CLINICAL THYROIDOLOGY

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EDITOR'S COMMENTS

This is the seventh 2009 issue of *Clinical Thyroidology*. As you may know, each issue will be sent to you by email as a separate list of articles that can be downloaded individually or as the entire document.

SEARCH FOR PREVIOUS ISSUES of *Clinical Thyroidology* A number of our readers have asked for a quick way to find articles published in this journal over the past years. Now you can access previous issues using key words, author names, and categories such as thyroid cancer, or other terms. You will find this by simply right clicking the following: http://thyroid.org/professionals/publications/clinthy/index.html

FIGURES The articles in Clinical Thyroidology contain figures with the ATA logo and a CT citation with the volume and issue numbers. We encourage you to continue using these figures in your lectures, which we hope will be useful to you and your students.

WHATS NEW The last page now has a set of references to REVIEWS & HOT ARTICLES which contains references to important reviews and very recent articles that look especially important to the Editors.

EDITOR'S CHOICE ARTICLES are particularly important studies that we recommend you read in their entirety.

We welcome your feedback and suggestions on these changes.

CONCISE REVIEW CITATIONS CONCISE REVIEWS can be cited by using the electronic citation at the end of each review.

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

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Sorafenib has clinical activity against metastatic papillary thyroid cancer but requires close monitoring and aggressive management of drug toxicity

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SUMMARY

BACKGROUND This phase II clinical trial of sorafenib is based on the central role of the Ras-Raf-MAP-ERK signaling pathway and vascular endothelial growth factor (VEGF) in papillary thyroid cancer (PTC). Although sorafenib was initially considered to be a selective RAF kinase inhibitor, it is now known to be a multikinase inhibitor that targets several receptor tyrosine kinases at submicromolar concentrations, including VEGF receptors (VEGFRs) 1 to 3 and platelet-derived growth factor receptor.

METHODS The primary end point of the study was the objective response rate. Secondary end points were the correlation of serum thyroglobulin (Tg), functional imaging, tumor genotype, and signaling inhibition in tumor biopsies. The study used a Simon minimax two-stage design. In a typical two-stage design of a phase II clinical trial of cancer, a fixed number of patients are initially enrolled. The trial may be terminated for lack of therapeutic efficacy if the number of treatment successes after the first stage is too small. If so, an additional fixed number of patients are enrolled to accumulate additional information on efficacy. Accrual to arm B in the Kloos study was designed to stop as soon as arm A was fully accrued. The study subjects were patients who were 18 years of age or older with adequate performance status and measurable tumor. Treatment with chemotherapy or radiation therapy was not permitted within 4 weeks before entry into the study, and radioiodine therapy (with ^{131}I) was not allowed within 24 weeks before entry into the study, or within 4 weeks if the patient had a negative posttreatment ^{131}I scan. Also required were a leukocyte level ≥3000/L, an absolute neutrophil count ≥1500/L, a platelet count ≥100,000/μL, and serum bilirubin, aspartate aminotransferase and alanine aminotransferase, and creatinine levels 1.5-fold the upper limit of normal. To study the effects on tumor perfusion, dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) scans were obtained within 4 weeks before and every 8 weeks while on therapy, and fluorodeoxyglucose positron-emission tomography scans were obtained at similar time points when possible.

Patients were observed every 4 weeks for 1 year and if stable, every 12 weeks thereafter. Therapy was withheld if the patients had a grade ≥3 or recurrent grade ≥2 drug-related toxicity other than hematologic toxicity, or a grade ≥2 hand–foot–skin reaction until the toxicity resolved to grade ≤1. Sorafenib was generally tolerated; however, a dose reduction to 600 or 400 mg/day of sorafenib and a subsequent dose reescalation up to 800 mg/day was allowed. Sorafenib was continued until one of the following occurred: progressive disease, patient off sorafenib longer than 24 consecutive days for any reason, intercurrent illness that prevented further therapy, unacceptable adverse events, or patient withdrawal from the study. The response was assessed every 2 months using the Response Evaluation Criteria in Solid Tumors (RECIST) (Figure 1).

RESULTS A total of 56 patients were selected for study; 31 (55%) were men and 25 (44%) were women. The median age of the patients in arm A was 67 years (range, 33 to 90), and in arm B 56 years (range, 27 to 76). In all, 41 (73%) had PTC, 19 (46%) of whom were in arm A and 22 (54%) in arm B.

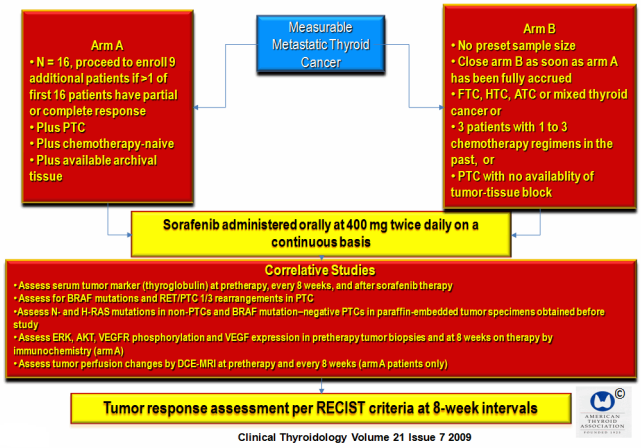

Figure 1. This figure shows the study cohort and study arms and patient demographics, and tumor histology. ATC = anaplastic thyroid cancer; DCE = dynamic contrast-enhanced; FTC = follicular thyroid cancer; HTC = Hürthle-cell cancer; MRI = magnetic resonance imaging; PTC = papillary thyroid cancer; RECIST = Response Evaluation Criteria in Solid Tumors. (Derived from data in Figure 1 of Kloos et al.)

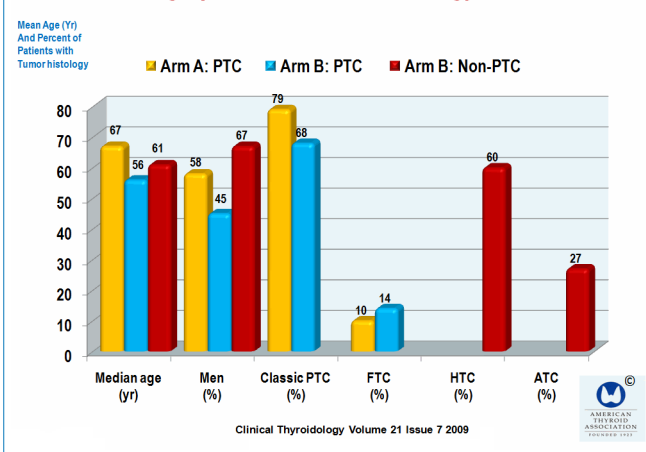

Figure 2. Patient demographics and tumor histology in arms A and B. ATC = anaplastic thyroid cancer; FTC = follicular thyroid cancer; HTC = Hürthle-cell cancer; PTC = papillary thyroid cancer. (Derived from data in Table 1 of Kloos et al.)

Thirty patients (73%) had classic PTC, 5 (12%) had follicular variant PTC, 4 (10%) had tall-cell-variant PTC, and 2 (5%) had poorly differentiated PTC. The distribution of tumor histologies in both arms of the study is shown in Figure 2. Two patients (4%) had follicular thyroid cancer (FTC), 9 (16%) had Hürthle-cell carcinoma, and 4 (7%) had anaplastic thyroid cancer. Arm A comprised 19 patients with PTC and 2 with FTC; arm B comprised 22 patients with PTC, 2 with FTC, 9 with Hürthle-cell carcinoma, and 4 with anaplastic thyroid cancer. The site of tumor metastases is shown in Figure 3.

TREATMENT ADMINISTERED The median duration of therapy was 14 months in arm A patients and 10, 8, and 2 months in patients with PTC, HTC/FTC, and ATC in arm B, respectively (Figure 4). Common grade 3 adverse events included hand–foot–skin reaction and musculoskeletal pain and fatigue. The reasons for dose reduction were hand–foot–skin reaction, diarrhea and weight loss, hypertension, fatigue, arthralgia, musculoskeletal chest pain, and mouth pain.

TUMOR RESPONSE ACCORDING TO RECIST

Of 41 patients with PTC, 6 had a partial response (PR; 15%; 95% confidence interval [CI], 6 to 29) and 23 (56%; 95% CI, 40 to 72) had stable disease for longer than 6 months. Median duration of PR was 7.5 months (range, 6 to 14). Median progression-free survival was 15 months (95% CI, 10 to 27.5) (Figures 5, 6 and 7).

BRAF mutation was detected in 17 (77%) of the 22 PTCs that were analyzed. Four of 10 paired tumor biopsies showed a reduction in VEGFR phosphorylation levels, ERK phosphorylation, and in VEGF expression during sorafenib therapy. No partial responses were noted among non-PTC patients. Clinical adverse events are shown in Figure 8.

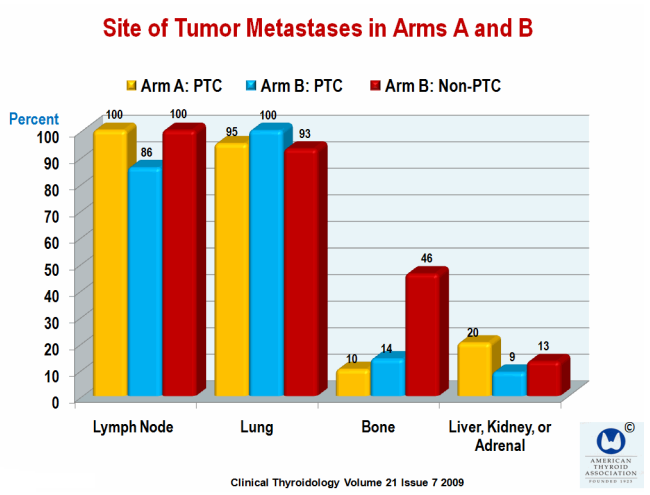

Figure 3. Site of tumor metastases in arms A and B. (Derived from data in Table 1 of Kloos et al.)

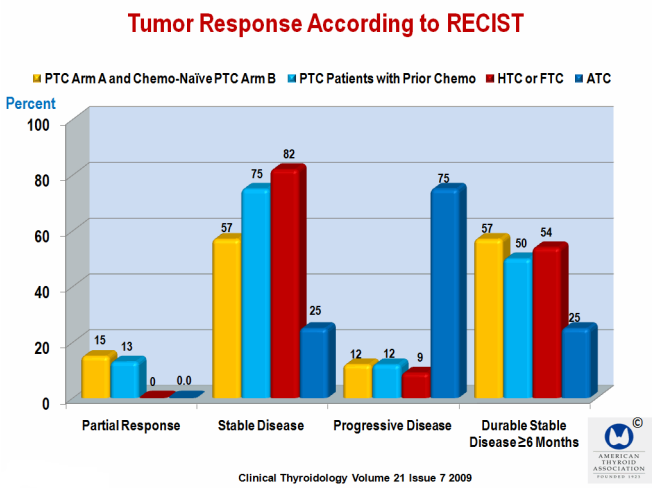

Figure 5. Tumor response is measured according to the RECIST (Response Evaluation Criteria in Solid Tumors).

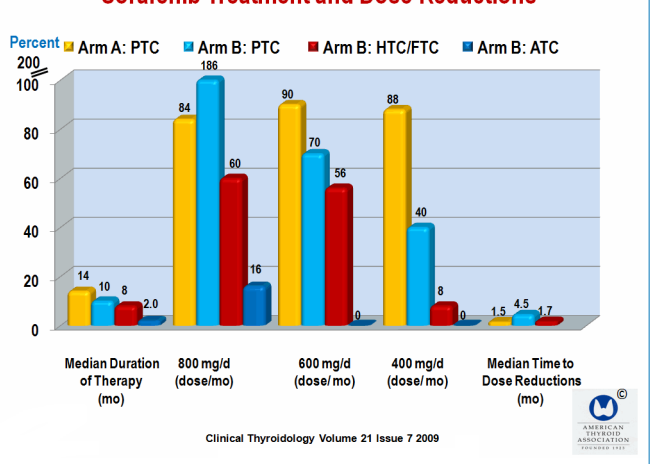

Figure 4. This is a summary of sorafenib treatment administered and the median duration of therapy and the median time to dose reductions (derived from data in Table 2 of Kloos et al.).

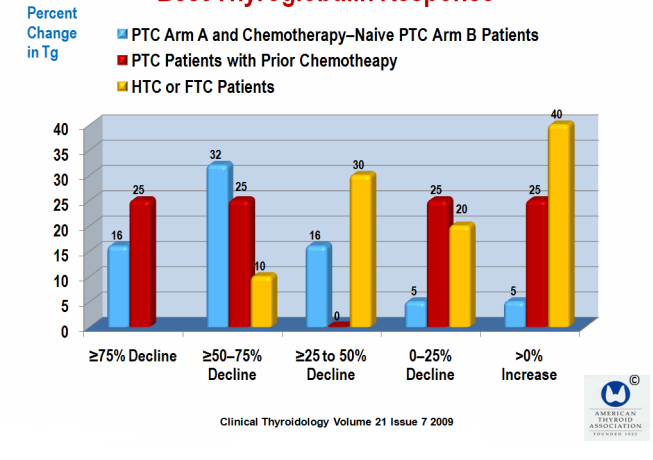

Figure 6. This shows the best thyroglobulin response to therapy.

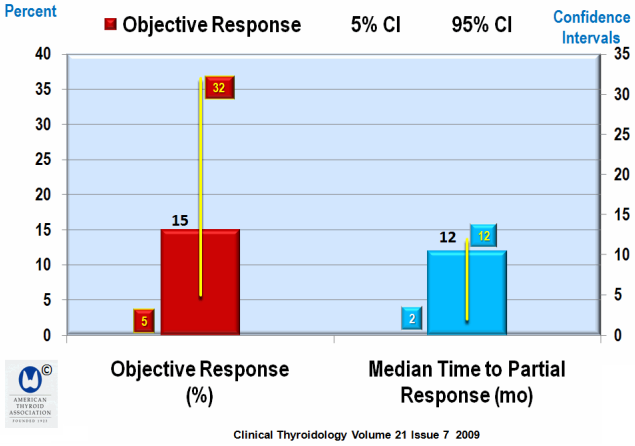

Figure 7. The objective response to sorafenib therapy is shown. Yellow bars = 5% to 95% confidence interval. The median time to partial response is shown; the top yellow flag is the 95% confidence interval (CI) and the lower left boxes are the 5% CI. The objective response (percent) and the median time to partial response (months) for sorafenib therapy is shown .

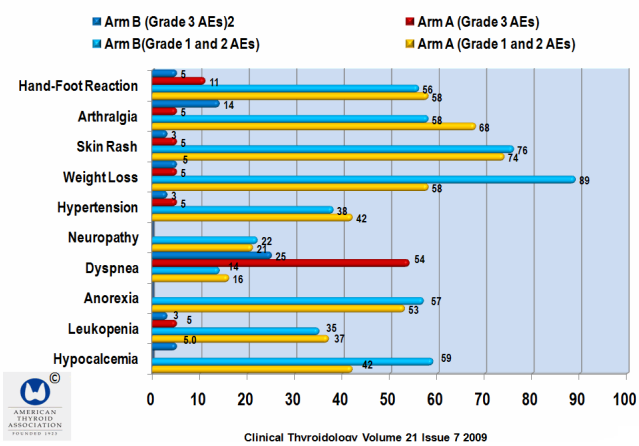

Figure 8. Some of the more common complications of sorafenib therapy. AE = adverse event.

SERUM THYROGLOBULIN CHANGES

In 14 of 18 patients (78%) the serum Tg was assessable, and declined more than 25% (Figure 6). In 10 of 14 assessable patients with PTC (71%), the 8- or 16-week DCE-MRI scans showed a median decrease of 46% (range, 27 to 92) during therapy, whereas no change was noted in the remaining four patients, none of whom had an objective response as compared with baseline. Among eight patients who had assessable results for paired biopsies and serial DCE-MRIs, there was no correlation between VEGFR levels or signaling response of VEGFR and pharmacokinetic parameters of DCE-MRI measurements.

CONCLUSION Sorafenib is relatively well-tolerated, with clinical and biologic antitumor activity in patients with metastatic papillary thyroid cancer, but it requires close surveillance and aggressive management of drug toxicity.

COMMENTARY

Studies of sorafenib have found the drug to have an impact on patients with metastatic tumor. Ratain et al. (1) found that patients with metastatic renal-cell carcinoma treated with sorafenib had median progression-free survival of 24 weeks as compared with 6 weeks for placebo (P = 0.007). Given the molecular pathophysiology of thyroid cancer and the spectrum of kinases inhibited by sorafenib, including Raf kinase, VEGFR, PDFR, and RET tyrosine kinases, Gupta-Abramson (2) conducted an open-label phase II trial to determine the efficacy of sorafenib in patients with advanced thyroid carcinoma. Patients with metastatic, iodine-refractory thyroid carcinoma received 400 mg of sorafenib orally twice daily. Thirty patients were entered into the study and treated for a minimum of 16 weeks. Seven patients (23%; 95% CI, 0.10 to 0.42) had a partial response lasting 18 to 84 weeks. Sixteen patients (53%; 95% CI, 0.34 to 0.72) had stable disease lasting 14 to 89 or more weeks. Seventeen (95%) of the 19 patients for whom serial thyroglobulin levels were available showed a rapid response in serum thyroglobulin levels, which decreased by a mean of 70%. Median progression-free survival was 79 weeks. Toxicity in this study was consistent with other sorafenib trials, although a single patient died of liver failure that was likely related to the treatment. The authors concluded that sorafenib has clinically relevant antitumor activity in patients with metastatic, radioiodine-refractory thyroid carcinoma, with an overall clinical benefit (partial response + stable disease) of 77%, a median progression-free survival of 79 weeks, and an overall acceptable safety profile. The authors opined that the results of this study represent a significant advance over chemotherapy in both response rate and progression-free survival, supporting further investigation of this drug in patients with thyroid cancer.

The Kloos et al. study is one of the first phase II clinical trials using an oral small-molecule multikinase inhibitor in patients with iodine-refractory metastatic PTC. The authors decided that sorafenib would be worthy of further study if the likelihood of a true response or target response rate was 30% or higher. The drug did not meet this expectation, and only 5 (15%) of 33 patients demonstrated a partial tumor response. Still, 23 patients had stable disease for longer than 6 months, and the median duration of the partial responses was 7.5 months, ranging from 6 to 14 months, and median progression-free survival was 15 months. Thyroglobulin declined more than 25% in 14 (78%) of 18 patients with PTC that had assessable thyroglobulin measurements.

Common grade 3 adverse events included hand–foot–skin reaction, musculoskeletal pain, fatigue, weight loss and diarrhea, and other adverse events. BRAF was detected in 17 (77%) of 22 PTCs analyzed. Four of 10 paired tumor biopsies

from patients with PTC showed a reduction in the levels of vascular VEGF phosphorylation, ERK phosphorylation, and VEGF expression during sorafenib therapy. No partial responses were found among patients with other forms of thyroid cancer. Stable disease and partial responses suggest a greater clinical benefit than that based on partial responses and stable disease of 6 months or more in 23 patients with PTC. Also, a better response is inferred from the serum Tg response.

Although the dose schedule used in this study was generally well tolerated, dose reductions were necessary in about half the patients. The authors suggest that the higher frequency of dose reductions in their study might be a result of relatively lower acceptability of long-term toxicities by patients with thyroid cancer. Still, the tumor response was generally maintained despite dose reductions.

Endocrinologists are not widely trained in the use of these drugs, but this study shows that the drug has benefits but also important complications. Physicians using these drugs must be aware of the adverse events of the drug and capable of quickly responding to this problem.

Ernest L. Mazzaferri, MD, MACP

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Methimazole-induced agranulocytosis in patients with Graves' disease is more likely with a daily dose of 30 mg than with 15 mg

Takata K, Kubota S, Fukata S, Kudo T, Nishihara E, Ito M, Amino N, Miyauchi A. Methimazole-induced agranulocytosis in patients with Graves' disease is more frequent with an initial dose of 30 mg daily than with 15 mg daily. Thyroid 2009;19:559-63.

SUMMARY

BACKGROUND One of the most serious side effects of antithyroid drugs (ATDs) is agranulocytosis; however, there is no conclusive evidence that the prevalence of this serious complication is related to the dose of ATDs. Although it has been reported that the side effects of methimazole (MMI) are dose-related, the studies remain inconclusive, perhaps because of the low frequency of agranulocytosis in patients treated with MMI. The aim of this study was to determine whether the prevalence of agranulocytosis is dependent on the dose of MMI.

METHODS From 1991 through 2005, 9104 patients with newly diagnosed Graves' disease were treated at Kuma Hospital in Japan. Of this group, 8260 patients received MMI as the initial therapy. Patients who dropped out within 1 year after the start of therapy (n = 1125) were excluded from the study, mainly because the authors believed that it was necessary to confirm that the side effects occurred at least 1 year after starting treatment. An additional 477 patients who were changed to propylthiouracil (PTU) or had surgery because of pregnancy or other complications were also excluded from the study. The remaining 6658 patients were enrolled into the study.

The diagnosis of Graves' disease was based on the laboratory features of hyperthyroidism, including suppressed serum thyrotropin (TSH), elevated levels of serum free triiodothyronine (T_3), and the presence of thyrotropin-binding inhibitor with or without an increase in radioiodine uptake. Agranulocytosis was defined as a neutrophil count less than 1000 per microliter. Patients were treated with an MMI dosage that was gradually tapered to maintain the euthyroid state. In some cases the MMI dosage was increased when the serum thyroid hormone levels were not declining. If a patient had fever, MMI was immediately discontinued and the white-cell count was measured.

RESULTS In all, 28 of 6658 patients (0.4%) had agranulocytosis; 30 (0.5%) neutropenia, and 650 (10%) minor side effects resulting in a switch to other treatments. In all, 5950 patients (89%) had follow-up for more than 1 year. The patients who could be followed for at least 1 year and others who had side effects during the observation period were selected as study subjects. As a result, 2087 subjects were treated with 30 mg/day of MMI and 2739 were treated with 15 mg/day of MMI.

Agranulocytosis developed in 17 patients (0.8%) in the 30-mg group, and 6 patients (0.3%) in the 15-mg group (P<0.01, comparing the prevalence of agranulocytosis in the two groups) (Figure 1). When severe agranulocytosis was defined as a neutrophil count less than 200 per microliter, there were 11 such patients (0.5%) in the 30mg group and 3 (0.1%) in the 15-mg group (P<0.05).

Neutropenia occurred in 16 patients (0.8%) in the 30-mg group and 7 (0.3%) in the 15-mg group (P<0.05). Of the 33 patients (2%) affected with agranulocytosis and neutropenia, 33 (1.6%) were in the 30-mg group and 13 (0.5%) were in the 15-mg group (P<0.001).

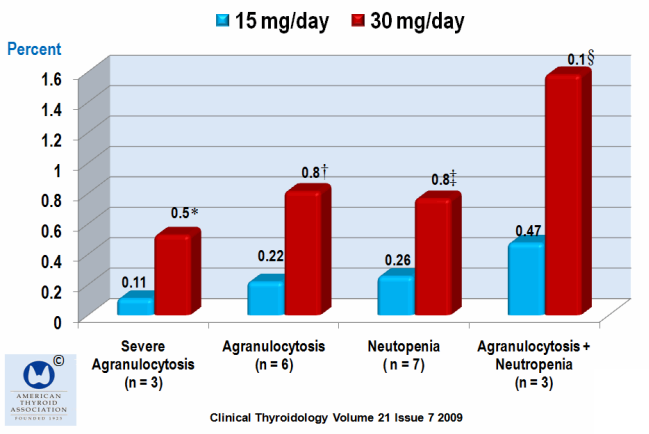

Figure 1. The incidence of side effects with 15 vs. 30 mg/day of methimazole *P = 0.02, †P = 0.006, ‡P = 0.002, §P = 0.0002) comparing 15 mg/day with 30 mg/day of MMI. Severe agranulocytosis is a neutrophil count less than 200 per microliter, agranulocytosis a neutrophil count less than 500 per microliter, and neutropenia a neutrophil count less than 1,000 per microliter.

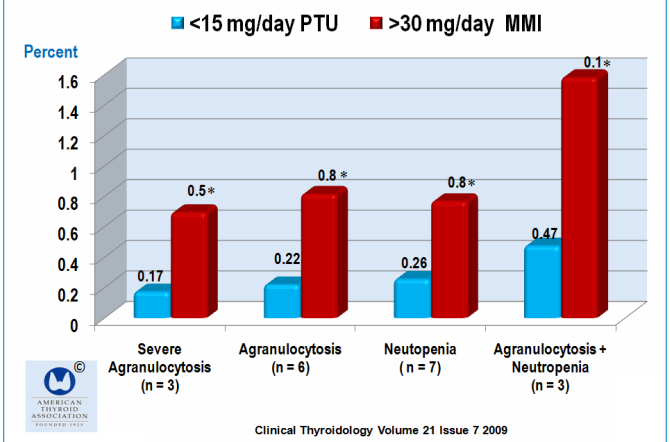

Figure 2. The incidence of side effects in the group of patients treated with less than 15 mg/day of PTU versus patients treated with more than 30 mg/day of MMI. *P<0.001 comparing <15 mg PTU with >30 mg MMI.

When the group treated with more than 20 mg/day of MMI was compared with those treated with less than 15 mg of PTU, 22 (0.7%) of 3174 patients had agranulocytosis in the high-dose group, and 6 (0.2%) of 3484 patients had agranulocytosis in the low-dose group (Figure 2). No patients treated with less than 10 mg/day of MMI had agranulocytosis, and 3 had neutropenia. No deaths from agranulocytosis occurred in the study subjects.

CONCLUSION Methimazole-induced agranulocytosis in patients with Graves' disease is more likely with a daily dose of 30 mg than with 15 mg.

COMMENTARY

The initial treatment of Graves' disease varies according to geographic location. Nonetheless, antithyroid drugs are the initial therapy of choice for the majority of patients with Graves' disease treated in Europe and Japan and elsewhere in Asia (1, 2). Although the superiority of either PTU or MMI is not fully established (3), MMI is in many ways better than PTU. For example, with MMI serious toxicity is less common, adherence rates to treatment are higher, and the thyroid hormones levels fall faster as compared with PTU (4, 5). Moreover, MMI is generally preferred when antithyroid drugs are given to prepare a patient for radioiodine therapy or surgery.

Yet, PTU is still the drug of choice during pregnancy as a consequence of the rare reports of birth defects, especially MMI-related aplasia cutis, that occur in women treated with MMI during the first trimester. In addition, PTU is most commonly recommended for patients with life-threatening thyrotoxicosis, mainly because of the reduction of T_3 production, although the clinical response to this effect is difficult to prove.

The most important issue concerning the choice of antithyroid drugs is the occurrence of life-threatening complications. MMI has less toxicity than PTU, especially when prescribed in lower doses (6, 7). In contrast, PTU can produce life-threatening hepatotoxicity that seems especially severe in children and has been reported to occur in pregnant women and in the fetus (7). A recent editorial by Cooper and Rivkees (7) suggests that approximately 4000 pregnant women per year would be expected to be treated with antithyroid drugs, most of whom would be treated with PTU, according to current practice guidelines. They also estimated that 15 adults with Graves' disease will develop severe PTU-related hepatotoxicity and that each year one or two individuals with Graves' disease in the United States will die or require a liver transplant after PTU exposure. Although MMI also can cause liver injury, it typically produces serious cholestatic dysfunction rather than severe hepatocellular inflammation. Cooper and Rivkees (7) concluded that considering the intricacies of care and risks involved for a pregnant women with thyrotoxicosis, treatment with radioactive iodine or surgery before pregnancy should be strongly considered for women who desire future pregnancy.

Agranulocytosis is the other life-threatening complication of antithyroid drugs that is of great concern. In this issue of Clinical Thyroidology, Takata et al. suggest that although a few studies suggest that agranulocytosis is related to the dose of MMI, the data are sparse (8).

The study by Takata et al. of 2087 subjects treated with 30 mg/day of MMI and 2739 treated with 15 mg/day of MMI found that the prevalence of agranulocytosis in the 30-mg group was almost fivefold greater than that in the 15-mg group ($P<0.01$). Likewise, the prevalence of agranulocytosis plus neutropenia was also about fivefold greater in the 30-mg group as compared with that in the 15-mg group ($P<0.001$). The authors' conclusions that MMI-induced agranulocytosis is dose-related is underpinned by their large study, which provides robust evidence to support this conclusion. Considering both the effectiveness of MMI and the risk of serious side effects with larger doses, the authors recommend 15 mg/day of MMI as the starting dose for the treatment of Graves' disease. This makes sense.

Ernest L. Mazzaferri, MD, MACP

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Nodule hypoechogenicity, microcalcifications, and a height-to-width ratio ≥1 are independent factors predicting malignancy in thyroid nodules regardless of nodule size

Popowicz B, Klencki M, Lewinski A, Slowinska-Klencka D. The usefulness of sonographic features in selection of thyroid nodules for biopsy in relation to the nodule's size. Eur J Endocrinol 2009;161:103-11.

SUMMARY

BACKGROUND The wide use of neck ultrasonography has altered the diagnostic approach to thyroid nodules, often revealing many small nodules of uncertain clinical significance on the one hand, and multiple large thyroid nodules on the other, posing the question as to which nodules should undergo fine-needle aspiration biopsy (FNAB). The aim of this study was to evaluate the diagnostic efficacy of ultrasound features that are most useful in establishing the indication for FNAB as it relates to the size of thyroid nodules.

METHODS This is a retrospective study of thyroid nodules diagnosed from 2000 through 2005 in 672 patients who were referred to thyroid surgeons for the management of thyroid nodules at the Medical University of Lodz in Poland. Many of these patients had large multinodular goiters, some of which had benign FNAB cytologic features and others that were suspected of having malignancy. Patients with a history of external-beam or ionizing radiation were excluded from the study. All of the ultrasound examinations were performed by three physicians with at least 5 years of experience with the same ultrasound equipment. Based on the postoperative histopathology, the thyroid nodules were classified as malignant or benign to facilitate an analysis of the nodule ultrasound features, including nodule shape, echogenicity, and intranodular blood flow pattern, and the presence of microcalcifications and multiple nodularity and tumor palpability. The following ultrasound features were analyzed: nodule shape (anterior–posterior dimension [height] compared with the transverse dimension [width] of the nodule to provide a height-to-width ratio in two diagnostic categories [≥1 and <1], nodule echogenicity, solidity and hypoechoic patterns, Doppler blood-flow patterns (intranodular vascular vs. other patterns) and the presence of other thyroid nodules in the thyroid gland. The features of malignancy were evaluated separately according to nodule size, which was categorized as small (<15 mm) and large (≥15 mm). In addition, the study included all accompanying nodules described in the ultrasound report and the postoperative histology report. Nodule margins were not described in a uniform fashion and thus could not be included in the analysis.

RESULTS The study comprised 1141 nodules in 672 patients whose mean (±SD) age was 49.5±11.4 years and for whom data on nodule palpability and histopathology were available. The analysis included 316 nodules for which Doppler blood-flow patterns were available and only 210 nodules for which data were available concerning the nodule shape. In all, 881 nodules were benign follicular adenomas and 96 were malignant (72 papillary, 11 medullary, 5 oxyphilic [Hürthle cell], 2 follicular thyroid, and 4 anaplastic thyroid). Among the 96 cancers, 33 (34%) had diameters less than 10 mm. There were 462 large nodules (40.5%) and 679 small nodules (59.5%).The mean nodule diameter was 32.97±14.31 mm (median, 28; range, 15 to 80) in the large-nodule group, and 11.25±2.7 mm (median, 10; range, 4 to 15) in the small-nodule group. As compared with the benign tumors, the malignant tumors were more often hypoechoic (61.5

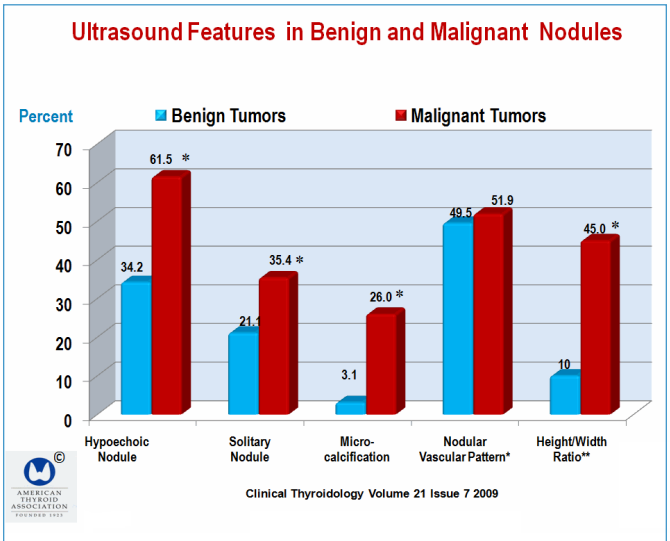

Figure 1. This figure shows the difference in accuracy of sonographic features in benign and malignant tumors, *P <0.001, comparing malignant and benign nodules, regardless of nodule size.

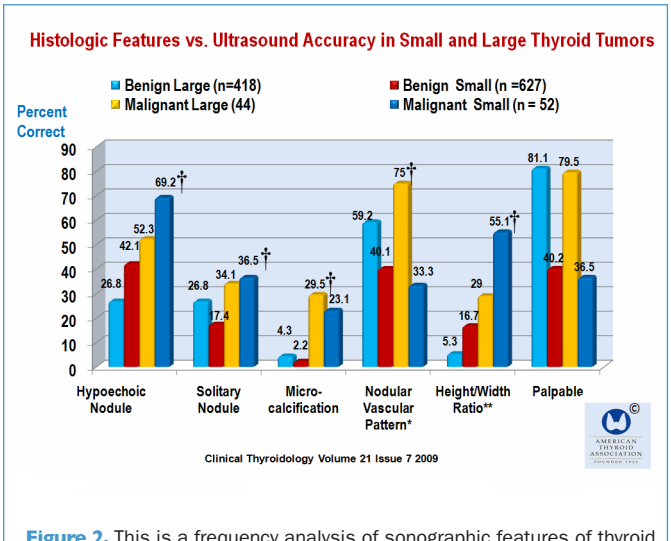

Figure 2. This is a frequency analysis of sonographic features of thyroid nodules and their size in groups of benign and malignant tumors. Small = <10 mm; large = ≥10 mm. * 316 nodules; ** 210 nodules. †P < 0.001, comparing malignant small nodules with malignant large nodules. Data for this figure is derived from Table 1 of Popowicz et al.

vs. 34.2%, P<0.0001) and solitary (35.4 vs. 21.1%, P<0.005) and more contained small calcifications (26.0 vs. 3.1%, P<0.001), and the malignant nodules more often had a height-to-width ratio that was ≥1, versus <1 (45.0 vs. 10%, P<0.0001) (Figure 1). Also, in a separate analysis of the malignant and benign nodules, the same ultrasound features were found in the small nodules as compared with the large nodules. As compared with small benign tumors, small malignant tumors were more likely to be hypoechoic (P<0.001), to have a height-to-width ratio ≥1 (P<0.0001), and to have microcalcifications (P<0.001). As compared with the benign nodules, small malignant tumors were more often solitary (36.5 vs. 17.4%; P<0.001), but this was found only with large nodules. An intranodular vascular pattern was significantly more common in large nodules as compared with small nodules (75 vs. 33.3%, P<0.05); however, there were no significant differences in Doppler blood flow in malignant and benign nodules (Figure 2).

The small nodules were divided by size into two groups: ≤10 mm and 11 to 15 mm. Features such as hypoechogenicity, solitary occurrence. and height-to-width ratio ≥1 tended to be more sensitive for the diagnosis of thyroid cancer in smaller nodules (Figure 3) The single most sensitive ultrasound feature allowing selection of nodules for FNAB in both small and large nodules was hypoechogenicity (Figures 4 and 5). Nonetheless, selecting only hypoechoic nodules for biopsy would have missed 31% of the small malignant tumors and 49% of the large tumors. The specificity of this criterion was significantly lower for small nodules than for large nodules (57.9 vs. 77.7%, P<0.0001) (Figures 5 and 6). Although the most specific criterion for malignancy in both small and large tumors was the presence of microcalcifications (>95%), the sensitivity of this feature was only 29.5% in both small and large tumors. The height-to-width ratio of a nodule had a higher sensitivity for malignant tumors in the large tumor group than the small tumor group (55.1 vs. 29.0%, P<0.002) (Figure 4) but had lower specificity (83.3%). A solitary nodule was more specific for malignancy in a small nodule than in a large tumor (82.6 vs. 73.2%, P<0.001).

Multivariate logistic-regression analysis (Figure 7) found in the small-nodule group that at least one of the ultrasound tumor features significantly differentiated malignant and benign nodules, which would have led to aspiration of 98% of malignant nodules, while lowering the number of examinations by 24.3%. Also in the small-tumor group, a sensitivity of >90% was found for an FNAB selection of malignant tumors that included all hypoechoic nodules and those with a height-to-width ratio ≥1. However, with these selection criteria, the specificity would be only 46.3% and the number of FNABs would decline by 28%. In the group of small nodules with diameters ≤10 mm, these ultrasound selection criteria (hypoechogenicity and height-to-width ratio ≥1) would result in a sensitivity of 90% with a specificity as low as 34.6%. If the selection criteria included

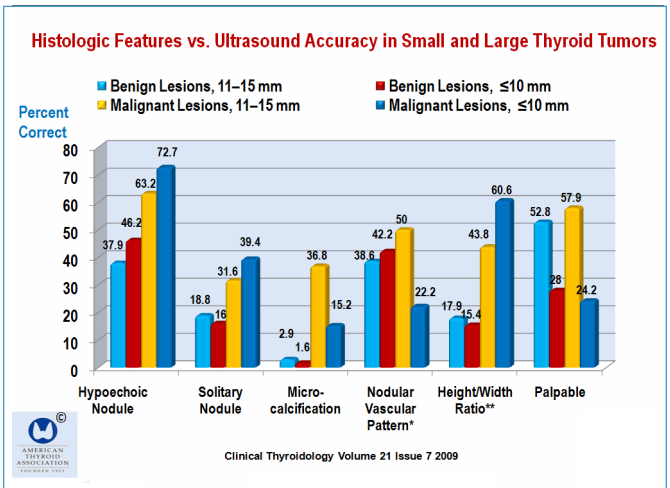

Figure 3. This figure shows the results of a detailed analysis of small nodules divided into lesions with diameters ≤ 10 mm and 11-15 mm. It shows that features like hypogenicity, solitary nodules, and height-to-width ratio ≥ 1 tended to be more sensitive in smaller nodules whereas nodule microcalcifications were less sensitive. Neither nodule palpability nor size > 10 mm was significantly associated with the histology diagnosis. * 3125 nodules; ** 103 nodules. Data for this figure were derived from Table 2 of Popowicz et al.

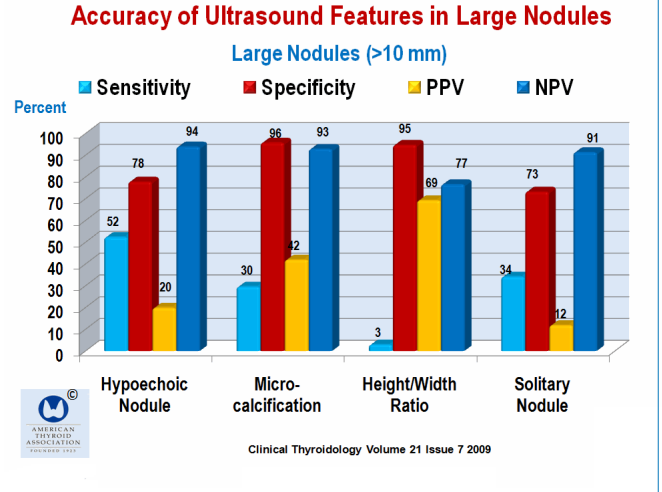

Figure 4. This figure shows the diagnostic accuracy of the ultrasound features in large thyroid nodules. Data for this figure were derived from Table 3 of Popowicz et al.

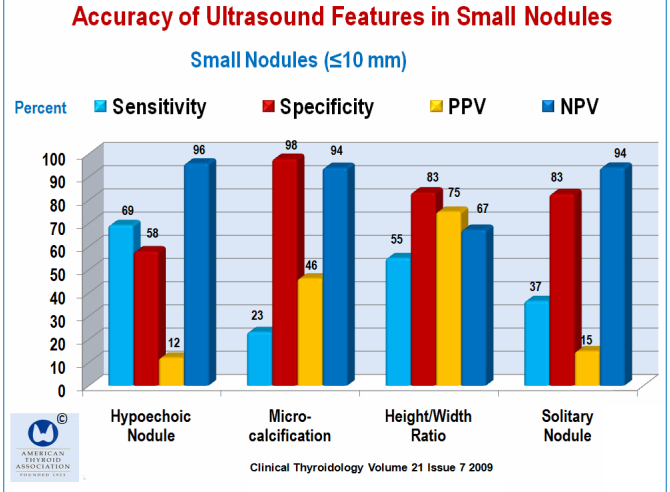

Figure 5. This figure shows the diagnostic accuracy of the ultrasound features in small thyroid nodules. Data for this figure were derived from Table 4 of Popowicz et al.

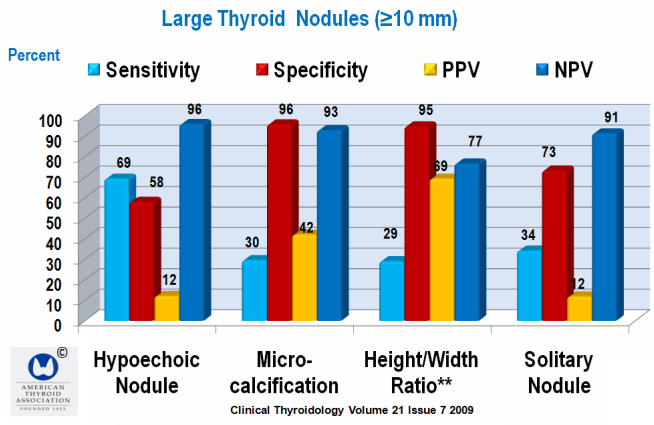

Figure 6. This figure shows the ultrasound features that independently identify malignant thyroid nodules. Data for this figure was derived from Table 5 of Popowicz et al.

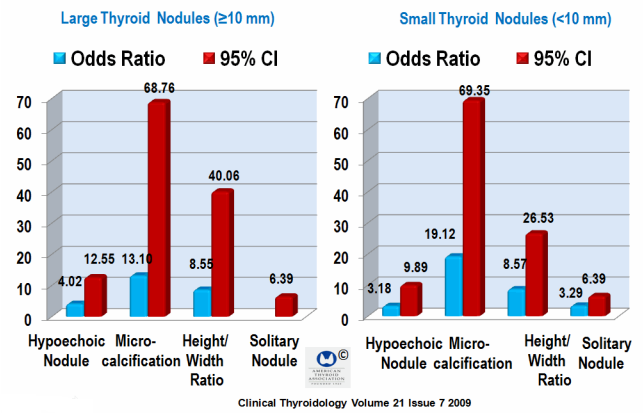

Figure 7. This figure shows the odds ratios for ultrasound features suggesting malignancy in a thyroid nodule in patients with large thyroid nodules or small thyroid nodules. Data for this figure was derived from Table 5 of Popowicz et al.

all nodules that were solitary or had microcalcifications, or had a height-to-width ratio ≥1, the specificity would increase to 77.8% in nodules ≤10 mm with a sensitivity of 81.6%; however, hypoechogenicity was the only feature among those analyzed that differed significantly between invasive and noninvasive cancers. The FNAB of all hypoechoic nodules or those containing calcifications or a height-to-width ratio ≥ 1 would lead to a 55.1% decline in the number of FNABs performed, while maintaining a high sensitivity and specificity of 83.9% and 72.4%, respectively.

CONCLUSION There is strong rationale for using thyroid ultrasound features to select large or small thyroid nodules for fine-needle aspiration biopsy. Nodule hypoechogenicity, microcalcifications, and a height-to-width ratio ≥1 are independent factors predicting malignancy in thyroid nodules regardless of nodule size.

COMMENTARY

A variety of ultrasound findings have been identified as independent features suggesting malignancy in a thyroid nodule. The study by Popowicz et al. provides further insight into this problem. This study found that lesional hypoechogenicity and the presence of microcalcifications were independent factors that suggested malignancy with a high degree of accuracy, regardless of nodule size. Widely recognized features portending malignancy in a thyroid nodule are hypoechogenicity (1-3), microcalcification (1, 3, 4), and irregular nodule margins (3, 4).

In addition to these ultrasound features, Popowicz et al. found on multivariate analysis that the shape of thyroid nodules determined by a height-to-width ratio ≥1 was also an independent factor suggesting malignancy. However, this has not been as widely accepted and varies according to the way it is measured in various studies. For example, Alexander et al. (5) found that a long-to–short-nodule axis ratio >2.5 was 100% predictive of a benign process; however, this was present in only 4% of the study cohort but was confirmed by a prospective validation with consistent results (P<0.01). In another study, Berker et al. (6) found that a long-to-short-nodule axis ratio <1.5 was associated with malignancy in subcentimeter thyroid nodules. Still others have determined the nodule configuration by measuring the anterior–posterior -to-width ratio. For example, Moon et al. (7) found that malignancy was identified by a taller-than-wide shape, which had a specificity of 91%, but a sensitivity of only 40%. Cappelli et al. (8) also found that a nodule shape that was more tall than wide determined by the anteroposterior-transverse diameter ratio >1 was a good predictor of malignancy independent of the nodule size, but concluded that microcalcification, blurred margins, and a hypoechoic nodule pattern was the best compromise between missing cancers and cost–benefit.

Popowicz et al. did not find Doppler blood-flow characteristics of the nodule to be useful for identifying malignancy in small nodules, which is in keeping with the findings in some studies (2, 9, 10) but not in others (8). For example, Papini et al. (11) found that an intranodular vascular pattern, was an independent risk factor of malignancy. Chan et al. (12) also found that hypoechogenicity (86%), microcalcifications (42%) and intranodular hypervascularity (69%) were uncommon features of papillary thyroid cancer. Thus, the findings on this feature are highly variable.

Popowicz et al. also found that a solitary nodule was also an ultrasound feature that suggested malignancy in small nodules, which has been found by some (5, 13) but not all (2,

11) studies. Still other studies (14) find that the cancer risk for patients with one or two nodules >1 cm decreases with three or more thyroid nodules.

Popowicz et al. found no single criterion to be optimal for selecting nodules for FNAB, a conclusion reached by others (8, 11, 15, 16). Popowicz concluded that the results of this study provide a rationale for using ultrasound features in selecting nodules for FNAB, such as the shape of nodules with a height-to-width ratio ≥1, hypoechogenicity, microcalcifications and a solitary nodule, but these ultrasound features have different predictive diagnostic values and different sensitivity and specificity according to nodule size. The authors offer the caveat that although the set of ultrasound features proposed in this study for small nodules is greater than that for large nodules, it does not mean that FNAB of very small nodules (microcarcinomas) should be performed more often than for larger nodules. Rather, it shows what ultrasound features should be considered to obtain the maximal sensitivity, and that small nodules presenting with such features should be biopsied or followed by repeat ultrasound examinations (17).

This is a very thoughtful study that provides important information about ultrasound-guided FNAB, not only in the sense of guiding the biopsy needle, but also in guiding the physician who will be performing the biopsy.

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Angiolymphatic tumor invasion is the main predictor of recurrence for papillary thyroid microcarcinoma

Arora N, Turbendian HK, Kato MA, Moo TA, Zarnegar R, Fahey TJ. Papillary thyroid carcinoma and microcarcinoma: is there a need to distinguish the two? Thyroid 2009;19:473-47.

SUMMARY

BACKGROUND Papillary thyroid microcarcinoma (PTMC) is defined as papillary cancer ≤1 cm, thus ranging in size from microscopic to as large as 1 cm in diameter. Some have suggested that tumors ranging in size from 1 to 5 mm have less aggressive clinical manifestations than tumors 6 to 10 mm in diameter. There is an even greater difference of opinion concerning the clinical behavior of classic papillary thyroid cancers (PTC) 1 to 2 cm or larger. The aim of this study was to compare classic PTC with PTMC.

METHODS The study subjects were patients with PTC referred to the New York Presbyterian Hospital–Cornell who had total or near-total thyroidectomy from January 1995 through January 2005 and had follow-up for at least 3 years after surgery. Patients with distant metastases unresponsive to ^{131}I therapy, or for whom clinical information was incomplete, were excluded from the study. PTMC was defined as a tumor ≤1 cm and PTC was defined as classic or follicular variant PTC. Incidental PTMC was defined as a tumor found during thyroid or neck surgery for conditions other than thyroid cancer, while nonincidental PTMC was defined as tumor that was resected in patients who had surgery for suspicious malignancy based on fine-needle aspiration biopsy (FNAB). Lymph-node metastases were identified either in the surgical histology specimens or on postoperative radioactive iodine imaging. Likewise, angiolymphatic invasion was defined by histologic evidence of tumor cell within a vessel, either attached to the vessel wall or associated with thrombosis. Extrathyroidal extension was defined as gross tumor extension found at surgery and confirmed on the surgical histology specimens.

RESULTS Of the 202 patients in the study, 66 (33%) had PTMC and 136 (67%) had PTC. There were 46 women (70%) with PTMC, the mean age of whom was 50 years (range, 24 to 78) as compared with a mean age of 46 years (range, 15 to 78) in the 136 patients with PTC. Complete tumor resection was accomplished in 59 patients (89%) with PTMC, and 115 patients (85%) with PTC. Approximately half of the patients in both the PTMC and the PTC group had central lymph-node dissections. Radioiodine therapy was given to 117 of the 136 patients (86%) with PTC and 44 of the 66 (67%) with PTMC (P<0.003).

Mean tumor size was 0.67 cm (range, 0.1 to 1) in the group with PTMC and 2.58 cm (range, 1.1 to 7) in the group with PTC. Multifocal tumor was found in 37 of 66 patients (56%) with PTMC and 71 (52%) with PTC. Extrathyroidal extension was found in 3 patients (4.5%) in the PTMC group and 19 (14%) in the PTC group. Angiolytic invasion was found in 4 (6%) of the PTMC group and in 18 (13%) of the PTC group. Except for average tumor size, all comparisons of PTMC and PTC were not statistically different.

Lymph-node metastases were found in 26 of 60 patients (43%) with PTMC and 63 of 124 patients (51%) with PTC (P = 0.35), and distant metastases were found in 3 of 47 patients (6%) with PTMC and 12 of 111 patients (11%) with PTC (P = 0.56). (Figure 1). Forty patients (19.8%) had tumor recurrence an average of 2.7 years after surgery (range, 6 months to 8.3 years). Tumor recurrence was found in 11 patients (17%) with PTMC and 29 patients (21.3%) with classic PTC (P = 0.57). The types of recurrence are shown in Figure 1. Approximately one third of recurrences in both groups were expressed only as a rise in

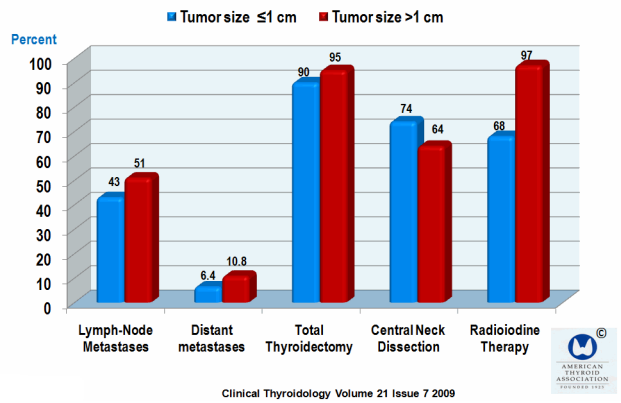

Figure 1. This figure shows the type of metastases, initial surgery, and ^{131}I therapy.

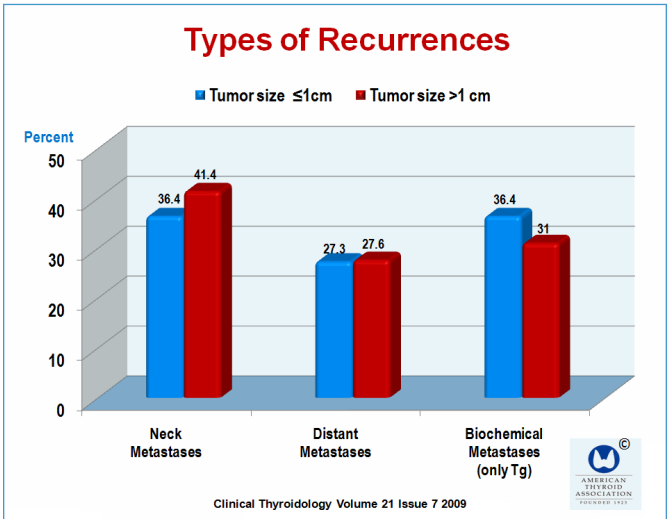

Figure 2. This figure summarizes the types of recurrences that occurred in patients with PTMC and PTC. None of the differences are statistically significant. Tg = Thyroglobulin.

serum thyroglobulin concentrations, with no identifiable source on imaging, while recurrence in the neck was the most common identifiable site in either group (Figure 2). There were several important differences in recurrence and disease-free outcomes among patients with PTMC and PTC. Tumors that recurred were significantly larger as compared with tumors that did not recur (0.81 cm vs. 0.64 cm, P<0.05); however, tumor size >8 mm was not found to be a significant marker for recurrence.

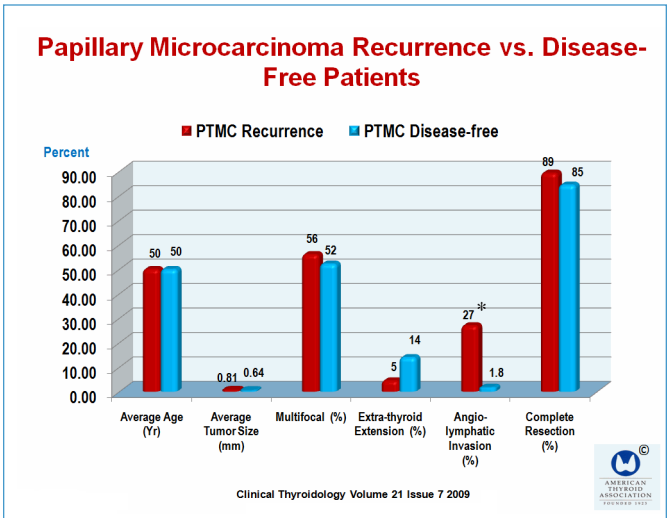

Figure 3. This figure shows that patients with PTMC had no significant difference in any of the parameters shown, except that 27% of patients with tumor recurrence had angiolymphatic invasion of tumor and only 2% who had angiolymphatic invasion remained free of disease (*P = 0.001)).

Among the patients with PTMC recurrence, tumors that recurred were significantly larger than those in patients who remained disease-free (8.1 mm vs. 6.4 mm, P<0.05), and patients with lymph-node metastases were significantly more likely to have angiolytic tumor invasion than those without lymph-node recurrence (3 of 11 [27%] vs. 1 of 55 [1.8]), respectively; P = 0.01).

None of the patients with incidental PTMC (n = 14) had tumor recurrence (P = 0.1), and tumors that recurred were more likely to be multifocal or to have lymph-node or distant metastases; however, this difference was not statistically significant (Figure 3). The types of recurrence in patients with PTMC and PTC were not significantly different. Multivariate logistic-regression analysis found that the presence of angiolymphatic invasion of PTMC was the only predictor of disease recurrence (P<0.02). However, the recurrence rates for PTMC and classic PTC were not significantly different (17% vs. 21%; P = 0.57)

CONCLUSION This study found that PTMC had a similar rate of poor prognostic features as compared with PTC, including lymph-node metastases and extrathyroidal extension, and recurrence rates in the two types of tumor were not significantly different. Angiolymphatic tumor invasion was the main predictor of recurrence.

COMMENTARY

This is an interesting study that compares the presentations and outcomes of patients with classic PTC and papillary microcarcinoma (PTMC). Before commenting on this paper, it is worthwhile to clarify the definition of papillary microcarcinoma, as it is not quite as clear as one might think. According to the World Health Organization (WHO) classification of tumors (1), the term microcarcinoma should be used for only papillary thyroid carcinoma that is found incidentally and that measures ≤1 cm in diameter. In some schemes, papillary carcinoma measuring <1 cm in diameter is considered a variant of papillary carcinoma (2-4). Also, the WHO definition concerning the caveat that this should be an incidentally discovered cancer, is more often than not considered in discussions of PTMC. The article by Arora uses the usual definition of PTMC without adding the term incidental. Of greater concern, the 6th edition of the TNM staging system endorsed by the American Joint Commission on Cancer (AJCC) (5, 6) and the International Union Against Cancer (UICC), which changed the definition of T1 from a tumor of ≤1 cm to a tumor of ≤2 cm, no longer is consistent with the WHO pathological definition of microcarcinoma. This only serves to add confusion concerning the management of papillary microcarcinoma.

Although there is debate concerning the management of PTMC, both the American and European Thyroid Associations (7, 8) suggest that lobectomy is sufficient therapy for patients with PTMC, providing the tumor is not multifocal, invasive or metastatic, or associated with familial papillary thyroid cancer in a patient who has not had head and neck irradiation. Still, there is a wide range of opinions concerning the management and general outcome of PTMC (9, 10). The tumor recurrence rates for PTMC are in the range of 5% (9, 11) 1 year after initial therapy (9), and the 10-year cancer-specific mortality rate in one of the largest studies published was 2% (11).

Yet over time, the recurrence rates of PTMC may be even higher than 5%. A study by Noguchi et al. (12) of 2070 patients with PTMC concluded that PTMC is essentially very similar to PTC that is ≥11 mm and has a very good prognosis. Smaller tumors and younger patients had a better prognosis. Among tumors ranging from 6 to 10 mm, the recurrence rates were 14% at 35 years, as compared with 3.3% in patients with smaller tumors. Patients older than 55 years had recurrence rates of 40% at 30 years, which is worse than those found in younger patients, who have a recurrence rates of less than 10%. Extracapsular invasion by the primary tumor also was found to have a higher recurrence rate. The authors of the study concluded that papillary microcarcinoma is similar to larger papillary carcinomas with tumor characteristics and age-based recurrence rates that extend for many years, justifying long surveillance after surgery.

The main findings of Arora et al. were an overall recurrence rate of approximately 20%; it was 17% in patients with PTMC. Tumors that recurred were significantly larger as compared with those that did not recur, fitting in with the notion that there is a range of outcomes in tumors ranging from 1 to 10 mm. None of the patients with incidental PTMCs had recurrence, suggesting that these tumors are less virulent than tumors that are apparent

at the time of diagnosis. The main finding of the multivariate analysis was that angiolymphatic tumor invasion portends a high rate of tumor recurrence, much like the findings reported by Noguchi et al.

Lastly, it should not go unnoticed that although all of the patients in this study had total thyroidectomy, approximately half had central compartment lymph-node dissection, and 68% with PTMC had postoperative ^{131}I therapy, yet about 20% of patients still had tumor recurrence.

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Ultrasound-guided fine-needle aspiration biopsy of thyroid nodules in children and adolescents has high diagnostic accuracy

Izquierdo R, Shankar R, Kort K, Khurana K.Ultrasound-guided fine-needle aspiration in the management of thyroid nodules in children and adolescents. Thyroid 2009;19:703-5.

SUMMARY

BACKGROUND The incidence of thyroid nodules in children and adolescents ranges from 1% to 2%. The aim of this study was to assess the diagnostic accuracy, sensitivity, and specificity of ultrasound-guided fine-needle aspiration biopsy (US-FNAB) in children and adolescents with thyroid nodules.

METHODS This is a retrospective analysis of the efficacy of US-FNAB in 42 children and adolescents in whom 52 thyroid nodules were identified. US-FNAB was performed with a 25-gauge needle attached to a 10-ml syringe. Up to four needle passes were performed per nodule and two slides were made from each aspiration for all nodules >1 cm. The cytology specimens were air-dried and stained with Diff-Quick or fixed immediately in 95% ethanol and stained by the Papanicolaou method. All thyroid examinations and US-FNAB studies were performed in a similar manner by one endocrinologist. The cytology and histopathology diagnoses were compared in all patients who had thyroid surgery. The diagnostic accuracy, sensitivity, and specificity were calculated from the results from each nodule. A cytology diagnosis of indeterminate or malignant was considered positive, a nonneoplastic result was considered negative, and a nodule confirmed as benign on the histopathology specimen was defined as true negative. Cytology specimens that were inadequate for diagnosis were not included in the calculations of accuracy.

RESULTS A total of 52 nodules in 42 patients underwent US-FNAB. The mean age of the patients was 14.75 years (range, 8.67 to 19.75); 29 patients (69%) were female, and 13 (31%) were male. The surgical histology results were available in 16 thyroid nodules. The US-FNAB cytology specimens were papillary thyroid cancer in 6 nodules (12%), indeterminate in 2 (4%), nonneoplastic in 42 (83%), and inadequate for diagnosis in 1 (2%) (Figure 1). Twenty-two of 36 nodules with benign cytology (61%) had follow-up with clinical and ultrasound examinations for an average of 20 months without any significant change in nodule size. Among the 16 patients who had thyroid surgery for which the histology diagnosis was available, the US-FNAB sensitivity was 100% and the specificity was 89%. There were no known false-negative cytology specimens, but there was one false-positive case. The overall diagnostic accuracy was 94%, which compares favorably with the results in a previous publication by these authors of historical controls that had fine-needle aspiration biopsy by palpation (Figure 2).

CONCLUSION Ultrasound-guided fine-needle aspiration biopsy of thyroid nodules in children and adolescents has high diagnostic accuracy.

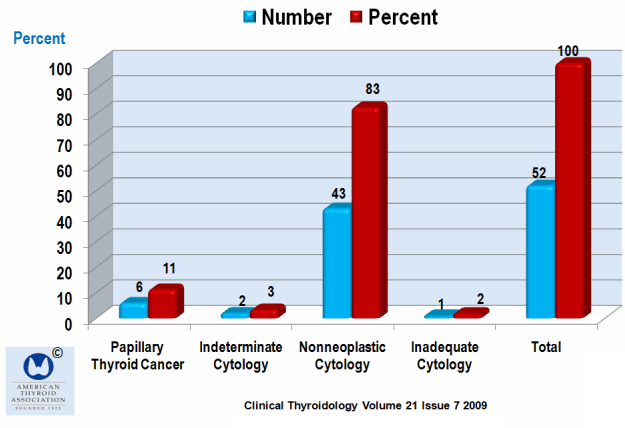

Figure 1. The cytology diagnosis of ultrasound-guided fine-needle aspiration biopsies in children

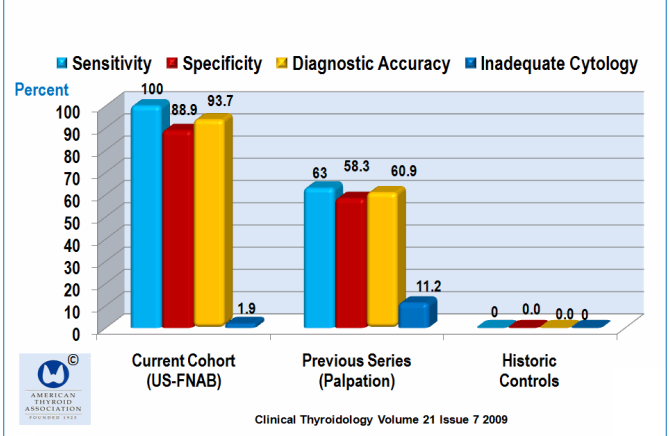

Figure 2. A comparison of the sensitivity, specificity, diagnostic accuracy and rate of inadequate cytology specimens in the current cohort as compared with a previous series in which fine-needle aspiration biopsy was done with palpation, and historic controls.

COMMENTARY

A number of studies show that US-FNAB is more precise and provides greater diagnostic accuracy than does FNAB performed by palpation to guide placement of the aspiration needle. Danese et al. (1) found that the sensitivity, specificity, and diagnostic accuracy was 92% vs. 97%, 69% vs. 70%, and 73% vs. 76%. In another study, by Carmeci et al. (2). The cancer yield at surgery for palpation-FNAB was 40%, and the cancer yield at surgery for US-FNAB was 59%. A study by Redman et al. (3) concluded that US-FNAB with on-site evaluation of cytology specimens substantially increases the adequacy of cytology specimens and decreases the number of required needle passes, which ultimately reduces patient discomfort and diagnostic errors, thus raising the question as to whether this should eventually become the standard of care. I think this is a goal that training programs should strive to achieve.

The study by Izquierdo et al. shows that the advantage of ultrasound guidance for FNAB extends to children, although the study is limited by the small number of patients and the lack of a contemporary control group. Still, the findings are in line with more robust studies in adults.

The current American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer (4) makes the following recommendations concerning neck ultrasound in the workup of thyroid nodules: Ultrasound guidance for FNAB is recommended for those nodules that are nonpalpable, predominantly cystic, or located posteriorly in the thyroid lobe. Recommendation B

R6a Ultrasound guidance should be used when repeating the FNAB procedure for a nodule with an initial nondiagnostic cytology result. Recommendation A

My opinion is that most thyroid nodules that require fine-needle aspiration biopsy should be performed under ultrasound guidance and with assessment for cytology adequacy.

Ernest L. Mazzaferri, MD, MACP

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DISCLOSURE

Dr. Mazzaferri receives honorari from Genzyme for providing lectures,

Dr. Sipos receives honoraria from Abbott and Genzyme for providing lectures.

Annual 80th Meeting

September 23-27, 2009 Palm Beach • Florida

AMERICAN THYROID ASSOCIATION

KEY DATES AND DEADLINES

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- **Short Call Submission:**
  August 8, 2009 - August 22, 2009
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Additional policies:

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- Authors of accepted posters are required to be present during the assigned poster sessions.
- Scientific materials presented at the ATA Annual Meeting must not have been submitted for publication at the time of abstract submission or presented at a scientific meeting before the 80th Annual Meeting of the ATA (local and regional meetings excluded).
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- Short Call Abstracts are reserved for the presentation of the very latest, important thyroid-related research with high impact. Submission of a Short Call Abstract does not guarantee acceptance for presentation. (Please note that regular research reports should be submitted by the Regular Abstract deadline.)
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Description
The 80th Annual Meeting of the ATA in Palm Beach will include the 5th Annual Clinical Fellows' Track and 3rd Annual Basic Fellows' Tracks, parallel and integrated programs designed for clinical (case studies, ultrasound, editorial and career development) and basic post-doctoral (basic science, grantsmanship, editorial and career development) fellows. In addition to participating in the regular meeting program, the fellows will attend special presentations, lectures and skill enhancement opportunities offered by ATA program faculty.

Objective
To encourage participation in the highly regarded Annual Meeting through faculty presentations, panels, case presentations, workshops during the 3 ½ day fellows' tracks.

Registration policies and procedures
- Detailed registration information for the ATA Fellows' Track is online at www.thyroid.org.
- Join the ATA now! All fellows' track applicants must be members of the ATA – go online to www.thyroid.org to submit an application (free for length of fellowship).
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- Must be first author on regular abstract submission or from accredited program in endocrinology.
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- Letter received by ATA from the Laboratory or Program Director (Fax: 703.998.8893).
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