

CLINICAL THYROIDOLOGY FOR PATIENTS



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THYROID CANCER Motesanib diphosphate can induce partial remissions in patients with progressive advanced metastatic DTC unresponsive to surgery, external beam radiotherapy and ¹³¹I. Sherman SI, Wirth LJ, Droz JP, Hofmann M, Bastholt L, Martins RG, Licitra L, Eschenberg MJ, Sun YN, Juan T, Stepan DE, Schlumberger MJ. Motesanib diphosphate in progressive differentiated thyroid cancer. *N Engl J Med* 2008;359:31-42. 23

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THYROID CANCER Papillary thyroid cancer (PTC) recurs in up to 30% of patients. Surgery and radioactive iodine therapy are the mainstays of therapy in such cases. The current ATA treatment guidelines recommend compartment-directed neck surgery for patients with lymph node metastases and no evidence of distant metastases (lung or bone) as the first line of therapy. Schuff, K. G., Weber, S. M., Givi, B., Samuels, M. H., Andersen, P. E., and Cohen, J. I. Efficacy of nodal dissection for treatment of persistent/recurrent papillary thyroid cancer. *Laryngoscope* 118(5), 768-775. 2008. 29

GRAVES' DISEASE IN CHILDREN Relapse of hyperthyroidism in children with Graves' disease treated with antithyroid drugs Kaguclidou F, Alberti C, Castanet M, Guitteny MA, Czernichow P, Leger J. Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. *J Clin Endocrinol Metab* 2008;93: 3817 30

GRAVES' DISEASE IN PREGNANCY Pregnant women with Graves' disease in remission after antithyroid drug therapy are at high risk of developing recurrent hyperthyroidism during the postpartum period Rotondi M, Cappelli C, Pirali B, Pirola I, Magri F, Fonte R, Castellano M, Rosei EA, Chiovato L. The effect of pregnancy on subsequent relapse from Graves' disease after a successful course of antithyroid drug therapy. *J Clin Endocr* 31



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CLINICAL THYROIDOLOGY FOR PATIENTS

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EDITOR'S COMMENTS

Clinical Thyroidology for Patients is a collection of summaries of recently published articles from the medical literature that covers the broad spectrum of thyroid disorders. A similar but more technical publication exists for physicians. This is written expressly for patients, although you are welcome to read the physician version which has considerably more technical information and is also available at the American Thyroid Association website at www.thyroid.org.

This issue provides brief summaries of papers published from medical centers around the world, including new studies on the treatment of thyroid cancer, subclinical hypothyroidism and subacute thyroiditis.

Throughout the summaries there are links to abstracts in the literature and to websites that provide educational material that we think may be helpful. Simply click on the URL and the information will appear.

This is a service provided by the American Thyroid Association to help patients understand the complicated and often bewildering language of modern medicine. This publication is for informational purposes and is meant to serve as a link between patients and their doctors, to help you understand difficult and sometimes baffling thyroid problems. Knowledge is a powerful means of dealing with difficult problems and we hope this journal will provide a source of strength and light that will assist patients in making day-to-day decisions about their thyroid health.

Ernest L. Mazzaferri, MD, MACP

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THYROID CANCER

WHAT IS THE STUDY ABOUT?

Motesanib diphosphate can induce partial remissions in patients with progressive advanced metastatic DTC unresponsive to surgery, external beam radiotherapy and ¹³¹I.

THE FULL ARTICLE TITLE: Sherman SI, Wirth LJ, Droz JP, Hofmann M, Bastholt L, Martins RG, Licitra L, Eschenberg MJ, Sun YN, Juan T, Stepan DE, Schlumberger MJ. Motesanib diphosphate in progressive differentiated thyroid cancer. *N Engl J Med* 2008;359:31-42. <http://www.ncbi.nlm.nih.gov/pubmed/18596272?dopt=Citation>

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Differentiated thyroid cancers such as papillary or follicular thyroid cancer, as well as other thyroid cancers express vascular endothelial growth factor (VEGF) and tyrosine kinases and other genetic features that regulate the growth and invasion of malignant tumors. This is a study of a new drug that appears to be helpful in patients with advanced cancer that is unresponsive to standard therapy.

WHAT WAS THE AIM OF THE STUDY?

The study was done to evaluate the efficacy and tolerability of motesanib diphosphate in patients with progressive, locally advanced or metastatic differentiated thyroid cancer.

WHO WAS STUDIED?

The study subjects were 93 patients who had progressive, locally advanced, or metastatic, radioactive iodine-resistant papillary, follicular, Hürthle cell, or other forms of thyroid cancer that were not amenable to standard therapeutic measures.

HOW WAS THE STUDY DONE?

The patients were treated with 125 mg of motesanib diphosphate, administered orally once daily. The main end point of the study was an objective response as assessed by an independent radiographic review using the RECIST Criteria as well as additional end points including the duration of the response, progression-free survival and safety.

WHAT WERE THE RESULTS OF THE STUDY?

The objective response rate was 14%. Stable disease was achieved in 67% of the patients, and was maintained for 24 weeks or longer in 35%; 8% had progressive disease as the best response. The most common treatment-related complications were diarrhea (59%) high blood pressure (56%) fatigue (46%) and weight loss (40%). There are other complications (see the website link above under the full title of the article).

HOW DOES THIS COMPARE WITH OTHER STUDIES?

There are no published studies to compare with this excellent study published in the *New England Journal of Medicine*. The full study information can be retrieved at the following web link: <http://content.nejm.org>

WHAT ARE THE LIMITATIONS OF THIS STUDY?

The decrease in serum thyroglobulin levels and its correlation with the tumor response, although consistent with other findings with radioiodine therapy, probably underestimated the efficacy of the study because thyroglobulin secretion and treatment with motesanib diphosphate caused increases in serum thyrotropin (TSH).

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This new drug can induce partial responses in patients with advanced tumor disease.

ABBREVIATIONS & DEFINITIONS

VEGF is vascular endothelial growth factor. VEGF has been shown to be responsible for the development and maintenance of a vascular network that promotes tumor growth and metastasis. A large and growing body of evidence indicates that both VEGF gene expression and VEGF production are associated closely with poor prognosis of thyroid cancer.

Motesanib diphosphate (AMG 706) is a novel oral inhibitor of VEGF receptors, platelet-derived growth-factor receptor, and KIT, all of which are involved in tumor growth and invasion

RECIST is Response Evaluation Criteria in Solid Tumors. Which is recommended for National Cancer Institute sponsored trials and involves formalized rules for measurement of tumor target lesions. Further explanation can be found at the NCI website: <http://imaging.cancer.gov/clinicaltrials/imaging/>

Web links are provided to provide further information



THYROID CANCER

WHAT IS THE STUDY ABOUT?

Radiation doses delivered to extrathyroidal tissues by ^{131}I is significantly lower in euthyroid patients treated with recombinant human thyrotropin than in hypothyroid patients undergoing thyroid hormone withdrawal.

THE FULL ARTICLE TITLE: Radiation doses delivered to extrathyroidal tissues by ^{131}I is significantly lower in euthyroid patients treated with recombinant human thyrotropin than in hypothyroid patients undergoing thyroid hormone withdrawal. Remy H, Borget I, Leboulleux S, Guilabert N, Lavielle F, Garsi J, Bournaud C, Gupta S, Schlumberger M, Ricard M. ^{131}I Effective Half-Life and Dosimetry in Thyroid Cancer Patients. *J Nucl Med* 2008;49:1445-50. <http://www.ncbi.nlm.nih.gov/pubmed/18703593?dopt=Citation>

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

There is strong evidence that ^{131}I treatment of thyroid cancer may induce a very small number of extrathyroidal cancers and leukemia, making it imperative that precautionary measures be exercised in the use of ^{131}I treatment of patients with differentiated thyroid carcinoma, especially young patients who generally have a good prognosis and long life expectancy, leaving them at risk of second tumors over many years. One measure is to use the smallest amount of ^{131}I that can effectively treat the patient. The other measure is to employ safeguards that might lower the extent of total body radiation from ^{131}I . Recent studies suggest that preparing patients with recombinant human thyrotropin (rhTSH) may favorably influence the effective half-life of ^{131}I and the absorbed doses by extrathyroidal organs. However, there still are uncertainties about the extent to which this occurs, and this issue requires further study.

WHAT WAS THE AIM OF THE STUDY?

This study was aimed at identifying the extent of tissue radiation that was delivered after preparation with thyroid hormone withdrawal (THW) and with rhTSH.

WHO WAS STUDIED?

Whole-body retention of ^{131}I was measured in 254 patients with papillary or follicular thyroid cancer, and repeated quantitative whole-body scans and measurements of the urinary excretion of ^{131}I were performed on 30 of these patients.

HOW WAS THE STUDY DONE?

This is a prospective study of patients with differentiated thyroid carcinoma treated with ^{131}I at Institut Gustave Roussy in Paris between December 2004 and June 2007, some of whom were prepared for treatment by THW for 5 weeks, during which triiodothyronine was administered for 3 weeks and total withdrawal was performed for 2 weeks, and others were treated

with 0.9 mg of rhTSH on two consecutive days during which the patients continued to take levothyroxine in preparation for treatment with ^{131}I . The amount of tissue radiation was compared in patients undergoing THW in preparation for ^{131}I therapy, with those undergoing preparation with recombinant human TSH.

WHAT WERE THE RESULTS OF THE STUDY?

The Mean effective half-life of ^{131}I is shorter by 31% in euthyroid patients treated with rhTSH compared with that in hypothyroid patients undergoing THW, which significantly decreases the radiation doses delivered to extrathyroidal tissues. Combined with smaller amounts of ^{131}I , the amount of whole body radiation delivered by ^{131}I remnant ablation can be substantially reduced. What this means is that much less irradiation is delivered to normal tissues with rhTSH without interfering with the effectiveness of the drug in treating thyroid tissues.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

The results of this study added complementary new information to studies done on this subject

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Preparation with rhTSH and using lower doses of ^{131}I reduces the risk of developing non-thyroid tissue and organ damage from ^{131}I .

ABBREVIATIONS & DEFINITIONS

TSH Thyroid stimulating hormone (thyrotropin) is a pituitary hormone that stimulates the release of thyroid hormone from the thyroid gland. TSH levels increase when the thyroid gland fails to make sufficient thyroid hormone.

Recombinant human TSH Diagnostic and treatment tools have also improved in recent years such as sensitive assays for serum thyroglobulin measurement, neck ultrasonography, and recombinant human thyrotropin (rhTSH). This drug is now approved by the Federal Drug Administration (FDA) for both diagnostic use and for treatment with ^{131}I for thyroid remnant ablation after initial surgery. More information about the guidelines for the use of this drug are available at the following Web links for the American Thyroid Association Guidelines for the management of thyroid cancer: <http://www.thyroid.org/professionals/publications/documents/Guidelinsthy2006.pdf>

Euthyroid is normal thyroid function.

Effective Half-life is a combination of the time (hours) that radioiodine remains in a cell and the half life of the radioisotope (^{131}I) which is about 8 hours during which the radioactivity slowly abates.



THYROID CANCER

WHAT IS THE STUDY ABOUT?

Extrathyroidal tissue radiation damage from ^{131}I remnant ablation is significantly less with rhTSH preparation than with thyroid hormone withdrawal.

THE FULL ARTICLE TITLE: Rosario PW, Borges MA, Purisch S. Preparation with recombinant human thyroid-stimulating hormone for thyroid remnant ablation with ^{131}I is associated with lowered radiotoxicity. *J Nucl Med* 2008;49:1776-82. <http://www.ncbi.nlm.nih.gov/pubmed/18927337?dopt=Citation>

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Although it is well established that preparation with recombinant human thyroid-stimulating hormone (rhTSH) for thyroid remnant ablation results in lower extrathyroidal radiation than hypothyroidism does, there are no studies directly connecting this information with tissue damage in patients treated with ^{131}I .

WHAT WAS THE AIM OF THE STUDY?

The aim of this prospective study was to compare the tissue damage caused by ^{131}I (100 mCi) when patients were prepared with rhTSH or thyroid hormone withdrawal for ^{131}I remnant ablation

WHO WAS STUDIED?

The study subjects were consecutive patients with papillary thyroid cancer (PTC) or follicular thyroid cancer who underwent total thyroidectomy and remnant ablation with 100 mCi (3.7 MBq).

HOW WAS THE STUDY DONE?

Damage to salivary glands, ovaries and testes, bone marrow and to other tissues was evaluated after preparation with rhTSH or thyroid hormone withdrawal. The serum amylase for salivary gland studies were obtained before and 48 h after ^{131}I ; and salivary pain was evaluated at 2 and 7 days after ^{131}I . Follicle stimulating hormone (FSH) was measured immediately before and 6 months after ^{131}I in both men and women.

WHAT WERE THE RESULTS OF THE STUDY?

There was significantly less damage to the salivary glands, ovaries, testes, bone marrow and other tissues when patients underwent preparation with rhTSH compared with thyroid hormone withdrawal.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

The results of this study added complimentary new information to studies done on the subject of non-thyroid tissue injury by ^{131}I .

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Preparation with rhTSH and using lower doses of ^{131}I reduces the risk of damage to non-thyroid tissues in response to ^{131}I therapy for remnant ablation.

ABBREVIATIONS & DEFINITIONS

FSH This is a pituitary hormone that rises when there is damage to the ovary or testes from a variety of conditions.

Recombinant human TSH Diagnostic and treatment tools have also improved in recent years such as sensitive assays for serum thyroglobulin measurement, neck ultrasonography, and recombinant human thyrotropin (rhTSH). This drug is now approved by the Federal Drug Administration (FDA) for both diagnostic use and for treatment with ^{131}I for thyroid remnant ablation after initial surgery. More information about the guidelines for the use of rhTSH are available at the following Web links for the American and European Thyroid Association Guidelines for the management of thyroid cancer. <http://www.thyroid.org/professionals/publications/documents/Guidelinsthy2006.pdf>

Euthyroid is normal thyroid function



THYROID NODULES

WHAT IS THE STUDY ABOUT?

There is debate about the management of patients who have a thyroid nodule that yields indeterminate follicular cytology on fine-needle aspiration biopsy (FNAB). One of the options is to perform a frozen section diagnosis (FSD) at the time of thyroid lobectomy, which might spare an unnecessary second operation in the 20% of patients with malignant nodules. This study analyzed the option of FSD in this situation.

THE FULL ARTICLE TITLE: Peng Y, Wang HH. A meta-analysis of comparing fine-needle aspiration and frozen section for evaluating thyroid nodules. *Diagn Cytopathol.*2008;36:916-920. <http://www.ncbi.nlm.nih.gov/pubmed/18855886?dopt=Citation>

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

There is debate about the management of patients who have a thyroid nodule that yields indeterminate follicular cytology on fine-needle aspiration biopsy (FNAB). Among the options is frozen section diagnosis (FSD) at the time of thyroid lobectomy, which might spare an unnecessary second operation in the 20% of patients with malignant nodules that have indeterminate FNAB cytology.

WHAT WAS THE AIM OF THE STUDY?

The aim of this study was to perform a meta-analysis of the literature related to this problem using FNAB and FSD.

WHO WAS STUDIED?

Patients who underwent thyroid FNAB or FSD, some of whom had indeterminate cytology on FNAB examination.

HOW WAS THE STUDY DONE?

This is an analysis of the medical literature. A PubMed search was performed to identify articles in English published from January 1982 to April 2007 that permitted comparisons of the diagnostic accuracy of FNAB and FSD specimens in the same study. The literature search yielded 62 publications, 52 of which met the study criteria.

WHAT WERE THE RESULTS OF THE STUDY?

The meta-analysis failed to demonstrate superiority of FNAB over FSD. Although FSD appears to have a higher specificity (99%) and positive predictive value than FNAB, its low sensitivity of FSD (21%) significantly limits its applicability in practice.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

There are no other meta-analyses of this problem.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Frozen section diagnosis of follicular thyroid nodules may have higher specificity and positive predictive value than fine-needle aspiration biopsy, but FSD is not sensitive enough in most hospitals to use the test for routine clinical use. There also is a major difference in the accuracy of FSD among hospitals and pathologists, mainly owing to the frequency with which the test is run in each hospital.

ABBREVIATIONS & DEFINITIONS

FSD is frozen section diagnosis At the time of surgery a pathologist can perform a rapid analysis of tissue that the surgeon has removed, which has literally been frozen to prepare for a microscopic examination by a pathologist. It can make a major difference in the extent of surgery performed during the operation. For example this could be the difference between lobectomy and total thyroidectomy at the first operation.

Sensitivity This is the percent of thyroid cancers that are accurately identified by a test (true positive).

Specificity This the percent of thyroid cancers that are correctly identified as a negative test which is identified as such (true negative).

Positive Predictive Value The percent that have the disease when the test is positive

Negative Predictive Value The percent that do not have the disease when the test is negative



THYROIDITIS

WHAT IS THE STUDY ABOUT?

Subacute thyroiditis (SAT) is a self-limited inflammatory disorder of the thyroid. This is a study aimed at further documenting the clinical characteristics of the disorder based on laboratory and imaging studies before treatment.

THE FULL ARTICLE TITLE: Nishihara E, Ohye H, Amino N, Takata K, Arishima T, Kudo T, Ito M, Kubota S, Fukata S, Miyauchi A. Clinical characteristics of 852 patients with subacute thyroiditis before treatment. *Intern Med* 2008;47:725-9.
<http://www.ncbi.nlm.nih.gov/pubmed/18421188?dopt=Citation>

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

SAT is a self-limiting inflammatory disorder of the thyroid. It is the most common cause of painful thyroid and may account for up to 5% of clinical thyroid abnormalities. This is a study aimed at further documenting the clinical characteristics of the disorder based on laboratory and imaging studies before treatment.

WHAT WAS THE AIM OF THE STUDY?

The aim of the study was to document the laboratory and clinical features of SAT.

WHO WAS STUDIED?

The subjects are 852 patients with SAT who were cared for at the Thyroid Clinic at Kuma Hospital in Japan from 1996 to 2004. The diagnosis was based on clinical features of thyroid swelling, pain and tenderness and an elevated C-reactive protein (CRP) and elevated serum free thyroxine (FT₄) and decreased serum thyrotropin (TSH) or suppressed 24-hour radioiodine uptake (RAIU), negative or weakly positive serum anti-thyroid antibodies, and an ultrasound hypoechoic area in a region of thyroid tenderness.

HOW WAS THE STUDY DONE?

The onset of SAT was defined as the time at which thyroid pain and tenderness developed. Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and CRP were also measured. To evaluate the acute phase of SAT before treatment, laboratory and imaging studies were divided into three groups: <7 days, 30±5 days and >60 days.

WHAT WERE THE RESULTS OF THE STUDY?

The monthly distribution during which SAT occurred clustered mainly from summer to early autumn. In all, 68% of the patients developed unilateral or bilateral neck pain at the onset, and 23% experienced nasal discharge, cough and sputum within 1 month before the onset of SAT, and 28% had temperatures >38°C (100.4°F). A total of 62% of the patients developed typical

symptoms of thyrotoxicosis, including palpitations, increased sweating, and weight loss. Within 1 month of the onset of SAT, the serum TSH and ALT declined significantly (<0.05), compared with TSH and ALT levels measured within 7 days of onset, and were clearly different in the three time periods. The other laboratory tests did not change significantly. Nine patients (1.6%) in the cohort had episodes of recurrent SAT with an interval of 13±5.6 years between the first and second episodes. Ultrasound examination showed that half of the patients with unilateral thyroid pain presented with bilateral hypoechoic area in the thyroid and the rate of bilateral hypoechoic area tended to increase 2 months after onset.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

The results of this study are comparable to other studies, although most other reviews recommend glucocorticoid or nonsteroidal anti-inflammatory therapy.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The principle finding in this study is that few abnormal laboratory tests occur in the first 30 days following the initial manifestations of SAT, with the exception of serum TSH levels, which are significantly suppressed within 30 days of the initial symptoms of SAT, and remained suppressed for more than 60 days. Before treatment, most of the abnormal laboratory findings associated with thyrotoxicosis, inflammation, and liver dysfunction reached peak levels within 1 week after onset.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Serum TSH levels are significantly lower within 30 days after the onset of subacute thyroiditis but other routine laboratory tests show little change.

ABBREVIATIONS & DEFINITIONS

TSH is thyroid stimulating hormone, a pituitary tumor that stimulates the thyroid gland. It rises when the thyroid fails to make sufficient thyroid hormone and declines when thyroid hormone secretion is low

AST (aspartate aminotransferase) is a blood test that rises with liver damage

ALT (alanine amino transferase) is a blood test that rises with liver damage

FT₄ is one of the thyroid hormones circulating in the blood stream

CRP is C-reactive protein, which rises in the blood stream when inflammation occurs



SUBCLINICAL HYPOTHYROIDISM

WHAT IS THE STUDY ABOUT?

Subclinical hyperthyroidism is the most prevalent thyroid dysfunction in older Italians living in Italy and is associated with cognitive impairment. This is a population-based study of persons living in Chianti (Tuscany, Italy).

THE FULL ARTICLE TITLE: Ceresini G, Lauretani F, Maggio M, Ceda GP, Morganti S, Usberti E, Chezzi C, Valcavi R, Bandinelli S, Guralnik JM, Cappola AR, Valenti G, Ferrucci L. Thyroid Function Abnormalities and Cognitive Impairment in Elderly People: Results of the Invecchiare in Chianti Study. *J Am Geriatr Soc* 2008. <http://www.ncbi.nlm.nih.gov/pubmed/19054181?dopt=Citation>

WHAT WAS THE AIM OF THE STUDY?

The study was done to investigate the relationship between thyroid dysfunction and cognition.

WHO WAS STUDIED?

The study comprised 1208 participants who were not being treated with drugs known to interfere with thyroid function. Three patients with dementia were excluded. The final study population for the study of thyroid dysfunction comprised 1171 subjects (652 women and 519 men).

HOW WAS THE STUDY DONE?

Blood samples collected in the morning after a 12-hour fast and plasma samples were analyzed for thyrotropin (TSH), free thyroxine (FT₄), and triiodothyronine (T₃). Global cognitive performance was assessed using the Mini-Mental Status Examination (MMSE).

WHAT WERE THE RESULTS OF THE STUDY?

Subclinical hypothyroidism and subclinical hyperthyroidism were more prevalent in older than in younger participants (subclinical hypothyroidism, 3.5% vs 0.4%, $P < .03$; subclinical hyperthyroidism, 7.8% vs 1.9%, $P < .002$). In euthyroid participants, TSH and FT₃ declined with age, while FT₄ increased. Older participants with subclinical hyperthyroidism had lower mean \pm SD MMSE scores than euthyroid subjects (22.61 \pm 6.88 vs. 24.72 \pm 4.52, $P < .03$). In adjusted analyses, participants with subclinical hyperthyroidism were significantly more likely to have cognitive dysfunction (hazard rate 52.26, $P = 0.003$). Subclinical hypothyroidism and subclinical hyperthyroidism were both more prevalent in older than in younger individuals.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

The results of this study added complementary new information to studies done on this subject

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The main finding is that subclinical hyperthyroidism is the most prevalent thyroid dysfunction in older Italian persons and is associated with cognitive impairment. No studies have addressed treating elderly patients with subclinical hyperthyroidism to improve dementia. Whether treating the subclinical hyperthyroidism—or for that matter, subclinical hypothyroidism—would ameliorate cognitive dysfunction is unknown, but some studies suggest such treatment might not be efficacious.

ABBREVIATIONS & DEFINITIONS

TSH Thyroid stimulating hormone (thyrotropin) is a pituitary hormone that stimulates the release of thyroid hormone from the thyroid gland. TSH levels increase when the thyroid gland fails to make sufficient thyroid hormone.

T₃ is triiodothyronine which is the most powerful form of thyroid hormone, accounting for most of the immediate activity of thyroid hormone.

T₄ is levothyroxine, the second main form of thyroid hormone, much of which is transformed to T₃ by enzymes situated in various organs.

Euthyroid is normal thyroid function

Mini-Mental Status Examination (MMSE) is a brief, quantitative measure of cognitive status in adults. It can be used to screen for cognitive impairment, to estimate the severity of cognitive impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individual's response to treatment. see this web link for further information: <http://www.minimental.com/>



THYROID CANCER

WHAT IS THE STUDY ABOUT?

Papillary thyroid cancer (PTC) recurs in up to 30% of patients. Surgery and radioactive iodine therapy are the mainstays of therapy in such cases. The current ATA treatment guidelines recommend compartment-directed neck surgery for patients with lymph node metastases and no evidence of distant metastases (lung or bone) as the first line of therapy. The likelihood of repeat surgical interventions in rendering patients free of disease is currently unknown. The aim of this retrospective study was to determine the efficacy and safety of central or lateral neck lymph node dissection in patients with recurrent PTC.

THE FULL ARTICLE TITLE: Schuff, K. G., Weber, S. M., Givi, B., Samuels, M. H., Andersen, P. E., and Cohen, J. I. Efficacy of nodal dissection for treatment of persistent/recurrent papillary thyroid cancer. *Laryngoscope* 118(5), 768-775. 2008. <http://www.ncbi.nlm.nih.gov/pubmed/18197134?dopt=Citation>

WHO WAS STUDIED?

The study subjects were 75 patients who had 79 lymph node dissections for persistent/residual papillary thyroid carcinoma.

HOW WAS THE STUDY DONE?

The primary outcome was the thyroglobulin (Tg) response to lymph node dissection. The secondary outcomes were surgical complications.

WHAT WERE THE RESULTS OF THE STUDY?

Of the 39 classifiable resections, 16 (41%) resulted in undetectable postoperative TSH-stimulated Tg levels. An

additional 12 resections resulted in significant (50% or more) reductions in suppressed or TSH-stimulated Tg levels for an overall improvement rate of 72%. Of all 79 resections, 25 (32%) resulted in minor and 7 (9%) resulted in major complications. The 7 (9%) major complications, included permanent hypoparathyroidism (7% of resections at risk), significant abscess requiring tracheostomy for airway and management and operative drainage, and pulmonary embolism after deep venous thrombosis LND for persistent/recurrent PTC is a relatively safe procedure in experienced hands. It can lead to an undetectable Tg in 41% of cases and produce a major Tg reduction in an additional 31%.

WHAT WAS THE AIM OF THE STUDY?

This study was done to evaluate the efficacy and morbidity of lymph node dissection in recurrent/persistent papillary thyroid short-term follow-up is comparable with that reported for I-131, and it should be considered in the management of persistent/recurrent PTC.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

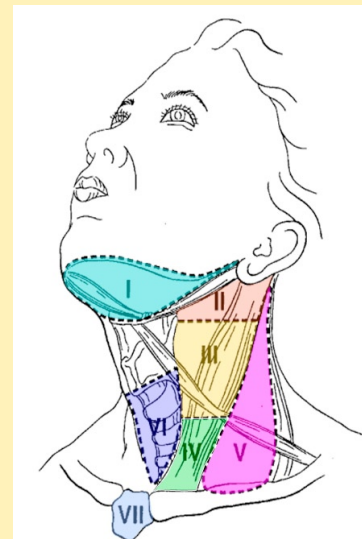
The data in this study, as well as some previous reports, suggest that in experienced hands, central compartment dissection does not increase the risk of hypoparathyroidism compared with lateral nodal dissection

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

In experienced hands, systematic compartment-based nodal dissection is a safe and efficacious treatment for persistent/recurrent PTC.

This figure shows the neck compartments used by surgeons to delineate the areas of lymph node metastases.

- Level I:** Contains the nodes of the submental and submandibular triangles, defined inferiorly by the digastric muscles.
- Level II:** Contains the upper jugular nodes from the base of skull to hyoid bone.
- Level III:** Contains the middle jugular nodes from the hyoid bone to the inferior edge of the cricoid cartilage.
- Level IV:** Contains the low jugular nodes from the cricoid cartilage to the clavicle.
- Level V:** Contains the nodes of the posterior triangle that is bounded anteriorly by the sternocleidomastoid muscle and posteriorly by the trapezius.
- Level VI:** Contains the nodes of the anterior central compartment from the hyoid bone to the manubrium with lateral boundaries being the carotid arteries
- Level VII:** Contains the superior mediastinal nodes from the level of the superior edge of the manubrium to the innominate vein.





GRAVES' DISEASE IN CHILDREN

WHAT IS THE STUDY ABOUT?

Relapse of hyperthyroidism in children with Graves' disease treated with antithyroid drugs

THE FULL ARTICLE TITLE: Kaguelidou F, Alberti C, Castanet M, Guittény MA, Czernichow P, Leger J. Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. *J Clin Endocrinol Metab* 2008;93:3817
<http://www.ncbi.nlm.nih.gov/pubmed/18628515?dopt=Citation>

WHAT WAS THE AIM OF THE STUDY?

This study was done to identify factors that predict relapse of hyperthyroidism in children with Graves' disease treated with antithyroid drugs (ATDs).

WHO WAS STUDIED?

This is a prospective, multicenter cohort study of 154 children with Graves' disease treated with carbimazole (an antithyroid drug). They were all younger than 19 years of age, and no neonatal thyrotoxic babies were included in the study.

HOW WAS THE STUDY DONE?

The intent was to treat all patients with one or two daily doses of carbimazole at a starting dose of 0.5 mg/kg per day, but over time this was decreased by 20 to 40% to maintain euthyroidism. The primary outcome was relapse of hyperthyroidism. Patients had clinical evaluations on months 1, 2, 3, 6, 9, 12, 18 and 24 months.

WHAT WERE THE RESULTS OF THE STUDY?

Older children were less likely to experience a relapse of hyperthyroidism after ATD withdrawal with a decrease in risk of 26% for every 5-year increase in age. Non-Caucasian patients were found to be 2.5-fold more likely to suffer a relapse than Caucasian patients. Also, a 10-point increase in serum FT₄ and a 10-unit increase in the multiple of upper normal limit for serum TRAb levels at diagnosis resulted in an 18 and 21% increase of relapse risk, respectively.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

A number of studies suggest that antithyroid drugs should be used for 12 to 18 months, and longer duration of treatment generally has no advantage. There are few studies of hyperthyroid Graves' disease, but several others also suggest that extending the duration of treatment may be beneficial.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The main implication of the study is that children may require longer periods of treatment with antithyroid drugs, although this study was not structured to determine how much longer children should be treated. Also, there are a number of studies in adults that find no advantage in treating a patient with hyperthyroid Graves' disease longer than 18 months. A European multicenter trial found that the dose of methimazole in Graves' disease can safely be kept to the minimal required dose, which will provide the same chance of remission as higher doses, thus providing the best balance of risk and benefit. The other uncertainty in the management of hyperthyroid children is compliance. The evidence suggests that treatment adherence is generally lower in children than in adults, particularly in adolescents as they approach independence.

ABBREVIATIONS & DEFINITIONS

Carbimazole is a form of antithyroid drug used in Europe, which is closely related to and comparable with methimazole that is used in the United States.

TSH Thyroid stimulating hormone (thyrotropin) is a pituitary hormone that stimulates the release of thyroid hormone from the thyroid gland. TSH levels increase when the thyroid gland fails to make sufficient thyroid hormone.

FT₃ is triiodothyronine is the most powerful form of thyroid hormone, accounting for most of the immediate activity of this hormone.

FT₄ is free levothyroxine, the second main form of thyroid hormone, much of which is transformed to T₃ by enzymes situated in various organs.

Euthyroid is normal thyroid function.

TRAb is anti-thyrotropin receptor antibodies. This is a key antibody that stimulates thyroid secretion of thyroid hormones in patients with Graves' disease.



GRAVES' DISEASE IN PREGNANCY

WHAT IS THE STUDY ABOUT?

Pregnant women with Graves' disease in remission after antithyroid drug therapy are at high risk of developing recurrent hyperthyroidism during the postpartum period

THE FULL ARTICLE TITLE: Rotondi M, Cappelli C, Piralì B, Pirola I, Magri F, Fonte R, Castellano M, Rosei EA, Chiovato L. The effect of pregnancy on subsequent relapse from Graves' disease after a successful course of antithyroid drug therapy. *J Clin Endocrinol Metab* 2008;93:3985-8.
<http://www.ncbi.nlm.nih.gov/pubmed/18483014?dopt=Citation>

WHAT WAS THE AIM OF THE STUDY?

This study was done to evaluate the effect of pregnancy and the postpartum (PP) period upon the clinical relapse of hyperthyroidism in patients with Graves' disease who are in remission after antithyroid drug treatment (ATD).

WHO WAS STUDIED?

In all, 150 females with Graves' disease were studied. All had completed a full course of at least 12 months of methimazole (MMI) therapy with restoration of euthyroidism lasting for at least 6 months after withdrawal of ATD.

HOW WAS THE STUDY DONE?

To evaluate the role of pregnancy and the PP period, patients were divided into two groups: those in group I did not become pregnant after stopping MMI, and patients in group II had at least one successful pregnancy after stopping MMI.

WHAT WERE THE RESULTS OF THE STUDY?

There was a significantly lower relapse rate in group I (56%) than in group II patients (84%, $P < 0.05$). Further analysis found that the time to relapse after MMI was significantly shorter in Group I than in Group II ($P < 0.0001$), indicating that only the number of pregnancies after ATD withdrawal was significantly related to the occurrence of relapsing hyperthyroidism. To discriminate the role of pregnancy and the PP period, the timing of the relapse was further evaluated in the patients in group II. During gestation, none of the patients in group II had a relapse of hyperthyroidism; however, 20 of 21 patients (95.2%), had a relapse during the PP period, between 4 and 8 months after delivery, whereas only 1 of 21 women (4.8%) had a relapse of hyperthyroidism after the PP period (24 months after delivery). Pregnancy was recorded after MMII withdrawal in only 4 of 59 patients (6.8%) who remained in remission throughout the study period. The overall relapse rate of hyperthyroidism after ATD treatment was 60.1%. The relative risk for relapsing Graves' disease after ATD was only

significantly higher in pregnancies after ATD withdrawal and was not related to a positive family history of autoimmune thyroid disease, duration of MMI treatment or the number of pregnancies at diagnosis of Graves' disease.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

Other studies also find that the relapses of Graves' hyperthyroidism generally occur during the PP period.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Pregnant women with Graves' disease in remission after antithyroid drug therapy are at high risk of developing recurrent hyperthyroidism during the postpartum period.

ABBREVIATIONS & DEFINITIONS

Methimazole is an anti-thyroid drug that is used to treat hyperthyroidism (an over-active thyroid gland) which is generally not used in pregnancy because of certain rare complications in the fetus.

Propylthiouracil is another type of antithyroid drug that usually is preferred for treatment of Graves' hyperthyroidism during pregnancy.

Graves' disease is an autoimmune thyroid disease with several manifestations, including hyperthyroid goiter, eye and skin involvement and other manifestations. It is self-limited and can be treated with antithyroid drugs, radioiodine, or surgery.

The **National Graves' Disease Foundation** can be reached at the following:
<http://www.ngdf.org/>

For further definitions see the following:
http://en.wikipedia.org/wiki/Graves-Basedow_disease

T₃ is triiodothyronine, the most powerful form of thyroid hormone, accounting for most of the immediate activity of this hormone.

T₄ is levothyroxine, the second main form of thyroid hormone, much of which is transformed to T₃ by enzymes situated in various organs.

Euthyroid is normal thyroid function.