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EDITOR'S COMMENTS

This first issue of *Clinical Thyroidology* in 2009 will mark the beginning of several new features of the journal. As you may know, we have solved the problems with our electronic delivery. Each issue will be sent to you as a separate list of articles that can be downloaded separately or as the entire document.

WHATS NEW Beginning with this issue, *Clinical Thyroidology* will be delivered monthly. You will receive approximately 5 to 10 articles each month, providing nearly double the number of articles that we have sent in the past. You will also notice that the articles contain figures with the ATA logo and a citation with the volume and issue numbers. We encourage you to continue using figures from *Clinical Thyroidology* in your lectures, which we hope will be useful to you and your students. Also, we have changed the look of the journal. The font is larger and hopefully easier to read in an electronic and paper format. Lastly, we have designed a patient version of *Clinical Thyroidology*, which is *Clinical Thyroidology for Patients*. The journal for patients is now available on the American Thyroid Association website and physicians are welcome to distribute it to their patients.

Although not new to this issue, we have designated some articles as EDITOR'S CHOICE which we think are especially important articles that should be read in their entirety

We welcome your feedback and suggestions on these changes.

THANK YOU The editors thank Dr. Tuttle for the thoughtful *Concise Review* in this issue of *Clinical Thyroidology*. Beginning with the first review article by Dr. Elaine Ron, authors can cite our CONCISE REVIEWS by using the electronic citation at the end of each review.

We and our staff wish you all a happy, healthy and productive New Year.

Ernest L. Mazzaferri, MD, MACP
Jennifer A. Sipos, MD

How to navigate this document: The Table of Contents and the Bookmarks are linked to the articles. To navigate, move your cursor over the article title you wish to see (either in the Contents or in the Bookmarks panel) and the hand will show a pointing finger, indicating a link. Left-click the title and the article will instantly appear on your screen. To return to the Contents, move the cursor to the bottom of the page and left-click Back to Contents which appears on every page. If you would like more information about using Bookmarks please see the help feature on the menu bar of Acrobat Reader.

Citations: Several of our readers have asked that we provide the correct citation for Concise Reviews and Editorials written for *Clinical Thyroidology*. Beginning with this issue, an electronic citation will be appended at the end of each Concise Review and each Editorial. If our readers wish to cite commentaries at the end of each article, we can format the journal to do this as well.

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Novel therapeutic options for aggressive thyroid cancer: Integrating information from the recent clinical trials into clinical practice

INTRODUCTION

The vast majority of thyroid cancer patients respond very well to our initial therapeutic interventions which usually include total thyroidectomy with appropriate lymph node dissection and selective use of radioactive iodine (^{131}I) ablation (1). In patients responding to this initial therapy, disease specific survival rates of more than 90 to 95% can be expected at 30 to 40 years of follow up (2; 3).

Unfortunately, there is a small cohort of thyroid cancer patients that have structurally progressive disease that is refractory to additional ^{131}I therapy and not amenable to further surgery or external beam irradiation. Most of these are older patients with either poorly differentiated thyroid cancer or one of the aggressive forms of differentiated thyroid cancer such as the tall cell, insular, or Hürthle cell variants. The most aggressive cases have disease that is markedly positive on 18FDG PET scanning (4). It is in this group of patients with ^{131}I-refractory, structurally progressive thyroid cancer that novel therapies are most urgently needed because without an effective systemic therapy, the 3 to 5-year survival rates can be less than 50% (5; 6).

TRADITIONAL APPROACH TO SYSTEMIC THERAPY IN THYROID CANCER

Currently, the only FDA approved drug for the treatment of ^{131}I-refractory thyroid cancer is doxorubicin (Adriamycin®). This approval was granted on the basis of several case series and relatively small uncontrolled trials in the 1970's and 1980's that demonstrated largely short term (usually less than a few months) partial response rates as high as 20 to 30% when doxorubicin was used either as a single agent or combined with other cytotoxic chemotherapy (7). None of these studies were done using the modern, standardized definitions of complete response, partial response, and disease progression (8) and therefore it is difficult to compare the clinical outcomes described in these older studies with the new phase 2 studies published over the last several years. However it is important to note that because of the toxicity profile and the lack of clinically meaningful durable responses, these agents are currently seldom used in clinical practice at major cancer centers and neither the American Thyroid Association (ATA) (9) nor the National Comprehensive Cancer Network (NCCN) guidelines (10) require patients to fail doxorubicin chemotherapy prior to enrollment in clinical trials.

WHAT ARE THE POTENTIAL TARGETS?

Over the last several years, our understanding of the pathophysiology of thyroid cancer has increased dramatically (11; 12). It is becoming increasingly apparent that the receptor tyrosine kinase/MAP kinase pathway is important in the initiation and progression of thyroid cancer. The descriptions of non-overlapping mutations in ret/PTC, ras, and BRAF in as many as 70% of differentiated thyroid cancers emphasize the central role of this pathway in the pathophysiology of differentiated thyroid cancer. Furthermore, angiogenesis appears to play a key role in tumor growth making inhibition of the vascular endothelial growth factor tyrosine kinase receptor pathway an attractive target for many experimental therapies (13).

PHASE 2 CLINICAL TRIALS IN THYROID CANCER

TRIAL DESIGN ISSUES

Over the last 10 years, at least nine Phase 2 clinical trials have been published that have examined the therapeutic effects of a wide variety of anti-neoplastic agents on structurally measurable disease in patients with ^{131}I-refractory differentiated thyroid cancer (15-23). Clinical trials designed primarily to evaluate re-differentiation therapy or medullary thyroid cancer therapies are not included in this review. In most phase 2 trials, a cohort of 20 to100 patients with the same malignancy are treated with a selected dose of the drug in question. Usually these studies are non-randomized trials that do not include an untreated control group.

Table 1 presents a summary of the design of the 9 most recently published phase 2 clinical trials (15-23). Most of the trials enrolled primarily differentiated thyroid cancer patients (papillary thyroid cancer, follicular variants of papillary thyroid cancer, follicular thyroid cancers and other aggressive variants including poorly differentiated thyroid cancers) while often including an exploratory arm that allowed enrollment of patients with medullary thyroid cancer or anaplastic thyroid cancer. All of the trials required structurally identifiable disease, usually at least one lesion larger than 1 cm in diameter, but varied widely in the requirement (and definition) of disease progression prior to entry.

Structural responses to anti-neoplastic agents in modern clinical trials are most commonly reported using a standardized set of definitions commonly referred to as RECIST (response evaluation criteria in solid tumors) criteria (8). A defined set of "target" lesions is identified that will be carefully measured (usually with CT or MRI) prior to therapy and at specific intervals during the trial. Other visible lesions that are not part of this initial measurement set are referred to as non-target lesions. A complete response is defined as the disappearance of all target and non target lesions (these findings must be confirmed 4 weeks later to meet this definition) A partial response requires at least a 30% decrease in the longest diameter of a single tumor or the sum of longest diameters of multiple target lesions (also confirmed at 4 weeks). Progressive disease is defined as a greater than 20% increase in the longest diameter of a single tumor or the sum of longest diameters in multiple target lesions or the appearance of new lesions. By default, stable disease means that the patient did not meet criteria of complete response, partial response or progressive disease. It is important to note that an increase in longest diameter of up to 19% or a decrease as much 29% would be classified as "stable disease" using RECIST criteria. In most studies, a graph (waterfall plot) is presented showing the best response obtained during therapy (expressed as percent decrease or increase in the longest diameter) for each individual patient.

Table 1: Study Design

	Ain 2000	Mrozek 2006	Ain 2007	Woyach 2008	Argiris 2008	Pennell 2008	Sherman 2008	Cohen 2008	Gupta-Abramson 2008
Agent	Paclitaxel	Celecoxib	Thalidomide	Vorinostat	Doxorubicin and interferon alpha 2b	Gefitinib	Motesanib	Axitinib	Sorafenib
Target*	Anti-microtubule agent	Cox-2 inhibitor	Anti-angiogenesis	Histone deactylase inhibitor	Cytotoxic + immune modulatory agent	EGFR	VEGFR, PDGFR, Kit	VEGFR	VEGFR, BRAF
Histology**	Anaplastic	DTC	DTC MTC	DTC MTC	DTC Anaplastic	DTC Anaplastic MTC	DTC	DTC MTC Anaplastic	DTC MTC Anaplastic
Entry Criteria	Measureable locally advanced or metastatic disease	Measureable locally advanced or metastatic disease	Unresectable distant metastases	Measureable locally advanced or metastatic disease	Measureable locally advanced or metastatic disease	Measureable locally advanced or metastatic disease	Measureable locally advanced or metastatic disease	Measureable locally advanced or metastatic disease	Measureable locally advanced or metastatic disease
Progression requirement for entry	Identification of persistent, recurrent, or metastatic disease	Structural progression or rising thyroglobulin in previous year	30% increase in tumor volume in previous year	None specified	None specified	Not required, but 89% had radiographic evidence of disease progression in previous 6 months	Documented disease progression by RECIST within 6 months	None specified	Structural progression in previous year (93% had FDG PET positive disease)
Primary Endpoint***	2 week durable response	Objective response by RECIST	Tumor volume	Objective response by RECIST	Structural response (not RECIST)	Objective response by RECIST	Objective response by RECIST	Objective response by RECIST	Objective response by RECIST

* EGFR (Epidermal growth factor receptor), VEGFR (Vascular endothelial growth factor receptor), PDGFR (Platelet derived growth factor receptor)

** DTC includes PTC, FVPTC, FTC, all variants including poorly differentiated (excludes anaplastic and medullary thyroid cancers).

*** Objective response by RECIST (response evaluation criteria in solid tumors) includes either complete or partial response

PHASE 2 CLINICAL TRIALS IN THYROID CANCER

OUTCOMES

As can be seen in Table 2, most of the phase 2 trials are relatively small and have enrolled primarily older patients (median age ranged from 57 to 69 yrs at the time of enrollment) with a disproportionate percentage of male patients compared to the usual 2:1 (female to male) distribution ratio seen at diagnosis (15-23). Only 1 complete response was seen in the 335 thyroid cancer patients enrolled in the 9 trials (15). Partial responses (as defined by RECIST) were more common, ranging from 3 to 30% (Table 2).

It is often difficult to determine if "stable disease" during a clinical trial represents an actual clinical benefit to the individual patient. Because of the relatively slow structural disease progression rate in many thyroid cancer patients, "stable disease" can only be considered a meaningful clinical endpoint if it can be documented that the patient would have reasonably been expected to progress over the time frame of the study based on documentation of disease progression prior to entry into the study, or possibly markedly positive 18FDG PET scanning at entry. If stable disease is a primary study endpoint, the pre-study evaluation of disease progression should be done using the same imaging modality and time frame used during the study. Accordingly, because of the stricter entry criteria requiring documented structural disease progression in the 6 to12 months prior to study entry, the relatively high stable disease best response rates reported with thalidomide (16), gefitinib (21), motesanib (22), and sorafenib (19) probably represent a true clinical benefit.

More clinically relevant than the best obtained response is an assessment of the duration of disease stabilization. To that end, Sherman et al. reported a durable stable disease rate (>24 weeks) of 35% of their cohort treated with motesanib yielding a clinical benefit of 49% (14% with partial response and 35% with durable stable disease) (22). Furthermore, a careful analysis of the waterfall plots (best obtained response expressed as percent change) demonstrate that most patients in the motesanib diphosphate (22), axitinib (18), and sorafenib (19) studies had some degree of tumor shrinkage as the best obtained response even though many did not reach the 30% decrease required for classification as a partial response.

While the precise rates of partial response and durable stable disease remains to be defined for each of these agents, it appears that these novel agents are more active than doxorubicin based cytotoxic chemotherapy. Unfortunately, it appears that these agents are more often cytostatic rather than tumoricidal since the rates of tumor stabilization far exceed the rates of partial or complete tumor responses. Therefore, the most common response that can be expected when patients are enrolled on these phase 2 trials is either stabilization of disease or minor decrease in tumor size that does not meet the RECIST definition of a partial response.

PHASE 2 CLINICAL TRIALS IN THYROID CANCER
TOXICITIES

Even though the clinical outcomes in some of these phase 2 trials are very promising, they are not achieved without significant toxicities. In the sorafenib (19), axitinib (18), and motesanib trials (22), 13 to 20% of patients discontinued the drug because of intolerable side effects. The likelihood of discontinuing the drug secondary to unacceptable side effects appeared slightly higher in the vorinostat study (56%) (23) and in the thalidomide study (16) than in the other phase 2 studies.

Fortunately, the vast majority of the side effects were reversible with discontinuation of the drug and often were dose related. As such, temporary interruption of the drugs with re-institution at lower dose levels was not an uncommon event in most of the studies. While the side effects varied depending on the drug, the most common side effects were fatigue, diarrhea, rash, weight loss, nausea, and hypertension. As would be expected, the vorinostat side effect profile included significant thrombocytopenia (23) and the doxorubicin/interferon-2b study had expected neutropenia, thrombocytopenia and cardiotoxicity (17). Although several patients died while on trial or shortly thereafter, only one death was thought to be possibly related to study medication (liver failure despite dose reduction and cessation of sorafenib) (19).

PHASE 2 CLINICAL TRIALS IN THYROID CANCER
FINDING THE TRIALS

With the widespread use of the internet search engines, patients and health care professionals are becoming very adept at identifying available clinical trials. Both the ATA (http://www.thyroidtrials.org) and the National Cancer Institute (http://www.cancer.gov/clinicaltrials) have specific web sites that will identify most thyroid cancer clinical trials that are open and enrolling patients.

PHASE 2 CLINICAL TRIALS IN THYROID CANCER
INTEGRATION INTO CLINICAL PRACTICE

When selecting patients for enrollment in clinical trials, it is of paramount importance that we differentiate those patients with stable, persistent disease from those that are having rapid structural disease progression (24). Because the most common clinical outcome in the phase 2 trials is stable disease, there seems to be little clinical benefit at this time in exposing patients that already have stable or very slowly progressive structural disease to the risks of experimental therapies. Likewise, patients

Table 2: Outcomes

	Ain 2000	Mrozek 2006	Ain 2007	Woyach 2008	Argiris 2008	Pennell 2008	Sherman 2008	Cohen 2008	Gupta-Abramson 2008
Agent	Paclitaxel	Celecoxib	Thalidomide	Vorinostat	Doxorubicin and interferon alpha 2b	Gefitinib	Motesanib	Axitinib	Sorafenib
Enrolled (n)	20	32	36	19	17	27	93	60	31
Histology*	20 ATC	32 DTC	29 DTC 7 MTC	16 DTC 3 MTC	15 DTC 2 ATC	18 DTC 5 ATC 4 MTC	93 DTC	46 DTC 12 MTC 2 ATC	27 DTC 1 MTC 2 ATC
Age at enrollment, median yrs (range)	58 (47-68)	65 (42-89)	57 (26-87)	62 (40-77)	69 (54-58)	65	62 (36-81)	59 (26-84)	63 (31-89)
Male Gender	65%	41%	67%	36%	47%	59%	53%	58%	50%
Outcome evaluable (n)	19	32	28	19	16	21	82	45	25
Best outcome **Complete response** **Partial response** **Stable Disease** **Progressive Disease**	 5% 47% 5% 42%	 0 3% 38% 59%	 0 18% 32% 50%	 0 0 56% 44%	 0 6% 63% 31%	 0 0 81% 19%	 0 14% 67% 8%	 0 40% 51% 9%	 0 23% 53% 3%

*DTC includes PTC, FVPTC, FTC, all variants including poorly differentiated (excludes anaplastic (ATC) and medullary thyroid cancers).

** Best outcome as a percentage of the evaluable patients.

whose only evidence of progressive disease is a rising serum thyroglobulin in the absence of localizable disease are also not generally eligible for clinical trials in which the primary endpoints are the effect of the drug on structurally identifiable disease.

In our practice, we select patients for clinical trials that have refractory differentiated thyroid cancer with structurally progressive lesions that cannot be adequately treated with additional local measures (such as surgery or external beam irradiation). While not an absolute requirement for entry onto a clinical trial, most patients have 18FDG-avid disease and negative ^{131}I diagnostic scans. Patients with metastatic disease that is either stable or very slowly progressive are followed with expectant observation and serial cross sectional imaging without additional treatments beyond TSH suppressive therapy.

In most cases, we define structurally progressive disease as a 20% or greater increase in size of the dominant lesion over a 6 month period, or as new metastatic lesions in the setting of at least one measurable lesion greater than 1 cm. Patients meeting these criteria would likely qualify for most clinical trials. However, the final decision about whether or not to begin a clinical trial (once these inclusion criteria are met) is based on the preferences of the patient, the rate of structural disease progression, other co-morbidities, the sites of progressive disease, and toxicities of the proposed therapy.

Over the last several years we have often been in the position of helping our patients decide which one of several available clinical trials would be best for them. Unfortunately, this decision usually has to be made based on estimates of side effects and logistical issues (such as location of the trial, number of visits required, and potential impact on work/family) rather than a specific knowledge of clinical benefit (partial response or disease stabilization). While it is attractive to select specific agents on the basis of the specific molecular abnormalities in the patient's individual tumor (11), it remains unknown whether this approach will lead to better outcomes than using one of the multi-targeted tyrosine kinase agents currently in clinical trials. To address this important issue, it is imperative that clinical trials include an assessment of clinical response based on the specific molecular profile of primary/metastatic tumor.

In keeping with the ATA and NCCN thyroid cancer guidelines, we offer Phase 2 clinical trials (and some Phase 1 clinical trials) as the preferred alternative to traditional doxorubicin based cytotoxic chemotherapy for patients with ^{131}I-refractory, structurally progressive disease. Patients ineligible or unwilling to participate in clinical trials are offered either a cytotoxic chemotherapy regimen or off label use of sorafenib depending on the specific details of the patient involved.

As with most of solid tumor oncology, it is logical to assume that combination therapies will be required to produce clinically meaningful disease regression and cures. With the promising results seen in the recent trials of the multi-targeted tyrosine kinase inhibitors and the expanding understanding of the molecular pathophysiology of thyroid cancer, we anticipate clinical trials in the near future that combine agents that block several different key steps in these important pathways.

It is now readily apparent that thyroid cancer has much more in common with other human solid tumors than we previously appreciated. As such, many of the lessons learned in solid tumor biology can be translated into our understanding of the treatment of thyroid cancer. Given the complexity of the treatment choices available, effective care of these patients with rapidly progressive, ^{131}I-refractory thyroid cancers require a multidisciplinary approach in which a wide variety of sub-specialty knowledge is brought to bear on the needs of an individual patient.

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Motesanib diphosphate can induce partial remissions in patients with progressive advanced metastatic differentiated thyroid cancer unresponsive to surgery, external beam radiotherapy and ^{131}I

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.

SUMMARY

BACKGROUND Thyroid cancers are highly vascular, overexpressing vascular endothelial growth factor (VEGF), which is a potent angiogenesis stimulator associated with aggressive tumor behavior and a poor clinical outcome. Inhibition of VEGF receptor (VEGFR) signaling inhibits the growth of thyroid tumors. This is a study of motesanib diphosphate, an oral, small-molecule tyrosine kinase inhibitor of VEGFR-1, 2, and 3; platelet-derived growth-factor receptor, and KIT in the management of differentiated thyroid cancer (DTC).

METHODS This is an open-label single-group, phase 2 study of motesanib diphosphate in the management of thyroid cancer. Study subjects were patients with progressive, ^{131}I-resistant, metastatic or locally advanced DTC that was not amenable to conventional therapy, who within 6 months before entry into the study, had at least one tumor defined as measurable according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. None had untreated brain metastases and all had disease progression of at least one tumor according to the RECIST criteria. The primary end point of the study was an objective response to 125 mg of motesanib diphosphate administered orally once daily. Secondary end points were the duration of the response, progression-free survival, and changes in serum thyroglobulin (Tg) concentrations, although a rising serum thyroglobulin level was insufficient evidence for disease progression.

RESULTS Study subjects were 93 patients (44 female [47%] and 49 male [53%]) with a median age of 62 years (range, 36 to 81). All had thyroidectomy and external-beam radiotherapy, and 90 (97%) had one or more courses of ^{131}I therapy prior to enrolling in the study. In all, 57 patients (61%) had papillary thyroid cancer, 17 (18%) had Hürthle-cell cancer, 15 (16%) had follicular cancer, and 4 (4%) had other forms of DTC. Tumor was locally advanced in 1 patient (1%) and metastatic in 92 others (99%). All patients received one or more doses of the drug, and 32 (34%) completed 48 weeks of treatment. The other 61 patients discontinued the drug prematurely because of disease progression (35), adverse events (12), patient request (6), or death (5), and 1 each because of withdrawal of consent, an administrative decision, or protocol deviation. The median duration of treatment of all patients was 35 weeks (range, 0.4 to 56), and the median follow-up was 50 weeks (range, 1 to 77). The median time to response was 15 weeks (95% confidence interval [CI], 8 to 27). For all patients, the median duration of progressive-free survival was 32 weeks for a response and 40 weeks for progression-free survival.

Thirteen patients (14%) achieved the primary end point of a confirmed objective response (14%; 95% CI, 7.7 to 22.7), all of which were partial responses (Figure 1). In all, 62 patients (67%) had durable stable disease (24 weeks or more) and 9 others (10%) had unconfirmed partial responses classified as stable disease (Figure 1). In all, 49% of the patients had either durable stable disease or a confirmed partial response, and 7 patients (8%) had disease progression as the best response (Figure 1).Tumor measurements decreased in 69 patients (74%). Median progression-free survival was 40 weeks (95 % CI, 32 to 50; Figure 2). The survival rate at 12 months was 73% (95 % CI, 63 to 83).

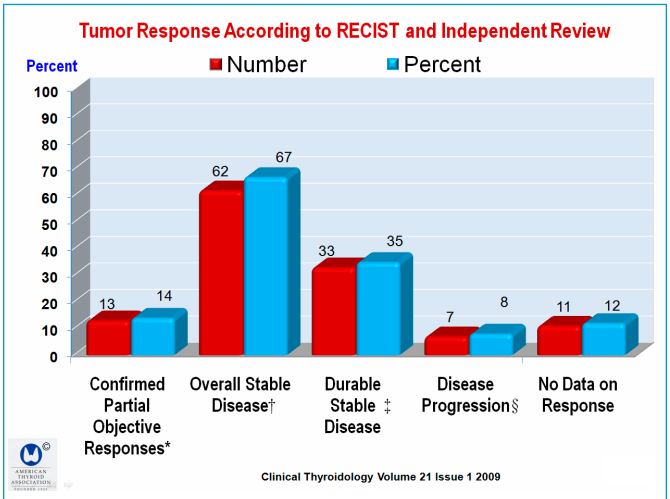

Figure 1. *All confirmed responses were partial. †Nine (10%) unconfirmed responses were classified as stable disease. ‡Durable stable disease is 24 weeks or more. §The best observed response in seven patients (8%). This figure is derived from data in Table 2 in Sherman et al.

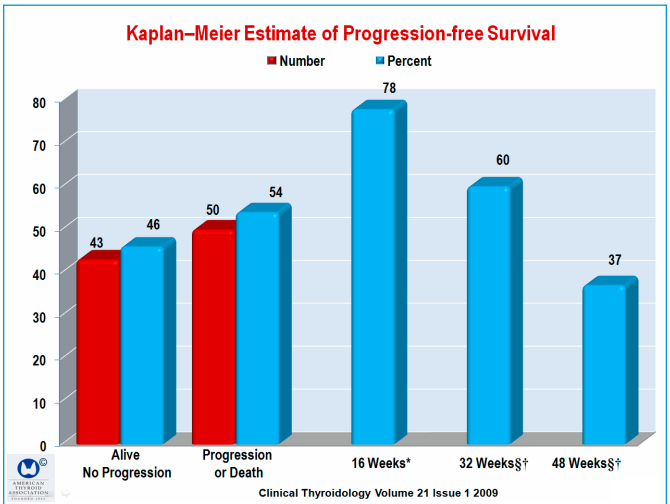

Figure 2. §The Kaplan–Meier estimate of the median duration of progression-free survival was 32 weeks. *Kaplan-Meier progression-free survival at three time periods are shown as percent and †95% Confidence Intervals: 78% (95% CI 69 to 87) 60 (95% CI 50 to 71 and 37 (95% CI 24 to 50) for 16, 32 and 48 wks, respectively. Figure is derived from data in Table 2 in Sherman et al.

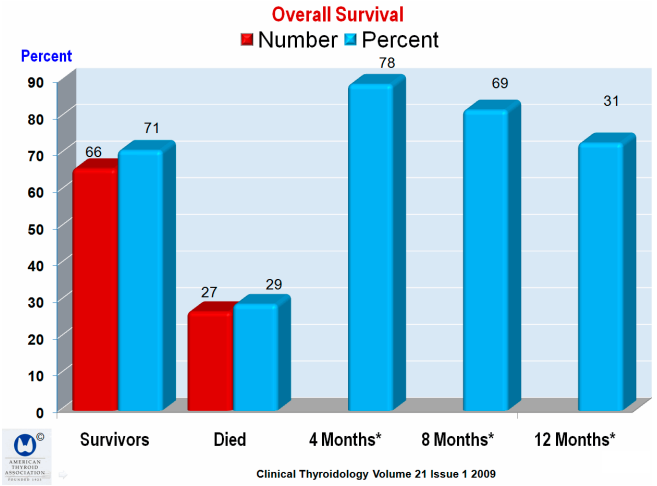

Figure 3. Overall Survival. *Kaplan-Meier estimate of survival at three time periods. This figure is derived from data in Table 2 in Sherman et al.

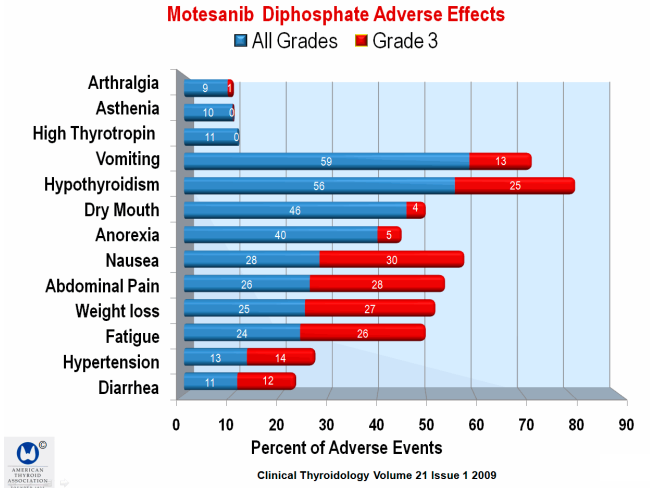

Figure 4. A total of 87 patients (94%) had at least one treatment-related adverse event. The most common treatment-related adverse events were diarrhea in 59% of the patients, hypertension in 56%, fatigue in 46%, and weight loss in 40%. This figure is derived from data in Table 2 in Sherman et al.

Overall, 46 (49%) of the patients had either a confirmed partial response or durable stable disease (Figure 1) and 27 (29%) died of disease (Figure 3).

A total of 87 patients (94%) had at least one treatment-related adverse event, and 2 patients died of disease (Figure 4). In all, 62 patients (67%) had stable disease. Among the 75 patients in whom thyroglobulin (Tg) analysis was performed, 81% had decreased serum Tg concentrations during treatment, as compared with baseline levels.

CONCLUSION Motesanib diphosphate can induce partial responses in patients with progressive advanced ^{131}I-nonresponsive metastatic DTC.

COMMENTARY

Until recently there has been little interest in the development of new drugs for the treatment of thyroid cancer, largely because the vast majority of patients (approximately 80%) have papillary thyroid cancer associated with about a 7% 10-year cancer-specific mortality rate (1). Although cancer death rates are higher in other forms of DTC, most follicular cell tumors can be effectively treated with total thyroidectomy and ^{131}I. As a consequence, even patients with distant or locoregional metastases may have a good prognosis. Yet when deaths do occur, they are caused by metastases that fail to take up enough ^{131}I to make treatment effective, which occurs in up to 75% of the patients, especially older patients and those with tumors that have BRAF mutations. The mainstay of therapy for this advanced stage is usually surgery, external-beam radiotherapy and tumor embolization. When this becomes ineffective, chemotherapy until now has had little impact on outcome, often leaving oncologists and endocrinologists less than enthusiastic about this option for progressive disease. However, the treatment of refractory thyroid cancer is likely to change dramatically in the next year or two. A thoughtful editorial by Pfister and Fagin (2) earlier this year predicted that translation of the advances in our understanding of tumor biology and drug development for thyroid cancer will lead to a paradigm shift in treatment that is likely to benefit patients who until recently have had few therapeutic options. This prediction is already coming true.

This important study by Sherman et al. shows that motesanib diphosphate can induce objective responses among patients with refractory thyroid cancer. The study underscores why oncologists must become involved in the treatment of these patients and why endocrinologists must become familiar with the new drugs that are becoming available, which may have serious adverse effects. This has important implications for the patient concerning day-to-day management. Who is best suited for such treatment? It is likely that the best approach is for both groups of physicians to forge close liaisons, bringing to bear the best expertise of two specialties. Among the myriad management issues, perhaps the most complex is the slow growth of some thyroid cancers, which makes it difficult to know exactly when to treat patients with a new drug. Endocrinologists who have cared for patients over an extended time generally have a good feel for the progression of tumor in their patients. Sherman et al. used a model that practitioners might follow, using the explicit and reproducible RECIST criteria to know when patients should be considered for clinical trials or placed on new drugs known to be effective.

In this issue of Clinical Thyroidology, Dr. R. Michael Tuttle, an expert in the management of advanced thyroid cancer, reviews the changing paradigms that are developing as a consequence of the availability of new thyroid cancer drugs.

Ernest L. Mazzaferri, MD, MACP

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The whole-body radiation delivered by ^{131}I remnant ablation can be significantly reduced by preparing patients with recombinant human thyrotropin rather than with 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.

SUMMARY

BACKGROUND There is compelling evidence that ^{131}I treatment of thyroid cancer may induce extrathyroidal cancers and leukemias. This makes it imperative that precautionary measures be taken when using ^{131}I treatment in 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 effective amount of ^{131}I to treat the patient. The other measure is to use safeguards that lower the extent of total-body radiation derived from ^{131}I. Recent studies suggest that preparing patients by administering recombinant human thyrotropin (rhTSH) may favorably influence the effective half-life of ^{131}I and reduce the radiation doses absorbed by extrathyroidal organs. However, there still are uncertainties about the extent to which this occurs, requiring further study of this issue.

METHODS This is a prospective study of patients with differentiated thyroid carcinoma treated with ^{131}I at the Institut Gustave Roussy from December 2004 through June 2007. Some of the patients were prepared for treatment by thyroid hormone withdrawal (THW) for 5 weeks, during which triiodothyronine (T_3) was administered for 3 weeks, and total withdrawal of thyroid hormone was performed for 2 weeks. The others remained on levothyroxine and were treated with 0.9 mg of rhTSH on 2 consecutive days in preparation for treatment with 100 mCi (3700 MBq) of ^{131}I. Twenty patients with low-risk cancer were treated with 30 mCi (1110 MBq). All had abundant hydration and were treated with laxatives during hospitalization. Three types of measurement were performed: whole-body counting in 245 patients, quantitative whole-body scans with total urinary ^{131}I excretion in 30, and urine samples from 19 who had THW and 11 treated with rhTSH. Whole-body retention of ^{131}I was measured by a probe fixed on the ceiling of each hospital room. From the three sets of available data (whole-body retention, whole-body scans, and urinary excretion), it was possible to extract dosimetry data on the organs of interest. The half-life (T1/2) is the time radioiodine remains in a body target divided by a factor of 2. The effective T1/2 is determined from the combination of physical isotope decay and the biologic T1/2 of ^{131}I (retention time of ^{131}I within the target cell), which is not dependent on the administered activity of ^{131}I (100 mCi or 30 mCi (Figure 1). Data from 254 patients were pooled for analysis.

RESULTS The mean effective whole-body half-life for the 30 patients who underwent repeated whole-body scans was 10.6 hr for the 11 who received rhTSH and 16.0 hr for the 19 who underwent THW (P = 0.0006), which was similar to those in corresponding patients in the entire series. The ^{131}I residence times for bladder, stomach, and colon were significantly different (Figure 2). The whole-body residence time was 15.2 hr in patients treated with rhTSH and 23.0 hr in the patients who underwent THW. The residence time in the stomach was significantly shorter (P = 0.01) in the patients treated with rhTSH as compared with those who underwent THW; however, there was no difference for the colon (P = 0.07), urinary bladder (P = 0.9), or breast (P = 0.53) (Figures 2 and 3). The residence time in the remainder of the

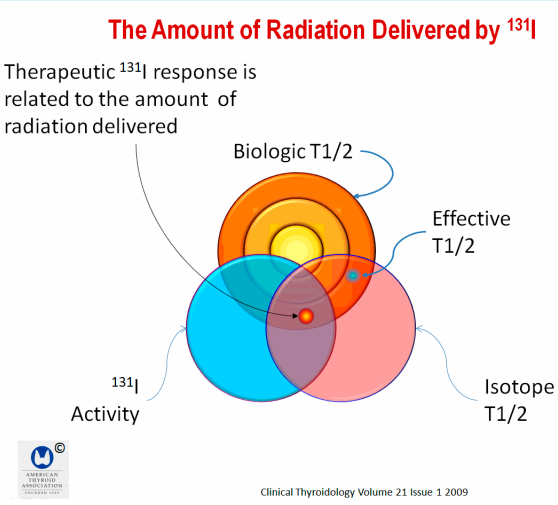

Figure 1. The effective half-life (T½) is a combination of the biologic T½ , (the residence time in the follicular cell or other body cell that concentrates ^{131}I) and the half-life of the isotope, which is approximately 8.1 days for ^{131}I. Activity is the "dose" of thyroid hormone (e.g., 30 mCi). Together, the three account for the total amount of iodine delivered to thyroid and other tissues, especially tissues that harbor sodium iodide symporters that facilitate movement of ^{131}I into a cell.

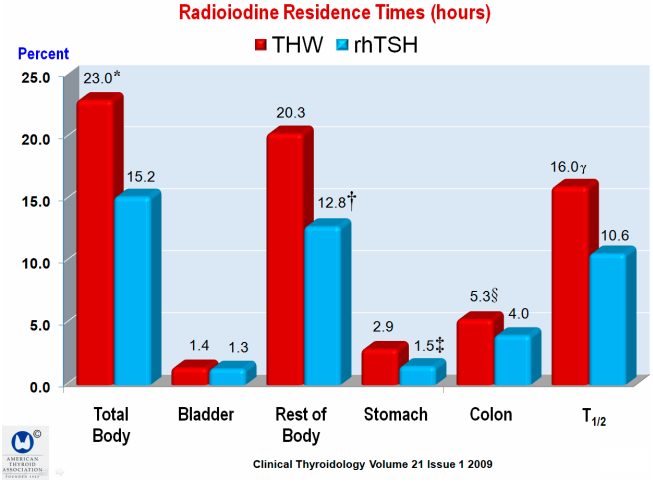

Figure 2. This depicts the residence times of ^{131}I within a cell from various tissues. THW denotes thyroid hormone withdrawal, and rhTSH recombinant human TSH. *P= 0.0006; †P = 0.04; ‡P = 0.01; §P = 0.07; γP = 0.0006. All comparisons are between rhTSH and THW. Data for this graph are derived from Table 3 in Remy et al.

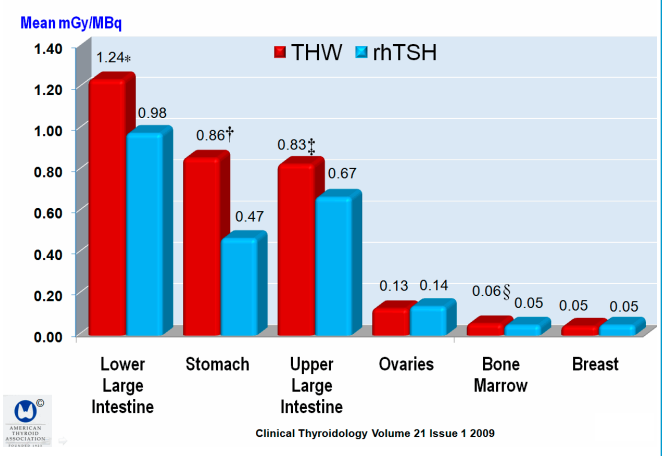

Figure 3. This figure depicts the dosimetry in terms of mean mGy of irradiation delivered to tissues per MBq of ^{131}I. *P = 0.09 †P= 0.009, ‡P = 0.05, *P = 0.05, †P = 0.009 ‡P = 0.05; §0.06. All comparisons are between rhTSH and THW. Data for this graph are derived from Table 4 in Remy et al.

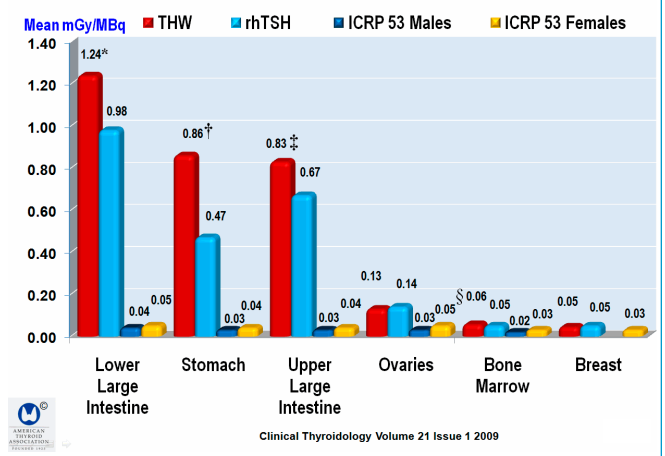

Figure 4. This is the same graph as shown in Figure 3, with the addition of data from the Commission on Radiological Protection (ICRP) that can be used for safe dose estimates in healthy subjects.*P = 0.09 †P= 0.009, ‡P = 0.05, *P = 0.05, †P = 0.009 ‡P = 0.05; §0.06; all comparisons are between rhTSH and THW. Data for this graph are derived from Table 4 in Remy et al.

body was shorter in patients treated with rhTSH as compared with those who underwent THW (P = 0.04) (Figure 3). The dose estimates were lower for the stomach (P = 0.009) and were of borderline significance for the upper large intestine (P = 0.05) and the bone marrow (P = 0.05) (Figures 3 and 4).

CONCLUSION The mean effective half-life of ^{131}I is shorter by 31% in euthyroid patients treated with rhTSH as 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.

COMMENTARY

This study is of major importance. It confirms and extends the previous report by Hänscheid et al. (1) on body retention of ^{131}I and elaborates on the radiation doses to blood and bone marrow and whole-body radiation following preparation with rhTSH and THW. The side effects of ^{131}I therapy are well known and are directly related to the amount of tissue radiation. As a consequence, patients can sustain considerable nonthyroidal tissue injury from ^{131}I, making them susceptible to a significantly higher risk of second nonthyroidal cancers as compared with the general population (2). There is a linear relationship between the amount of administered ^{131}I and the rate of second cancers (3) and tissue damage. Retrospective studies suggest that empiric ^{131}I dosing regimens, the most common approach used, frequently exceed the maximum tolerated radiation levels, especially in elderly patients (4, 5). One way to decrease these adverse effects is to substantially reduce the amount of ^{131}I for remnant ablation. The ATA guidelines suggest that the minimum ^{131}I activity (30 to 100 mCi) necessary to achieve successful remnant ablation should be used, particularly for patients at low risk (6). This recommendation is based on the fact that ^{131}I activities between 30 and 100 mCi generally show similar rates of successful remnant ablation (7-12) and recurrence (11), suggesting that 30 mCi is the preferred amount of ^{131}I for patients at low risk of adverse tumor outcomes.

The Remy study confirms that using rhTSH reduces the amount of radiation exposure by about one-third (13). It confirms previous reports on body ^{131}I retention (1) and on estimated doses to the blood and bone marrow, and that whole-body residence time is shorter in patients treated with rhTSH than in those who undergo THW, in whom residence time was longer than the 11.1 hr reported in the International Commission on Radiological Protection (ICRP) report 53. Although the ICRP data are usually considered the standard in the field of internal dosimetry, it does not provide powerful information when residence times are needed for calculations after the administration of therapeutic ^{131}I. In the Remy and Hänscheid (1) studies, the mean whole-body residence time was shorter in patients pretreated with rhTSH (17.3±3.9 hr and 15.2±3.1 hr, respectively) than in patients who had THW (24.1±7.8 hr and 23.0±7.7 hr).

In summary, these studies collectively provide robust evidence that the use of rhTSH in euthyroid patients significantly reduces the amount of whole-body radiation and radiation to tissues such as the lacrimal glands, stomach, breast, salivary glands and other organs that contain sodium iodine symporters and thus concentrate ^{131}I more avidly than other tissues. Taken together, these data suggest that ^{131}I for remnant ablation should routinely be administered with the smallest amount of ^{131}I that is effective, in the range of 30 mCi in patients at low risk, and that patients should be prepared with rhTSH for remnant ablation.

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Frozen-section diagnosis of follicular thyroid nodules may have higher specificity and positive predictive value than fine-needle aspiration biopsy, but is not sensitive enough for routine clinical use in most hospitals

Peng Y, Wang HH. A meta-analysis of comparing fine-needle aspiration and frozen section for evaluating thyroid nodules. Diagn Cytopathol 2008;36:916-20.

SUMMARY

BACKGROUND The treatment of patients who have a thyroid nodule that yields indeterminate follicular cytology on fine-needle aspiration biopsy (FNAB) is under debate. Among the options is to perform a frozen-section diagnosis (FSD) at the time of thyroid lobectomy, which might avoid an unnecessary second operation in the 20% of patients with indeterminate cytology that have malignant nodules. These authors performed a meta-analysis of the literature related to this problem.

METHODS A PubMed search was performed to identify English-language articles published from January 1982 through April 2007 that permitted comparisons of the diagnostic accuracy of FNAB and FSD specimens in the same study. Only publications providing sufficient information to determine the number of true positive and true negative tests and false positive and false negative tests were included in the study. FNAB diagnoses were stratified into three FNAB diagnostic categories: (1) follicular lesion/neoplasms and intermediate cytology with special findings such as follicular proliferation with atypia; (2) nonfollicular lesions (predominantly papillary thyroid cancer); and (3) thyroid carcinoma not otherwise specified (NOS). All three FNAB cytology terms were considered positive tests. Accuracy of FNAB and FSD were based on findings in the thyroidectomy specimen.

RESULTS The literature yielded 62 publications, 52 of which met the study criteria. There were 29 studies with 3027 cases with FNAB cytology in the group designated as a follicular lesion/neoplasm that were compared with 23 FSD studies with 2531 cases. In this group, the mean (±SD) sensitivity for FNAB as compared with FSD was 69±32 and 21±23 (P<0.0001), specificity 60±32 and 99±2.4 (P = 0.004), positive predictive value (PPV) 35±28 and 86±26 (P = 0.002), and negative predictive value (NPV) 84±19 and 83±16% (P = 0.03), comparing FNA and FSD, respectively (Figure 1).

In the follicular-lesion category there were only 4 studies and 646 cases in which the FNA cytology was categorized as intermediate. As compared with the 23 FSD studies, there were no statistically significant differences between FNAB and FSD. In the nonfollicular-lesion category there were 20 studies with 2307 cases and 20 FSD studies with 3533 cases. In this group, the mean (±SD) sensitivity of FNAB vs. FSD was 67±25 vs. 66±22, specificity 95±5.1 vs. 98±5.3, PPV 94±7.9 vs. 96±11, and NPV 79±16 vs. 84±13%, comparing FNAB with FSD; all comparisons in this group were statistically nonsignificant. In the nonfollicular-lesion category, there were 12 studies with 941 cases in which FNAB cytology was designated as suspicious. In this group, the FNAB and FSD sensitivity was 83±19 vs. 66±22 (P = 0.0003), specificity 67±23 vs. 98±5.3 (P = 0.005), PPV 81±16 vs. 96±11 (P = 0.0003), and NPV 85±17 vs. 84±13% (P = 0.67) (Figure 2).

In the thyroid cancer lesion termed NOS, there were 21 FNAB studies with 4704 cases compared with 21 FSD studies with 4970 cases. In this category, the sensitivity of FNAB and FSD was 54±19 vs. 71±13 (P = 0.0004), specificity 96±7.2 vs. 99±1.2 (P = 0.08), PPV 88±19 vs. 98±3.5 (P = 0.001), and NPV 87±8.5 vs. 92±6.4% (P = 0.002) comparing FNAB with FSD (Figure 3). In the thyroid cancer group designated only as suspicious, the

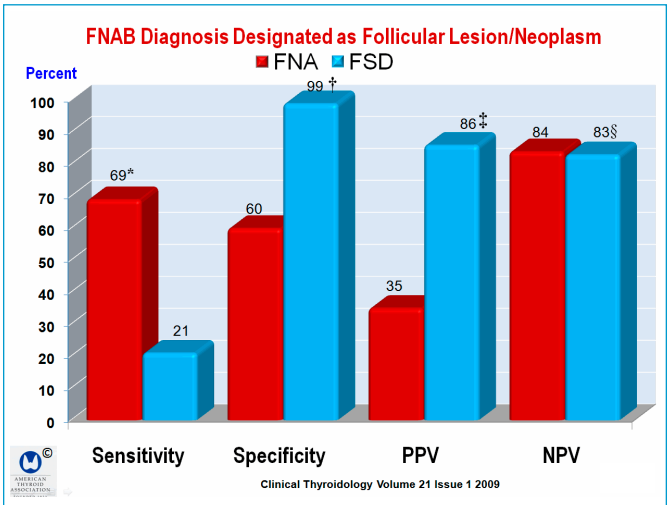

Figure 1. The diagnostic accuracy of fine-needle aspiration biopsy (FNAB) cytologic diagnosis of follicular lesion vs. frozen-section diagnosis (FSD). *P<0.0001., †P = 0.004. ‡P = 0.002.§Negative predictive value (NPV) = 0.03. Here and in the other figures, all comparisons are FNAB vs. FSD. The data in this figure are derived from Table 1 in Peng et al.

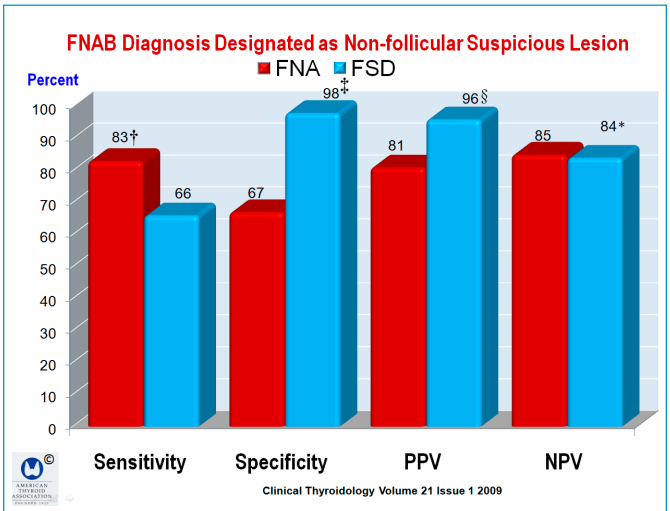

Figure 2. Diagnostic accuracy of FNAB and FSD.*P<0.0003, †P = 0.005, ‡P = 0.003, §P = 0.67. The data in this figure are derived from Table 2 in Peng et al.

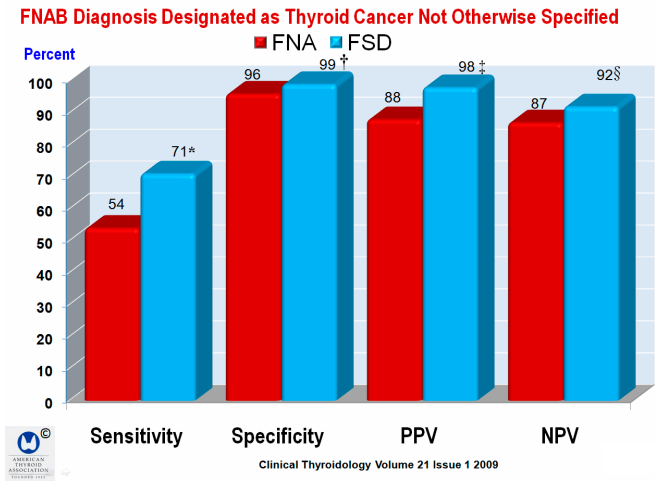

Figure 3. *P = 0.002, †P=0.0004, ‡P = 0.08, §P = 0.001. The data in this figure are derived from Table 3 in Peng et al.

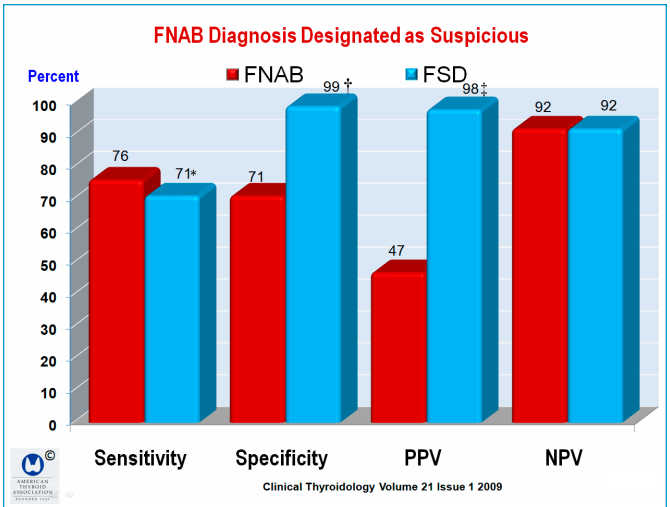

Figure 4. †P=0.0004, ‡P = 0.004 §0.002, *P = 0.002. The data in this figure are derived from Table 3 in Peng et al.

sensitivity of FNAB and FSD was 76±23 vs. 71±13 (P<0.001), specificity 71±21 vs. 99±1.2 (P = 0.004), PPV 47±19 vs. 98±3.5 (P = 0.002), and NPV 92±6.4 vs. 92±6.4% (P = 0.03), comparing FNAB with FSD (Figure 4).

CONCLUSION This meta-analysis fails to demonstrate superiority of FNAB over FSD. Although FSD appears to have a higher specificity and positive predictive value than fine-needle aspiration biopsy, its low sensitivity significantly limits its applicability in practice in most hospitals.

COMMENTARY

The only reason to raise the question asked in this study is how can one gauge the accuracy of identifying follicular thyroid cancer at the time of thyroid lobectomy in order to avoid patients undergoing needless completion thyroidectomy? What is the magnitude of this problem? Indeterminate cytology, often reported as “follicular neoplasm” or “Hürthle-cell neoplasm” can be found in approximately 15 to 30% of FNAB specimens, only 20% of which turn out to be malignant (1). While certain FNA and clinical features such as male sex, nodule size > 4 cm, older age, and cytologic features such as cellular atypia may improve the FNAB diagnostic accuracy for malignancy, the overall predictive values are low (2;3).

Peng et al. found that the specificity and positive predictive value of FSD is significantly higher than that of FNAB; however, the diagnostic sensitivity of FNAB, which ranges from 71 to 21 % (Figures 1 and 4) is generally higher than that of FSD, depending on exactly how the FNAB features are described by the cytopathologist. Although the diagnostic sensitivity of FSD is slightly greater than that of FNAB in some cases (Figure 3), there is a much more fundamental issue: FSD has a major advantage over FNAB because vascular or thyroid invasion is not apparent on FNAB, making it virtually impossible to meaningfully compare the two diagnostic approaches. In the final analysis, this study fails to demonstrate the superiority of FSD over FNAB, if for no other reason than that 1 to 2% of patients would still undergo unnecessary total thyroidectomy using FSD (Figures 1 to 4). It is doubtful that many patients would opt for this choice. Furthermore, there are widely divergent opinions in various centers concerning the use of FSD for thyroid nodules, which is likely to reflect the frequency with which FSD is practiced for thyroid nodules (4-10).

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Pregnant women with Graves' disease in remission after antithyroid drug therapy are at high risk of recurrent hyperthyroidism developing 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 Endocrinol Metab 2008;93:3985-8.

SUMMARY

BACKGROUND Pregnancy and the postpartum (PP) period induce major changes in the immune system that influence the clinical activity of autoimmune diseases. The aim of this study was to evaluate the effect of the PP period on the relapse of hyperthyroidism in patients with Graves' disease who were in remission after the withdrawal of antithyroid drug treatment (ATD).

METHODS This is a retrospective study of 150 women with Graves' disease. 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 ATD withdrawal. To evaluate the role of pregnancy and the PP period, patients were divided into two groups: those in group 1 did not become pregnant after stopping MMI, and patients in group 2 had at least one successful pregnancy after stopping MMI.

RESULTS A total of 214 women with Graves' disease fulfilled the study criteria. All were white. Their median age was 32 years (range, 19 to 43). There were 189 patients in group 1 and 25 in group 2. Because the mean (±SD) age was significantly greater in group 1 (32.1±5.3) than in group 2 (27.3±5.8) (P = 0.001), the patients in group 1 were stratified according to their age at diagnosis and, starting from the oldest patient, were excluded from the study until there were no significant differences in the mean ages of the two groups. After this adjustment, there were 125 patients with Graves' disease in group 1 who did not become pregnant after stopping MMI for a median of 17.5 months (range, 12 to 120). The length of follow-up was 16 months (range, 6 to 360), including the patients who experienced a relapse of hyperthyroidism. The two groups did not differ significantly in age, duration of MMI therapy, and follow-up. The relapse rate

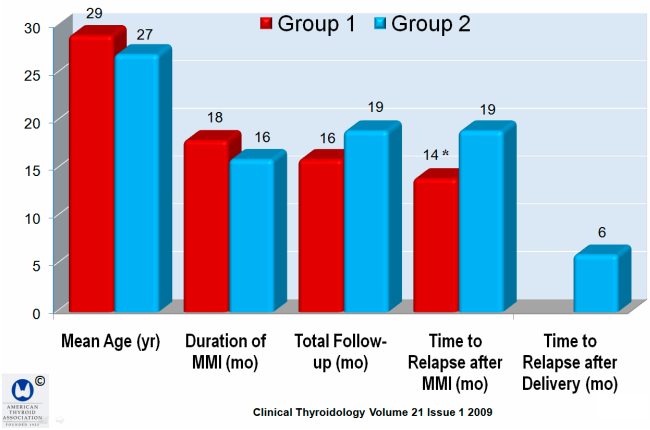

Figure 2. The only significant variable found on multivariate analysis is time to relapse after methimazole withdrawal, which was 14 months in group 1 (range, 6 to 144) and 19 months in group 2 (*P<0.0001). MMI denotes methimazole. Adapted from the data in Table 1 in Rotondi et al.

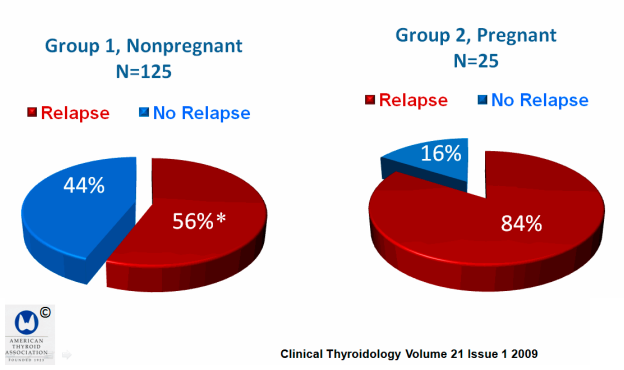

Figure 1. This figure shows relapsing Graves' hyperthyroidism in 21 of 25 patients who had a pregnancy after antithyroid drug (ATD) withdrawal (84.0%) and in 70 of 125 patients who did not become pregnant since ATD withdrawal (56.0%, *P<0.05). Adapted from the data in Figure 1 in Rotondi et al.

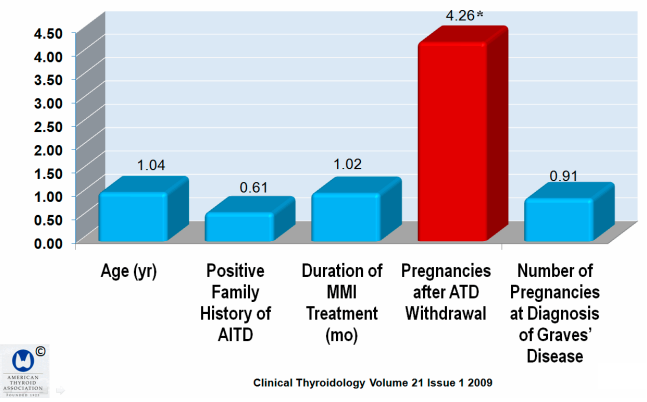

Figure 3. The relative risks for relapsing Graves' hyperthyroidism after antithyroid (ATD) drug withdrawal. MMI denotes methimazole. AITD is autoimmune thyroid disease. Adapted from the data in Table 2 in Rotondi et al.

was significantly lower in group 1 (56%) than in group 2 (84%) (P <0.05; Figure 1). Multiple regression analysis found that the time to relapse after MMI was significantly shorter in group 1 than in group 2 (P<0.0001; Figure 2), indicating that only the number of pregnancies after ATD withdrawal was significantly related to the occurrence of relapsing hyperthyroidism (Figure 3). To discriminate the role of pregnancy and the PP period, the timing of the relapse was further evaluated in the patients in group 2. During gestation, none of the patients in group 2 had a relapse of hyperthyroidism; however, 20 of 21 (95.2%) had a relapse during the PP period, between 4 and 8 months after delivery, whereas only 1 of 21 (4.8%) had a relapse of hyperthyroidism after the PP period (24 months after delivery). Pregnancy was recorded after MMI 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 (4.57, 95% confidence interval, 1.315 to 13.782, P = 0.016) 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 (Figure 3).

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

COMMENTARY

Relapse of Graves' hyperthyroidism usually occurs within the first 3 to 6 months after antithyroid drugs are stopped (1) and, over time, is approximately 50%, ranging from 30% to 60% in various studies (1-3). About 75% of women in remission after antithyroid drug therapy who become pregnant will have a relapse of Graves' hyperthyroidism or the development of postpartum thyroiditis 2 to 4 months postpartum (4).

The relapse rate of hyperthyroidism in the study by Rotondi et al. was 60% after antithyroid drug therapy was withdrawn and was significantly higher (84%) in patients who became pregnant after discontinuing the antithyroid drug therapy , compared with a 56% recurrence rate in women who did not became pregnant after discontinuing the drug. None of the patients had a relapse during the first trimester of gestation, whereas more than 95% of pregnant women in whom hyperthyroidism developed after antithyroid drug withdrawal did so during the PP period.

By multiple regression analysis, the relative risk of a relapse (4.26) of hyperthyroidism occurred almost exclusively in pregnant women after antithyroid drug withdrawal, and the results show that relapse of Graves' hyperthyroidism occurs almost exclusively during the postpartum period. None of the patients experienced a relapse of hyperthyroidism during gestation, and in 20 of 21 patients (95.2%), the relapse of Graves' hyperthyroidism occurred between 4 and 8 months after delivery.

Other studies have found that thyroid volume, serum levels of free thyroid hormones and antithyrotropin receptor antibody titers influence the recurrence rate of Graves' hyperthyroidism, but this group of variables was not explored in the Rotondi study. Rotondi et al. provide two caveats: first, thyroid function should be carefully monitored in women with Graves' disease who become pregnant, which is in accord with recent Endocrine Society guidelines (5), and second, definitive treatment with thyroidectomy or radioiodine should be strongly considered in women with Graves' disease who plan to become pregnant. Both seem like excellent options in this setting.

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Subclinical hyperthyroidism is the most prevalent thyroid dysfunction in older Italians and is associated with cognitive impairment

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 November 19, 2008. doi:10.1111/j.1532-5415.2008.02080.

SUMMARY

BACKGROUND The prevalence of overt and subclinical hypothyroidism in older populations is as high as 20%. Yet whether this affects health and functional status in older persons is uncertain. The aim of this study was to investigate thyroid function abnormalities in older persons and to explore the relationship between thyroid dysfunction and cognition.

METHODS The Invecchiare in Chianti, The InCHIANTI study, is a population-based study of persons living in the Chianti geographic area (Tuscany, Italy). The original study group comprised a total of 1453 persons whose age ranged from 20 to 102 years; representing 91.6% of the eligible population. The study was aimed at identifying measures clinicians could use to understand the causes of walking difficulties in older persons. Of the 1453 participants who had home interviews, 1343 (92%) donated a blood sample. Complete data on thyroid hormones and cognitive performance were available in 1208 participants who were not being treated with drugs known to interfere with thyroid function; also, 3 patients with dementia were excluded. The final study population for the study of thyroid dysfunction comprised 1171 subjects, 652 women (56%) and 519 men (44%). Blood and plasma samples collected in the morning after a 12-hour fast were analyzed for thyrotropin (TSH), free thyroxine (FT_4), and triiodothyronine (T_3). Global cognitive performance was assessed by the Mini–Mental State Examination (MMSE). A value less than 24 was considered to indicate cognitive impairment. Other information on demographics, smoking, and the use of medication were collected using standardized questionnaires. Weight, body-mass index (BMI), and the level of physical activity and exercise, nutrition and disease were also evaluated by standardized questionnaires. Participants were classified according to TSH and FT_4 and FT_3 concentrations into five categories: (1) overt hypothyroidism (TSH >4.68 μIU/ml, FT_4 <0.78 ng/dl); (2) subclinical hypothyroidism (TSH >4.68 μIU/ml, FT_4 = 0.77 to 2.19 ng/dl); (3) euthyroidism (TSH = 0.46 to 4.68 μIU/ml), (4) subclinical hyperthyroidism (TSH <0.46 μIU/ml, FT_4 = 0.77 to 2.19 ng/dl, FT_3 = 2.77 to 5.27 pg/ml); and (5) overt hyperthyroidism (TSH <0.46 μIU/ml, FT_4 >2.19 ng/dl, FT_3 >.27 pg/ml). Four patients with low T_3 syndrome with normal FT_3 and TSH levels were excluded from the analysis.

RESULTS Subclinical hypothyroidism was more prevalent in older than in younger participants (3.5% vs. 0.4%, P<0.03), as was subclinical hyperthyroidism (7.8% vs. 1.9%, P<002). Serum TSH and FT_3 declined with age in euthyroid participants, while FT_4 increased. Older participants (≥65 years) with subclinical hyperthyroidism had lower mean (±SD) MMSE scores than did euthyroid subjects (22.61±6.88 vs. 24.72±4.52, P<0.03). Participants with subclinical hyperthyroidism were, in an adjusted analysis, significantly more likely to have cognitive dysfunction (hazard rate [HR], 2.26; P = 0.003). Among 255 participants, 139

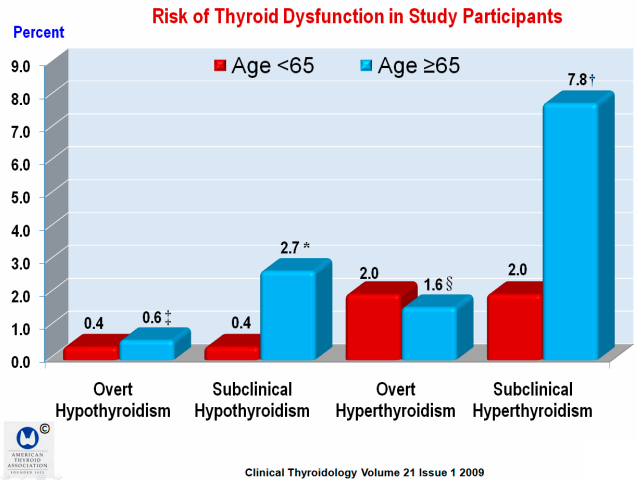

Figure 1. The risk of thyroid dysfunction in study participants younger than age 65 vs. participants 65 yr or older. 95% of the younger participants and 87% of the older participants were euthyroid. Subclinical hypothyroidism and subclinical hyperthyroidism were both more prevalent in older than in younger individuals, *P<0.03 and †P <0.002, respectively, while the prevalence of overt hypothyroidism and hyperthyroidism was similar in younger and older individuals. ‡P = 0.77, and §P = 0.93). Data from Ceresini et al.

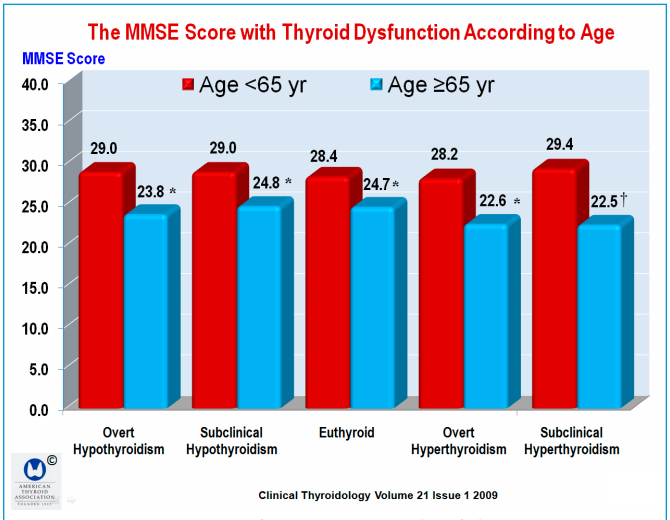

Figure 2. The Mini–Mental State Examination (MMSE) scores were significantly lower in participants age 65 or older as compared with younger participants. *P <0.03, †P = 0.002, from age-adjusted linear or logistic-regression models, as appropriate. Older participants (≥65 yr) with subclinical hyperthyroidism had lower mean (±SD) MMSE scores than did euthyroid subjects (22.61±6.88 vs. 24.72±4.52, P<0.03). Participants with subclinical hyperthyroidism were, in an adjusted analysis, significantly more likely to have cognitive dysfunction (hazard rate [HR], 2.26; *P = 0.003). Data are from Tables 1 and 2 in Ceresini et al.

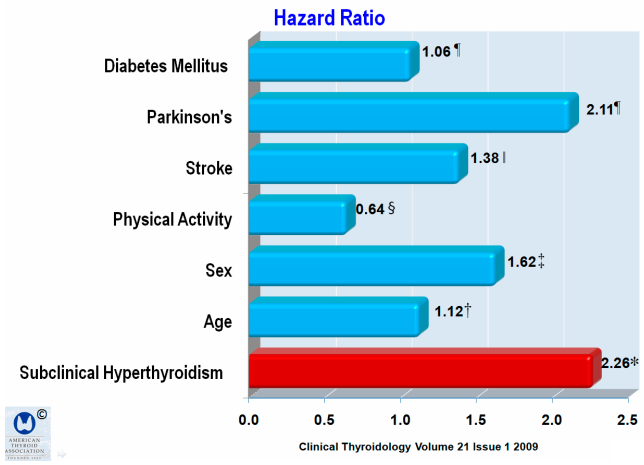

Figure 3. Multivariate regression analysis relating subclinical hyperthyroidism to the risk of having low Mini–Mental State Examination (MMSE) score <24 (considered to indicate cognitive impairment) *P = 0.003, †P = <0.001, ‡P= .05, §P =0.006, γP = 0.01, ¶P = 0.6. Data from Table 3 in Ceresini et al.

women (53%) and 116 men (46%) were younger than 65 years, 243 were euthyroid (95%), and 1 each had overt hypothyroidism (0.4%) and subclinical (0.4%) hypothyroidism (Figure 1). Five participants (2%) had subclinical hyperthyroidism and five (2%) had overt hyperthyroidism (Figure 1). Of the 916 participants aged 65 or older (513 women and 403 men), five (0.6%) had overt hypothyroidism, 25 (2.7%) had subclinical hypothyroidism, and 800 (87%) were euthyroid, 71 (7.8%) had subclinical hyperthyroidism, and 15 (1.6%) had overt hyperthyroidism (Figure 1). Subclinical hypothyroidism and subclinical hyperthyroidism were thus both more prevalent in older than in younger individuals (P<0.03 and P<0.002, respectively) while the prevalence of overt hypothyroidism was similar in younger and older individuals (P = 0.77; Figure 1). The MMSE score, adjusted for age, sex and other potential confounders was significantly lower in subclinically hyperthyroid than in euthyroid participants (22.61±6.88 vs. 24.72±4.52, P<0.03; Figure 2). Multivariate regression analysis found the hazard ratio of having cognitive impairment associated with subclinical hyperthyroidism versus euthyroidism was 2.26 (P<0.003) (Figure 3).

CONCLUSION Subclinical hyperthyroidism is the most prevalent thyroid dysfunction in older Italian persons and is associated with cognitive impairment.

COMMENTARY

The prevalence of overt and subclinical hypothyroidism in elderly populations is as high as 20% (1). With aging, the prevalence increases 1% or 2% in iodine-deficient geographic areas and up to 7% or 8% in iodine-sufficient areas (1). However, inconsistent findings have been found in epidemiologic studies investigating the relationship between subclinical hypothyroidism and cognitive dysfunction (2). In the present study, the odds of having poorer cognitive function were greater for subclinical hyperthyroidism than for stroke, diabetes mellitus, and Parkinson's disease. Thus, in this large population-based study, the overall prevalence of thyroid dysfunction tended to be higher in older than in younger persons, with subclinical hyperthyroidism being the most highly prevalent condition associated with cognitive deterioration. A study from the Netherlands found that subclinical hyperthyroidism in the elderly increased the risk of dementia and Alzheimer's disease. A recent study by Samuels et al. (3) found mild decrements in health status and mood in when subclinical hypothyroidism was induced in a blinded, randomized fashion. More importantly, there were independent decrements in working memory, which suggested to the authors that subclinical hypothyroidism specifically impacts brain areas responsible for working memory. Whether treating the subclinical hyperthyroidism—or for that matter, subclinical hypothyroidism—would ameliorate cognitive dysfunction is unknown, but some studies suggest this might not be the case (4). However, other cross-sectional or longitudinal observations have failed to demonstrate an association between thyroid dysfunction and cognition (2, 5). Still, there is a high prevalence of autoimmune thyroid disorders in patients with Alzheimer's disease (6), and other studies have found an association between autoimmune-associated subclinical hyperthyroidism and dementia (7). This intriguing observation by Ceresini et al. will certainly spark further investigation.

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The risk of hyperthyroidism relapse following antithyroid drug withdrawal in children with Graves' disease can be decreased only by a longer initial duration of therapy

Kaguelidou 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;93:3817-26

SUMMARY

BACKGROUND Predicting the outcome of antithyroid drug therapy (ATD) for Graves' disease is problematic. There are many retrospective studies in adults showing that patients with more severe degrees of hyperthyroidism, large goiters, a high triiodothyronine (T_3)-to-thyroxine (T_4) ratio, and higher levels of anti-thyrotropin (TSH) receptor antibodies (TRAb) are less likely to have a remission than are patients with milder disease and smaller goiters. Yet none of these features accurately predict outcome. In children there is even more uncertainty about factors that predict outcome. Such studies in children are limited. As a result, there is debate concerning how Graves' disease in children should be treated. The aim of this study was to identify factors that predict relapse of hyperthyroidism in children with Graves' disease treated with ATDs.

METHODS This was a prospective, multicenter cohort study of children with Graves' disease treated with carbimazole. The intention was to treat all patients for a total of 24±3 months. All consecutive patients with Graves' hyperthyroidism who were younger than 18 years of age were included in the study, but children with neonatal hyperthyroidism were excluded. The diagnosis was based on clinical signs of hyperthyroidism, a TSH <0.05 μIU/ml, and a serum free T_4 (FT_4) >21 pmol/L (1.6 ng/dl) with or without a serum free T_3 (FT_3) >11 pmol/L (0.71 ng/dl) and the presence of significant serum TRAb levels with or without serum antithyroid peroxidase antibodies. The intent was to treat all patients with one or two daily doses of carbimazole at a starting dose of 0.5 mg/kg/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 at months 1, 2, 3, 6, 9, 12, 18, and 24.

RESULTS A total of 154 children were initially included; 17 (11%) were 5 years of age or younger and 137 (89%) were older than 5 years; 118 were female (77%), 36 were male (23%), and 65 were prepubertal (47%). Serum TRAb levels were significantly higher in patients younger than 5 years than in older patients (P<0.0001); they were also higher in patients with a severe initial clinical presentation as compared with those without a clinically severe presentation (P = 0.03). Serum TRAb and FT_3 levels were significantly correlated (P = 0.005) but there was no correlation between TRAb levels and goiter size or gender. Most patients (147; 95%) completed one course of therapy. Seven patients who did not complete one course of ATDs were excluded from the analysis. The median duration of ATD treatment was 25 months (range, 23 to 28), but only 83 patients (56%) received ATDs according to the protocol for 21 to 27 months. A total of 64 children (44%) had deviations from the study protocol and 20 received antithyroid drugs for 12 to 20 months because of noncompliance; 44 patients received ATDs for more than 27 months. Overall, the estimated rate of hyperthyroidism relapse was 59% (95% confidence interval [CI], 52 to 67) at 1 year and 68% (95% CI, 60 to 76) at 2 years after the end of treatment (Figure 1). The median time to relapse was 8 months (95% CI, 5.4 to 11.4). In all, 64 of the 99 relapses (65%) occurred in the first 6 months and 87 of the 99 (88%) relapses occurred in the first year (Figure 1).

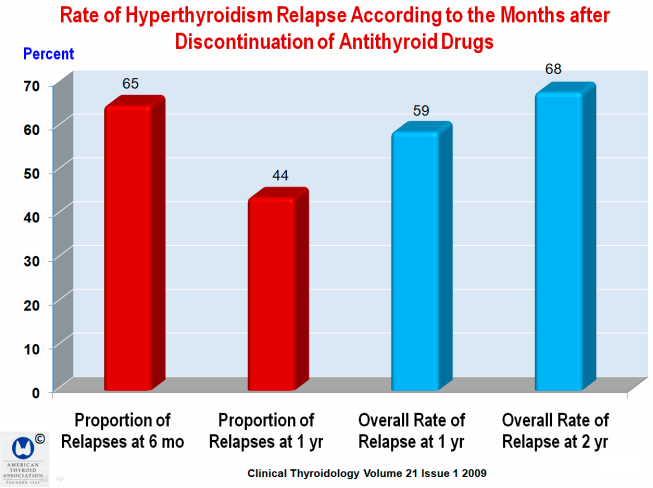

Figure 1. This shows the proportion of the 99 relapses of hyperthyroidism that occurred at 6 months and 1 year after the end of antithyroid drug treatment, and the overall rates of relapse at 1 and 2 years after antithyroid drug treatment. The median time to relapse was 8 months (95% CI 5.4 to 11.4 months). Derived from Kaguelidou et al data.

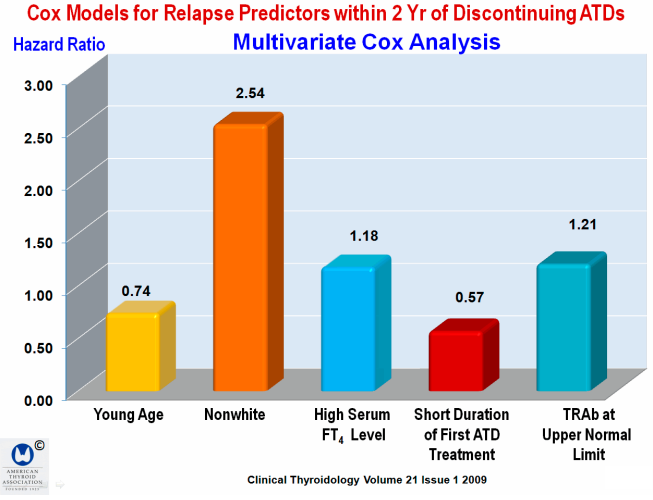

Figure 2. The results of a multivariate Cox analysis within 2 years of discontinuing ATDs. Derived from data in Table 2 by Kaguelidou et al.

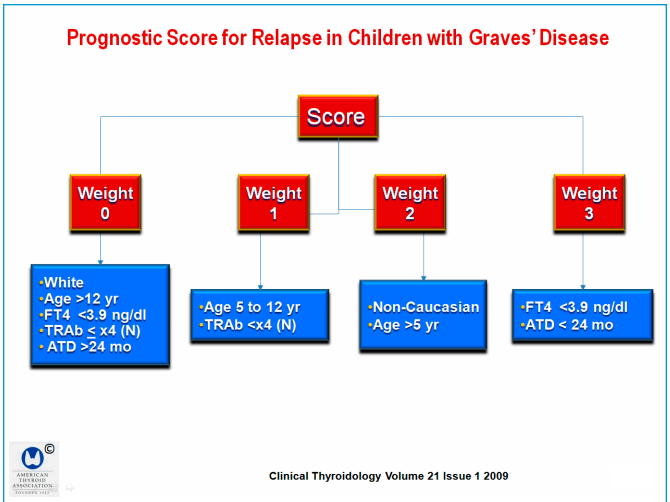

Figure 3. The prognostic scoring system devised by Kaguelidou et al. is derived from the results of this study. The data are derived from Table 3.

Five variables were identified as independent predictors of relapse in a multivariate Cox model: (1) patient age (hazard ratio [HR], 0.74; 95% CI, 0.56 to 0.97; P = 0.05); (2) nonwhite patients (HR, 2.54; 95% C,I 1.50 to 4.3; P = 0.0003; (3) serum FT_4 levels (HR, 1.18; CI, 1.07 to 1.30; P<0.0001); (4) duration of the first course of ATD treatment (HR, 0.57; 95% CI, 0.39 to 0.84; P = 0.007); (5) upper normal limit for TRAB concentration (HR, 1.21; 95% CI, 1.02 to 1.45; P<0.0001 (Figure 2). 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. Nonwhite patients were found to be 2.5-fold more likely to suffer a relapse than white patients. Also, a 10-point increase in serum FT_4 and a 10-unit increase in the multiple of upper normal limit for serum TRAb levels at diagnosis resulted in an 18% and a 21% increase of relapse risk, respectively. A prognostic score, which was derived from the regression coefficient of each variable retained in the final model, is shown in Figure 3.

CONCLUSION The risk of relapse of hyperthyroidism after antithyroid drug withdrawal in children with Graves' disease can be decreased only by a longer initial duration of antithyroid drug therapy

COMMENTARY

The principle finding in this study is that five independent variables (Figure 2) had a significant effect on the recurrence rates in children with Graves' hyperthyroidism. As a practical matter, however, the only variable that might be amenable to clinical manipulation is the duration of ATD therapy. The authors suggest that long courses of ATD are associated with a better-than-usual outcome, but acknowledge that their study was not designed to answer just how long ATD therapy should be continued. The study did, nonetheless, find that every additional year of treatment was associated with a decrease in the rate of relapses.

In adults with Graves' hyperthyroidism, ATD treatment for 12 to 18 months is the usual practice (1, 2). The evidence that prolonging ATD therapy improves the relapse rates of Graves' hyperthyroidism is inconsistent. One prospective randomized trial found that after 2 years of follow-up, there was significant improvement in the hyperthyroidism relapse rate when patients were treated with ATDs for 18 months, as compared with only 6 months (42% vs. 62%, P<0.05) (3). Another study found, after a 2-year follow-up, that relapse rates were 46% in patients treated with ATDs for 12 months and 54% in those treated for 24 months (P = 0.36); however, after a 5-year follow-up, the relapse rates were almost identical after 12 and 24 months of ATD treatment (83 vs. 86%, P = 0.7) (4). Still another prospective study, which compared the relapse rates of Graves' hyperthyroidism in patients treated for either 42 or 18 months, found the relapse rates after 2 years of follow-up were 36% and 29% (P not significant) in the two groups, respectively (5). An evidence-based study of the literature found that the optimal duration of ATD therapy is 12 to 18 months (6). A multicenter European 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 resulting in the best balance of risk and benefit (7).

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 the age of independence (8). With this aside, relapse of Graves' hyperthyroidism in children poses a substantial health problem that requires ongoing study such as the important study by Kaguelidou et al.

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Serum TSH levels are significantly lower within 30 days after the onset of subacute thyroiditis and remain so for over 60 days, but other routine laboratory tests show little change

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.

SUMMARY

BACKGROUND Subacute thyroiditis (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 study of 852 patients aimed at further documenting the clinical characteristics of the disorder based on laboratory and imaging studies before treatment.

METHODS The subjects were patients with SAT who were cared for at the Thyroid Clinic at Kuma Hospital in Japan from 1996 through 2004. The diagnosis was based on clinical features of thyroid swelling, pain, and tenderness; an elevated C-reactive protein (CRP), elevated serum free thyroxine (FT_4), and decreased serum thyrotropin (TSH) levels or suppressed 24-hour radioiodine uptake (RAIU); negative or weakly positive serum antithyroid antibodies; and an ultrasound hypoechogenic area in a region of thyroid tenderness. 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.

RESULTS A total of 852 patients were retrospectively enrolled in the study. There were 745 women (87%) and 107 men (13%) whose mean (±SD) age was 47.8±9.4 years (range, 22 to 83; median, 48) (Figure 1). Almost all the patients (96%) visited the hospital within 45 days after the onset of neck pain. The monthly distribution during which SAT occurred clustered mainly from summer to early autumn (P<0.001) (Figure 2). In all, unilateral or bilateral neck pain developed at the onset in 68% of the patients, 23% experienced nasal discharge, cough, and sputum within 1 month before the onset of SAT, and 28% had temperatures >38°C (100.4°F). The rate of bilateral ultrasound hypoechoic areas tended to increase over time, but the changes are not statistically significant (Figure 3). Typical symptoms of thyrotoxicosis, including palpitations, increased sweating, and weight loss, developed in 62% of the patients (Figure 3). Within 1 month after the onset of SAT, the serum TSH and ALT declined significantly (P<0.05), as compared with TSH and ALT levels measured within 7 days of onset, and were clearly different in the three time periods (Figure 4). The other laboratory tests did not change significantly. The rates of virus infection and other diseases did not differ from those in the general population. There were 9 patients (1.6%) in the cohort who had episodes of recurrent SAT with an interval of 13±5.6 years between the first and second episodes.

CONCLUSION Serum TSH levels are statistically lower within 30 days and remain so for over 60 days after the onset of SAT but other routine laboratory tests show little significant change.

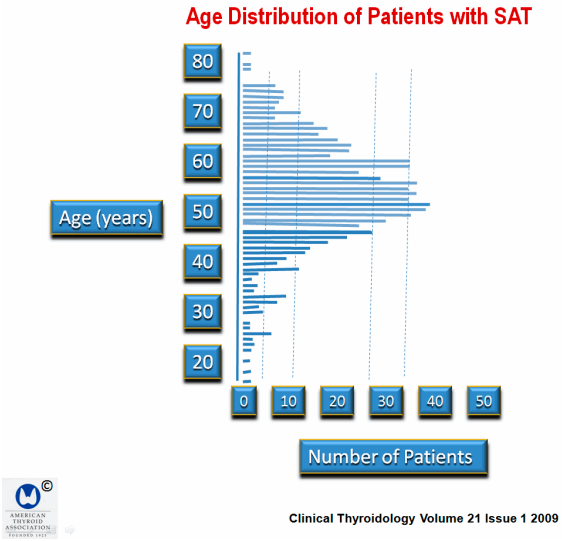

Figure 1. The peak age distribution of patients with SAT was between about 40 and 50 years. The majority were female (87%). This graph is adapted from Nishihara et al.

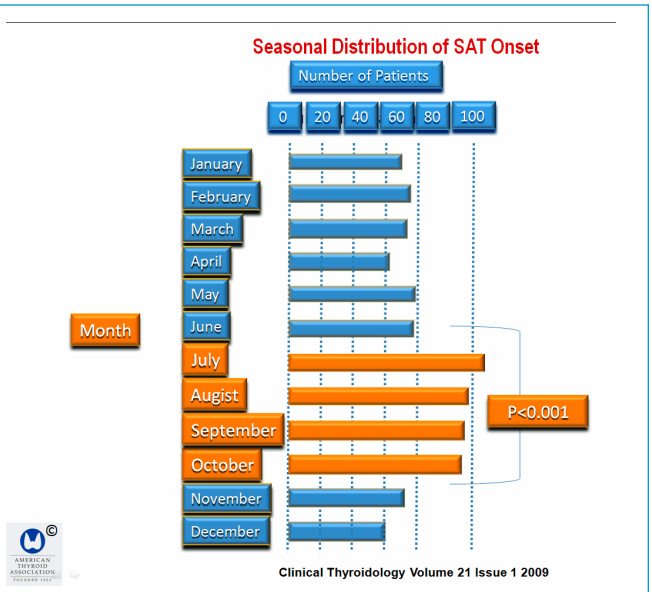

Figure 2. There was a significant increase (P<0.001) in SAT cases from early summer to late fall that did not correlate with viral infections. This graph is adapted from Nishihara et al.

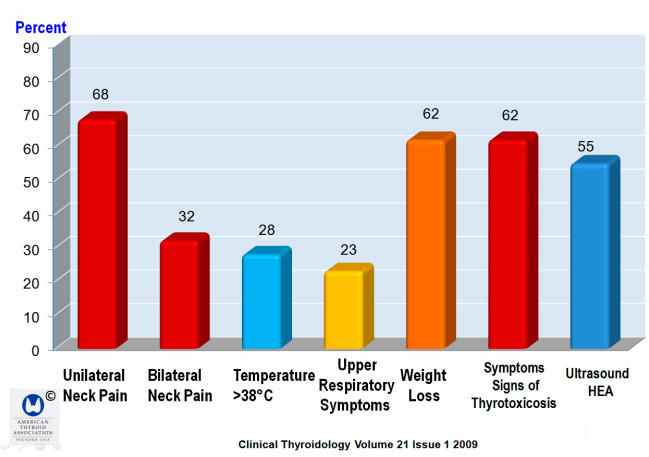

Figure 3. The rate of bilateral hypoechoic ultrasound areas (HEA) tended to increase over time after the onset of pain, but the difference was not statistically significant. This figure is derived from the data of Nishihara et al.

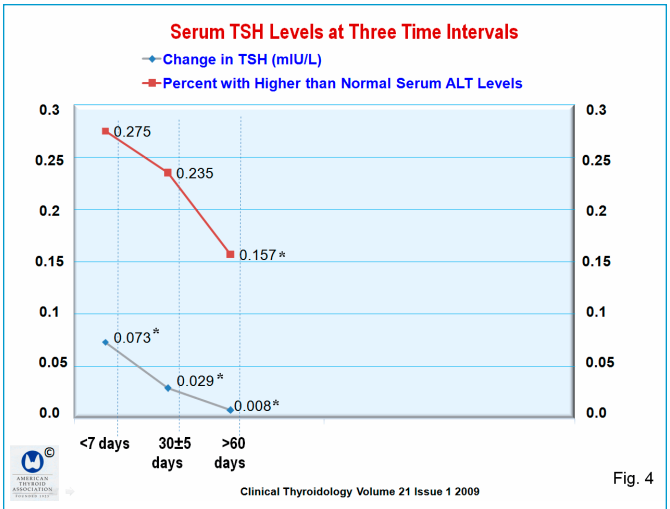

Fig. 4

Figure 4. All laboratory measurements remained statistically unchanged over time except for TSH. *P<0.05. Serum ALT (alanine aminotransferase) was slightly but not statistically above normal levels at <7 days and 30 days after the onset of SAT. This figure is derived from the data of Nishihara et al.

COMMENTARY

The principal finding in this study is that few abnormal laboratory tests occurred in the first 30 days following the initial manifestations of SAT, with the exception of serum TSH levels, which were significantly suppressed within a week after the patients sought medical attention and remained suppressed for more than 60 days. The study did not review the treatment of SAT, which is probably the most controversial issue concerning this disorder.

One review (1) of 160 patients with SAT found, as reported by Nishihara et al., that thyroid pain was the presenting symptom in 96% of the patients, and 4% had a relapse of SAT 6 to 21 years after the initial episode. Although corticosteroid therapy was given to 36% of the patients, early-onset hypothyroidism occurred both in patients receiving (29%) and in those not receiving (37%) the drug. Moreover, at the last follow-up, more patients who had hypothyroidism had received corticosteroid therapy as compared with the group that had not received corticosteroid therapy (25% vs. 10%) (P<0.05). Although the study found that corticosteroid therapy may relieve symptoms, it did not prevent the onset of both early and late hypothyroidism.

Another retrospective review (2) of 56 consecutive patients (70% of whom were female with a mean [±SD] age of 48.6±12 years) found that 9% had recurrent disease, although differences in occurrence by season were not significant (P = 0.28). Ten patients received no treatment, and 43 others received either nonsteroidal antiinflammatory drugs (NSAIDs; 25 patients) or glucocorticoids (18 patients). However, the duration of hyperthyroidism was similar in patients given NSAIDs and glucocorticoids, and untreated patients had less severe clinical disease than those who were treated. The authors concluded that SAT follows an unpredictable clinical course that is hardly affected by its treatment.

A third retrospective review (3) of 176 patients with SAT found that thyroid pain was present in 97% of female patients and 100% of male patients, and 78 patients (46%) had high fever. Among patients who were treated with NSAIDs, recurrence developed in 10% and there was no significant difference in recurrence rates between patients who had been treated with NSAIDs and those who had been treated with prednisolone.

Thus, studies show that the presenting symptoms are reasonably predictable, as are the changes in thyroid-function tests reflecting early manifestations of hyperthyroidism that may persist for up to several months, and that treatment has little effect on outcome. The ultrasound changes described by Nishihara et al. are important and provide guidance as to what to expect on ultrasonography.

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Acute radiation thyroiditis that sometimes occurs with postthyroidectomy remnant ablation is directly related to thyroidal ^{131}I uptake and not to the amount of ^{131}I used for ablation

Cherk MH, Kalff V, Yap KS, Bailey M, Topliss D, Kelly MJ. Incidence of radiation thyroiditis and thyroid remnant ablation success rates following 1110 MBq (30 mCi) and 3700 MBq (100 mCi) post-surgical ^{131}I ablation therapy for differentiated thyroid carcinoma. Clin Endocrinol (Oxf) 2008;69:957-62.

SUMMARY

BACKGROUND Radiation thyroiditis may be observed when a patient with thyroid cancer has a large postsurgical thyroid remnant that is treated with radioactive iodine (^{131}I) or external-beam radiotherapy. When this occurs, possibly dangerous acute neck pain and swelling may develop. The aim of this study was to evaluate the relationships between thyroid remnant ^{131}I uptake and radiation thyroiditis, and the rate of thyroiditis with 30 and 100 mCi of ^{131}I (1110 and 3700 MBq [mCi x 37 = MBq]).

METHODS This was a retrospective study of patients who were treated postoperatively with either 30 mCi or 100 mCi of ^{131}I to destroy the thyroid remnant. The amount of ^{131}I was chosen according to the clinical features of the tumor and patient risk factors. Patients were classified as having insignificant thyroiditis if no treatment was required, mild thyroiditis if simple analgesics such as nonsteroidal antiinflammatory drugs (NSAIDs) were required, and severe thyroiditis if steroids were required. The criterion for successful thyroid remnant ablation was an absence of visible ^{131}I uptake in the thyroid bed on a 2-mCi whole-body scan performed 6 to 12 months after ^{131}I therapy.

RESULTS The study subjects comprised 183 patients (143 female [78%] and 40 male [22%]) ranging in age from 16 to 87 years; 139 (76%) had papillary thyroid cancer and 44 (24%) had follicular cancer. Sixty-eight patients (37%) were treated with 30 mCi of ^{131}I and 115 (63%) were treated with 100 mCi.

Median ^{131}I uptake by the thyroid remnant was 1 mCi (range, 0.4 to 2.1) in the entire group, 0.5 mCi (range, 0.25 to 1.4) in the 30-mCi group, and 1.4 mCi (range, 0.6 to 2.5) in the 100-mCi group. Median ^{131}I uptake by the thyroid remnant was 1.8% (range, 0.85 to 4.6) in the 68 patients who received 30 mCi, and 1.4% (range, 0.6 to 2.5) in the group that received 100 mCi. Thyroiditis requiring treatment developed in 39 patients (21%), which was mild in 29 (16%) and severe, lasting 2 to 3 days, in 10 patients (5%). The incidence of thyroiditis was 12% in patients treated with 30 mCi and 27% in those treated with 100 mCi (P = 0.02) (Figure 1).

In patients who had follow-up, thyroid remnant ablation was incomplete in 8 of 35 (23%) with thyroiditis, and in 22 of 123 (18%) without thyroiditis (relative risk, 1.28; 95% confidence interval, 0.63 to 2.63; P = 0.51).The levels of thyroid remnant ^{131}I uptake correlated with the incidence of thyroiditis (r = 0.51, P≤0.0001), and for every 1-mCi increase in the remnant ^{131}I uptake, the risk of thyroiditis increased by 64%. Severe thyroiditis did not occur with remnant ^{131}I uptake <2 mCi. Thyroiditis developed in 21 of 30 patients (70%) with remnant ^{131}I uptake >3 mCi; 9 cases (30%) were severe (Figure 2).There was no significant difference in remnant ablation success rates for patients treated with 30 or 100 mCi (Figure 3). Among 58 of the 68 patients with follow-up who were treated with 30 mCi, the success rate of thyroid remnant ablation was 76%, as compared with an 84% success rate in the 100 of 115 patients with follow-up who were treated with 100 mCi (P = 0.30) (Figure 3).

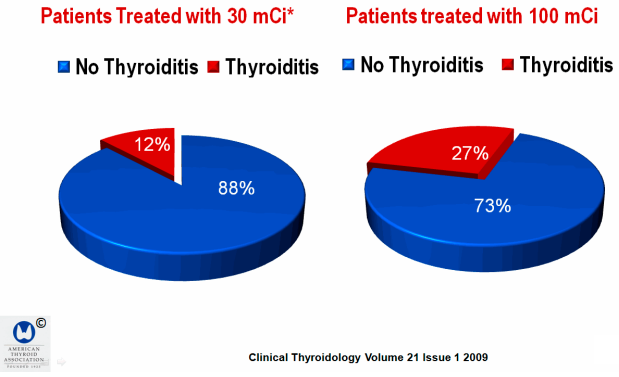

Figure 1. Thyroiditis developed in 39 of 183 patients (21%); it was mild in 29 (16%) and severe, lasting 2 to 3 days, in 10 (5%). The incidence of thyroiditis was 12% in patients treated with 30 mCi and 27% in those treated with 100 mCi. *P = 0.02.

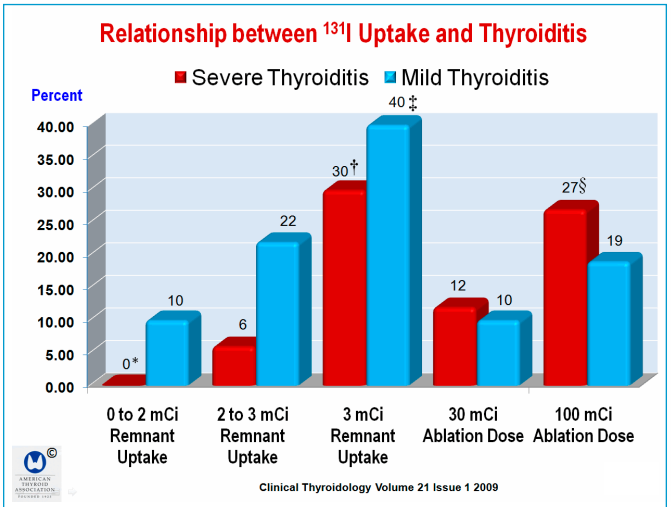

Figure 2. The levels of thyroid remnant ^{131}I uptake correlated with the incidence of thyroiditis (r = 0.51). The risk of thyroiditis increased 64% for every 1 mCi taken up by the thyroid remnant. *P≤0.001. †P<0.02. Severe thyroiditis occurred only with remnant 131I uptake >2 mCi. Thyroiditis developed in 21 of 30 patients (70%) with remnant ^{131}I uptake >3 mCi; 9 cases (30%) were severe.

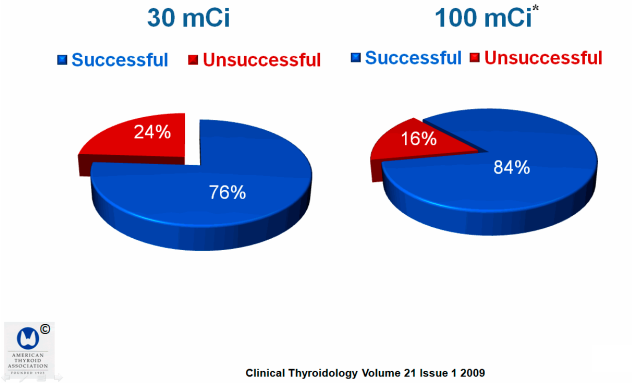

Figure 3. The success rates of remnant ablation with 30 and 100 mCi were not significantly different.*

CONCLUSION In patients with differentiated thyroid carcinoma, acute thyroiditis that sometimes occurs with postthyroidectomy remnant ablation is directly related to the amount of uptake of ^{131}I by the thyroid and not the amount of ^{131}I used for ablation.

COMMENTARY

Although acute thyroiditis that occurs when a large thyroid remnant is treated with ^{131}I is well recognized by clinicians, little is written about the subject. Most of the time, radiation thyroiditis causes painful thyroid with the usual features of subacute thyroiditis. Still, symptoms vary from mild cases of pain and swelling to acute thyroid swelling requiring glucocorticoid therapy. There are few systematic studies of the incidence and clinical manifestations of radiation-induced thyroiditis caused by radionuclides or external-beam radiation. In one study, Burmeister et al. (1) found that radiation-induced thyroiditis occurred in 6 of 10 patients (60%) who were treated with 50 to 185 mCi of ^{131}I after having undergone hemithyroidectomy or lobectomy. In contrast, there was only a 6% rate of thyroiditis in patients who had more extensive thyroidectomy—total or near-total thyroidectomy. The authors opined that the evidence supports a dose effect for the pathogenesis of these complications, and recommend <30 mCi of ^{131}I for the initial thyroid remnant ablation in patients with substantial residual thyroid tissue remaining after surgery. The same caveat relates to external-beam radiation that inadvertently radiates the thyroid gland or is applied to the neck in patients with residual differentiated thyroid cancer in the thyroid bed. The symptoms of radiation thyroiditis vary, but generally comprise acute neck pain and swelling, with release of thyroid hormones from the gland, rarely causing acute thyrotoxicosis.

Nishiyama et al. (2) explored the incidence, effects and outcome of radiation-induced thyroiditis in a cohort of 22 patients undergoing external-beam radiation to the neck for nonthyroid problems, which incidentally exposed the thyroid gland to therapeutic doses of radiation. Measurements were made of serum thyrotropin (TSH), free triiodothyronine (FT_3) and total triiodothyronine (T_3), thyroxine (T_4), thyroglobulin, and antithyroid antibodies at baseline and after approximately 40 Gy had been administered to the thyroid, after which the laboratory studies were repeated 3 and 6 months later. TSH underwent two phases of change. First, a significant change in serum TSH occurred right after radiotherapy, initiating a thyrotoxicosis phase, during which the TSH reached a nadir in 1 month, and later increased well above normal, in the range of 10 μIU/ml after 6 months during the hypothyroid phase. During the acute phase, T_3, FT_3, and T_4 increased only slightly and symptoms were minimal, but hypothyroidism later developed in some patients.

Bal et al. (3) performed ^{131}I lobar ablation as an alternative to completion thyroidectomy in patients with differentiated thyroid carcinoma, using 15 to 60 mCi of ^{131}I, depending on the size of the lobe and other patient features. Six months later, patients were evaluated with a whole-body ^{131}I scan, a 48-hr ^{131}I neck uptake, and a serum thyroglobulin measurement after levothyroxine withdrawal. The thyroid lobe was completely ablated in 53 patients (57%) after one dose of ^{131}I and the remaining patients had partial thyroid ablation, with the mean radioiodine neck uptake being reduced to 3.1±2.4%. The mean first dose of ^{131}I was 31.8±11.7 mCi, and the estimated mean absorbed dose was 251.3±149.3 Gy (range, 120 to 790). Approximately 30% of the patients in whom the remnant thyroid lobe was ablated with a single dose of ^{131}I received ≤200 Gy. Moreover, the cumulative ablation rate was 92.1% after two doses of ^{131}I, and only 7 patients needed a third dose of ^{131}I. In all, 15 patients (16.1%) reported throat discomfort and neck pain. All were treated with mild analgesics, except for three patients who needed additional oral prednisolone for 7 to 10 days to overcome neck edema. Bal et al. concluded that ^{131}I ablation of an intact thyroid lobe is possible and that it can be achieved with much smaller doses of radioiodine than previously believed. However, a systematic survey of patient symptoms and signs was not performed.

The main conclusion of the study by Cherk et al. is that radiation thyroiditis is directly related to the amount of ^{131}I uptake by the thyroid and not the amount of ^{131}I used for ablation. While this seems to be somewhat counterintuitive and at odds with the findings by Burmeister et al., the size of the thyroid remnant is directly related to the amount of ^{131}I radiation given to the residual thyroid, which in turn is affected by the amount of ^{131}I that is administered. There are several shortcomings in the study by Cherk et al. First, there are no data on thyroid-function tests or descriptions of the symptoms experienced by patients in whom severe thyroiditis developed. Second, follow-up was incomplete in a relatively large number of patients. Third, the extent of surgery was quite variable in patients treated outside the authors' medical center. Lastly, given the incomplete follow-up, it is not possible to reach a meaningful conclusion about the efficacy of using 30 mCi of ^{131}I for remnant ablation. However, there are several prospective, randomized studies that clearly show that 30 to 50 mCi is sufficient for thyroid remnant ablation in the vast majority of patients, usually in the range of 80 to 90%, whether patients are prepared by thyroid hormone withdrawal or recombinant human TSH (4-7) . The advice provided by Burmeister et al. appears to remain relevant.

Ernest L. Mazzaferri, MD, MACP

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

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.

SUMMARY

BACKGROUND Preparation for ^{131}I remnant ablation using recombinant human thyrotropin (rhTSH) in patients with differentiated thyroid cancer results in lower extrathyroidal radiation than occurs in patients prepared by thyroid hormone withdrawal (THW). However, there are no studies that directly demonstrate differences in tissue damage using the two forms of preparation. This is a retrospective study aimed at comparing the damage caused by remnant ablation when patients receive one or the other form of preparation.

METHODS The study subjects were consecutive patients with papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC) who underwent total thyroidectomy and remnant ablation with 100 mCi (3.7 MBq) of ^{131}I from August 2003 through December 2006. Damage to salivary glands and ovaries and testes, hematologic damage, and oxidative injury were evaluated. The serum amylase for salivary gland studies were obtained before and 48 hours 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. A complete blood count was performed immediately before and 30, 45, and 60 days after ^{131}I. Plasma 8-epi-prostaglandin F2α (PGF2α), a marker of dose-dependent in vivo oxidation injury, was measured immediately before and 4 days after ^{131}I therapy. Patients were divided into two groups, one that received rhTSH (group A) and another that underwent THW (group B) in preparation of remnant ablation.

RESULTS A total of 94 patients with PTC or FTC were enrolled in the study, 30 in group A, and 64 in group B; 64 were female (47%) and 30 male (21%), with a mean (±SD) age of 45±9.5 and 44±11 years, respectively. There were no significant differences in tumor histology, size, or extrathyroidal invasion or the interval between thyroidectomy and remnant ablation in the two groups; however, the serum TSH level immediately before the administration of ^{131}I was 118±28.5 μIU/ml in group A and 85±23 in group B (P<0.05). Uptake of ^{131}I was no more than 2% in any patient. In groups A and B, serum FSH was elevated 105% and 236% in men, and 65% and 125% in women, in the groups A and B, respectively (P<0.001, Figure 1). In groups A and B, amylase was elevated 48 hours after ^{131}I in 36.6% and 80% (P<0.001) of the patients, and symptoms of acute sialoadenitis occurred in 30% and 58.3% (P = 0.01, Figure 1). Thrombocytopenia (<1000,000/mm^3) or neutropenia (<1500/mm3) (lowest count) occurred up to 60 days after ^{131}I in 7% of group A and 21.4% of group B (P = 0.01). The mean decrease (lowest count) of neutrophils was 20% and 45%, and the mean decrease in platelets was 25% and 52% (P<0.01 for both). The increase in plasma 8-epi-PGF2α was 56% and 100%, and the mean increase was 60% and 125%. (Figure 2)

After a follow-up of approximately 2 to 5 years, FSH was normal in 20 of 27 patients (74%) who had elevated levels of FSH after ablation, and platelet and neutrophil counts returned to normal in 10 of 12 (83%) with early neutropenia or thrombocytopenia.

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

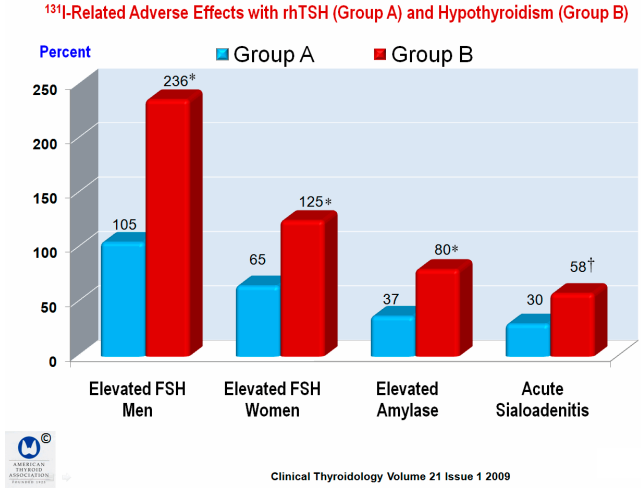

Figure 1. The adverse effects of ^{131}I on gonads and salivary glands are greater in patients prepared with rhTSH (group A) than in those prepared with thyroid hormone withdrawal (group B). *P = 0.001. †P = 0.01. This figure was drawn from the data in Table 4 by Rosario et al.

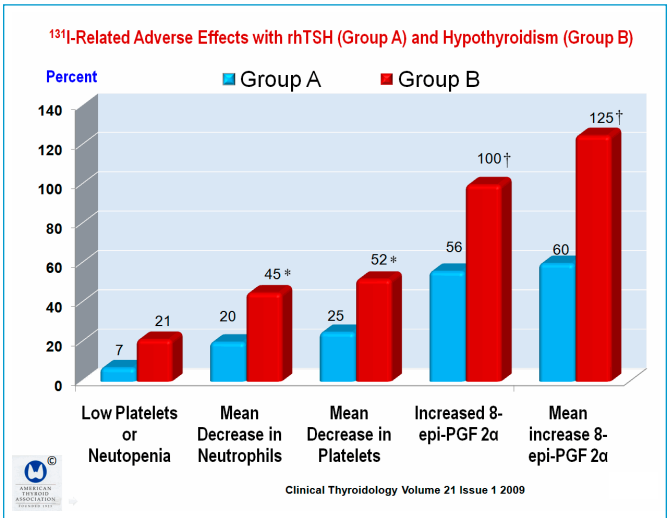

Figure 2. The adverse effects of ^{131}I on bone marrow and oxidative tissue damage (epi-prostaglandin F2α [PGF2α]). Thrombocytopenia or neutropenia was observed 30, 45, and 60 d after ^{131}I administration in 4, 8, and 2 patients, respectively. Mean decrease in neutrophils and platelets is the lowest count. Lowest platelet count was observed 30, 45, and 60 days after ablation in 20, 44, and 20 patients, respectively. Lowest neutrophil count was observed 30, 45, and 60 days after ablation in 16, 40, and 28 patients, respectively. *P <0.01, †P<0.001. This figure was drawn from the data in Table 4 by Rosario et al.

COMMENTARY

This study directly compares the tissue injury caused by 100 mCi (3.7 GBq) of ^{131}I administered for remnant ablation in patients prepared with rhTSH as compared with THW. The differences in injury caused by the two types of preparation are impressive. In all, six of the seven patients who continued to show elevated FSH levels and the two patients with persistent hematologic abnormalities were in group B. Hyperamylasemia persisted in only two patients, also from group B, and recurrent or persistent pain or xerostomia was observed in four patients, one from group A and three from group B, all of whom showed elevated amylase levels or acute sialoadenitis after ablation.

There is robust evidence that the mean effective half-life of ^{131}I is shorter by 31% in euthyroid patients treated with rhTSH as compared with that in hypothyroid patients undergoing THW (1-3). This significantly decreases the radiation doses delivered to extrathyroidal tissues. Combined with smaller amounts of ^{131}I, in the range of 30 mCi, the amount of whole-body radiation delivered by ^{131}I for remnant ablation can be substantially reduced. The ATA guidelines suggest that the minimum ^{131}I activity (30 to 100 mCi) necessary to achieve successful remnant ablation should be used, particularly for low-risk patients (4). This recommendation is based on the fact that ^{131}I activities between 30 and 100 mCi generally show similar rates of successful remnant ablation (5-10). Also, recurrence rates are comparable following THW and rhTSH preparation (11). These data directly imply that 30 mCi is the preferred amount of ^{131}I for patients at low risk of adverse outcomes. This study by Rosario et al. adds one more piece of evidence to support the notion that the smallest amount of ^{131}I in patients prepared with rhTSH is likely to provide the lowest risk of nonthyroidal tissue injury.

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Rising serum antithyroglobulin antibody levels predict recurrence of differentiated thyroid carcinoma in thyroglobulin-negative patients

Kim WG, Yoon JH, Kim WB, Kim TY, Kim EY, Kim JM, Ryu JS, Gong G, Hong SJ, Shong YK. Change of serum antithyroglobulin antibody levels is useful for prediction of clinical recurrence in thyroglobulin-negative patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 2008;93:4683-9.

SUMMARY

BACKGROUND Serum antithyroglobulin antibodies (TgAbs) are found in 10 to 25% of patients with differentiated thyroid carcinoma (DTC), as compared with an incidence of approximately 10% in the general population. This poses a serious problem in the follow-up of patients with DTC, as circulating TgAb interferes with serum thyroglobulin (Tg) measurements performed by immunometric assays. Thyroid cancer management guidelines suggest that TgAb levels serve as a surrogate for serum Tg measurement during follow-up, providing TgAb is measured in the same laboratory. Kim et al. hypothesize that changes in serum TgAb might predict tumor outcome, which has been a point of contention in previous studies. The aim of this study was to determine whether a changing pattern of TgAb levels found soon after thyroidectomy could serve as a prognostic indicator.

METHODS This retrospective study was performed on 1499 consecutive patients treated for DTC in the authors' hospital from 1995 through 2003. All had total thyroidectomy followed by remnant ablation with 100 to 150 mCi (3.7 to 5.55 GBq) of ^{131}I about 6 weeks after surgery. Patients selected for study had no preoperative evidence of extracervical tumor, or ^{131}I uptake outside the thyroid bed on the posttreatment whole-body scan (RxWBS) or in the thyroid bed on the first diagnostic whole-body scan (DxWBS) during follow-up. Patients with extracervical metastases or poorly differentiated or anaplastic thyroid cancer were excluded from the study. Follow-up DxWBS was performed with 4 mCi (148 MBq) of ^{131}I after thyroid hormone withdrawal every 3 to 6 months along with serum Tg and TgAb measurements. When serum Tg was above 2 μg/L, other imaging studies were performed according to the clinical findings. Recurrence was defined as tumor reappearance after complete remnant ablation and undetectable serum Tg and TgAb. Persistent disease was defined as the identification of tumor confirmed by cytology or histopathology after complete ^{131}I ablation. Lymphocytic thyroiditis was diagnosed according to the classic histologic findings of Hashimoto's disease. Serum Tg measurements were performed by an immunometric assay with a functional sensitivity of 1 μg/L, and TgAb was performed by a radioligand assay in which a TgAb value greater than 100 U/ml was considered positive. Tumors were staged by the TNM (tumor–node–metastasis) classification system of the International Union Against Cancer and the American Joint Committee on Cancer, revised in 2002 (6th edition). The change in TgAb concentrations measured between the time of remnant ablation (TgAb1) and 6 to 12 months later (TgAb2) was evaluated as a possible prognostic indicator.

RESULTS A total of 824 patients were selected for study, 747 (91%) women and 77 (9%) men, all of whom had undetectable serum Tg values after thyroid hormone withdrawal and no visible uptake on the first DxWBS. Their mean (±SD) age was 46±11.6 years (range, 13.0 to 76.4). In all 88% had papillary thyroid cancer, 6% had follicular variant papillary thyroid cancer, and 7% had follicular thyroid cancer. Tumors were >4 cm in 7%, were multifocal in 35%, had extrathyroidal invasion in 53%, and had lymph-node metastases in 50%.

Twenty patients (24%) had recurrent or persistent tumor (1 man and 19 women). Their mean age was 51.5±12.8 years (range, 33.1 to 73.8). A mean interval of 50.4±21.7 months (range,

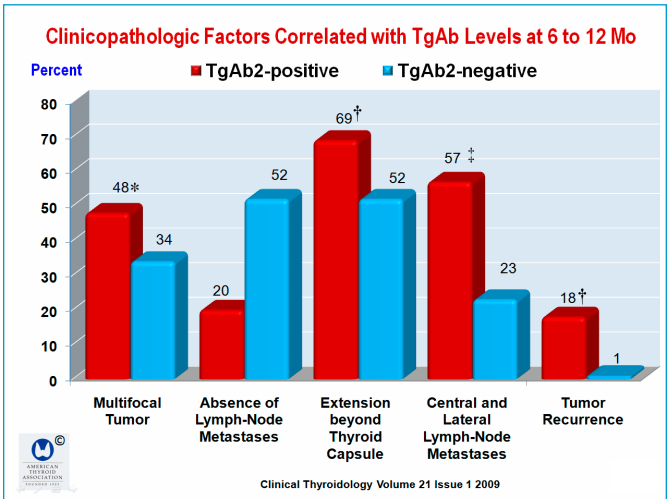

Figure 1. Clinical factors that correlate with TgAb levels at 6 to 12 months of follow-up *P = 0.04, †P< 0.001, ‡P = 0.01 comparing outcome in positive versus negative TgAb2. Not shown in the figure, 22 patients (39%) in the TgAb2-positive group and 150 (20%) in the TgAb2-negative group had lymphocytic thyroiditis (P<0.001). Figure is derived from data in Table 2 of Kim et al.

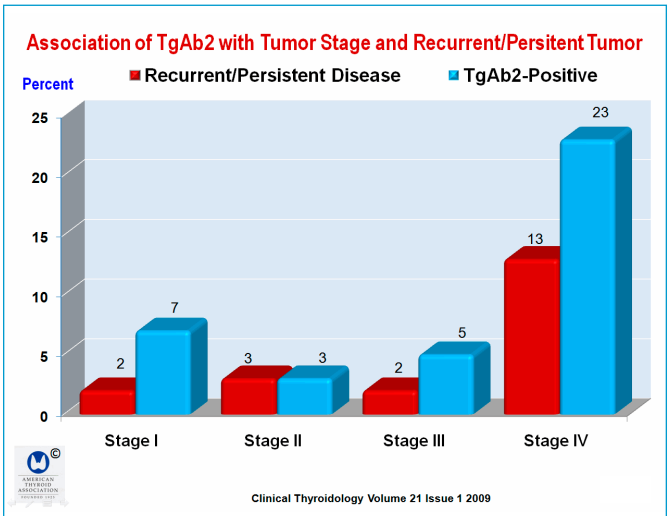

Figure 2. The association of TgAb2 with tumor stage and recurrent/persistent disease

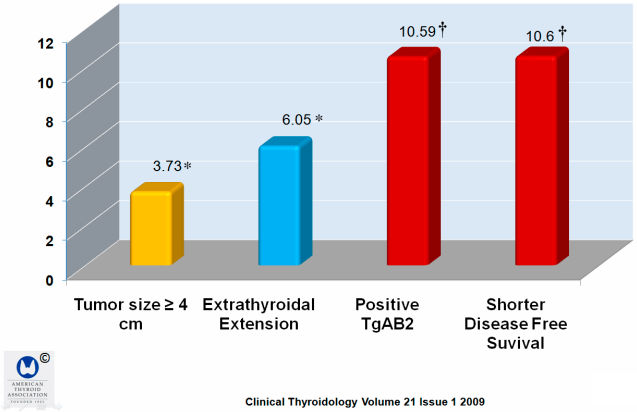

Figure 3. Clinicopathologic factors independently associated with persistent/recurrent tumor. *P<0.0.02, †P = 0.01. Figure is derived from multivariate analysis data in Table 3 of Kim et al.

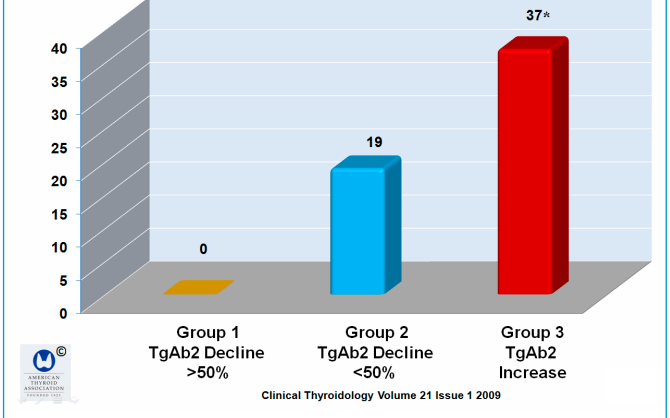

Figure 4. The association of recurrent/persistent disease with changing TgAb2 values *P = 0.016

16.2 to 118.5) transpired from the time of TgAb2 measurement and confirmation of recurrent or persistent disease. In all, 56 of the 824 patients (6.8%) had TgAb values >100 U/ml at the time of the first DxWBS (TgAb2). At 6 to 12 months there were no significant differences in age, gender, or tumor size in TgAb2-positive and TgAb-negative patients; however, compared with the TgAb2-negative patients, a greater number of TgAb2-positive patients had multifocal tumors (48 vs. 34%, P<0.04, Figure 1) and tumors with extension beyond the thyroid capsule (69 vs. 52%, P = 0.01) and central and lateral cervical lymph-node metastases (57% vs 23%, P<0.001) (Figure 1). Twenty-two patients (39%) in the TgAb2-positive group and 150 (20%) in the TgAb2-negative group had lymphocytic thyroiditis (P<0.001). There was an association between TgAb2-positivity and tumor stage (Figure 2).

TgAb2 was positive in 56 patients, 10 of whom (18%) had recurrence, while TgAb2 was negative in 768 patients, only 10 of whom (1%) had recurrence during 73.6 months of follow-up (P<0.001). Univariate analysis found that recurrent/persistent tumor was associated with tumor size (P = 0.02) and extrathyroidal extension (P<0.001) (Figure 3). Multivariate analysis found an independent association between recurrent/persistent disease and extrathyroidal extension of tumor (hazard ratio [HR], 6.05; 95% confidence interval [CI], 1.4 to 26.5; P<0.02) and larger tumor size (HR, 3.73; 95% CI, 1.2 to 11.2; P< 0.02) and that TgAb2 was independently associated with shorter disease-free survival (HR, 10.6; 95% CI, 4.4 to 25.7; P<0.001) (Figure 3).

The change between TgAb1 and TgAb2 levels was evaluated in TgAb2-positive patients divided into three groups. In 21 patients (group 1) the TgAb2 concentration decreased more than 50%, in 16 patients (group 2) it decreased less than 50%, and in 19 patients (group 3) it increased over the 6- to 12-month period. Among the three groups, there were no significant differences in the TgAb2 level, age, gender, tumor size, multifocality, lymph-node metastasis, or extrathyroidal extension. The recurrence rates in groups 1, 2, and 3 were 0, 19, and 37%, respectively (P = 0.06) (Figure 4).

CONCLUSION Changes in serum TgAb levels measured at 6 to 12 months after remnant ablation predict recurrence in patients with undetectable Tg values. Change in TgAb concentrations during the early postoperative period may be a prognostic indicator of recurrence.

COMMENTARY

This important study provides substantial information concerning the presence of TgAb in patients with DTC. For several decades it has been widely appreciated that immunometric Tg assays are prone to TgAb interference, commonly causing falsely low serum Tg measurements. Guidelines for the treatment of patients with DTC suggest that radioimmunoassays may be less prone to antibody interference, but they are not widely available and their role in the clinical care of patients is uncertain (1). Conflicting data concerning virtually every facet of TgAb surrounds this issue. For example, the prevalence of TgAb among patients with thyroid cancer ranges from 10 to nearly 30% in various publications (2,3), mainly because TgAb measurements are highly susceptible to differences among laboratories and TgAb methods. Serial TgAb studies must thus be performed in the same laboratory and assay. Even so, other issues plague the measurement of TgAb, including the timing and standardization of the test, without which results vary widely, similar to serum Tg measurements. What we have learned is that a spot serum Tg or TgAb is not nearly as accurate as performing serial tests in the same laboratory. Thus, different studies suggest that TgAb cannot reliably identify patients with persistent tumor.

For example, one study (3) found that the prevalence of TgAb at the initial examination was 29% (median, 130 U/ml); during follow-up the TgAb levels increased transiently in one-tenth of the patients, but thereafter the prevalence of TgAb decreased <10% after 3 years, leading the authors to conclude that the

development and course of TgAb cannot be predicted by initial or residual tumor volume and TgAb or Tg levels. Another study (4) of 1050 patients found circulating TgAbs in 102 patients (10%); these levels were elevated in 32 patients both before and after total thyroidectomy and ^{131}I ablation. As a result, no relationship could be found between preoperative serum TgAb levels and tumor stage at diagnosis or with outcome of the disease; yet during follow-up, TgAb serum levels decreased or disappeared in 21 patients who were considered tumor-free, while they remained unchanged or even increased among patients with proven metastases and others considered free of tumor. Among 102 TgAb-positive patients, serum TgAb levels measured after thyroid ablation were significantly higher in patients with metastases than in those considered tumor-free ($P<0.0001$). The problem is that the TgAb levels in this study were measured by different methods, and in some cases by the semiquantitative hemagglutination method, which is common in studies performed before the year 2000, underscoring how difficult it is to compare such studies (2,3,5)

A study performed in 2003 (6) by Chiovato et al. (6) investigated whether complete removal of thyroid antigens results in the abatement of humoral thyroid autoimmunity. A total of 182 patients with DTC who tested positive for serum TgAb and thyroid peroxidase antibodies (TPOAb) were treated with total thyroidectomy and ^{131}I to ablate residual or metastatic thyroid tissue. Mean (±SD) follow-up was 10.1 ± 4.1 years (range, 4 to 20). TPOAb, Tg, and TSH-receptor antibodies progressively disappeared after median of 6.3 years for thyroid peroxidase antibodies and 3.0 for TgAb. There was a statistically significant correlation between the disappearance of thyroid tissue and that of thyroid antibodies. The authors concluded that complete ablation of thyroid tissue with its antigenic components results in the disappearance of antibodies to all major thyroid antigens, thus supporting the concept that continued antibody production depends on the persistence of autoantigen in the body. Still, most studies have reported that TgAb levels did not show any association with a poor prognosis. In most cases, the studies were just after surgery or remnant ablation and did not exclude patients with metastatic disease (6-8).

Kim et al. present robust data that a change of serum TgAb levels detected between the time of remnant ablation and 6 to 12 months later is useful for predicting clinical recurrence in patients with undetectable serum Tg levels with positive TgAb concentrations, while decreasing TgAb levels suggest that the tumor is responding to therapy.

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Disclosure

Dr. Mazzaferri receives honoraria from Genzyme for providing lectures.

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