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## EDITORIAL

# Surgeon Performance in Thyroidectomy: Older Is Not Necessarily Better

In the January 2012 issue of the *British Medical Journal*, Duclos and associates reported the findings of a prospective, multicenter trial examining the influence of a surgeon's experience on the outcomes of thyroid surgery (1). The study examined 28 high-volume thyroid surgeons at various points in their careers across five centers in France over a 1.5-year period. Rates of two complications, recurrent laryngeal-nerve palsy and hypoparathyroidism, were the primary end points. Using a mixed-model analysis, the authors determined that surgeons with 5 to 19 years of experience had the best outcomes, with complication rates of less than 1%. After adjustment for patient- and hospital-centered variables, surgeon experience in excess of 20 years emerged as the sole predictor of higher complication rates, carrying an odds ratio of 3.06 for recurrent laryngeal-nerve palsy and 7.56 for hypoparathyroidism.

Prior studies have demonstrated that high-volume surgeons have superior outcomes in thyroidectomy (2,3). However, the study by Duclos et al. is the first to compare individual surgeons at different stages in their careers. Their somewhat arbitrary experience categories, likely chosen to divide the study participants into rough quartiles, describe a rather broad "phase of excellence" for midcareer surgeons, between the ages of 30 and 50 years. Thyroidectomy is a procedure that lends itself to this type of study because it is a very pure test of technical skill. The complications are very well defined and can be measured objectively.

The concept of expert performance is not new. It has been previously described in violinists, pilots, ballerinas, athletes, surgeons, and other similar professions that require coordination of advanced cognitive function with completion of a complex physical task (4). Expert performance arises after a dedicated period (generally more than 10 years) of deliberate practice, that is, practice purposefully focused on improving performance (5). Performance improvement is closely linked to timely feedback, frequent repetition, and the presence of well-defined goals. The practice of medicine is generally lacking in these three features, which may explain the observation that the quality of care delivered tends to decline with increasing physician experience (6). In contrast, surgery, replete with daily opportunities for performance improvement, was thought to be an exception to that rule—at least until now.

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# EDITORIAL — Surgeon Performance in Thyroidectomy: Older Is Not Necessarily Better

Manual dexterity, strength, visuospatial ability, hearing, attention, memory, and cognitive skills decline with age. All these factors may adversely affect surgeon performance and contribute to higher operative mortality rates among patients of surgeons over age 60 for certain complex procedures (7). Adding increased thyroidectomy complications to this list creates a potentially worrisome picture with regard to patient safety, especially when one considers that: (a) surgeons' reputations (and hence their ability to attract new patients) tend to grow with time, (b) no defined system exists to monitor or ensure surgical quality as practitioners age, and (c) the decision to retire is left to the individual surgeon rather than to any type of oversight body. In contrast, commercial airline pilots are not permitted to act as the pilot in command past the age of 65 in Europe and the United States (8). Given that one in five Americans undergoes elective surgery each year (9), some degree of parity might be expected in the treatment of surgeons and pilots.

Having said that, knowledge and experience count for a great deal in surgery. Older surgeons play a crucial role in mentoring their less experienced colleagues; hence, they must stay active professionally. The contributions of Duclos et al. do not call for regulation of surgeon retirement. Rather, the paper represents just one voice in a growing chorus that is actively calling for transparent reporting of surgical outcomes. What health care consumers (patients and insurers) currently have are surrogate indicators for surgical quality: hospital volume, surgeon volume, surgeon subspecialization, and now surgeon age. But these surrogates are a poor substitute for the individual outcome data that are sorely needed to create a value-based health care delivery system (10). Transparency would pave the way for virtuoso surgeons of all experience levels to be rewarded according to the same single criterion that determines the salaries of superstar athletes, perhaps the only factor that patients really care about: current performance.

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# The Evidence for Performing Universal Screening for Detection of Thyroid Disease in Pregnancy Continues to Be "Soft"

Lazarus JH, Bestwick JP, Channon S, Paradice R, Maina,A, Rees R, Chiusano E, John R, Guaraldo V, George LM, Perona M, Dall'Amico D, Parkes AB, Joomun M, Wald NJ. Antenatal thyroid screening and childhood cognitive function. N Engl J Med 2012;366:493-501.

## SUMMARY

### Background

Active secretion of thyroid hormone by the fetal thyroid does not start until about 18 to 20 weeks' gestation. Until then, the fetus is dependent on $T_4$ from the mother for growth and development, including central nervous system maturation. High levels of thyrotropin and/or low levels of $FT_4$ in women during pregnancy have been associated with impaired cognitive development in their offspring, suggesting that antenatal screening and treatment of thyroid deficiency may be worthwhile.

### Methods

The authors conducted a randomized, controlled trial to assess the effects of a high thyrotropin level, a low $FT_4$ level, or both on cognitive function of the 3-year-old offspring of women who underwent thyroid screening in early pregnancy and received treatment.

Pregnant women were recruited from 10 centers in the United Kingdom and 1 center in Italy. Exclusion criteria were an age of less than 18 years, a gestational age of more than 15 weeks 6 days, twin pregnancies, and known thyroid disease. After blood samples were drawn and sent to a reference lab, the women were randomly assigned to a group whose blood was immediately tested for $FT_4$ and TSH and who were treated with L-$T_4$ if the screening results were positive or to a control group whose blood was stored at –40°C and was tested only after delivery. Women were classified as positive if the serum thyrotropin concentration was above the 97.5th percentile, the serum $FT_4$ concentration was below the 2.5th percentile, or both. Patients in the group who were treated with L-$T_4$ (starting at 150 µg per day) had thyroid function rechecked 6 weeks after the start of L-$T_4$ therapy and at 30 weeks' gestation, with adjustment of the dose as necessary. The target thyrotropin level was 0.1 to 1.0 mIU per liter. All women received routine obstetrical care. The primary outcome was the IQ, at 3 years of age, of children of the women who tested positive. Based on the results of a 1999 study by Haddow et al. (1), 22 (5%) of the children of the women who received L-$T_4$ would have been expected to have an IQ of 85 or less, as compared with 66 children (15%) of women in the control group.

### Results

A total of 21,846 women were recruited and underwent randomization; 10,924 were assigned to the screening group and 10,922 were assigned to the control group. The proportion of women who had positive results on screening tests was 4.6% in the group given L-$T_4$, and 5.0% in the control group. About 5% of women classified as having positive screening results had both a high thyrotropin level and a low $FT_4$ level. L-$T_4$ was started at a median gestation of 13 weeks 3 days. Psychological testing was completed in 78.2% of the children of women who tested positive in the group receiving L-$T_4$, and in 73.3% of the children of women who tested positive in the control group. There were no significant differences between the screening and control groups with respect to gestational age at delivery (median, 40.1 and 40.2 weeks, respectively; P = 0.10), rates of preterm birth (<37 weeks' gestation) (5.6% and 7.9%; P = 0.20), and birth weight (mean, 3.5 kg and 3.3 kg; P = 0.15).

### Cognitive Function

The mean standardized IQ in the children of the control group was 100.0 (by definition), and was 99.2 in the children of the women who received L-$T_4$ (P = 0.40). The proportion of children with an IQ of less

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than 85 was 12.1% in the L-$T_4$-treated group and 14.1% in the control group (P = 0.39). An analysis adjusting for initial thyrotropin measurements (log-transformed) also did not show a significant association between thyrotropin and IQ. There were no significant between-group differences in the results of other psychological assessments (Child Behavior Checklist [CBCL] and Behavior Rating Inventory of Executive Function, preschool version [Brief-P] scores).

Post hoc analyses were performed in the following subgroups: women with a positive screening results according to TSH level only, women with positive screening results according to $FT_4$ level only, and women with positive screening results according to both TSH and $FT_4$ levels, women who began to receive treatment before 14 weeks' gestation, women who began to receive treatment at 14 weeks' gestation or later, women in whom the target TSH level was achieved by 6 weeks after screening, and women in whom the target thyrotropin level was achieved at 30 weeks' gestation. There were no significant differences in IQ scores between the L-$T_4$-treated group and the control group in any of these subgroup analyses.

### Conclusions

The authors found no significant difference in IQ scores between the 3-year-old children born to women who were randomly assigned to the screening group at about 12 weeks' gestation and who were treated for reduced thyroid function before 20 weeks' gestation (median, 13 weeks 3 days) and the children born to women with reduced thyroid function who were randomly assigned to the control group and received no L-$T_4$ treatment during pregnancy. There were also no significant between-group differences in analyses limited to the women who adhered to treatment. Current guidelines do not recommend routine antenatal screening for hypothyroidism in pregnancy; this study provides support for these guidelines, since the authors found no benefit of routine screening for maternal hypothyroidism at about 12 to 13 weeks' gestation in the prevention of impaired childhood cognitive function.

## ANALYSIS AND COMMENTARY

The noninterventional study of Haddow et al. published in 1999 concluded that children of untreated pregnant women with hypothyroidism had a lower IQ score at age 7 to 9 than children from euthyroid mothers (1). The mean (±SD) serum TSH in the women with hypothyroidism was 13.2±0.3 mU/L (geometric means and logarithmic standard deviations) as compared with 1.4 ±0.2 mU/L in control euthyroid mothers (P<0.001), with 9 of 62 women having TSH values over 30 mU/L (1). Serum $T_4$ and $FT_4$ were also significantly different between hypothyroid and euthyroid women. In the current study, the median serum TSH in women with hypothyroidism was 3.8 mIU/L in the screening group and 3.2 mIU/L in the women in the control group (not treated) (interquartile ranges, 1.5 to 4.7 and 1.2 to 4.2, respectively).

In the past decade, multiple cohort and observational studies have been published, which have suggested a significant increase in obstetrical complications in mothers with subclinical hypothyroidism or hypothyroxinemia, in areas reported as iodine-sufficient. Most of the women were tested in the first trimester and/or early second trimester of gestation. In the vast majority of the studies, only a single determination of thyroid tests was available for the whole length of the pregnancy (reviewed in 2). The complications most frequently reported were miscarriages and preterm delivery (<37 weeks' gestation), with other complications reported in some but not all studies, including preeclampsia, breech delivery, infants who were small for gestational age, and postpartum bleeding. The suggestion that early screening for detection and treatment of maternal hypothyroidism, with the intent to prevent obstetric and offspring complica-

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tions, became a hot and controversial issue among physicians caring for these patients. Guidelines for the management of thyroid disease in pregnancy were published by other endocrine societies (3,4), with the recommendation for target or case-finding instead of universal screening in the first obstetrical visit, which is also the position of the American Congress of Obstetricians and Gynecologists (5). The lack of justification for universal screening was based on the fact that only a single control study of less than 100 pregnant women was available in the literature, which showed a significant decrease in miscarriage rate and preterm delivery in euthyroid women with evidence of chronic thyroiditis who had been treated with L-$T_4$, as compared with a nontreated group (6). The authors of the current study acknowledge that other studies have found more specific cognitive impairments associated with maternal hypothyroidism or hypothyroxinemia, among them psychomotor deficit, delays in the development of expressive language, vision abnormalities, and behavioral changes. In addition to the difference in the degree of thyroid dysfunction (only 5% of the women suffered clinical hypothyroidism in the Lazarus study), and IQs were measured at 3 years of age, whereas in Haddow study, testing was done between 7 and 9 years of age.

Additional randomized studies are needed to answer three important clinical questions: (1) Does starting L-$T_4$ therapy early in pregnancy, in women with subclinical hypothyroidism—and also in euthyroid women with chronic thyroiditis—prevent obstetrical and/or long-term complications in offspring? (2) If so, is universal or case-finding early in pregnancy cost-effective in preventing such complications? and (3) What initial screening tests should be performed: TSH, $FT_4$ or equivalent, and/or TPO antibodies? In the meantime, physicians treating women of reproductive age should be aware that a significant number of them have symptoms that could indicate thyroid disease, that prompt assessment of thyroid status is in order, and if there is evidence of hypothyroidism, L-$T_4$ therapy is of potential benefit not only to the patient during the current pregnancy, but also if there is a subsequent pregnancy. At this point, once a woman is pregnant, whether to perform universal screening or case finding is a decision based on personal experience.

**— Jorge H. Mestman, MD**

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# Neurodevelopment May Be Entirely Normal in Children Born to Women with Hypothyroidism Who Are Restored to Euthyroidism by Late Pregnancy

Momotani N, Iwama S, Momotani K. Neurodevelopment in children born to hypothyroid mothers restored to normal thyroxine ($T_4$) concentration by late pregnancy in Japan: No apparent influence of maternal $T_4$ deficiency. J Clin Endocrinol Metab. February 8, 2012 [Epub ahead of print].

## SUMMARY

### Background

Thyroid hormone is essential for brain development both before and after birth. Maternal $T_4$ has been shown to have a crucial role in brain development in fetuses with sporadic congenital hypothyroidism. The importance of maternal $T_4$ has also been shown in basic studies in fetal neurodevelopment before the onset of fetal thyroid function, which corresponds to the first trimester in humans. Moreover, the correlation between mild maternal $T_4$ deficiency at 12 to 17 weeks' gestation and disturbance of neurodevelopment in progeny has been shown in case–control studies in The Netherlands and the United States. These observations have given rise to the perception that maternal hypothyroidism or $T_4$ deficiency in early pregnancy leads to a defect in neuropsychological development. On the other hand, the absence of intellectual impairment among children, irrespective of the severity of $T_4$ deficiency in the mother in early pregnancy after $T_4$ normalization by late pregnancy, has been reported from Japan. This points to uncertainty about whether the neurologic impairment is a result of reduced availability of maternal $T_4$ in early pregnancy. The authors reported five cases showing no apparent effect of maternal $T_4$ deficiency on neurodevelopment in progeny in whom low $T_4$ levels had been corrected by late pregnancy.

### Methods

Five women with overt hypothyroidism detected at 6 to 16 weeks' gestation initiated $T_4$ treatment. The serum TSH levels at detection ranged from 23.3 to 657 mU/L and the serum $FT_4$ from 0.09 to 0.66 ng/dl. In four women, euthyroidism was restored by the 20th week. One remained in a subclinical hypothyroid state. Developmental scores of their children were evaluated between 25 months and 11 years of age by either the Tsumori-Inage Infant's Developmental Test or the Wechsler Intelligence Scale for Children-Third Edition (WISC-III) and compared with those of siblings with no exposure to maternal hypothyroidism.

### Results

Initial serum TSH and $FT_4$ levels were monitored at 2- to 6-week intervals; they normalized by 20 weeks in 4 patients; in the other woman, subclinical hypothyroidism remained for the rest her gestation. The WISC-III scores of 3 children were compared with their 3 siblings born when mothers were euthyroid during a subsequent pregnancy; the scores were within the normal range and not significantly different between the siblings. In the other 2 infants, the score on the Tsumori-Inage infant psychomotor development test was within the normal range at age 25 and 35 months. Their siblings were not tested.

### Conclusions

In iodine-sufficient areas, maternal $T_4$ deficiency in early pregnancy does not necessarily affect neurodevelopment. However, early detection by routine screening would be crucial where recovery from hypothyroidism by late pregnancy is essential for normal brain development. Therefore, other factors that could potentially alter neurodevelopment, such as iodine deficiency, must be investigated.

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# Neurodevelopment May Be Entirely Normal in Children Born to Women with Hypothyroidism Who Are Restored to Euthyroidism by Late Pregnancy



## ANALYSIS AND COMMENTARY

In this study, IQ and DQ (development quotient) scores indicated no apparent neurodevelopmental deficit in children whose mothers had overt hypothyroidism during the first trimester of pregnancy and were restored to normal serum $T_4$ levels by late pregnancy. Haddow et al. (1) reported lower IQs in children of untreated pregnant women with hypothyroidism. At about the same time, Pop et al. (2) described impaired psychomotor development in infants of women with hypothyroxinemia who had serum TSH levels within the reference range. In the Pop study, children of women with hypothyroxinemia with $FT_4$levels below the 5th percentile (11 mothers) and below the 10th percentile (22 mothers) at 12 weeks' gestation were evaluated at 10 months of age using the Bailey Psychomotor Development Index scale; they had significantly lower scores as compared with children of mothers with higher $FT_4$ values. Since this study was carried out in an area with iodine sufficiency, there was no clear cause to explain isolated cases of hypothyroxinemia. It is well known that in areas of chronic iodine deficiency, serum iodine and $T_4$ are low, with a corresponding increase in T3 production (3). Other studies from areas of iodine deficiency describe deleterious neurocognitive defects in offspring of women with hypothyroxinemia (4). In Japan in 1994, Liu et al. (5) studied IQs of eight children born of women with severe hypothyroidism (mean [±SD] serum TSH, 116±59 μU/ml; $FT_4$, <0.5 ng/dl) detected during the 5th to 10th week of gestation and compared them with IQs of their siblings born when mothers were euthyroid. All women with hypothyroidism had normal $FT_4$levels by 28 week' gestation. The IQ scores of these children at 4 and 10 years were normal and comparable to their siblings studied at comparable ages. It is surprising that this study published in an American journal was not cited by Haddow or Pop in their publications. Momotani et al. now confirm the original observation by Liu et al (both populations were from the same geographic area in Japan); the degree of hypothyroidism was much more severe in the patients reported by Liu et al. (5) and Momotani than in those included in the series by Haddow et al. (1) and Pop et al. (2). Furthermore, in a 2003 study by Pop et al. (6), no apparent neurodevelopment delay was seen in children when maternal $FT_4$ levels spontaneously increased after the first trimester. As suggested by the authors, the discrepancies between other studies and their own may reside in the amount of dietary iodine intake, which is very high in Japan (7). It was recently reported that iodine concentration is low in the formula given to premature infants in the Boston area (8). The importance of iodine replacement in women of childbearing age is underestimated; it was proposed that proper iodine supplementation should be started years before conception in order to achieve normal thyroid function in early pregnancy (9).

**— Jorge H. Mestman, MD**

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# Plasma C-Type Natriuretic Peptide Is a Biological Marker of Velocity of Skeletal Growth during Treatment of Acquired Hyperthyroidism and Hypothyroidism in Preadolescent Children

Reh CS, Olney RC, Azen C, Prickett TC, Espiner EA, Geffner ME. Plasma C-type natriuretic peptide forms and thyroid status in prepubertal children with acquired thyroid disease. Clin Endocrinol (Oxf) 2012;76:228-35.

## SUMMARY

### Background

There are at least three different natriuretic peptides. Atrial natriuretic peptide (ANP) is primarily released from the atria in response to volume expansion (1,2). As indicated by its name, ANP has a natriuretic effect, but this effect is minor and can be overwhelmed by severe sodium load such as in some cases of decompensated cirrhosis and cardiac insufficiency. B-type natriuretic peptide (BNP) was initially discovered in the brain but it can also be produced elsewhere—for example, in cardiac ventricles. The structurally similar C-type natriuretic peptide (CNP) is produced by the vascular endothelium and the kidney. Its physiological action is so far largely unknown. There is, however, a clear correlation between its blood levels and skeletal growth rate (3,4).

In children, hypothyroidism is associated with markedly slowed skeletal growth and hyperthyroidism is associated with markedly accelerated skeletal growth. In animal models, synthesis and secretion of growth hormone are strongly dependent on thyroid hormones. Yet, insulin-like growth factor I (IGF-I) levels are not affected by hyperthyroidism and hypothyroidism. Therefore, the pathophysiological relationship between the plasma levels of the C-type natriuretic peptide and thyroid status is certainly worth exploring.

### Methods and Results

Children older than 3 years of age were studied; 27 were prepubertal, 15 had hypothyroidism, and 12 had hyperthyroidism. Neonatal hypothyroidism was excluded. At each visit, anthropometric measurements were performed and the height was measured with an accuracy of 0.1 cm. CNP and the more stable amino terminal propeptides of CNP (NTproCNP) were determined by radioimmunoassay (RIA). The two groups had a similar mean age.

Mean bone age was younger in children with hypothyroidism than in those with hyperthyroidism (6.8 years versus 9.5 years); height velocity (HV) was also lower in hypothyroid children. The IGF-I levels were identical in the two groups. NTproCNP was clearly lower in children with hypothyroidism than in those with hyperthyroidism. During the 6 to 8 weeks necessary for normalization of thyroid status, HV and NTproCNP responded more rapidly in children with hyperthyroidism than in those with hypothyroidism. Within 6 to 8 weeks, NTproCNP decreased from a mean of 58 pmol/L by approximately 15 pmol/L, while in children with hypothyroidism the increase in NTproCNP was less impressive and more variable. For hyperthyroidism and hypothyroidism, the deviation from the expected bone age correlated well with the concentration of NTproCNP, which increased proportionally with increasing bone age. No significant changes in the IGF-I levels were observed.

### Conclusions

CNP and its more stable serum cognate NTproCNP reflect the severe alterations of bone age in hyperthyroidism and hypothyroidism, the levels being higher in hyperthyroidism and lower in hypothyroidism. The values directly correlate with the delay or the acceleration of bone growth rate. The changes occur

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within weeks of treatment, which compares favorably with other parameters related to changes in growth velocity (HV), which seem to respond more slowly. In contrast, IGF-I levels are unreliable as a biologic parameter of growth retardation or acceleration in thyroid disease. The authors do not suggest any clinical usefulness of the measurement but rather stress the pathophysiological importance of these new findings.

## ANALYSIS AND COMMENTARY

The alteration of bone age in hyperthyroidism or hypothyroidism can be clinically impressive. The clinical response to treatment takes time, since HV and catch-up growth in children with hypothyroidism need months of treatment. They are delayed as compared with changes in serum thyroid hormone levels. In this report, the authors describe a new finding—the good correlation of CNP, measured by the more stable NTproCNP, with the severity of either delayed or accelerated skeletal growth. NTproCNP has the advantage of responding rapidly in close correlation with the changes in serum thyroxine levels, particularly in hyperthyroidism. These findings contrast with the lack of correlation between IGF-I levels and thyroid disease in children. They suggest an important interaction between thyroid hormones and CNP, which is probably generated in part within growth plates. Thyroid hormones can therefore be added to the list of factors already known to interact at the level of growth plates, such as growth hormone, testosterone, cortisol, and nutrients. Is there any clinical benefit from measuring NTproCNP? The critical clinical end point is catch-up growth and HV. The small number of subjects in this study does not allow a firm conclusion as to the value of this biologic parameter in comparison with anthropometric measurements.

**— Albert G. Burger, MD**

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# A Large Case–Control Study Confirms that Development of Abnormal Thyroid Function Is Associated with Iodinated Contrast Material

Rhee CM, Bhan I, Alexander, EK, Brunelli SM. Association between iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism. Arch Intern Med. 2012;172:153-9.

## SUMMARY


### Background

From the first days of our endocrine fellowship we are taught about the acute Wolff–Chaikoff effect, escape from it, and its opposite, the Jod–Basedow phenomenon, which can result when the thyroid is exposed to high levels of iodide. Prolonged hyperthyroidism can develop after patients are exposed to iodinated contrast material during computed tomography (CT) scanning or cardiac catheterization (CC), but there have been no large controlled studies examining the incidence of this complication (1-3). This study queried a database of 4.5 million patients in Boston, an iodine-sufficient area, and used a nested case–control study to assess the frequency with which abnormal thyroid function tests were associated with exposure to iodinated contrast materials.

### Methods and Results

This carefully constructed retrospective case–control study examined the records of adults who had a normal TSH value obtained from January 1, 1990, through June 30, 2010, who had no known history of thyroid dysfunction, thyroid surgery, radioactive iodine thyroid ablation, or use of L-$T_4$ or antithyroid medication, and who had a second TSH measurement performed 2 weeks to 2 years after the first determination. Patients whose TSH values did not change between the two determinations were used as controls, matched for age sex, race, follow-up TSH interval, and estimated glomerular filtration rate. If the second TSH value was below the lower limit of the reference range, the patient was considered to have hyperthyroidism, whereas if the second TSH value was above the upper limit the patient was considered to have hypothyroidism. During 4096 patient intervals, iodinated contrast material was administered 361 times, leaving 3678 patient intervals that could be used as controls. In the source cohort, 361 subjects (8.8%) received iodinated contrast material in the interval between the two TSH tests (CT alone, 80.9%; CC alone, 13.6%; both CT and CC, 5.5%). A suppressed TSH level occurred in 191 intervals; of those, 178 were matched to 655 controls. Matched analysis revealed a significant association between contrast exposure and incident hyperthyroidism (odds ratio [OR], 1.98; 95% CI, 1.08 to 3.60; P = 0.03). The number needed to harm was 23. In secondary analysis, patients with a TSH of <0.01 mIU/L (considered to have overt hyperthyroidism) were more likely to be female, to have renal dysfunction, and to be of nonwhite race/ethnicity. An elevated TSH occurred in 227 intervals; of those, 213 were matched to 779 controls. Matched analysis did not reveal a significant association (OR, 1.58; 95% CI, 0.95 to 2.62; P = 0.08). The number needed to harm was 33. However, if the interval for the second TSH determination was less than 180 days, or if the evaluation was limited to severe hypothyroidism (TSH >10), the association with exposure to contrast material did reach significance.

### Conclusions

This study demonstrated associations between exposure to iodinated contrast materials from CT scanning and cardiac catheterization and the development of thyroid dysfunction. The strengths of the study include the large number of controls and careful case definitions. The study is limited because of the retrospective nature of the analysis, the variability between the time of exposure to contrast material and the time that follow-up TSH values were obtained, and the lack of a complete set of peripheral hormone levels in most of the patients.


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# A Large Case–Control Study Confirms that Development of Abnormal Thyroid Function Is Associated with Iodinated Contrast Material



## ANALYSIS AND COMMENTARY

I admit my bias is that the study must be correct, based on the known Wolff–Chaikoff and Jod–Basedow effects and the very high iodine content of contrast media (4). This is a difficult study for a nonstatistician to tease apart, but over 20 years, there were 4096 patient intervals (1 patient can have more than 1 interval that is separated by time) during which the serum TSH was checked twice within 2 years. Only 361 of these intervals were associated with the administration of iodinated contrast material. This means that the study captured only a small percentage of patients who received contrast material. One could ask whether there was a patient bias, since the period of repeating a TSH test (from 2 weeks to 2 years later) is more frequent than the period routinely used to follow patients without thyroid symptoms. This study confirms an association between the development of thyroid dysfunction and the administration of contrast material (1-4), although the design does not allow it to be used to show causality; that would require a prospective study that fully characterizes the patient's thyroid status before and at set times after the administration of contrast material. If the number needed to harm is 1 in 23 for the development of hyperthyroidism, then a prospective study that obtained follow-up samples from at least 2000 patients after they received contrast material would be required in order to obtain a statistically significant difference, a study that would appear to be difficult to perform and fund.

**— Stephanie L. Lee, MD, PhD**

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Clinical THYROIDOLOGY
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# Successful Ablation of Thyroid Remnants Can Be Achieved with Two 20 mCi (740 MBq) Doses of $^{131}$I

Clerc J, Bienvenu-Perrard M, Pichard de Malleray C, Dagousset F, Delbot T, Dreyfuss M, Groussin L, Marlowe RJ, Leger FA, Chevalier A. Outpatient thyroid remnant ablation using repeated low 131-iodine activities (740 MBq/20 mCi x 2) in patients with low-risk differentiated thyroid cancer. J Clin Endocrinol Metab. 2012;97:871-80.

## SUMMARY

### Background

Differentiated thyroid carcinoma (DTC) classified as low risk has a low rate of recurrence and very low mortality. After surgical thyroidectomy, many patients with DTC currently are not treated with $^{131}$I for ablation of remnant thyroid tissue. On the other hand, there has been renewed interest in using the smallest effective dose of $^{131}$I for ablation rather than giving an arbitrary dose of 100 mCi (3.7 GBq) for these patients. The current paper describes the efficacy of using a minidose protocol of two doses of 20 mCi (740 MBq) $^{131}$I given 6 to 18 months apart.

### Methods

The study included 160 consecutive patients with well-differentiated thyroid cancer who underwent total thyroidectomy and were classified as pT1/N0-Nx disease during the period 2001–2011. After 2 weeks on a low-iodine diet, the patients were given an ablative dose of 740 MBq $^{131}$I and then had scans 2 or 3 days later. A second dose of 740 MBq $^{131}$I was given 6 to 18 months later. The doses were given after rhTSH or after 4 weeks of $T_4$ withdrawal. Ablation success at minidose 2 also was the end point of a multivariate analysis to identify factors present at minidose 1 that independently predicted this outcome. The ultimate objective of the analysis was to identify factors indicating that the second minidose of $^{131}$I might be omitted. Patients underwent ultrasonography in follow-up and measurements of Tg. Successful ablation was defined as the combination of: (1) no visible thyroid-bed uptake on whole-body scintigraphy with 740 MBq (740 WBS) or cervical uptake below 0.1%, and (2) undetectable Tg (<1 ng/ml).

### Results

Nine patients were found to have positive imaging in nodes or distant disease, five on the first scan and five others on the second scan, and were excluded from the analysis.

The ablation success rate was 75.9% after one 740-MBq dose in 145 patients and 90.2% after the second dose in 132 evaluable patients. About 10% had no thyroid remnant and had ablation by surgery alone. Patients who underwent successful $^{131}$I-ablation tended to be younger (P<0.02). Stimulation by rhTSH with the first minidose ablation was associated with more successful ablation (81%) than with thyroid hormone withdrawal (52%), but the opposite occurred with the second minidose (13% with rhTSH vs. 52% with thyroid hormone withdrawal). The strongest predictor of successful ablation at minidose 2 was Tg <10 ng/ml at minidose 1, which indicated a smaller remnant. Tumor size and multifocality did not predict successful ablation. There was no evidence of recurrent disease in 81 patients with prolonged follow-up.

### Conclusions

The minidose outpatient ablation protocol was effective and useful diagnostically in low-risk patients with DTC.

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## ANALYSIS AND COMMENTARY

The success of the 20 mCi (740 MBq) $^{131}$I ablation is probably attributable to the completeness of surgery. This is indicated by the stimulated Tg being <10 ng/ml at the time of the first ablation dose. The additional success of the second minidose is its administration without prior $^{131}$I diagnostic scan that could cause stunning of the tumor tissue and impair uptake of the treatment dose.

In recent years, there has been a trend to reduce the ablative dose of $^{131}$I to 30 mCi or even 50 mCi, doses that were once commonly used in the United States in order to avoid the high cost of hospitalization for the therapy. A study of 555 patients given doses of 15 to 50 mCi (in groups with progressive 5 mCi increments) for ablation in India showed that a dose of at least 25 mCi was equally as effective as higher doses (1). In a comparison of 30 mCi and 100 mCi $^{131}$I for ablation, the success rates were similar, but the higher dose caused more radiation thyroiditis (2). In addition, it is well-established that the incidence of dry mouth and lacrimal-duct obstruction increase with increasing doses of $^{131}$I, so lower doses cause fewer adverse reactions.

A criticism of the ablation method used in this study is that it requires two sets of rhTSH injections, which increases the cost and inconvenience to the patient, but one could argue that a stimulated measurement of Tg and a follow-up scan should be performed in follow-up for any ablation protocol.

In evaluating this retrospective study, it is difficult to avoid the conclusion that many of these patients classified as pT1 with no evidence of nodal disease would not be treated with $^{131}$I ablation at the current time because of a lack of evidence of efficacy in these patients who have an excellent prognosis. Nevertheless, when a low-risk patient is treated, a low dose is likely to be effective, as indicated by this study.

**— Jerome M. Hershman, MD**

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Clinical THYROIDOLOGY
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# Microscopic Extrathyroidal Extension Is Not a High Risk Factor for Differentiated Thyroid Cancers Smaller than 4 cm

Nixon IJ, Ganly I, Patel S, Palmer FL, Whitcher MM, Tuttle RM, Shaha AR, Shah JP. The impact of microscopic extrathyroid extension on outcome in patients with clinical T1 and T2 well-differentiated thyroid cancer. Surgery 2011;150:1242-49.

## SUMMARY

### Background

Studies of national databases and from large institutions have indicated that age and gross extrathyroidal extension (ETE) of tumor are important predictive factors for disease-specific survival for well-differentiated thyroid cancer. However, it has never been clear that microscopic ETE of the primary tumor has the same prognostic impact. In patents older than 45 years of age, small tumors (<4 cm; American Joint Committee on Cancer/Union for International Cancer control [AJCC/UICC] cT1 and cT2) found to have microscopic ETE are upgraded to AJCC/UICC stage 3. This upgrading suggests that such patients have a higher risk of mortality. The authors of this study examined the impact of microscopic ETE in patients with small (<4cm; cT1 and cT2) well-differentiated thyroid cancer (91% papillary, 5% follicular, and 4% Hürthle-cell) to determine the effect of the extent of surgery and of adjuvant radioactive iodine (RAI) treatment on outcome.

### Methods and Results

Patient records from 1986 to 2005 revealed that of 1810 patients who underwent initial surgery for thyroid cancer, 984 (54%) had well-differentiated thyroid cancer <4 cm (cT1/cT2) and no evidence of adenopathy, based on clinical examination at the time of operation plus central-neck node dissection, and no evidence of extension to fibroadipose tissue or strap muscles. Of the 984 patients, 869 (88.3%) were stage 1 and 2 (pT1 and pT2), while 115 (11.7%) were upstaged to stage 3 (pT3) because of microscopic ETE. There was less ETE in tumors <1 cm (6%), than in tumors 1 to 2 cm (16.4%), 2 to 3 cm (15.3%), and 3 to 4 cm (11.7%). Disease-specific survival (DSS) and recurrence-free survival (RFS) were estimated by means of Kaplan–Meier analysis. The entire group was followed for a median of 98 months (range, 6 to 291) with 95% 10-year overall survival, 99%DSS, and 98% RFS. There was no significant difference between the pT1/pT2 and pT3 groups in 10-year DSS (99% vs. 100%; P = 0.733) or RFS (98% vs. 95%; P = 0.188). Of the 869 stage 1 and 2 patients without ETE, 488 (56%) underwent total thyroidectomy, 350 (40%) had thyroid lobectomy, 15 (2%) had isthmusectomy, and 16 (2%) had subtotal thyroidectomy. Postoperative RAI was given to 186 (21%) of the 869 without microscopic ETE. Of the 115 with microscopic ETE, 86 underwent total or near-total thyroidectomy (77%), 26 had lobectomy (23%), and 2 (2%) had subtotal thyroidectomy. Postoperative RAI was given to 65 (57%, P<0.001). The extent of surgery or RAI ablation was not significant for recurrence on either univariate or multivariate analyses in the pT3 cohort. There were no disease-specific deaths in the group with microscopic ETE. There were 3 recurrences, all within cervical nodes, in the 115 with ETE (3%), whereas 5 of the 869 without ETE had cervical-node recurrence (0.5%, P = 0.032).

### Conclusions

This study indicates that microscopic ETE does not affect the disease-specific survival and recurrence-free survival in patients with small well-differentiated thyroid cancer <4 cm (cT1 or cT2) who do not have abnormal nodes (N0).

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## ANALYSIS AND COMMENTARY

The 2009 American Thyroid Association Guideline for Thyroid Nodule and Cancer suggests using both the TMN AJCC/UICC staging and risk factors to completely assess risk for death and persistence/recurrence of the tumor (1). These risk categories state that microscopic ETE places patients at medium risk while gross ETE places patients at high risk (2,3). In contrast, the current retrospective study shows that the excellent outcome expected for small tumors of differentiated thyroid cancer (cT1/cT2; <4 cm) without nodes (N0) is not affected by microscopic ETE. In the absence of other risk factors, such as lymphovascular invasion, aggressive histology, incomplete surgical removal, or clinically important metastatic nodes, it may not be necessary to upgrade tumors found to contain microscopic ETE to pT3. The impact of ultrasound examinations and thyroglobulin determinations was not assessed in this retrospective study, and they probably deserve to be included in future large multi-institution studies before guidelines for the management of thyroid cancer are altered.

**— Stephanie L. Lee, MD, PhD**

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Clinical THYROIDOLOGY
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# Patients Homozygous for Mutations in the Thyroid Hormone Receptor Beta Gene Have More Severe Symptoms of Thyroid Hormone Resistance

Ferrara AM, Onigata K, Ercan O, Woodhead H, Weiss RE, Refetoff S. Homozygous thyroid hormone receptor β-gene mutations in resistance to thyroid hormone: three new cases and review of the literature. J Clin Endocrinol Metab. February 8, 2012 [Epub ahead of print]. doi: 10.1210/jc.2011-2642.

## SUMMARY

### Background

Patients who have persistently high thyroid hormone levels but whose TSH values are persistently normal (or high) may be resistant to thyroid hormone. After ruling out other possible diagnoses, most cases of resistance turn out to be due to a single nucleotide mutation in one copy of the thyroid hormone receptor beta (THRB) gene. The mutations differ widely in their dominant negative effects and in the degree of resistance observed in different tissues. The same mutation can be associated with very different clinical manifestations, even in members of the same family. Some patients are unaware of symptoms or merely have a long-standing goiter, while others may be nervous, or have tremor, palpitations, insomnia, heat intolerance, weight loss, or increased appetite, suggesting hyperthyroidism, while in children, delays in neurologic and skeletal development can suggest hypothyroidism.

### Methods

Three children from two families were noted to have tachycardia, goiter, deafness, defective speech, and delays in growth and intellectual development. Thyroid-function tests strongly suggested resistance, so THRB was analyzed in family members.

### Results

Neonatal TSH levels in the first child were very high; her thyroid was normal in size but its 99mTc uptake was increased. She was treated with beta-blockade for tachycardia at 1 week of age, and by the age of 3 years, deafness, goiter and delayed skeletal and gross motor development had appeared. The consanguineous parents both had mild hearing defects. The putative father was taking L-$T_4$ for an unknown thyroid problem, but he did not undergo testing. The patient's mother, uncle, grandmother, and great grandmother had high total $T_4$, $T_3$, and $FT_4$ index (FTI) levels, yet their TSH levels were normal to high. They all had some degree of deafness and were found to be heterozygous for a point mutation (G347E) in thyroid receptor beta (TRβ), whereas the child was homozygous.

The G347E mutation had previously been found in a 36-year-old man who had undergone thyroidectomy and had started L-$T_3$ therapy to suppress his TSH; he was mildly mentally retarded, and his resting pulse was under 80. In vitro studies on the $T_3$-binding activity of the mutant receptor showed it to be 1/20 of the wild type receptor (1).

A girl and boy in a second family had birdlike faces and were deaf. At 3 years of age, the girl was noted to have a goiter with thyroid-function tests consistent with thyroid hormone resistance, and she was treated with propranolol for tachycardia. At 7 years of age, her $FT_4$ and $T_3$ levels were immeasurably high, yet her TSH was 14 μU/ml. She was given increasing doses of triiodothyroacetic acid (Triac), but her goiter continued to grow, necessitating a thyroidectomy before she was 9. Her skeletal and mental development were retarded. Her younger brother was deaf and had a goiter and developmental delays, but he did not have tachycardia. His TSH was 91 μU/ml despite having an elevated serum $T_4$. These two siblings were homozygous for a point mutation in TRβ (R316C), while the consanguineous parents

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were heterozygous, as were the paternal grandfather and maternal uncle. The father had undergone thyroidectomy at age 28, and his TSH was 37 μU/ml despite an elevated FTI. The mother did not have a goiter or tachycardia, but her $FT_4$ was high; she also had a positive TPO antibody titer [interestingly, autoimmune thyroiditis is more common in patients with thyroid hormone resistance, which can further complicate evaluation of their thyroid status (2)]. A girl who had hypothyroidism at birth with only a lingual thyroid was found to be heterozygous for R316C (3). L-$T_4$ at 350 μg/day eventually normalized her TSH levels. In vitro studies on the mutated receptor showed its affinity for $T_3$ to be about one third of that of the wild type; it was also unable to form homodimers and it impaired the transcription of $T_3$-responsive genes.

## Conclusions

The greater severity of laboratory and clinical abnormalities in the homozygous members of these two families with point mutations in TRβ resembles what was previously reported in the homozygote of a family bearing a 3-base-pair deletion in THRB (4). The lesser biochemical and clinical severity in the heterozygotes, who have one normal allele, suggests that the mutant protein has less opportunity to disturb the function of TRα1,which predominates in the conduction system of the heart, and with which TRβs commonly heterodimerize.

## ANALYSIS AND COMMENTARY

The single-point mutations found in these two families are known to affect the affinity of the receptor for $T_3$, but many THRB mutations that do not affect $T_3$ binding still cause resistance. Some disturb heterodimerization between TRs, RARs, or RXRs, or interactions with coactivators or coinhibitors. The TRβ1 isoform predominates in many peripheral tissues, whereas the TRβ2 isoform predominates in the hypothalamus and pituitary. However, there are several other splice variants from both the TRα and β genes that do not bind $T_3$ but do form dominant negative heterodimers and are expressed at varying levels in certain tissues (5). Covalent modifications such as phosphorylation also influence the activity, subcellular distribution, and stability of the TRs, and also need to be included in assessing mechanisms of resistance. However, TR mutations are not the whole story. Thyroid hormone responsiveness is also influenced by nongenomic actions of thyroid hormones, and the activity of thyronine transporters and deiodinases in different cell types, so unraveling all the players involved will be an arduous undertaking. In the case of the pituitary, thyrotroph sensitivity can be estimated by the product of the TSH and the $FT_4$ levels, but no simple tests for resistance in other organs are available yet.

Severe cases of resistance are unusual, but there may be more subtle patients in one's practice whose diagnosis of hyperthyroidism needs to be reassessed. Such patients may have had a goiter, palpitations, and a high $T_4$ level in the days before the TSH assay was sensitive enough to be meaningful at low levels. Those patients may have received "definitive treatment" and then were given enough thyroid hormone to make them "clinically euthyroid." If their TSH is in the normal range, and their $FT_4$ is only slightly high, what should be done? We recognize that TSH should be undetectable if the $FT_4$ is high, but we also know that the $FT_4$ test can give questionable results, and that TSH levels can vary by 40% on repeat testing. However, if the two tests disagree consistently, shouldn't one reassess the diagnosis? Before proceeding to a muta-

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tional analysis of THRB, the possibility of interfering human antimouse antibodies should be ruled out. However, in their absence—and particularly if other family members have similar histories—establishing the diagnosis of thyroid hormone resistance could avert surgical or radioiodine ablations in future generations. In about 15% of cases, no mutation is found in THRB. In such cases, it may be reasonable to determine the ratio of the level of the alpha subunit of pituitary glycoprotein hormones to the level of TSH, since TSH-secreting pituitary adenomas, although very rare, can occur. In such a case, a formal test of TSH sensitivity using increasing doses of $T_3$ may be in order. The test can provoke hyperthyroid symptoms or have cardiac effects, although cautious use of beta blockade may be somewhat protective.

**— Stephen W. Spaulding, MD**

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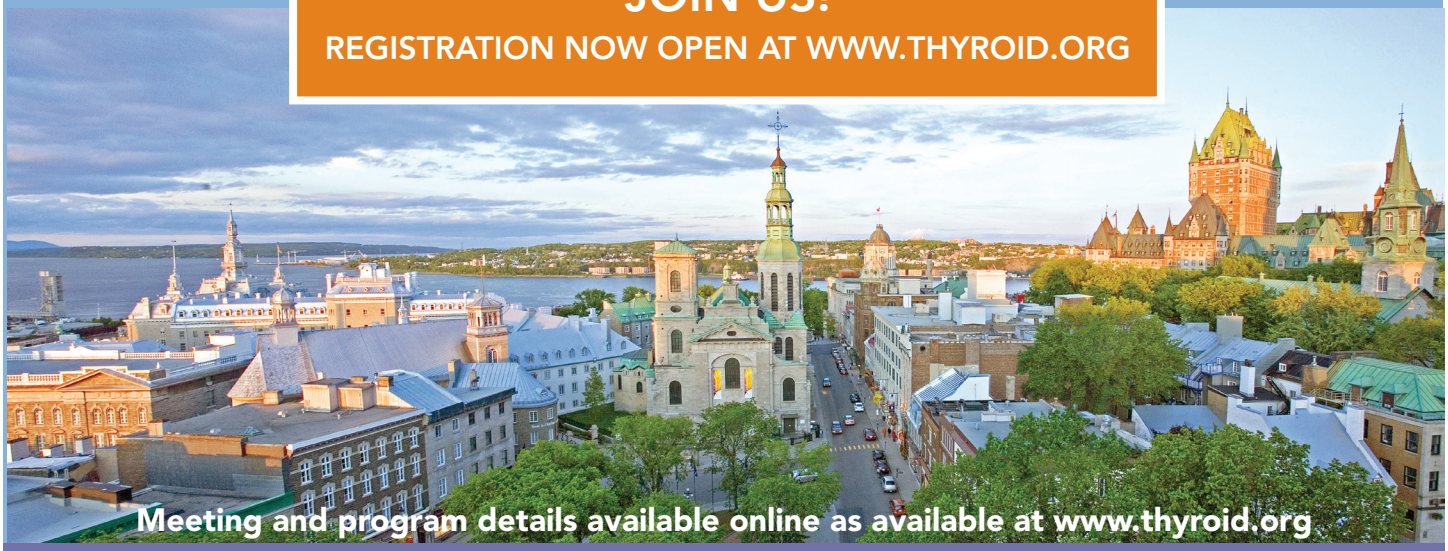


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