Thyroid Nodule Size and Prediction of Cancer

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Context: Thyroid nodule size is routinely measured, although its impact on thyroid cancer risk is unclear.

Objective: Our objective was to evaluate the association of nodule size upon cancer risk.

Design, Setting, and Patients: We conducted a retrospective cohort analysis at an academic hospital with 4955 consecutive patients evaluated between 1995 and 2009.

Intervention: Ultrasound and ultrasound-guided fine-needle aspiration of nodules >1 cm was done. Indeterminate and malignant nodules were referred for surgery, and histopathology was reviewed.

Main Outcome Measure: The presence and histological subtype of cancer was evaluated.

Results: Of 7348 evaluated nodules, 927 (13%) were cancerous. Of those 1.0 to 1.9 cm in diameter, 10.5% were cancerous. In contrast, of those >2.0 cm, 15% were cancerous ($P < .01$). However, nodules 2.0 to 2.9, 3.0 to 3.9, and >4 cm were cancerous in 14%, 16%, and 15% of cases ($P = .14$), respectively, demonstrating no graded increase in risk beyond the 2-cm threshold. When malignant, the proportion of papillary carcinoma decreased (nodules 1.0–1.9 cm, 92% of cases; 2.0–2.9 cm, 88%; 3.0–3.9 cm, 83%; >4 cm, 74% [$P < .01$]), while follicular carcinoma increased (1.0–1.9 cm, 6%; 2.0–2.9 cm, 7%; 3.0–3.9 cm, 12%; >4 cm, 16% [$P < .01$]) as nodules enlarged. Nodules size did not influence cytology distribution or risk of false-negative aspirates.

Conclusions: Increasing thyroid nodule size impacts cancer risk in a nonlinear fashion. A threshold is detected at 2.0 cm, beyond which cancer risk is unchanged. However, the risk of follicular carcinomas and other rare thyroid malignancies increases as nodules enlarge. ***(J Clin Endocrinol Metab* 98: 564–570, 2013)**

Thyroid nodules are common, and prevalence increases with age (1). Although most are benign, ~10%-15% prove malignant. It is estimated that 56 000 new cases of thyroid cancer will be diagnosed in the United States annually, and over 2000 patients will die from this disease. The goal of thyroid nodule evaluation is to accurately assess the risk such a nodule is cancerous via methods that are accurate and precise, yet also safe, cost-effective, and without morbidity (2).

Fine-needle aspiration (FNA) is the primary diagnostic methodology used for thyroid nodule evaluation. First introduced over 50 years ago, thyroid nodule FNA has proven to be of high value because nearly 70% of aspirates return benign. These results are highly accurate and allow for conservative management. However, FNA is imperfect because 20%–25% of samples return indeterminate (3–5). Such samples are cytologically abnormal reflecting an increased risk of malignancy, although without diagnostic

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2012-2968 Received August 1, 2012. Accepted November 7, 2012.
First Published Online December 28, 2012

Abbreviation: FNA, Fine-needle aspiration.

certainty. Most cytologically indeterminate aspirates are referred for surgery, yet more than half prove to have benign disease (1, 6, 7). These data confirm the need for improved preoperative assessment.

Both clinical and sonographic variables have been investigated with regard to their ability to modify preoperative risk. Young age and male sex increase the risk a nodule may prove cancerous (8, 9). High-risk clinical features such as new-onset hoarseness of voice (albeit rare) also predict malignancy. Over the last 20 years, ultrasound assessment of thyroid nodules has demonstrated similar ability to predict malignant disease. The sonographic findings of microcalcifications, hypoechogenicity, absence of a halo, and irregular nodular margins all increase cancer risk (10). But although the clinical value in detecting these features remains high, moderately poor inter-rater reliability poses a challenge. Even among blinded experts, congruent reporting of these findings is suboptimal with only moderate interobserver agreement (11). Only one widely used sonographic feature, the proportion of cystic content within a thyroid nodule, appears highly reproducible. Together, the above data confirm the need to identify other variables that can influence preoperative risk assessment. One such hypothesized variable is thyroid nodule size, which can be easily measured with great accuracy and precision.

Previous studies suggested that nodule size may assist in cancer risk assessment, although data are conflicting (12, 13). Most recently, a study from 2006 concluded that no association exists (10). Large thyroid nodules (>4 cm) are frequently referred for surgical removal because of concern for cancer, even if they demonstrate no structural impingement upon surrounding neck structures (14–16). This may in part be due to the fact that size has proven to be a powerful predictor of malignancy when masses are discovered in other tissue types, such as the lung or adrenal gland (17). If found to be similarly predictive of malignant thyroid disease, such an easily performed, accurate, and precise measurement could prove an important variable in the preoperative assessment of affected patients.

Since 1995, we have prospectively cataloged all patients referred to the Brigham and Women's Hospital thyroid nodule clinic (10). This clinic was designed to provide an integrative assessment of thyroid cancer risk, as clinical, sonographic, and cytologic assessment could be provided during a single visit. Patients are referred upon clinical suspicion (or known detection) of a thyroid nodule. Previous analyses confirm that 95% of thyroid nodules evaluated within our hospital system are referred to this clinic (5, 10), strongly suggesting no referral or selection bias. From 1995 through 2009, this database has grown to include nearly 5000 patients with over 9000 nodules. These data provide an unparalleled means of assessing the impact of nodule size on thyroid cancer risk. Furthermore, by investigating such a large sample of unselected, consecutive nodules, we hypothesized that this investigation may also provide insight into our understanding of thyroid malignancy itself.

Materials and Methods

We reviewed the records of 4955 consecutive patients referred to the Thyroid Nodule Clinic at the Brigham and Women's hospital from 1995–2009. All patients underwent thyroid ultrasonography, with 3 measurements of all nodules over 5 mm in size (length, width, anteroposterior dimension). Serum TSH was measured, and if normal or elevated, patients with nodules ≥10 mm in diameter were advised to undergo ultrasound-guided FNA. If serum TSH was <0.5 μU/mL, patients were referred for thyroid scintigraphy to identify autonomously functioning nodules.

One of 5 radiologists, each with expertise in thyroid sonography, performed thyroid ultrasonography. A 10- to 17-mHz transducer was used for the procedure. FNA was performed by 1 of 4 thyroidologists under ultrasound guidance. A 25-gauge needle was used to obtain typically 3 needle samples per nodule. With rare exception, a maximum of 2 nodules were aspirated during a single visit. If FNA results were nondiagnostic, a reaspiration was performed 1 or more times until a cytological diagnosis was successfully obtained or the patient elected surgical resection prior to a cytological diagnosis.

FNA cytology slides were evaluated by a Brigham and Women's Hospital cytopathologist. Results were classified based on criteria and terminology analogous to those of the Bethesda System for Reporting Thyroid Cytopathology (18, 19). Specifically, all thyroid FNAs were classified into one of the following categories: nondiagnostic, negative for malignant cells (benign), atypical cells of undetermined significance, suggestive of a follicular neoplasm, suggestive of a Hurthle cell neoplasm, suspicious for malignancy, and positive for malignant cells. FNA results are tabulated here in the analogous Bethesda System for Reporting Thyroid Cytopathology categories. Patients with indeterminate or malignant cytology were recommended for hemithyroidectomy or near-total thyroidectomy. In cases that underwent surgery, the final diagnosis was based on histopathological analysis of the surgical specimen by a staff pathologist. Although all nodules evaluated were ≥1 cm sonographically, in rare circumstances, the histopathology measurement was <1 cm. In such circumstances, the nodule was still included for study analysis so long as the referential integrity of the nodule could be confirmed from ultrasound to histopathology.

Nodules >1 cm were considered benign if no abnormal cells (benign cytology) were found on an adequate FNA, if no evidence of cancer was found on histologic examination of the resected nodule, if thyroid scintigraphy indicated the nodule functioned autonomously, or if cystic, there was greater than a 50% reduction in nodule diameter on follow-up ultrasound. In patients with more than one nodule, each nodule >1 cm was individually classified as benign or malignant based on the above criteria. For each nodule, maximal size, corresponding FNA cytology, and ultimate benign vs malignant categorization were

Table 1. Study Cohort Depicting the Demographics and Ultrasound Characteristics of 4955 Patients With 9339 Nodules ≥1 cm

	Entire Cohort	Evaluated Nodules
Patients, n	4955	
Sex, n (%)		
Male	696 (14)	
Female	4259 (86)	
Age, n (%)		
18–30 y	511 (10)	
31–40 y	787 (16)	
41–50 y	1152 (23)	
51–60 y	1150 (23)	
61–70 y	843 (17)	
71–99 y	512 (10)	
Mean age, y	51.2	
Median age, y	51.3	
Nodules, n	9339	7348
Size, n (%)		
1.0–1.9 cm	5343 (57)	3621 (49)
2.0–2.9 cm	2158 (23)	1956 (27)
3.0–3.9 cm	1044 (11)	998 (14)
≥4.0 cm	794 (9)	773 (11)
Mean size, cm	2.6	2.3
Median size, cm	2.3	2.0
Cystic content, n (%)		
Solid (<25%)	6900 (74)	5492 (75)
25–75%	1520 (16)	1227 (17)
>75%	919 (10)	629 (9)

determined. The influence of thyroid nodule size upon cancer risk was evaluated.

Permission for this review and analysis was granted from the Investigational Review Board at the Brigham and Women's Hospital. Results are presented according to nodule or according to patient and compared using χ^2 or *t* test as appropriate. *P* values < .05 were considered significant.

Results

A total of 4955 consecutive patients with 9339 thyroid nodules ≥1 cm presented for evaluation between 1995 and 2009. Of these patients, 3842 (78%) underwent complete evaluation of all nodules >1 cm. The remaining 1113 patients had at least one but not all nodules >1 cm evaluated, usually because of high cystic content or low-risk features in a nodules of borderline size (10–15 mm). Therefore, a total of 7348 nodules (79% of total detected) from 4955 patients formed the basis for this evaluation. Patient demographics and nodule characteristics are depicted in Table 1. The mean nodule diameter was 2.6 cm, although 20%–25% of the cohort (n = 1838 total nodules; n = 1771 evaluable) presented with nodules larger than 3 cm, and 11% (n = 794 total nodules; n = 773 evaluable) with nodules larger than 4 cm. Most nodules were solitary (54%) and solid (75%).

The distribution of FNA cytology is shown in Table 2. Thyroid nodule size had no influence upon the distribution of cytology aspirates in each Bethesda category ($P = .63$). Specifically, 72% of nodules 1.0 to 1.9 cm were classified benign; 67% of nodules 2.0 to 2.9 cm were classified benign; 65% of nodules 3.0 to 3.9 cm were classified benign; and 64% of nodules ≥4 cm were classified benign. Similar findings were found for indeterminate classifications (atypical cells of an undetermined significance, suggestive of a follicular or Hurthle cell neoplasm, and suspicious for malignancy) as well as those positive for malignancy. Importantly, thyroid nodule size also did not impact the risk of a nondiagnostic aspirate ($P = .93$).

Of 4955 patients, 813 (16%) were diagnosed with clinically relevant thyroid cancer >1 cm as follows: 697 of 813 (86%) papillary carcinoma (including follicular variant), 66 of 813 (8%) follicular or Hurthle cell carcinoma, 42 of 813 (5%) other carcinoma (including medullary, anaplastic carcinoma, follicular lymphoma, and metastatic disease), and 8 of 812 (1%) with two types of pathology. Among all evaluated thyroid nodules ≥1 cm, 927 of 7348 (13%) proved cancerous, and 375 patients were found to have 2 or more cancerous nodules simultaneously in their multinodular gland.

Table 2. Distribution of FNA Cytology

Cytology, n (%)	Thyroid Nodule Size, cm 1.0–1.9	2.0–2.9	3.0–3.9	≥4.0
No malignant cells	2595 (72)	1317 (67)	648 (65)	494 (64)
Atypica of undetermined significance	159 (4)	111 (6)	51 (5)	60 (7)
Suspicious for a follicular or Hurthle cell neoplasm	203 (6)	147 (8)	112 (11)	70 (9)
Suspicious for papillary carcinoma	221 (6)	154 (8)	85 (9)	61 (8)
Positive for malignancy	186 (5)	106 (5)	49 (5)	40 (5)
Nondiagnostic	257 (7)	121 (6)	53 (5)	58 (7)
Total (n = 7348)	3621	1956	998	773
FNA not performed	1722	202	46	21
All nodules (n = 9339)	5343	2158	1044	794

Table 3. Thyroid Nodule Size and Risk of Cancer, Demonstrating a Threshold Effect

Nodule Size	No. of Nodules	No. Cancerous (%)	P
1.0–1.9 cm	3621	383 (11)	<.01
≥2.0 cm	3727	544 (15)	
2.0–2.9 cm	1956	265 (14)	
3.0–3.9 cm	998	163 (16)	.14
≥4.0 cm	773	116 (15)	

For the purposes of this investigation, thyroid nodules 1.0 to 1.9 cm in diameter provided baseline cancer risk for comparison (10.5% risk of cancer). The overall prevalence of cancer in nodules 2.0 to 2.9 cm was 13.5%; in nodules 3.0 to 3.9 cm, 16.3%; and in nodules ≥4.0 cm, 15.0%. This was statistically significant ($P <$ .01). However, the primary influence of this association was the low malignancy rate in nodules 1.0 to 1.9 cm. When comparing nodules 2.0 to 2.9 cm, 3.0 to 3.9 cm, or ≥4.0 cm, no difference in malignancy rate was demonstrated ($P = .14$). This suggests a possible threshold effect (Table 3).

Importantly, the proportion of cytologically benign nodules that proved cancerous after surgical removal (false-negative aspirates) was not different between groups. A total of 1502 nodules were surgically removed despite benign FNA. In these circumstances, clinical concern (based on all available clinical, biologic, and sonographic data) was used to decide upon need for nodule removal, or they were removed as part of a multinodular goiter. Of these nodules, 79 of 7348 (1.1%) proved to be malignant on final histology as follows: for nodules 1.0 to 1.9 cm, 41 of 3621 (1.1%) were false-negative aspirates; for those 2.0 to 2.9 cm, 13 of 1956 (0.7%) were false-negative aspirates; for those 3.0 to 3.9, 15 of 998 (1.5%) were false-negative aspirates; and for those ≥4 cm, 10 of 773 (1.3%) were false-negative aspirates ($P = .15$ for difference between group). We note that neither surgery nor repeat FNA was performed on most cytologically benign nodules during follow-up assessment.

When analysis of nodule size was compared with the type and distribution of thyroid malignancy, discordance was detected (Table 4 and Figure 1). Specifically, increasing nodule size was associated with a lower proportion of of papillary carcinomas ($P < .01$). In contrast, the proportion of follicular or Hurthle cell carcinomas increased linearly as diameter increased ($P < .01$). Only 7% of cancers in nodules <4 cm were follicular or Hurthle cell carcinoma (6% for nodules 1.0–1.9 cm, 7% for nodules 2.0–2.9, and 12% for nodules 3.0–3.9), whereas 16% of cancerous nodules >4 cm were follicular or Hurthle cell carcinoma ($P = .03$). A similar increase in the proportion of other rare cancers (such as medullary and anaplastic carcinoma, thyroid lymphoma, and metastatic disease from other organs) was also noted with increasing nodule size.

Table 4. Thyroid Cancer Size and the Distribution and Histologic Subtype of Malignancy

Nodule size	Cancer	Type of Thyroid Carcinoma, n (%): Papillary Carcinoma	Follicular/Hurthle Cell Carcinoma	Other Malignancy
1.0–1.9 cm	383	353 (92)	22 (6)	8 (2)
2.0–2.9 cm	265	235 (88)	18 (7)	12 (5)
3.0–3.9 cm	163	135 (83)	20 (12)	8 (5)
≥4.0 cm	116	85 (74)[a]	18 (16)[a]	12 (10)

[a] $P < .01$ for trend.

Because cystic fluid can significantly influence nodule size even though it is felt to be a benign characteristic, we also considered whether the proportion of cystic content in nodules influenced the above findings of size and malignancy. No association was found. Specifically, of the 383 thyroid cancers measuring 1.0 to 1.9 cm in diameter, 29 (7.6%) were >50% cystic; of 265 cancers measuring 2.0 to 2.9 cm in diameter, 11 (4.2%) were >50% cystic; of 163 cancers measuring 3.0 to 3.9 cm in diameter, 10 (6.1%) were >50% cystic; and of 116 cancers measuring >4 cm, 9 (8.0%) were >50% cystic ($P = .91$ for difference).

Discussion

This analysis of nearly 5000 patients with over 7000 clinically relevant thyroid nodules provides the largest unbiased assessment of thyroid nodule size and risk of cancer. Greater nodule size influences cancer risk, although the increase in absolute risk between small (1.0–1.9 cm) and large (>4.0 cm) nodules is modest. Notably, a threshold effect is detected at approximately 2.0 cm in nodule diameter. Thereafter, larger nodule size imparts no further malignant risk, even if 4.0 cm or larger. However, larger nodules, if cancerous, are significantly more likely to be follicular or Hurthle cell carcinomas (or other rare malignancies) in comparison with smaller nodules. This was not influenced by the cystic content. These data clarify previously conflicting reports as to whether nodule size influences thyroid cancer risk (10, 12, 13, 20–23) and impact clinical care recommendations. Equally important, theses data demonstrate the reliability and accuracy of diagnostic FNA for the evaluation of nodules regardless of size, while

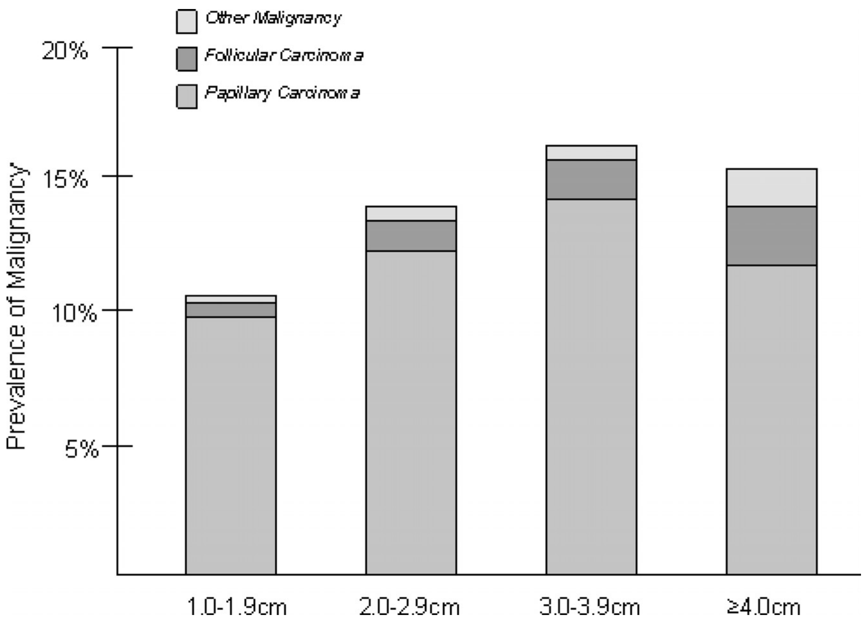

Figure 1. Thyroid nodule size and the types and distribution of thyroid malignancy. Data from 7348 evaluated nodules are presented.

also providing insight into the biology of thyroid cancer itself.

Sixteen percent of patients (and 13% of thyroid nodules) in our population proved to have clinically relevant (>1 cm) thyroid cancer. Although this prevalence was increased once nodules grew larger than 2 cm, a notable finding is that the distribution of follicular and Hurthle cell carcinoma increased linearly from 6% in nodules 1 to 1.9 cm to 15% in nodules ≥4 cm in diameter (Table 4 and Figure 1). This implies that the most common form of thyroid malignancy (papillary carcinoma) is largely predetermined at its inception and does not transform with growth. A similar phenotype correlation applies to benign thyroid nodules. In contrast, the increasing proportion of follicular and Hurthle cell carcinoma in larger nodules confers a different meaning. One explanation is that nodule growth increases the risk of secondary genomic mutations that transform a benign nodule (such as a follicular adenoma) into a malignant nodule (such as a follicular carcinoma). Although possible, an alternative explanation seems more plausible. The histologic hallmarks of follicular carcinoma (capsular and/or vascular invasion) may occur only once a nodule expands beyond a certain size (or cellular number), even if oncogenic mutations are present at its inception. Indeed, several prior investigators have argued that histologically benign nodules that harbor known oncogenic mutations (such as RAS or PAX8: PPARg mutations) may be best characterized as carcinoma in situ (24). Our large-scale, epidemiologic data support this hypothesis. This finding must be contrasted with papillary carcinoma, in which malignancy is histologically determined on the basis of nuclear and cellular morphologic changes. Such findings would likely be apparent in thyroid nodules regardless of their size.

Many clinicians currently recommend surgical resection when nodules grow larger than 4 cm. This is primarily because of a heightened concern for malignancy and false-negative aspiration (which in a large nodule would allow undetected, yet later-stage disease to remain untreated) or separately because of mass effect from the nodule itself. Our data refine the former recommendation, demonstrating that nodules larger than 2 cm are at increased risk for cancer compared with those measuring 1.0 to 1.9 cm, although further risk is not imparted if the nodules measure 2, 3, or >4 cm in diameter. Furthermore, we documented false-negative aspirates in only 1.3% of nodules >4 cm. This rate was similar to nodules measuring 1 to 1.9, 2 to 2.9, or 3 to 3.9 cm (1.1%, 0.7%, or 1.5% false-negative rates, respectively), although we note that only selected thyroid nodules were subject to repeat FNA or surgical resection to define these calculations. Translation of these data to clinical practice must therefore be done cautiously. Other data have demonstrated a higher rate of false-negative aspirates in larger nodules, which may reflect a clinician's ability to incorporate multiple variables (such as ultrasound and clinical characteristics) into care decisions, even if cytology is benign. Therefore, we acknowledge that a large nodule (even if cytologically benign) may require resection based on cosmetic, symptomatic, or clinical concerns alone. This approach remains reasonable, although such a recommendation given to a patient with a nonmalignant, low-risk lesion must be weighed against the small but not inconsequential risk of surgical complications (25). This concern is amplified in centers where thyroid surgery is performed infrequently (26).

Our data refine the recommended diagnostic evaluation of patients with multiple thyroid nodules. Traditionally, the largest (or so-called dominant) nodule is recommended for aspiration. Our above findings confirm that preferentially aspirating solid or partially cystic nodules >2.0 cm may enhance detection of malignancy. However, if multiple nodules >2 cm are present, our data support the continued use of sonographic criteria (such as hypoechoic parenchyma, microcalcifications, and irregular margins) to guide selection of nodules for aspiration. We also note that our data demonstrate the reliability and accuracy of diagnostic FNA regardless of thyroid nodule size, because the distribution of cytologic results is not influenced by nodule diameter (including the proportion of nondiagnostic aspirates).

We acknowledge limitations to this study. Our data are from a single institution and retrospective in nature. Furthermore, only 79% of nodules were completely evaluated. Nonetheless, this cohort represents the largest available analysis of consecutive patients referred for ultrasound assessment and ultrasound-guided FNA of all clinically relevant nodules. We have also detected no evidence of selection or referral bias within our sample cohort, because >95% of all patients with thyroid nodules in our healthcare system are evaluated in our multidisciplinary center and are accounted for in this analysis. We also acknowledge that cytologically benign nodules were classified as benign although in most cases did not undergo repeat FNA or surgical resection to confirm the accuracy of this cytologic diagnosis. However, the low but consistent rate of false-negative aspirates among all size categories argues against an intrinsic error otherwise unaccounted for, and it is also not feasible to expect removal of all such nodules given their benign cytology results.

In summary, these data provide strong evidence that thyroid nodule size >2 cm is associated with an increased risk of well-differentiated thyroid cancer. However, further growth beyond 2 cm no longer influences malignant risk, suggesting a threshold effect. Separately, however, our findings also suggest that large nodule size, when cancerous, influences the specific type of thyroid carcinoma itself. Papillary carcinoma is largely predetermined at its inception and not influenced by growth or cellular expansion. In contrast, follicular carcinoma is much more likely in larger nodules. Although the significance of this remains uncertain, this implies the current histologic parameters used to distinguish follicular adenomas and carcinomas may be an incomplete assessment of malignant potential. This lends further support for the use of molecular analysis to better understand the underlying mechanisms of disease and to improve the accuracy of thyroid cancer diagnosis.

Acknowledgments

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Disclosure Summary: The authors have nothing to disclose related to the subject matter of this paper.

References

1. **Mazzaferri EL.** Management of a solitary thyroid nodule. *N Engl J Med*. 1993;328(8):553–559.
2. **Cooper DS, Doherty GM, Haugen BR, et al.** Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2009;19(11):1167–1213.
3. **Gharib H, Goellner JR.** Fine-needle aspiration biopsy of the thyroid: an appraisal. *Ann Intern Med*. 1993;118(4):282–289.
4. **Miller B, Burkey S, Lindberg G, Snyder WH 3rd, Nwariaku FE.** Prevalence of malignancy within cytologically indeterminate thyroid nodules. *Am J Surg*. 2004;188(5):459–462.
5. **Yassa L, Cibas ES, Benson CB, et al.** Long-term assessment of a multidisciplinary approach to thyroid nodule diagnostic evaluation. *Cancer*. 2007;111(6):508–516.
6. **Baloch ZW, LiVolsi VA, Asa SL, et al.** Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the national cancer institute thyroid fine-needle aspiration state of the science conference. *Diagn Cytopathol*. 2008;36(6):425–437.
7. **Baloch ZW, Fleisher S, LiVolsi VA, Gupta PK.** Diagnosis of "follicular neoplasm": a gray zone in thyroid fine-needle aspiration cytology. *Diagn Cytopathol*. 2002;26(1):41–44.
8. **Hung W, Anderson KD, Chandra RS, et al.** Solitary thyroid nodules in 71 children and adolescents. *J Pediatr Surg*. 1992;27(11):1407–1409.
9. **Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA.** Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. *J Clin Endocrinol Metab*. 2006;91(11):4295–4301.
10. **Frates MC, Benson CB, Doubilet PM, et al.** Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. *J Clin Endocrinol Metab*. 2006;91(9):3411–3417.
11. **Moon WJ, Jung SL, Lee JH, et al; and Thyroid Study Group, Korean Society of Neuro- and Head and Neck Radiology.** Benign and malignant thyroid nodules: US differentiation–multicenter retrospective study. *Radiology*. 2008;247(3):762–770.
12. **Raparia K, Min SK, Mody DR, Anton R, Amrikachi M.** Clinical outcomes for "suspicious" category in thyroid fine-needle aspiration biopsy: Patient's sex and nodule size are possible predictors of malignancy. *Arch Pathol Lab Med*. 2009;133(5):787–790.
13. **Mendelson AA, Tamilia M, Rivera J, et al.** Predictors of malignancy in preoperative nondiagnostic biopsies of the thyroid. *J Otolaryngol Head Neck Surg*. 2009;38(3):395–400.
14. **Alexopoulou O, Beguin C, Buysschaert M, et al.** Predictive factors of thyroid carcinoma in non-toxic multinodular goitre. *Acta Clin Belg*. 2004;59(2):84–89.
15. **Park JH, Choi KH, Lee HB, Rhee YK, Lee YC, Chung MJ.** Intrathoracic malignant peripheral nerve sheath tumor in von Recklinghausen's disease. *Korean J Intern Med*. 2001;16(3):201–204.
16. **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(10):913–916.
17. **Gould MK, Ananth L, Barnett PG; Veterans Affairs SNAP Cooperative Study Group.** A clinical model to estimate the pretest probability of lung cancer in patients with solitary pulmonary nodules. *Chest*. 2007;131(2):383–388.
18. **Cibas ES, Ali SZ.** The Bethesda System for Reporting Thyroid Cytopathology. *Thyroid*. 2009;19(11):1159–1165.

19. **Ali SZ Cibas ES, eds.** *The Bethesda System for Reporting Thyroid Cytopathology*. New York, NY: Springer; 2009.
20. **Stang MT, Carty SE.** Recent developments in predicting thyroid malignancy. *Curr Opin Oncol*. 2009;21(1):11–17.
21. **Banks ND, Kowalski J, Tsai HL, et al.** A diagnostic predictor model for indeterminate or suspicious thyroid FNA samples. *Thyroid*. 2008;18(9):933–941.
22. **McHenry CR, Huh ES, Machekano RN.** Is nodule size an independent predictor of thyroid malignancy? *Surgery*. 2008;144(6):1062–1068; discussion 1068–1069.
23. **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(6):837–844; discussion 844.e1–e3.
24. **Nikiforov YE, Ohori NP, Hodak SP, et al.** Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples. *J Clin Endocrinol Metab*. 2011;96(11):3390–3397.
25. **Bergenfelz A, Jansson S, Kristoffersson A, et al.** Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. *Langenbecks Arch Surg*. 2008;393(5):667–673.
26. **Sosa JA, Bowman HM, Tielsch JM, Powe NR, Gordon TA, Udelsman R.** The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. *Ann Surg*. 1998;228(3):320–330.