The Diagnostic Accuracy of Ultrasound-Guided Fine-Needle Aspiration Biopsy for Thyroid Nodules Three Centimeters or Larger in Size

Rıfkı Ucler, M.D.,[1]* Celil Alper Usluogulları, M.D.,[1] Abbas Ali Tam, M.D.,[1] Didem Ozdemir, M.D.,[1] Fevzi Balkan, M.D.,[1] Samet Yalcın, M.D.,[2] Gulten Kıyak, M.D.,[2] Pamir Eren Ersoy, M.D.,[2] Gulnur Guler, M.D.,[3] Reyhan Ersoy, M.D.,[1] and Bekir Cakır, M.D.[1]

Background and Purpose: *Whether under ultrasonography (US) guidance or not, fine-needle aspiration biopsy (FNAB) has some limitations, particularly in larger nodules. In this study, we aimed to evaluate the diagnostic value of US-guided fine-needle aspiration biopsy (US-FNAB) in thyroid nodules equal to or larger than 3 cm.*

Materials and Methods: *Data of 267 patients operated for nodular goiter in the period of January 2006 and March 2012 were reviewed retrospectively. The study group (40 males, 104 females; mean age 42.3 ± 12.3, between 17 and 71) consisted of patients with nodules with a diameter of 3 cm or larger. Patients with nodules less than 3 cm in diameter were considered as the control group (27 males, 96 females; mean age 44.4 ± 11.9, between 18 and 71).*

Results: *For nodules smaller than 3 cm, US-FNAB had an accuracy rate of 60% and a false negativity rate of 21.9%. In nodules equal to or larger than 3 cm, the accuracy rate of US-FNAB was 80%, with a false negativity rate of 6.7%. Malignancy was observed in 16% of the study group and 42.3% of the control group.*

Conclusion: *This study showed that increased nodule diameter is not associated with limitations in the diagnostic value of US-FNAB. We also found that the malignancy rate was smaller for larger nodules. This finding reflects the importance of accurate and rational diagnostic work-up and clinical management for detecting malignancy and surgical decision-making.* Diagn. Cytopathol. 2015;43:622–628. © 2015 Wiley Periodicals, Inc.

Key Words: thyroid nodule; fine-needle aspiration biopsy; diagnostic accuracy; ultrasonography; histopathology

A prevalence of thyroid nodules of up to 50% has been defined in autopsy series,[1] and >60% in healthy adults detected with sonography.[2] Several factors have been identified to predict the presence of malignancy in thyroid nodules including age, gender, history of radiotherapy in the head and neck region, family history of thyroid cancer, and morphological characteristics of the nodule detected by thyroid ultrasonography (US). While still controversial, a larger nodule size has been associated with the presence of thyroid carcinoma.[3,4]

Fine-needle aspiration biopsy (FNAB) is widely used during the process of diagnosing thyroid nodules. It is a valuable aid in establishing the need for thyroid surgery and diagnosis and for treatment of malignancies.[5–7] FNAB has a reported diagnostic sensitivity of 89 to 98% and a specificity of 92% for thyroid nodules.[3,6,8,9] However, FNAB has several limitations, particularly when used for larger thyroid nodules,[3,4,7,10,11] Thus, the diagnostic role of FNAB for larger thyroid nodules is still debated. While some authors advocate that ultrasound-guided FNAB gives accurate results irrespective of the size of the nodule,[12,13] others have claimed that this procedure is associated with a high rate of false-negative results.[3,10,11] These claims were supported by one study, which showed that nodules larger than 3 cm in size were more likely to be associated with nondiagnostic biopsy

[1]Department of Endocrinology and Metabolism, Ataturk Education and Research Hospital, Ankara, Turkey
[2]Department of General Surgery, Ataturk Education and Research Hospital, Ankara, Turkey
[3]Department of Pathology, Ataturk Education and Research Hospital, Ankara, Turkey
*Correspondence to: Rıfkı Ucler, MD, Department of Endocrinology and Metabolism, Ataturk Education and Research Hospital, Ankara, Turkey. E-mail: rifkiucler@gmail.com
Received 13 November 2014; Revised 5 February 2015; Accepted 30 March 2015
DOI: 10.1002/dc.23289
Published online 25 April 2015 in Wiley Online Library (wileyonlinelibrary.com).

results in comparison with smaller nodules.[14] Despite these data, full consensus has not yet been reached for the appropriate treatment and follow-up of large thyroid nodules.

In this study, we aimed to evaluate the diagnostic value of US-FNAB in thyroid nodules $\geq$3 cm.

Materials and Methods

Study Population

This retrospective study evaluated patients with nodular goiter who were referred to the Adult Outpatient Clinic for Endocrinology; 267 patients were evaluated by a committee composed of general surgery, pathology, and endocrinology specialists and had undergone thyroidectomy performed by the surgeons in the same committee between January 2006 and March 2012.

This study was a retrospective review of 267 consecutive patients who had been operated for solitary thyroid nodules (67 males, 200 females; mean age 43.3 $\pm$ 12.1, between 17 and 71). The approval of the medical ethics committee was obtained. The requirement for patient informed consent was waived. Patients with nodules with a diameter $\geq$3 cm, based on recordings of standard ultrasonographic measurements, were accepted as the study group, and patients who had nodules <3 cm in diameter were enrolled as the control group. Ultrasonographic features of the nodules, risk factors for malignancy, criteria for surgical therapy, and thyroid functional status in both groups were evaluated.

Exclusion Criteria

The patients not included in the study were those with more than one thyroid nodule, no cytology report before surgery, history of thyroid surgery, history of radioactive iodine therapy, or history of percutaneous invasive intervention to the thyroid.

Analysis of Ultrasonographic Findings

The size of the nodule was based on the largest size measured by ultrasonography. The size (mm), presence of halo, echogenicity, content, and calcification type of the nodule were evaluated. The lesions were grouped as hypoechoic, isoechoic, isohypoechoic, hyperechoic, and anechoic (purely cystic) according to their echogenicity. The content of the nodule was described as solid (with no cystic component), mixt (with cystic component) or purely cystic (with only mural solid component in a small area). The calcification types of the lesions were classified as microcalcification, macrocalcification, micro-macrocalcification, eggshell-like (eggy) calcification or no calcification.

Risk Factors for Malignancy

Evaluation of risk factors for malignancy included the following: young age (<20) or advanced age (>60); male gender; history of radiotherapy of the neck in childhood or adolescence; pressure symptoms such as recent changes in speaking, breathing, and swallowing; family history of thyroid cancer and multiple endocrine neoplasia type 2 (MEN-2); and presence of regional lymphadenopathy.

Criteria for Surgical Therapy

The criteria for surgical treatment were as follows (the most appropriate single criterion for each patient): malignancy; suspected malignancy; undetermined and nondiagnostic biopsy result (in at least two biopsies performed at different times); benign result in biopsy but large-sized nodule; benign biopsy result but with high suspicions of malignancy in ultrasonographic and clinical examinations; overt hyperthyroidism; and thyroidectomy made during excision of parathyroid adenoma.

Thyroid Functional Status

Based on thyroid function tests, the patients were divided into groups of euthyroidism, overt hypothyroidism, overt hyperthyroidism, subclinical hypothyroidism, and subclinical hyperthyroidism. All patients in the hyperthyroidism group (84 patients) had undergone scintillation. According to their scintillation results, the patients in the overt hyperthyroidism group (81 patients) were divided into two subgroups, namely, those with increased activity of the nodule (toxic nodular goiter, TNG) and those with increased activity of the parenchyma (toxic diffuse nodular goiter, TDNG).

FNAB Procedures

Biopsy was performed with the guidance of US by direct visualization of the needle tip, and a specimen was obtained from the solid region within the thyroid mass or by targeting the remaining solid region after aspirating the fluid part before carrying out the biopsy if the mass consisted mostly of cystic component. Two different sites of the nodules were sampled, in the case of large nodules, and both sites were guided by US. In patients with overt hyperthyroidism, euthyroidism was provided with antithyroid therapy before biopsying.

Cytological Examination

In light of previous studies,[15–17] cytological results were categorized into five groups including malignant, suspicious for malignancy, undetermined, benign, and nondiagnostic. Samples with an adequate number of cells and typical cytological characteristics of malignancy were considered malignant.[17] Inadequate cellularity was not used for the diagnosis of malignancy.[17–19] Samples were considered suspicious for malignancy if they were pleomorphic, juxtaposed, compressed, or had cells with large nuclei.[16,17] Follicular neoplasia and Hurthle cell neoplasia

with a uniform cellular population and scant colloid lacking typical features of carcinoma were considered as undetermined cytology.[17,20] Colloidal nodule, nodular hyperplasia, and lymphocytic thyroiditis were benign cytological findings. Samples with less than six cell groups at a minimum with each group having >10 well-preserved thyroid cells were considered as nondiagnostic cytology.[17]

Statistical Analysis

The results are expressed as the means ± standard deviation. Parametric variables were compared using Student's *t* test. χ^2 test was used to compare gender distribution. Associations between categorical variables (US features, cytological and histopathological results) and their variations among study groups were compared using the χ^2 test or a likelihood ratio. For the analysis of sensitivity and specificity of US-FNAB and diagnostic power of the test in studied patient groups, undetermined, suspicious for malignancy and malignant cytological results were obtained from the malignant group and benign cytological results from the benign group, based on the prior studies[15,17] that used histopathological results as a benchmark. Inadequate biopsy results were not included into these analyses. Differences were considered to be statistically significant when the $P < 0.05$. Statistical analysis was conducted using SPSS® for Windows 15.0 (SPSS, Chicago, IL).

Results

The mean age was 44.4 ± 11.9 years and 42.3 ± 12.3 years for control group subjects and case group subjects, respectively. There was no significant difference between control and case groups with respect to mean age ($t = 1.400$; $P = 0.163$). Female patients represented 78.0% of the control group and 72.2% of the case group. The gender distribution rate was statistically similar for control and case groups ($\chi^2 = 1.198$; $\pi = 0.274$).

The control group consisted of 123 patients (46.1%) with a nodule size less than 30 mm, and 144 patients (53.9%) with a nodule size equal to or greater than 30 mm formed the case group. The median nodule size was 14.7 mm (interquartile range = 10.1) in the control group and 43.1 mm (interquartile range = 14.9) in the case group.

The distribution of risk factors for malignancy in the study groups is shown in Table I. The pressure symptoms such as recent changes in speaking, breathing, and swallowing were significantly higher in the case group ($P = 0.001$).

Criteria for surgical management in case and control groups are given in Table II. There was a significant difference in surgical management criteria between the groups ($\chi^2 = 118.124$; $P = 0.001$).

Table I. Risk Factors for Malignancy in Case and Control Groups

Risk factors	*Controls, N (%)*	*Cases, N (%)*	*P*
Young age (<20) or advanced age (>60)	12(9.8)	18 (12.5)	>0.05
Male gender	27 (22)	40 (27.8)	>0.05
History of radiotherapy of the neck region	0 (0)	0 (0)	-
Presence of pressure symptoms	0 (0)	34 (23.6)	0.001
Thyroid cancer or MEN-2 in family history	2 (1.6)	0 (0)	N/A
Regional lymphadenopathy	1 (0.8)	2 (1.4)	N/A

MEN: multiple endocrine neoplasia; N/A: not eligible for statistical evaluation.

Table II. Criteria for Surgical Management in Case and Control Groups

Criteria for surgical management	*Controls, N (%)*	*Cases, N (%)*
FNAB:Malignant	20 (16.3)	6 (4.2)
FNAB:Suspicious for malignancy	23 (18.7)	8 (5.6)
FNAB:Undetermined	35 (28.7)	21 (14.6)
FNAB:Nondiagnostic	12 (9.8)	7 (4.9)
FNAB:Benign + large-sized nodule	0 (0)	48 (33.3)
FNAB:Benign + suspect malignancy in ultrasonographic and clinical examinations	9 (7.3)	0 (0)
Overt hyperthyroidism		
TDNG	16 (13)	6 (4.2)
TNG	4 (4.1)	48 (33.3)
Excision of parathyroid adenoma	3 (2.4)	0 (0)

FNAB: fine-needle aspiration biopsy; TDNG: toxic diffuse nodular goiter; TNG: toxic nodular goiter.
$\chi^2 = 118.124$; $P = 0.001$.

The thyroid functions in the study groups are shown in Table III. There was a significant difference in thyroid functions between the groups ($\chi^2 = 49.867$; $P = 0.001$).

The ultrasonographic features of nodules in the study groups are given in Table IV. All ultrasonographic features of the nodules including content, margin regularity, echogenicity, calcification type, and presence of halo showed statistically significant differences.

Cytological examination results and final histopathologic malignancy rates are shown in Table V, and distribution of histopathologic results are shown in Table VI for study groups. While the rate of malignant histopathologic results was 42.3% in control group subjects, the corresponding rate found in the case group patients (16.0%) was significantly lower ($\chi^2 = 22.723$; $P = 0.001$).

Among control group subjects with a nodule size less than 3 cm, US-FNAB was found to have a sensitivity of 85.4%, specificity of 40.3%, positive predictive value (PPV) of 52.6%, negative predictive value (NPV) 78.1%, accuracy rate of 60%, and a false-negativity rate of 21.9%. For case group patients with a nodule size equal to or greater than 3 cm, US-FNAB was found to have a sensitivity of 72.7%, specificity of 81.6%, PPV of 45.7%,

NPV 93.3%, accuracy rate of 80% and a false negativity rate of 6.7%.

Discussion

Several studies have demonstrated that FNAB is a sensitive and specific test for the diagnosis of thyroid cancer and is a useful method that provides guidance to primary surgery and prevents unnecessary procedures.[3,8,9] However, false-negative results may occur due to the inability to obtain adequate material from small nodules, and shortcomings in cytopathological interpretation of follicular neoplasia leads to increases in the diagnostic limitation of US-FNAB.[11] Additionally, the diagnostic accuracy of FNAB may be less for large nodules, particularly if the nodule size is greater than 3 cm.[3,4,10]

Consistent with previous studies,[17,21] in the present study, a greater diagnostic performance of US-FNAB was found for the case group when 144 patients in the case group with nodules equal to or greater than 3 cm and 123 control patients with nodules smaller than 3 cm were compared. The procedural accuracy rate was 60% for control group and 80% for the case group. Our results support the argument that there is no direct relationship between increased diagnostic limitation of US-FNAB and increased nodule size. Patients with multiple thyroid nodules were excluded in this study. We think this allows for more accurate and realistic calculations by preventing possible false evaluations in final histopathological comparisons that might occur secondary to malignancy of other nodules.

In the present study, the false-positivity rate of cytological data reported as "suspicious for malignancy" was found to be 25% in the case group, which was comparable to the rates reported in other studies (between 20 and 33.8%).[10,17,22–24] However, the false-positivity rate of cytological data reported as "suspicious for malignancy" was 30.4% in the control group. For nodules with malignant cytology, there were no false-positive results in the case group, but the false-positivity rate was 10% in the control group. Of the two patients representing 10% of the control group, one was identified as having a benign nodular goiter and the other as having Hurthle cell adenoma on the basis of final pathology results.

Our data question the accuracy of FNAB results, which are reported as benign irrespective of the nodule size. Similar to previous studies,[15,17,21,22,25] the false-negative biopsy rate was 6.7% for nodules 3 cm in diameter or greater in the present study, but the percentage of patients found to have follicular neoplasia that were originally

Table III. Thyroid Functions in Study Groups

Thyroid functional status	*Controls, N (%)*	*Cases, N (%)*
Euthyroidism	85 (69.1)	76 (52.8)
Overt hypothyroidism	10 (8.1)	5 (3.5)
Overt hyperthyroidism		
TDNG	18 (14.6)	6 (4.2)
TNG	5 (4.1)	52 (36.1)
Subclinical hypothyroidism	5 (4.1)	2 (1.4)
Subclinical hyperthyroidism[a]	0 (0)	3 (2.1)

TDNG: toxic diffuse nodular goiter; TNG: toxic nodular goiter.
$\chi^2 = 49.867$; $P = 0.001$.
[a]With scintigraphic examination active nodules were found in all three cases.

Table IV. The Ultrasonographic Features of Nodules in the Study Groups

Ultrasonographic features	*Controls, N (%)*	*Cases, N (%)*	χ^2	*P*
Content			61.311	**0.001**
Solid	75 (61)	22 (15.3)		
Mixed	47 (38.2)	113 (78.5)		
Cystic	1 (0.8)	9 (6.3)		
Margin regularity			5.530	**0.019**
Regular	72 (58.5)	140 (72.2)		
Irregular	51 (41.5)	40 (27.8)		
Echogenicity			59.514	**0.001**
Isoechoic	46 (37.4)	108 (75)		
Isohypoechoic	42 (34.1)	23 (16)		
Hypoechoic	30 (24.4)	4 (2.8)		
Hyperechoic	4 (3.3)	0 (0)		
Anechoic	1 (0.8)	9 (6.3)		
Calcification type			11.534	**0.021**
Micro	32 (26)	47 (32.6)		
Macro	7 (5.7)	5 (3.5)		
Micro-Macro	9 (7.3)	24 (16.7)		
Absent	72 (58.5)	68 (47.2)		
Eggy	3 (2.4)	0 (0)		
Halo			5.065	**0.024**
Yes	43 (35)	70 (48.6)		
No	80 (65)	74 (51.4)		

The bold values points to important findings of our results.

Table V. Cytological Results and Final Histopathologic Malignancy Rates of Study Groups

	Controls		*Cases*	
	Cytological results, N (%)	*Final malignancy rate (%)*	*Cytological results, N (%)*	*Final malignancy rate (%)*
Nondiagnostic	13 (10.5%)	30.8	19 (13.2%)	5.3
Benign	32 (26.0%)	21.9	90 (62.5%)	6.7
Undetermined	35 (28.4%)	20.0	21 (14.5%)	19.0
Suspicious for malignancy	23 (18.7%)	69.6	8 (5.6%)	75.0
Malignant	20 (16.3%)	90	6 (4.2%)	100
Total	**123 (100%)**	**42.3**	**144 (100%)**	**16**

The bold values points to important findings of our results.

Table VI. Distribution of Histopathologic Results of Study Groups

	Controls		*Cases*	
	N	%	*N*	%
Benign	**71**	**57.7**	**121**	**84.0**
Benign Nodular Goiter	54	76.0	96	79.3
Adenoma	13	18.4	22	18.2
Chronic Thyroiditis	4	5.6	3	2.5
Malignant	**52**	**42.3**	**23**	**16.0**
Papillar Thyroid Cancer	46	88.5	19	82.6
Follicular Thyroid Cancer	4	7.7	2	8.7
Hurthle Cell Cancer	1	1.9	1	4.4
Medullary Thyroid Cancer	1	1.9	1	4.4

The bold values points to important findings of our results.

diagnosed as benign was high (16.6%). This rate of false-negative results (16.6%) for follicular neoplasia found in the case group is similar to the rates reported by other studies (up to 30%).[10,17,26,27] This may be explained by the presence of intratumoral heterogeneous areas within large follicular neoplasia. Another important result was that the rate of false-negative biopsy results was considerably higher (21.9%) for nodules smaller than 3 cm. In 1995, Meko and Norton reported that FNAB had a false negativity rate of 11% and that this rate increased up to 30% for large, cystic/solid thyroid nodules that carried a high probability of being cancerous.[11] McCoy et al. reported that the false negativity rate was 13% for nodules greater than 4 cm, and it increased to 16% when multifocal micropapillary carcinomas were included.[3] Additionally, a number of other studies reported a high prevalence of malignancy for large thyroid nodules and a high rate of false-negative FNAB results (13–50%).[3,5]

In the present study, malignancy rate was 5.3% in the case group and 30.8% in the control group for nodules with ''nondiagnostic'' cytology, and the difference was statistically significant ($\chi^2 = 3.854$; $P = 0.049$). These rates are consistent with a wide range of malignancy (from 2% to 37%) rates reported previously for nondiagnostic cytological features.[15,28–30] Also, a recent article by Anderson et al. found a low rate of malignancy with repeated biopsy (0.6%) and with surgical pathologic examination (1.8%) for 393 single nodules with nondiagnostic FNA results.[31] However, the final malignancy rate was 10.2% (5/49) for those who underwent surgery among 49 patients with persistent nondiagnostic FNA results in the subgroup of the study, which is comparable to the rates reported in our study. The high malignancy rate observed in the control group versus the case group lends support for a limited diagnostic value of FNAB due to the inability to obtain sufficient amount of material from small nodules. Additionally, our results seem to be associated with the use of different selection criteria for surgical indications of large and small nodules and contain more functional nodules in the case group.

Whether increased nodule size is an independent risk factor for thyroid malignancy is still controversial. Although some studies suggest that nodule size is not an independent risk factor for predicting malignancy,[13,22,25,32–34] other studies advocate that enlarged nodule size increases the risk of malignancy[3,35–37] and, therefore, surgical therapy should be recommended to these patients without giving consideration to cytological results. Based on final histopathologic results, 16% of the case group patients and 42.3% of the control group patients had malignant nodules, representing a significant difference ($\chi^2 = 22.723$; $P < 0.001$). This study included only adult patients because it was planned to cover patients in the adult endocrinology clinic. Because young age (<20) is a risk factor for malignant thyroid nodules, inclusion of pediatric patients may have resulted in higher rates of malignancy than the rates found in this study. In the present study, it is interesting to note that the malignancy rate was substantially higher among nodules smaller than 3 cm, which was significantly different from the rate found for nodules equal to or greater than 3 cm. When we look at cytological results of case and control groups in the present study, it is observed that while nodules with benign cytology are more common in the case group, malignant nodules and nodules suspicious for malignancy are considerably more prevalent in the control group. Thus, the final histopathological results should not be surprising because criteria for surgical indication differed widely between small and large nodules in our patient group. While surgery was considered for large nodules mainly because of compression symptoms and autonomous hyperactivity which leads to hyperthyroidism, small nodules were operated due to a high level of suspicion for severe malignancy based on cytological, ultrasonographic and clinical features. Our study findings demonstrate the importance of accurate and rational diagnostic and clinical approach in surgical decision-making and malignancy detection.

Functional nodules were present in 38.2% (55 of 144 nodules) and 4.1% (5 of 123 nodules) of case and control groups, respectively. As noted above, this difference stems from the use of different selection criteria for surgical indications of large and small nodules. The final malignancy rates were 7.3% (4 of 55 nodules) for the case group and 60% (3 of 5 nodules) for the control group in these nodules. In a study published recently, the malignancy rate was 4.5% in single toxic nodule patients.[38] In fact, the choice of an appropriate treatment for toxic nodules is not easy because comprehensible criteria for therapy selection have not yet been established, owing to the lack of long-term prospective randomized studies comparing different treatment modalities. We have used FNAB of functional thyroid nodules to determine the appropriate treatment since it can detect

malignancy in functional nodules, supporting the findings of our study and previous studies.[38–40] Also, a surgical approach for patients with toxic nodules larger than 3 to 4 cm is generally suggested. We chose mostly a surgical treatment option given the higher risk of treatment failure with radioactive iodine.[41,42]

There are some limitations to our study. Firstly, our study did not include all the patients with solitary nodules who were referred to our outpatient clinic, since radioiodine ablation treatment was performed in some cases with small functional nodules and since some cases without suspected malignancy were followed. Our study includes only patients who had been operated. This probably influenced our final malignancy rate. Secondly, the malignancy rate and the diagnostic accuracy rate may have some errors since the number of active nodules was higher in the case group. It is possible that these nodules may have changed the malignancy rate and the diagnostic accuracy rate. Thirdly, since biopsy materials analyzed in this study were performed by multiple cytopathologists, the results of US-FNAB could have been affected by interpreter variability and this was not considered in the study.

In conclusion, we observed that there is no direct correlation between enlarged nodule size and increased diagnostic limitation of US-FNAB. A decision for performing surgery or whether a thyroid nodule is malignant should not be made solely on the basis of nodule size. Instead, consideration of all diagnostic and clinical data is necessary. Lower rates of false-negative and suspicious biopsy results could possibly be achieved owing to advances in imaging methods and FNAB techniques and by the use of new techniques of molecular cytopathological investigation.

References

1. Mortensen JD, Woolner LB, Bennett WA. Gross and microscopic findings in clinically normal thyroid glands. J Clin Endocrinol Metab 1955;15:1270–1280.
2. Tan GH, Gharib H. Thyroid incidentalomas: Management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Intern Med 1997;126:226–231.
3. McCoy KL, Jabbour N, Ogilvie JB, Ohori NP, Carty SE, Yim JH. The incidence of cancer and rate of false-negative cytology in thyroid nodules greater than or equal to 4 cm in size. Surgery 2007; 142:837–844.
4. Carrillo JF, Frias-Mendivil M, Ochoa-Carrillo FJ, Ibarra M. Accuracy of fine-needle aspiration biopsy of the thyroid combined with an evaluation of clinical and radiologic factors. Otolaryngol Head Neck Surg 2000;122:917–921.
5. Pinchot SN, Al-Wagih H, Schaefer S, Sippel R, Chen H. Accuracy of fine-needle aspiration biopsy for predicting neoplasm or carcinoma in thyroid nodules 4 cm or larger. Arch Surg 2009;144: 649–655.
6. Tee YY, Lowe AJ, Brand CA, Judson RT. Fine-needle aspiration may miss a third of all malignancy in palpable thyroid nodules: a comprehensive literature review. Ann Surg 2007;246:714–720.
7. Carmeci C, Jeffrey RB, McDougall IR, Nowels KW, Weigel RJ. Ultrasound-guided fine-needle aspiration biopsy of thyroid masses. Thyroid 1998;8:283–289.
8. Bhatki AM, Brewer B, Robinson-Smith T, Nikiforov Y, Steward DL. Adequacy of surgeonperformed ultrasound-guided thyroid fine-needle aspiration biopsy. Otolaryngol Head Neck Surg 2008;139: 27–31.
9. Greenblatt DY, Woltman T, Harter J, Starling J, Mack E, Chen H. Fine-needle aspiration optimizes surgical management in patients with thyroid cancer. Ann Surg Oncol 2006;13:859–863.
10. Gharib H, Goellner JR. Fine-needle aspiration biopsy of the thyroid: An appraisal. Ann Intern Med 1993;118:282–289.
11. Meko JB, Norton JA. Large cystic/solid thyroid nodules: A potential false-negative fine-needle aspiration. Surgery 1995;118:996–1004.
12. Porterfield JR, Jr, Grant CS, Dean DS, et al. Reliability of benign fine-needle aspiration cytology of large thyroid nodules. Surgery 2008;144:963–969.
13. Albuja-Cruz MB, Goldfarb M, Gondek SS, Allan BJ, Lew JI. Reliability of fine-needle aspiration for thyroid nodules greater than or equal to 4 cm. J Surg Res 2013;181:6–10.
14. Richards ML1, Bohnenblust E, Sirinek K, Bingener J. Nondiagnostic thyroid fine-needle aspiration biopsies are no longer a dilemma. Am J Surg 2008;196:398–402.
15. Seningen JL, Nassar A, Henry MR. Correlation of thyroid nodule fine-needle aspiration cytology with corresponding histology at Mayo Clinic, 2001–2007: An institutional experience of 1,945 cases. Diagn Cytopathol 2012;40(Suppl 1):E27–E32.
16. Kwak JY, Kim EK, Kim HJ, Kim MJ, Son EJ, Moon HJ. How to combine ultrasound and cytological information in decision making about thyroid nodules. Eur Radiol 2009;19:1923–1931.
17. Yoon JH, Kwak JY, Moon HJ, Kim MJ, Kim EK. The diagnostic accuracy of ultrasound-guided fine-needle aspiration biopsy and the sonographic differences between benign and malignant thyroid nodules 3 cm or larger. Thyroid 2011;21:993–1000.
18. Kwak JY, Kim EK, Kim MJ, et al. The role of ultrasound in thyroid nodules with a cytology reading of "suspicious for papillary thyroid carcinoma." Thyroid 2008;18:517–522.
19. Moon HJ, Kwak JY, Kim EK, et al. The combined role of ultrasound and frozen section in surgical management of thyroid nodules read as suspicious for papillary thyroid carcinoma on fine-needle aspiration biopsy: A retrospective study. World J Surg 2009; 33:950–957.
20. Baloch ZW, Sack MJ, Yu GH, Livolsi VA, Gupta PK. Fine-needle aspiration of thyroid: An institutional experience. Thyroid 1998;8: 565–569.
21. Lewis CM, Chang KP, Pitman M, Faquin WC, Randolph GW. Thyroid fine-needle aspiration biopsy: Variability in reporting. Thyroid 2009;19:717–723.
22. Shresta M, Crothers BA, Burch HB. The impact of thyroid nodule size on the risk of malignancy and accuracy of fine-needle aspiration: A 10-year study from a single institution. Thyroid 2012;22: 1251–1256.
23. Cibas ES, Ali SZ. The bethesda system for reporting thyroid cytopathology. Thyroid 2009;19:1159–1165.
24. Jo VY, Stelow EB, Dustin SM, Hanley KZ. Malignancy risk for fine-needle aspiration of thyroid lesions according to the Bethesda system for reporting thyroid cytopathology. Am J Clin Pathol 2010; 134:450–456.
25. Kihara M, Hirokawa M, Masuoka H, et al. Evaluation of cytologically benign solitary thyroid nodules by ultrasonography: a retrospective analysis of 1877 cases. Auris Nasus Larynx 2013;40:308–311.
26. Piromalli D, Martelli G, Del Prato I, Collini P, Pilotti S. The role of fine-needle aspiration in the diagnosis of thyroid nodules: Analysis of 795 consecutive cases. J Surg Oncol 1992;50:247–250.
27. Bahar G, Braslavsky D, Shpitzer T, et al. The cytological and clinical value of the thyroid "follicular lesion." Am J Otolaryngol 2003;24:217–220.

28. Alexander EK, Heering JP, Benson CB, et al. Assessment of nondiagnostic ultrasound-guided fine-needle aspirations of thyroid nodules. J Clin Endocrinol Metab 2002;87:4924–4927.
29. Chow LS, Gharib H, Goellner JR, van Heerden JA. Nondiagnostic thyroid fine-needle aspiration cytology: Management dilemmas. Thyroid 2001;11:1147–1151.
30. MacDonald L, Yazdi HM. Nondiagnostic fine-needle aspiration biopsy of the thyroid gland: A diagnostic dilemma. Acta Cytol 1996;40:423–428.
31. Anderson TJ, Atalay MK, Grand DJ, Baird GL, Cronan JJ, Beland MD. Management of nodules with initially nondiagnostic results of thyroid fine-needle aspiration: Can we avoid repeat biopsy?. Radiology 2014;272:777–784.
32. Sahin M, Gursoy A, Tutuncu NB, Guvener DN. Prevalence and prediction of malignancy in cytologically indeterminate thyroid nodules. Clin Endocrinol (Oxf) 2006;65:514–518.
33. McHenry CR, Huh ES, Machekano RN. Is nodule size an independent predictor of thyroid malignancy? Surgery 2008;144: 1062–1069.
34. Raber W, Kaserer K, Niederle B, Vierhapper H. Risk factors for malignancy of thyroid nodules initially identified as follicular neoplasia by fine-needle aspiration: Results of a prospective study of one hundred twenty patients. Thyroid 2000;10:709–712.
35. Schlinkert RT, van Heerden JA, Goellner JR, et al. Factors that predict malignant thyroid lesions when fine-needle aspiration is "suspicious for follicular neoplasm." Mayo Clin Proc 1997;72:913–916.
36. Sclabas GM, Staerkel GA, Shapiro SE, et al. Fine needle aspiration of the thyroid and correlation with histopathology in a contemporary series of 240 patients. Am J Surg 2003;186:702–710.
37. Tuttle RM, Lemar H, Burch HB. Clinical features associated with an increased risk of thyroid malignancy in patients with follicular neoplasia by fine-needle aspiration. Thyroid 1998;8:377–383.
38. Smith JJ, Chen X, Schneider DF, et al. Toxic nodular goiter and cancer: A compelling case for thyroidectomy. Ann Surg Oncol 2013;20:1336–1340.
39. Kang AS, Grant CS, Thompson GB, van Heerden JA. Current treatment of nodular goiter with hyperthyroidism (plummer's disease): Surgery versus radioiodine. Surgery 2002;132:916–923.
40. Cerci C, Cerci SS, Eroglu E, et al. Thyroid cancer in toxic and non-toxic multinodular goiter. J Postgrad Med 2007;53: 157–160.
41. Ferrari C, Reschini E, Paracchi A. Treatment of the autonomous thyroid nodule: A review. Eur J Endocrinol 1996;135:383–390.
42. Mazzaferri EL. Management of a solitary thyroid nodule. N Engl J Med 1993;328:553–559.