and 2001. Women and infants with known thyroid disease were excluded. Cord blood T_4, FT_4, and thyroglobulin (Tg), Tg antibody, and thyroperoxidase (TPO) antibody levels were measured. Maternal serum TSH, T_4, FT_4, TPO antibody, and Tg antibody were measured at 10 weeks of gestation, at 34 weeks of gestation, and at delivery. Neurodevelopment was assessed in all children at 5.5 years of age using McCarthy scales, which include Verbal, Perceptual Performance, Quantitative, Memory, Motor, and General Cognitive Index scales. Unadjusted associations were assessed using Pearson correlation coefficients. Univariate general linear models were used to assess associations adjusted for maternal verbal IQ, age, and smoking history, maternal depression, child's birth order, duration of breast-feeding, infant sex, gestational age at delivery, multiple gestation, cord-blood antithyroid antibody positivity, and significant life events (moving, death of close family member).

Results

Fifteen percent of women were TPO-antibody–positive and 12% were Tg-antibody–positive. Four percent of women had serum TSH >2.5 mIU/L at 10 weeks of gestation and 14% of the women had serum TSH levels >3 mIU/L at delivery. There were no associations between maternal TSH and cord TSH or FT_4. Maternal and cord TSH, FT_4, and TPO antibodies were not associated with children's developmental scores. Positive maternal Tg antibodies were associated with decreased scores on child Perceptual Performance and Motor scales. Positive cord-blood Tg antibodies were associated with lower Perceptual Performance scores in unadjusted, but not adjusted, analyses. In unadjusted and adjusted analyses, children with cord blood FT_4 in the lowest decile had higher scores on the General Cognitive Index, Quantitative, Verbal, and Memory scales. Sensitivity analyses demonstrated that there was a U-shaped relationship between cord-blood total T_4 levels and Memory and Verbal developmental subscales.

Conclusions

This study demonstrates that lower cord-blood total T_4 levels were associated with higher scores on several child neurodevelopmental scales.

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ANALYSIS AND COMMENTARY

The results of this study are surprising, and diametrically opposite to the authors' original hypothesis. The data are discordant with previous studies, which found associations between mild maternal hypothyroidism or hypothyroxinemia and lower child IQ (1-3), but similar to the previous study by Oken and colleagues (4), which also demonstrated paradoxically higher developmental scores in children with low neonatal total T_4 . The reasons for the observed inverse association between neonatal total T_4 and neurodevelopmental measures are unclear. The number of infants with low T_4 concentrations was relatively small in both studies that have demonstrated this finding, and it may simply be an artifact due to small sample size. Although their analyses were adjusted for gestational age at delivery, Williams and colleagues speculate that this finding may be due to higher T_4 levels in infants born at 41 to 42 weeks of gestation than in those born at 37 to 40 weeks and that perhaps overly long gestation is related to poorer developmental outcomes. They suggest that further studies are needed to determine relationships between gestational age, neonatal T_4 levels, and the postnatal T_4 surge.

Strengths of this study include its prospective design and adjustments for many possible confounders. Limitations include the loss to follow-up of 35 of 135 full-term infants, the lack of measurements of maternal urinary iodine concentration, and the small sample size (only 10 newborns were in the low total T_4 group). Further research in larger cohorts is needed to better understand the complex relationships between maternal and neonatal thyroid function and subsequent child development.

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Recurrence of Papillary Thyroid Cancer Was Found in 1.4% of Those Without Persistent Disease Within 8 Years

Jerome M. Hershman

Durante C, Montesano T, Torlontano M, Attard M, Monzani F, Tumino S, Costante G, Meringolo D, Bruno R, Trulli F, Massa M, Maniglia A, D'Apollo R, Giacomelli L, Ronga G, Filetti S; on behalf of the PTC Study Group. Papillary thyroid cancer: time course of recurrences during postsurgery surveillance. J Clin Endocrinol Metab 2013;98:636-42. Epub January 4, 2013.

SUMMARY

Background

Because some patients with papillary thyroid cancer (PTC) have late recurrences, these patients are followed for many years. Currently, most patients with PTC have small tumors and a very good prognosis. The tools for following these patients have improved in the past two decades, so recurrences are detected more easily. The question of how long and how frequently patients with PTC should be followed has not been addressed. The present study was conducted to identify times to recurrence of PTC and to define the rates of recurrences in order to provide data to improve the cost-effectiveness of postoperative surveillance.

Methods

This is a retrospective study of consecutive patients with PTC diagnosed since January 1990 in eight Italian referral centers. Inclusion criteria were negative antithyroglobulin levels and follow-up for at least 3 years before January 31, 2012. All patients had total thyroidectomy. The use of cervical-lymph-node dissection and radioiodine ablation (RAI) was based on institutional guidelines. Patients had follow-up within the first year and then yearly thereafter that included neck ultrasound and serum Tg, basal and stimulated. Suspicious lymph nodes were biopsied, and appropriate imaging studies were performed to identify structural disease.

Results

The study population consisted of 1020 patients, 80% of whom were female. The median tumor size was 15 mm; tumors were multifocal in 36% and bi-lateral in 25%. Extrathyroidal extension was found in 245 patients, positive lymph nodes in 255, and distant metastases in 3.2%; 82% were classified as AJCC stages I or II. The ATA risk level (1) based on the surgical findings and pathology was low in 61.3%, intermediate in 35.5%, and high in 3.2%. Radioiodine remnant ablation was performed in 88% of the patients.

In the first postoperative follow-up, persistent disease was found in 72 (7.2%), and 57 of them had positive serum Tg. Those with persistent disease comprised 16 (2.5%) of the 625 with low risk, 41 (11.3%) of the 362 with intermediate risk, and 23 (69.7%) of the 33 with high risk. At the end of the follow-up (5 to 20 years; median, 10 years), 20% of the group still had imaging-documented disease and 80% were disease-free. Imaging was negative and Tg positive in 18.5% who received RAI and in 15.2% of those who did not.

Of the 948 patients considered to be disease-free based on initial postoperative imaging, 185 (15%) had positive Tg. Disease recurred in only 1 of the 185 patients with detectable Tg and no structural disease. It recurred in 13 of the 948 (1.4%) within 8 years, half of them within the first 3 years; 5 were low-risk and 8 intermediate-risk patients. Only 6 of the 13 had positive Tg at recurrence.

Conclusions

Recurrence of PTC is uncommon but may occur within 8 years of follow-up in 1.3% of patients at intermediate and low risk.

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ANALYSIS AND COMMENTARY

This paper provides important data regarding long-term follow-up of patients with PTC, but it does not provide a definitive rationale for optimal management of these patients with regard to length of follow-up before saying that recurrent disease is very unlikely. Persistent disease in 2.5% and recurrence in 0.8% (5 of 625) of the low-risk group are cause for concern. The authors contrast their findings with the 1990 findings of Mazzaferri and Jhiang, who found a recurrence rate of 20%, with 19% detected more than 10 years after surgery (2).

Obviously, high-risk patients require long-term, perhaps 20 years, of careful follow-up. Those with low and intermediate risk should probably be followed for 10 years (at least 8, based on the data of this study) before being optimistic about cure, a term used very cautiously, even in patients with thyroid cancer.

Surprisingly, the authors do not comment on what happened to the185 patients with positive Tg at the initial (probably 1 year) follow-up. These patients are certainly a cause for concern and continued follow-up until the Tg declines and/or all imaging is repeatedly negative.

It is interesting that 88% received RAI. With less use of RAI in low-risk patients with PTC, as currently advocated, there may be more cause for concern. The serum Tg in patients who do not undergo ablation will then be detectable often, making this measurement useless as a biomarker for recurrence. The authors point out that 92% of those treated with RAI had negative imaging findings, as did 98% of those not given RAI; the small difference may be attributed to not using RAI in patients with a very good prognosis.

The role of TSH suppression with levothyroxine was not addressed in this report. Because of late recurrences, I am reluctant to allow the TSH to be in the normal range until there is good evidence of absence of disease.

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Clin Thyroidol 2013;25:62–63.

Clinical THYROIDOLOGY
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Life Expectancy Is Not Reduced in Patients With Differentiated Thyroid Cancer Who Are Younger Than Age 45

Jerome M. Hershman

Verburg FA, Mäder U, Tanase K, Thies ED, Diessl S, Buck AK, Luster M, Reiners C. Life expectancy is reduced in differentiated thyroid cancer patients >= 45 years old with extensive local tumor invasion, lateral lymph node, or distant metastases at diagnosis and normal in all other DTC patients. J Clin Endocrinol Metab 2013;98:172-80. Epub November 12, 2012 Nov 12.doi: 10.1210/jc.2012-2458.

SUMMARY

Background

Virtually all patients with cancer are concerned about their life expectancy. Although patients with thyroid cancer usually have normal life expectancy when treated appropriately, there are many whose life span is limited by the thyroid cancer. This paper is a review of a German database with careful analysis of clinical factors and life expectancy.

Methods

The Wurzburg Thyroid Cancer Database was established in 1980. Using this database, the authors analyzed clinical features and survival of 2011 patients with differentiated thyroid cancer (DTC) who had been treated and followed from January 1980 until December 2011. Patients were treated by total thyroidectomy with subsequent ^{131}I ablation, except for 391 who had isolated papillary microcarcinoma and were treated with hemithyroidectomy. During follow-up, patients underwent neck ultrasonography, radioiodine scans, and thyroglobulin measurements at 6-month intervals for 5 years and annually thereafter. Persistent disease or recurrence was generally treated with ^{131}I. Patients were classified as having papillary, follicular, or Hürthle-cell cancer. Those with poorly differentiated or insular carcinoma were not included. Survival rates were calculated by the Kaplan–Meier method and compared with standard mortality rates of the general German population adjusted for birth year and sex.

Results

The median age at diagnosis was 47.6 years and the median follow-up was 7.1 years. During the follow-up, 264 patients (13.1%) died. Overall 14% of the patients had reduced life expectancy. There was no reduction in life expectancy for those younger than age 45, but it was reduced in those older than age 45, especially in those over age 60. There was a statistically significant reduction in relative survival in patients with follicular thyroid carcinoma, those with extensive extrathyroidal invasion, those with lateral-compartment lymph-node metastases (but not central-compartment metastases), and those with distant metastases. The patients' sex had no influence on life expectancy.

Conclusions

Life expectancy is not significantly reduced in 86% of patients with DTC. Only patients who were at least 45 years old and had extensive local invasion, lateral lymph-node metastases, or distant metastases at diagnosis showed a clearly lower life expectancy.

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ANALYSIS AND COMMENTARY

The current report is the largest study of life expectancy in patients with DTC. It confirms and extends the findings in a similar study of 504 patients with DTC (1). Only older patients with risk factors of extrathyroidal extension, lateral lymph nodes, and distant metastases have shortened life expectancy. These patients are classified as stage 4 by the TNM system. However, there is concern that the TNM system inappropriately reduces the risk of patients younger than age 45 who have these more aggressive features because they are classified as stage 2. An analysis of the SEER database showed that mortality of stage 2 patients younger than age 45 was 11-fold greater than that for stage 1 patients (2).

I found it interesting that there was a lack of effect of sex because it is commonly stated that men with thyroid cancer have a worse prognosis than women.

There are several caveats to this study. Wurtzburg is in an area of iodine deficiency. The authors state that more than 50% of the DTC cases were discovered incidentally as a result of surgery for large goiters. This is certainly not the case in the United States and other areas without iodine deficiency. Another issue is that a mean follow-up of only 7.1 years may be too short to detect mortality. Also, the authors excluded from their analysis patients with more aggressive forms of DTC, such as insular carcinoma. In addition, a single institution study may be too narrow for a definitive study of life expectancy.

The authors note that, despite the liberal use of ^{131}I ablation for low-risk patients, there was no excess mortality due to secondary malignancies associated with the use of ^{131}I therapy in contrast with other studies (3,4).

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Clin Thyroidol 2013;25:64–65.

Clinical THYROIDOLOGY
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Are We Missing Salivary-Gland Dysfunction Years After a Single ^{131}I Treatment for Thyroid Cancer?

Albert G. Burger

Jeong SY, Kim HW, Lee SW, Ahn BC, Lee J. Salivary gland function five years after a radioiodine ablation in patients with differentiated thyroid cancer: direct comparison of pre and post-ablation scintigraphies and their relation to xerostomia symptoms. Thyroid. November 15, 2012 [Epub ahead of print].

SUMMARY

Background

Chronic sialadenitis is a frequent complication of radioactive iodine therapy (RAI), even after a single RAI application (1). Some patients report some minor transient symptoms during the first few weeks following treatment. Today, salivary-gland function can be assessed by 99mTc pertechnate scintigraphy (SGS). Its diagnostic yield can be improved if it is performed before and after ^{131}I treatment, thus reducing interindividual variability. Information can be obtained by both 99mTc pertechnate uptake as well as by its release pattern from the salivary glands.

Methods

In this study, 214 subjects were studied before and approximately 5 years after a single ^{131}I treatment. Patients with head surgery or external radiation were excluded. The uptake of 99mTc and the ejection fraction (EF) of the tracer were evaluated. For measuring EF, lemon juice was sprayed in the oral cavity and the decrease of radioactivity was followed over 10 minutes. Each salivary gland was scored as follows: 0, normal uptake and secretion; 1, slightly decreased uptake; 2, moderately decreased uptake but still above background; and 3, uptake equal to background. EF was expressed as a percentage of the activity before administering the lemon juice. The RAI treatment was done in hypothyroidism, with doses ranging between 3.7 and 5.55 GBq (100 to 150 mCi). During the first 2 days, the patients were instructed to suck sour candies whenever awake and to drink at least 2 L of liquid. In case of salivary-gland swelling, nonsteroidal antiinflammatory medications were given.

Results

Papillary thyroid cancer was present in 96% of the mainly female patients. In the majority of patients, the results for all four salivary glands were available. After 5 years, 35 patients (16%) reported a dry mouth. Symptoms of a dry mouth were more frequent with higher RAI doses (5.55 GBq, 18%; 3.7 GBq, 7.8%). The SGS before RAI was normal in 88% of 852 salivary glands. In the remaining glands, the uptake was slightly reduced but never undetectable (score, 3). Five years after ^{131}I treatment salivary-gland uptake was normal in 73.8% of patients (score, 0), slightly reduced in 7.9%, and moderately reduced in 6.7% of patients; no uptake was found in 11.6% (score, 3). A single salivary gland was affected in 78.6%, two glands in 49.5%, three glands in 6.9% and four glands in 8% of patients.

The EF after lemon juice was affected to a degree comparable to that of the uptake.

Subjective symptoms (dry mouth) were rarely reported in the presence of a minor decrease in SGS (score, 1). Clinical symptoms were mostly correlated with moderate to severe dysfunction of more than one salivary gland. Symptoms were more frequently reported with submandibular-gland dysfunction than with parotid-gland dysfunction.

Conclusions

In patients who underwent ^{131}I treatment of papillary cancer, salivary-gland scintigraphy was performed

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a few days before radioactive iodine treatment and approximately 5 years later. In most cases, the first scintigraphy was performed after withdrawal of thyroid hormone treatment, with a serum TSH of >30 mU/L. Patients received relatively large doses of ^{131}I—between 3.7 and 5.55 GBq of ^{131}I. Five years after a single radioactive iodine treatment, up to 20% of all patients had salivary-gland dysfunction, but only 16% reported a dry mouth. In the majority of cases, only one to two salivary glands were affected, perhaps explaining the scarcity of symptoms. No major morphologic alterations of the salivary glands, such as constrictions of the secretory channels, were observed.

ANALYSIS AND COMMENTARY

This large study certainly provides worthwhile information for endocrinologists who are treating patients with radioactive iodine. The currently recommended doses of ^{131}I are 1.1 to 1.85 GBq (30 to 50 mCi), which is markedly below the dose used in this study. Since the authors observed salivary-gland dysfunction more frequently in patients treated with the highest dose of 5.55 GBq, one is inclined to conclude that these complications will be rare, albeit not absent, with the currently recommended regimen.

No information was provided on how to improve salivary-gland dysfunction. The authors mention one study claiming improvement, but they rightly suggest that this should be tested on a larger scale (2).

The salivary glands are not the only tissue equipped with a mechanism for actively transporting iodide. For instance, the gastric and colonic mucosa avidly transport iodide and the follicular cells of the ovaries have the same capacity . Several relevant publications on this subject are available, but to my knowledge, little information obtained with modern technology, as used here, has yet been reported. The possibility of damage in tissues others than the thyroid after ^{131}I therapy, especially secondary malignancies, remains a major concern (3-5).

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Clin Thyroidol 2013;25:66–67.

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Socioeconomic Status and Access to Care Do Not Account for the Rising Incidence of Thyroid Cancer

Jerome M. Hershman

Li N, Du XL, Reitzel LR, Xu L, Sturgis EM. Impact of enhanced detection on the increase in thyroid cancer incidence in the United States: review of incidence trends by socioeconomic status within the Surveillance, Epidemiology, and End Results registry, 1980-2008. Thyroid 2013;23:103-10. doi: 10.1089/thy.2012.0392. PMID: 23043274.

SUMMARY

Background

The incidence of thyroid cancer has been increasing during the past three decades. Some attribute this to increased case finding through the widespread use of thyroid ultrasound and FNA of small thyroid nodules (1). However, there has also been an increase of thyroid cancers larger than 4 cm that should be palpable and easily discovered clinically (2). The debate continues as to whether the increased incidence of thyroid cancer is a true increase or due entirely to enhanced detection. Access to health care is likely associated with socioeconomic status (SES). To explore the contribution of enhanced detection to the recent increases in incidence of thyroid cancer, the authors compared thyroid cancer incidence trends between low- and high-SES counties in the United States during the past three decades.

Methods

The authors linked the U.S. Surveillance, Epidemiology, and End Results 9 cancer database (SEER 9) with the 2000 U.S. Census database that contained county-level SES data. The geographic areas were adjusted by a median household income index. To adjust for accessibility to health care, counties were divided into two categories: adjacent to a metropolitan area or not adjacent to a metropolitan area. Then counties were divided into quartiles based on economic data. The investigators created a composite index of county SES that included three indicators: cost-of-living-adjusted median household income, percentage of population with at least a high school education, and percentage of population with health insurance.

Results

The SEER 9 database contained 49,819 patients with thyroid cancer during 1980–2008. The distribution of SES indicators suggested that patients with thyroid cancer in the SEER 9 registries tended to reside in the areas that have higher SES than the average U.S. population. Among all the patients with thyroid cancer, 95% were from counties that are in or adjacent to metropolitan areas. In counties with a high composite SES score, the increase in incidence was moderate during the 1980s and 1990s but more pronounced after 1996. In contrast, in counties with a low composite SES score, the incidence increased moderately and steadily over the entire study period. The incidence of thyroid cancer of all sizes increased (1.1 to 2 cm, 2 to 4 cm, and > 4 cm) in both the lowest SES quartile and the high combined upper three quartiles during the time period 1980–2010. The incidence increases were similar in metropolitan counties and counties not adjacent to metropolitan areas.

Conclusions

The data show that socioeconomic factors and access to medical care do not explain the rising incidence of thyroid cancer. Therefore, it is likely that there is a true increase in thyroid cancer incidence.

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ANALYSIS AND COMMENTARY

This study is a sophisticated analysis of the role of socioeconomic status and access to care as factors that might explain the increased incidence of thyroid cancer in the past 30 years. Because there were no significant differences in rising incidence between those in the lowest SES quartile and the combination of the other three quartiles and because there were no differences between regions with different access to care, the authors conclude that SES and access to care do not explain the rising incidence of thyroid cancer. Therefore, it is likely that there is a real increase in the incidence of thyroid cancer.

A limitation of the study is that the SEER database does not contain economic data, so the data used was on a county basis rather than on an individual basis. In addition, only 4% of the patients were in the lowest SES quartile; the SEER registries tended to be in areas with higher SES than the average U.S. population. Nevertheless, the study provides reliable data showing that the rising incidence of thyroid cancer cannot easily be explained on the basis of ascertainment bias.

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NRAS Mutation in a FLUS FNA Mandates Thyroidectomy

Wendy Sacks

CASE PRESENTATION

A 40-year-old woman was found to have a thyroid nodule on examination by her internist. She presented to our center for further evaluation. A 2-cm nodule was palpated, and ultrasound revealed a solitary left lobe nodule measuring 1.2 by 1.83 by 2.5 cm. Ultrasound features suspicious for malignancy, such as microcalcifications, hypoechogenicity, and intranodular vascularity, were absent; a central area of hypoechogenicity was noted (Figure 1). Cytology from an ultrasound-guided fine-needle aspiration (FNA) biopsy suggested a hyperplastic (adenomatoid) nodule, but the SurePath slide showed high cellularity; therefore, the nodule was considered a follicular lesion of undetermined significance (FLUS) (Figure 2). SurePath is a liquid-based preparation in which the cell sediment is emulsified in suspension, the cells separated and laid out on a slide (one per nodule), while red blood cells are lysed to decrease their obscuring effect. Several studies have reported the efficacy of the SurePath preparation (1). A repeat biopsy showed benign cytology with a NRAS mutation by molecular testing.

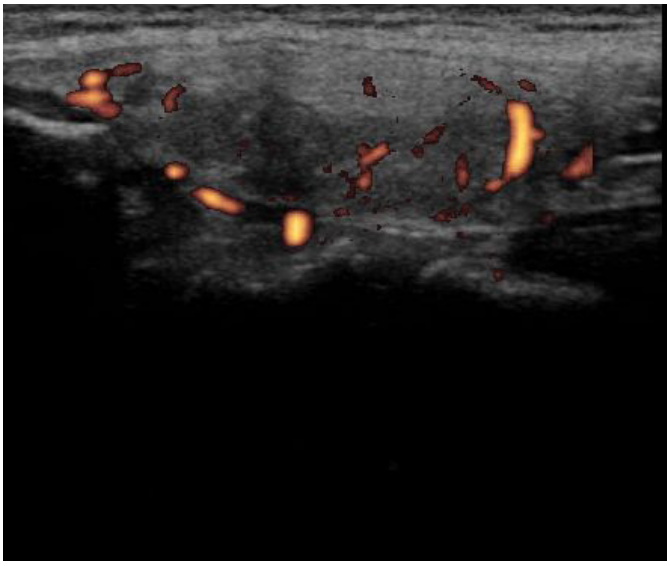

Figure 1. Ultrasound of 2.2cm left thyroid nodule, sagittal view. Features include a central hypoechogenic area within an isoechoic nodule and peripheral vascularity.

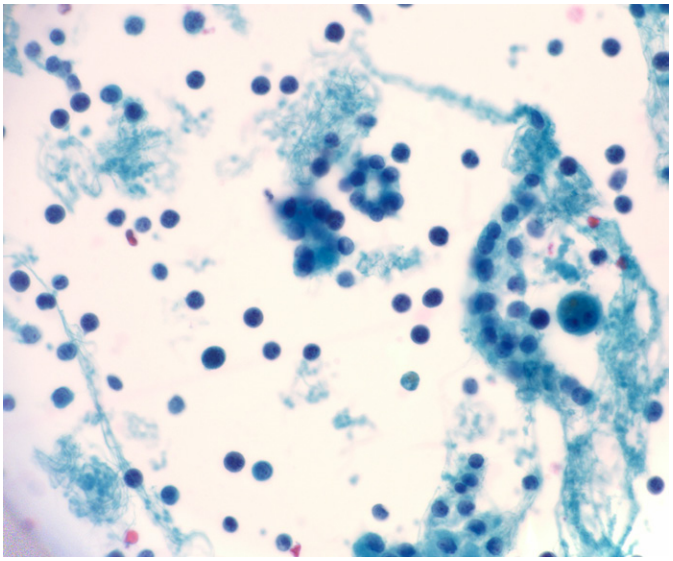

Figure 2. Cytopathology from thyroid nodule fine needle aspiration demonstrating isolated microfollicles in an otherwise bland appearing specimen.

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ANALYSIS AND COMMENTARY

With the availability of molecular testing, we see more cases similar to this patient. FNA cytology is still the most reliable method of diagnosing a thyroid nodule; however, approximately 25% of nodules fall in the indeterminate category, in which the risk for malignancy for the FLUS/AUS (atypia of undetermined significance) category ranges between 5 and 15% (2). The clinical treatment of these patients can be challenging, and many are sent for surgery even though their tumor is likely to be benign. The ability to test for molecular mutations in FNA specimens provides further information with which to refine our clinical decision-making. With specific reference to the patient presented above, (i) what is her risk for malignancy, (ii) should one recommend conservative management using close monitoring with serial ultrasounds, or (iii) is surgery indicated, and if so, lobectomy or total thyroidectomy?

Nikiforov and colleagues at the University of Pittsburgh evaluated both the incidence and the risk of malignancy in nodules with FLUS/AUS FNA cytology by studying oncogenic mutations (3). Of the 218 patients (247 FNA specimens) with a surgical histologic diagnosis, 32 nodules (35 FNA specimens) were malignant. The molecular panel performed on the FNA specimens demonstrated 21 mutations in 35 malignancies, including 16 RAS (16 follicular variant PTC), 5 BRAF (4 PTC, 1 follicular variant PTC) and 1 PAX8/PPARγ (1 follicular variant PTC) mutation. Three of the nodules with a RAS mutation were benign follicular adenomas on surgical histology. Thus, the positive predictive value (PPV) for malignancy in a FLUS/AUS lesion with any molecular mutation (RAS, BRAF, PAX8/PPARγ) is 88% with 63% sensitivity.

A major concern with the presence of a RAS mutation in a benign nodule is its potential for malignant transformation and dedifferentiation, since it is a potent oncogene (4, 5). The presence of the BRAF V600E mutation confers a 100% PPV for thyroid malignancy, so total thyroidectomy is the appropriate treatment even if the nodule has an indeterminate cytology. Except for BRAF V600E, the other molecular markers in the panel, or gene array studies, do not provide such certainty for indeterminate nodules. The American Thyroid Association guidelines recommend either a hemithyroidectomy or total thyroidectomy as the initial surgical approach for solitary indeterminate nodules (6).

Case Management

The initial cytology in this case conferred a 5% to 15% risk for malignancy, while the second sampling was benign. However, with the presence of an NRAS mutation, we felt the risk for malignancy increased significantly, up to 88% based on the Pittsburgh data. Therefore, we recommended that she have surgery. She opted for a hemithyroidectomy, with the understanding that a completion surgery may be necessary if the pathology proved malignant. Indeed, the final pathology demonstrated a 1.4-cm follicular variant of papillary thyroid carcinoma within a 2.2-cm nodule. For ease of future monitoring, she had a completion thyroidectomy. Whether to do a completion surgery could be debated in this case based on the small size of the tumor and the lack of lymph-node involvement, extrathyroidal extension, and lymphovascular invasion.

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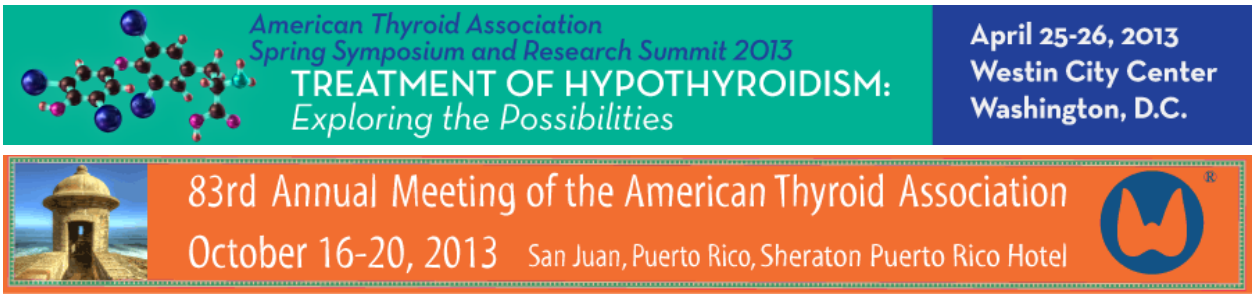

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Call for Nominations for 2013
American Thyroid Association
Board of Directors

In accordance with the Bylaws of the American Thyroid Association, the Nominating Committee is soliciting nominations from the membership for candidates for the offices of President and Directors (2) to serve on the ATA Board of Directors. Candidates will be selected by the Nominating Committee and submitted to the ATA Board for final approval.

A ballot will be sent to the membership electronically in August 2013. Newly elected Board members will be announced at the Annual Business Meeting on Thursday, October 17, 2013.

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The **President** will serve a one-year term as President-Elect (2013-2014), followed by one year as President (2014-2015), and another year as a Past-President (2015-2016). See job description in Policies and Procedures under "Members Only" at www.thyroid.org. *Election of the President will be competitive.*

Nominee: _____

ATA Board Director
Two **Directors** will each serve a four-year term (2013-2017). See job description in Policies and Procedures under "Members Only" at www.thyroid.org. *Election of directors will be competitive.*

Nominee: _____

Nominee: _____

Nominated by (please print or type): _____

Signature: Date:

All nominations must be submitted to the Executive Director, Bobbi Smith, by letter, fax, or e-mail bsmith@thyroid.org by March 31, 2013.

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Call for Nominations for the 2013 Awards
American Thyroid Association

▪ Distinguished Service Award ▪ Sidney H. Ingbar Distinguished Lectureship ▪
▪ Van Meter Lecture ▪ Paul Starr Lecture •
• Lewis E. Braverman Lectureship • John B. Stanbury Thyroid Pathophysiology Medal ▪

The Van Meter Award Lecture established in 1930, recognizes outstanding contributions to research on the thyroid gland or related subjects. The award is given each year to an investigator who is not older than the age of 45 in the year of the award. The Van Meter award winner is kept secret until the time of the award lecture during the annual meeting. An honorarium and expenses are awarded to the Van Meter recipient. This award receives support from Mary Ann Liebert, Inc., Publishers.

Nominee: Date of Birth

The Sidney H. Ingbar Distinguished Lectureship Award, endowed by contributions to honor the memory of Sidney H. Ingbar, recognizes outstanding academic achievements in thyroidology, in keeping with the innovation and vision that epitomized Dr. Ingbar's brilliant investigative career. The Ingbar award is conferred upon an established investigator who has made major contributions to thyroid-related research over many years. An honorarium will be presented to the recipient.

Nominee:

The Paul Starr Award Lecture recognizes an outstanding contributor to clinical thyroidology. An honorarium will be presented to the recipient. This award receives support from Dr. Boris Catz.

Nominee:

The Lewis E. Braverman Lectureship Award recognizes an individual who has demonstrated excellence and passion for mentoring fellows, students and junior faculty; has a long history of productive thyroid research; and is devoted to the ATA. The award is endowed by contributions to honor Dr. Lewis E. Braverman. An honorarium will be presented to the recipient.

Nominee:

The Distinguished Service Award (DSA) honors a member who has made important and continuing contributions to the American Thyroid Association (ATA). The DSA award certificate is presented at the ATA Annual Banquet.

Nominee:

The John B. Stanbury Thyroid Pathophysiology Medal recognizes outstanding research contributions, either conceptual or technical, to the understanding of thyroid physiology or the pathophysiology of thyroid disease, as evidenced by having a major impact on research or clinical practice related to thyroid diseases. A medal, funded by Dr. John Stanbury, is conferred at the Annual Banquet.

Nominee:

Nominated by: (print or type) *Signature:* *Date:*

Nominators must submit all of the following electronically to thyroid@thyroid.org to complete the nomination by the deadline of March 31, 2013:

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2. CV and brief nomination letter, emphasizing major accomplishments.
3. List of 2 to 4 most significant publications with PDF or URL to provide access to these papers.

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