A Cohort Analysis of Clinical and Ultrasound Variables Predicting Cancer Risk in 20,001 Consecutive Thyroid Nodules

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Context: Assessing thyroid nodules for malignancy is complex. The impact of patient and nodule factors on cancer evaluation is uncertain.

Objectives: To determine precise estimates of cancer risk associated with clinical and sonographic variables obtained during thyroid nodule assessment.

Design: Analysis of consecutive adult patients evaluated with ultrasound-guided fine-needle aspiration for a thyroid nodule ≥1 cm between 1995 and 2017. Demographics, nodule sonographic appearance, and pathologic findings were collected.

Main Outcome Measures: Estimated risk for thyroid nodule malignancy for patient and sonographic variables using mixed-effect logistic regression.

Results: In 9967 patients [84% women, median age 53 years (range 18 to 95)], thyroid cancer was confirmed in 1974 of 20,001 thyroid nodules (9.9%). Significant ORs for malignancy were demonstrated for patient age <52 years [OR: 1.82, 95% CI (1.63 to 2.05), $P < 0.0001$], male sex [OR: 1.68 (1.45 to 1.93), $P < 0.0001$], nodule size [OR: 1.30 (1.14 to 1.49) for 20 to 19 mm, OR: 1.59 (1.34 to 1.88) for 30 to 39 mm, and OR: 1.71 (1.43 to 2.04) for ≥40 mm compared with 10 to 19 mm, $P < 0.0001$ for all], cystic content [OR: 0.43 (0.37 to 0.50) for 25% to 75% cystic and OR: 0.21 (0.15 to 0.28) for >75% compared with predominantly solid, $P < 0.0001$ for both], and the presence of additional nodules ≥1 cm [OR: 0.69 (0.60 to 0.79) for two nodules, OR: 0.41 (0.34 to 0.49) for three nodules, and OR: 0.19 (0.16 to 0.22) for greater than or equal to four nodules compared with one nodule, $P < 0.0001$ for all]. A free online calculator was constructed to provide malignancy-risk estimates based on these variables.

Conclusions: Patient and nodule characteristics enable more precise thyroid nodule risk assessment. These variables are obtained during routine initial thyroid nodule evaluation and provide new insights into individualized thyroid nodule care. (***J Clin Endocrinol Metab*** **104: 5665–5672, 2019)**

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Abbreviations: AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; BWH, Brigham and Women's Hospital; FNA, fine-needle aspiration; RoM, risk of malignancy; SUSP, suspicious for malignancy; TBSRTC, The Bethesda System for Reporting Thyroid Cytopathology; UG-FNA, ultrasound-guided fine-needle aspiration; US, ultrasound.

Thyroid nodules are common. In adults, a palpable thyroid nodule is present in nearly 5% of women and 1% of men, but thyroid nodules can be identified on imaging in up to 68% of patients (1–5). In the United States, over 200 million individuals may be diagnosed with a nodule if subjected to sonographic imaging (6). The ultimate goal of thyroid nodule evaluation is to detect clinically meaningful thyroid cancer, although only the minority (10% to 15%) of nodules prove malignant (7–9).

The evaluation of a patient with a suspected or known thyroid nodule includes a careful medical history and physical examination, followed by ultrasound (US) evaluation. Clinical factors, such as patient age and sex, can influence the risk that a detected nodule is malignant (10–15). More recently, sonographic characteristics of thyroid nodules have been used to better assess the risk of malignancy (RoM). Although some sonographic features such as microcalcifications, hypoechogenicity, and irregular margins associate with malignant disease, the inter-rater variability on the interpretation of these findings remains high. In contrast, nodule size and presence of cystic fluid have much higher consistency when subjected to blinded review but have only variably been associated with increased RoM in selected populations (10–14, 16–20). Importantly, no investigation of an unselected, consecutive cohort has yet placed all of these commonly obtained and reproducible clinical variables (age, sex, nodule size, cystic component, and multinodularity) into a single model that can be applied to clinical care. The ability to do so would enable individualized integration of the risks posed by these variables and improve the approach to diagnostic fine-needle aspiration (FNA) biopsy.

Cytopathologic interpretation following US-guided FNA (UG-FNA) is currently the principle diagnostic approach to evaluate for malignancy (16, 21, 22). With the use of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), benign and malignant cytologic results are highly accurate for the exclusion or identification of cancer, respectively. Intermediate cytologic findings (TBSRTC Categories III–V), however, are common (22–25) and do not exclude or confirm the presence of malignancy (23, 25–27). Additionally, as current guidelines recommend the performance of UG-FNA in a more selected subset of thyroid nodules (16), many nodules may not have cytologic information available to assist in risk stratification. Thus, an improved understanding of how other patient and nodule characteristics impact risk would better inform the need (or lack of need) for UG-FNA and also better inform individualized RoM when integrated with cytology analysis.

Since 1995, there has been a prospectively maintained database of all consecutive patients evaluated at the Brigham and Women's Hospital (BWH) Thyroid Nodule Clinic for one or more clinically relevant (≥1 cm) nodules. This clinic captures nearly all patients evaluated for thyroid nodular disease in our healthcare system (Brigham Health), the preponderance of whom were receiving initial thyroid nodule evaluation. This large database of unselected consecutive patients, managed with a consistent clinical approach, allows a unique opportunity to analyze the interplay of numerous clinical, radiologic, and pathologic variables, as we seek to individualize patient care. This study describes the clinical landscape of nodule assessment in a large cohort of consecutive thyroid nodule patients and defines the precise impact of each variable upon malignancy risk.

Methods

This was a cohort study of consecutive adult patients, age ≥18 years of age, evaluated in the thyroid nodule clinic at BWH, with UG-FNA for one or more thyroid nodules ≥1 cm between 1995 and 2017. Approval to conduct this study was obtained from the Partners Institutional Review Board.

Patient evaluation included assessment of thyroid function and thyroid US performed by a radiologist with expertise in thyroid sonography, using a 10- to 18-MHz transducer. Nodule location, solid or degree of cystic content, and size in three dimensions were reported. UG-FNA was offered when a nodule that measured ≥1 to 1.5 cm in greatest dimension was identified. Rare instances in which UG-FNA of a nodule <1 cm with high sonographic suspicion for cancer was performed were excluded from the current analysis. FNA was performed by a thyroidologist under US guidance, using a 25-gauge needle following subcutaneous lidocaine administration. Typically, three aspirates per nodule constituted a single FNA. For cystic nodules, US guidance was used to direct sampling of the solid portion of the nodule.

All aspirates were processed using ThinPrep liquid-based cytology preparation (Hologic Corp, Marlborough, MA) for evaluation, as previously described (8). Aspiration specimens were interpreted by pathologists experienced in thyroid cytopathology. Although the period of this study partially predates TBSRTC, cytologic reporting throughout the study period used criteria and terminology later adopted for TBSRTC (22) with the same six categories used. Surgical pathology specimens obtained from thyroidectomy were reviewed and interpreted by a staff pathologist. Histopathology for each nodule was recorded. The extent of disease at diagnosis was classified according to the American Joint Committee on Cancer criteria at that time.

For this study, all patients with UG-FNA results for one or more nodules ≥1 cm were included. Patients were classified as having a solitary nodule (one nodule ≥1 cm) or multinodular thyroid (more than one nodule, each ≥1 cm). Nodules were categorized based on cystic content as predominantly solid (<25% cystic), partially cystic (25% to 75% cystic), or predominantly cystic (>75%). When the initial nodule assessment included repeat UG-FNA cytology, the actionable result that

guided clinical management was used for analysis. A small number of nodules were included as malignant without histologic confirmation when cytology confirmed thyroid or nonthyroid cancer, but the patient was not a candidate for surgery. As the majority of patients with benign aspirates are not referred for surgery, and the accuracy of benign cytology is extremely high, cytologically benign nodules that were not resected were classified as benign and included together with histologically benign nodules.

Statistical analysis

Data are shown as means ± SD or median with range for continuous variables and number and percentages for categorical variables. Comparison was performed using a parametric or nonparametric t test for continuous variables and χ^2 test for categorical variables. Changes for demographic, nodule size, and pathologic characteristics of nodules over time were assessed using linear or logistic regression with a mixed model. A 4-year interval was used for this analysis over time. Area under the receiver operator characteristic curve analysis was performed, and optimal cut-off values were defined by the Youden index J. Mixed-effect logistic regression (PROC GLIMMIX) was performed to identify risk factors for thyroid nodule malignancy while accounting for patients' correlation. Regression coefficients from our model were used to create a prediction equation. Analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC). Statistical significance was defined as a two-tailed $P < 0.05$ for all analyses. Figures were produced using GraphPad Prism (GraphPad Software, San Diego, CA) and Adobe Photoshop (Adobe Systems, Inc., San Jose, CA).

Results

Between 1995 and 2017, 9967 consecutive adult patients with 20,001 nodules ≥1 cm were evaluated with US and UG-FNA (Table 1). In this population, 8372 patients (84.0%) were women, and the median age was 53 years (18 to 95 years). The median nodule size was 1.7 cm (1.0 to 12.8 cm) in largest dimension, with 82.9% under 3.0 cm. Of all nodules, 14,708 (73.5%) were solid. Further details are shown in Table 1.

UG-FNA was performed in 14,389 of 20,001 nodules ≥1 cm (71.9%). Nodules typically were not subjected to UG-FNA if functional on radionuclide scanning, if UG-FNA of another nodule revealed a high-risk cytologic result [*e.g.*, suspicious for malignancy (SUSP) or malignant] leading to surgical intervention, or if <2 cm and mostly cystic. Over the two decades of cohort collection, thyroid nodule management has increasingly favored individualized decisionmaking regarding the need for UG-FNA, depending on nodule size and sonographic findings. Accordingly, nodules without UG-FNA were smaller and more cystic compared with those that underwent UG-FNA ($P < 0.0001$; Table 2).

Final cytology for thyroid nodules undergoing UG-FNA is shown in Table 3. The final nodule cytology was nondiagnostic in 919 (6.4%), benign in 10,154 (70.6%), atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) in 968 (6.7%), follicular neoplasm/suspicious for follicular or Hürthle neoplasm in 892 (6.2%), SUSP in 718 (5.0%), and malignant in 738 (5.1%). Histopathologically malignant nodules, as a proportion of total nodules or a proportion of resected nodules for each TBSRTC category, are shown in Table 3. Among the 10,154 nodules with benign cytology, 1512 (14.9%) were surgically resected (typically because of growth, concerning sonographic features, or persistent symptoms), of which, 106 (1.0%) proved malignant.

To obtain the most accurate overall assessment of malignant nodules, nodules with malignant histopathology (with or without UG-FNA) and those with malignant cytology but that remained unresected were combined. Of 20,001 nodules, a total of 1974 (9.9%) were malignant. On a per-patient basis, 1625 (16.3%) patients evaluated for thyroid nodular disease proved to have malignancy. Looking at the distribution of thyroid cancer types in this general thyroid nodule population showed that 1419 (87.4%) patients had papillary thyroid carcinoma, 96 (5.9%) had follicular

Table 1. Patient and Nodule Characteristics

	n (%)
Patients	9967
Sex	
Female (%)	8372 (84.0)
Male (%)	1595 (16.0)
Age	
Median (range)	53 (18–95)
18–30 y (%)	829 (8.3)
31–40 y (%)	1425 (14.3)
41–50 y (%)	2198 (22.1)
51–60 y (%)	2424 (24.3)
61–70 y (%)	1921 (19.3)
>70 y (%)	1170 (11.7)
No. of nodules per patient (≥1 cm)	
1 (%)	5269 (52.9)
2 (%)	2265 (22.7)
3 (%)	1069 (10.7)
≥ 4 (%)	1364 (13.7)
Median (range)	1 (1–14)
Thyroid nodules	20,001
Nodule diameter	
Median, cm (range)	1.7 (1.0–12.8)
1.0–1.9, cm (%)	12,284 (61.4)
2.0–2.9, cm (%)	4305 (21.5)
3.0–3.9, cm ($)	1875 (9.4)
≥4.0, cm (%)	1537 (7.7)
Cystic content	
Solid (%)	14,708 (73.5)
25%–75% cystic (%)	3760 (18.8)
>75% cystic (%)	1533 (7.7)

Table 2. Comparison of Nodules Undergoing FNA With Those That Did Not

	Nodule With FNA	Nodule Without FNA	
	n = 14,389	n = 5612	*P* Value
Mean nodule size, cm	1.9 (1.0–12.8)	1.3 (1.0–7.9)	<0.0001
Distribution, n (%)			<0.0001
1.0-1.9, cm	7436 (51.7)	4848 (86.4)	
2.0-2.9, cm	3750 (26.1)	555 (9.9)	
3.0-3.9, cm	1732 (12.0)	143 (2.5)	
≥ 4.0, cm	1471 (10.2)	66 (1.2)	
Cystic content, n (%)			<0.0001
Solid	10,830 (75.3)	3878 (69.1)	
25%–75%	2717 (18.9)	1043 (18.6)	
>75%	842 (5.8)	691 (12.3)	

thyroid carcinoma, and other forms of cancer, including metastases to the thyroid gland, each represented ~1% to 2% of affected patients (Table 4).

Demographic, nodule, and pathologic variables were assessed over time to identify trends in clinical care. The proportion of male patients evaluated (Fig. 1A) rose progressively from 9.1% (106/1171) in 1995 to 1998 to 16.9% (546/3238) in 2015 to 2017 ($P < 0.0001$). Mean patient age also increased (Fig. 1A) from 48.9 ± 14.3 in 1995 to 1998 to 55.2 ± 15.0 in 2015 to 2017 ($P < 0.0001$). Notably, the median size in the largest dimension of aspirated nodules (Fig. 1B) decreased over the study period ($P = 0.02$). Figure 1C shows the distribution of TBSRTC categories over time, which was notable for a small but progressive increase in TBSRTC III (AUS/FLUS) cytology compared with other categories. As shown in Fig. 1D, the malignancy rates for nodules that underwent surgical resection (*e.g.*, surgical yield) generally increased over the study period, from 26.1% (93/357) in 1995 to 1998 to 46.1% (233/505) in 2015 to 2017 ($P < 0.0001$).

We next sought to define the relative contribution of the clinical and US variables to the prediction of cancer in a thyroid nodule ≥1 cm. To do this, multivariable regression analysis was performed using commonly obtained and highly reproducible variables of age, sex, nodule size, and nodule cystic contents and the presence of multinodularity as factors (Table 5). Based on receiver operator characteristic analysis, age was dichotomized at 52 years to discriminate cancer risk best. All variables from the univariable analysis were statistically significant and included in multivariable analysis. In the multivariable model, increased risk was observed for age <52 years [OR: 1.82 (1.63 to 2.05), $P < 0.0001$] and male sex [OR: 1.68 (1.45 to 1.93), $P < 0.0001$]. A progressive increase in risk also was observed for larger nodule size compared with nodules measuring 1.0 to 1.9 cm [OR: 1.30 (1.14 to 1.49) for 2.0 to 2.9 cm, OR: 1.59 (1.34 to 1.88) for 3.0 to 3.9 cm, OR: 1.71 (1.43 to 2.04) for ≥4 cm, $P < 0.0001$ for all]. In contrast, significant reduction in the odds of malignancy was observed for nodules ≥1 cm when part of a multinodular gland [OR: 0.69 (0.60 to 0.79) for two nodules, OR: 0.41 (0.34 to 0.49) for three nodules, OR: 0.19 (0.16 to 0.22) for four or more nodules, $P < 0.0001$ for all]. Odds of malignancy were reduced with increasing cystic content compared with predominantly solid nodules [OR: 0.43

Table 3. Distribution of Cytologic Diagnoses After Final UG-FNA Evaluation

TBSRTC Category	Nodule Cytology, n (%)	Malignancy Rate in Resected Nodules, n (%)	% Histology-Confirmed Malignancy in All Nodules
I. Nondiagnostic	919 (6.4)	36/226 (16.8)	4.0
II. Benign	10,154 (70.6)	106/1512 (7.1)	1.0
III. AUS/FLUS	968 (6.7)	207/561 (37.4)	21.4
IV. FN/SFN	892 (6.2)	243/697 (34.9)	27.2
V. SUSP	718 (5.0)	477/670 (71.3)	66.4
VI. Malignant	738 (5.1)	674/681 (99.0)	91.3[a]

Abbreviations: AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN, follicular neoplasm/suspicious for follicular or Hürthle neoplasm.

[a]Because of the confirmed accuracy of a malignant cytology result, the cancer rate in this category for resected nodules (99%) is likely more accurate than the rate for all nodules (91.3%), which does not includ nodules for which histopathology was not obtained or available.

Table 4. Distribution of Malignant Histologies Among 9967 Patients

Patient Diagnosis	n (%)
Type of thyroid cancer	
Papillary carcinoma (all variants)	1419 (87.4)
Follicular carcinoma	96 (5.9)
Hürthle cell carcinoma	18 (1.1)
Medullary carcinoma	14 (0.9)
Poorly differentiated carcinoma	23 (1.4)
Anaplastic carcinoma	20 (1.2)
Thyroid lymphoma	1 (0.06)
Intrathyroidal metastasis of nonthyroid malignancy	34 (2.1)
Lymphoproliferative diseases[a]	12
Renal cell carcinoma	7
Squamous cell carcinoma	4
Esophageal cancer	5
Other[b]	4

[a]Lymphoproliferative disease: non-Hodgkin lymphoma (4), marginal lymphoma (1), chronic lymphocytic leukemia/small cell lymphoma (2), diffuse large B cell lymphoma (2), follicular lymphoma (2), Langerhans histiocytosis (1).

[b]Ewing sarcoma (1), melanoma (1), nonsmall cell lung (1), breast (1).

(0.37 to 0.50) for 25% to 75% cystic, OR: 0.21 (0.15 to 0.28) for >75% cystic, $P < 0.0001$ for both].

Finally, regression coefficients from the multivariable model were used to generate a prediction equation for the probability of malignancy for any given thyroid nodule based on the cumulative impact of these reproducible clinical and sonographic variables. This thyroid nodule cancer-risk calculator provides an estimated RoM for a given individual, once patient age and sex, nodule size (centimeter) and degree of cystic component, and the number of nodules ≥1 cm present are entered. Results are expressed as a percentage RoM. For example, a solitary, 1.5-cm thyroid nodule that is partially cystic (25% to 75%) in a 55-year-old woman has an estimated risk of 5.23%, whereas a 3.2-cm solid nodule in a 30-year-old man who has one other nodule ≥1 cm has a 29.9% risk of being malignant. This BWH Thyroid Nodule Risk Estimator is available at http://thyroidcancerrisk.brighamandwomens.org/.

Discussion

Thyroid nodules represent a common clinical dilemma. Whereas most nodules prove benign, evaluation is frequently necessary to exclude the possibility of cancer. Whereas many risk factors for malignancy have been suggested, our understanding of the specific risk attributable to these is not precisely known. Our results illustrate the landscape of thyroid nodule evaluation in current clinical practice. From this, our calculator allows commonly available and highly reproducible data to estimate the risk of thyroid cancer in each individual nodule. In this largest population of consecutive nodules yet reported, patient age, sex, nodule size, degree of multinodularity (counting nodules ≥1 cm), and degree of cystic content were all highly important predictors of thyroid cancer. These variables proved predictive in adjusted multivariable analysis, confirming their independent relevance to thyroid nodule evaluation.

Increasing patient age had previously been associated with a lower RoM in adults (15, 28), possibly as a result of the accumulation of benign nodules with aging or the greater incidental detection of lower-risk nodules in this population. The present data confirm younger patients' age as a notable predictor of malignancy and define an age cut-off of 52 years as the best discriminating binary cut-off. With the use of this cut-off, the adjusted odds of malignancy in any relevant nodule was 1.8 times higher in patients younger than 52 years than those older than 52 years. A greater risk of thyroid nodule malignancy in men compared with women also has been previously suggested (14), but this has not been consistently confirmed (13, 29). The precise data from our study confirm an increase in cancer risk in men compared with women. Although larger thyroid nodule size often provokes greater clinical concern, the relationship between nodule size and cancer risk has been inconsistent (12–14, 18, 30). Our study confirms an increasing cancer risk as nodules enlarge from 1 to 4 cm in diameter. It is uncertain why these findings for nodule size differ from the analysis of a partially overlapping cohort (18), but one possibility is a change in FNA performed for larger cystic nodules over time. Consistent with previous investigations (14, 20, 31), a decrease in RoM was observed for categories of greater multinodularity (solitary, vs two, three, or greater than or equal to four nodules), as well as an increasing cystic component (solid to <25%, 25% to 75%, >75%). Based on all of the above findings, we created the BWH Thyroid Nodule Risk Estimator for the determination of the RoM when all such variables are cumulatively considered.

Our data also depicted interesting diagnostic trends over the past 20 years, likely representative of national trends. We observed increasing patient age and decreasing nodule size over time, which both fit with increased incidental detection of nodules that were not otherwise clinically apparent. The observed increase in male patients, as well as the trends in the distribution of nodule cytology over time, are of uncertain significance. But, importantly, a gradual increase in the proportion of resected nodules proving malignant was observed (*e.g.*, surgical yield). This is highly encouraging and likely reflects improved, individualized risk assessment applied to management decisions, including US and molecular diagnostic testing.

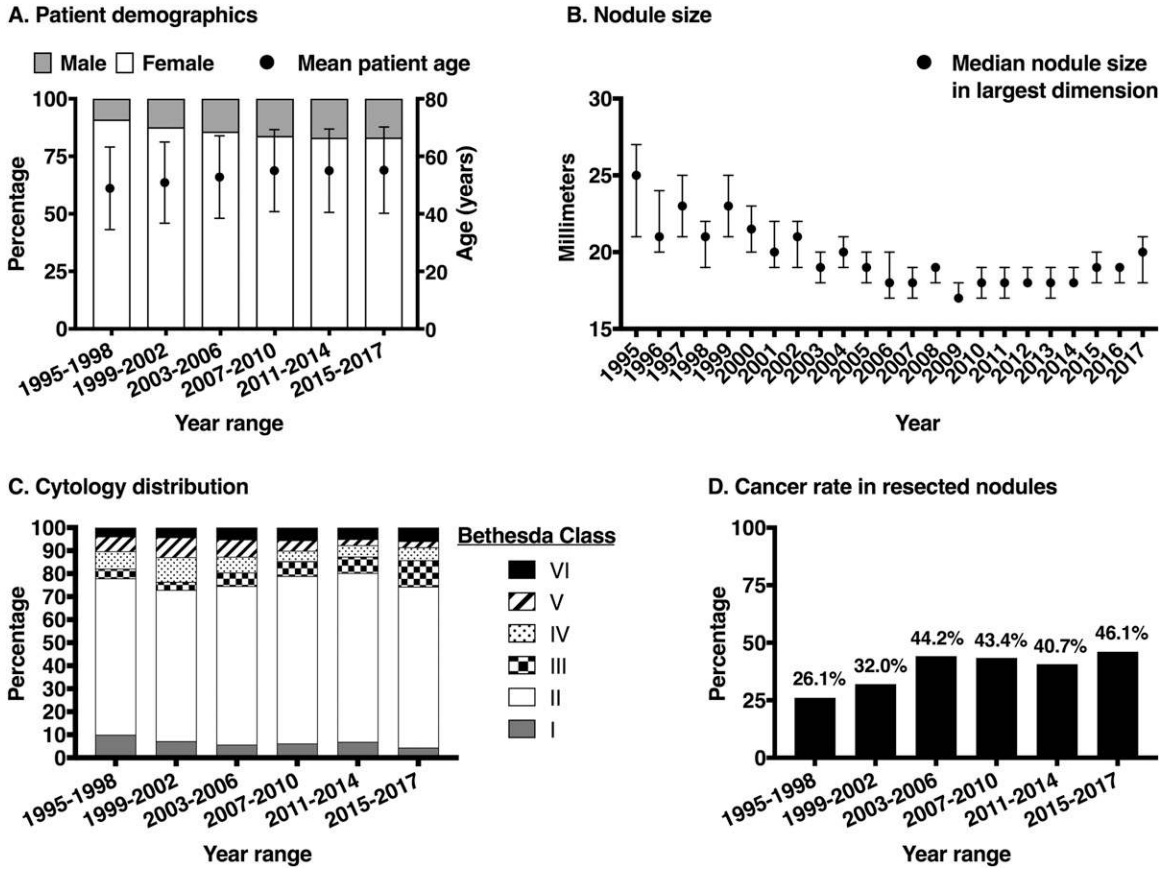

Figure 1. Trends in patient characteristics, nodule size, and pathology in nodules undergoing UG-FNA from 1995 to 2017. Trends in the clinical evaluation of thyroid nodules are shown for time intervals as shown. (A) Patient sex in bars shows a progressively increasing proportion of males (gray bar) compared with females (white bars) across the time intervals ($P < 0.0001$). A mean patient age at the time of UG-FNA with SD (black dot and whisker) shows a gradual increase over time ($P < 0.0001$). (B) Median nodule size (millimeters) and 95% CI are shown by year from 1995 to 2017, illustrating a decrease over time ($P < 0.0001$), although this trend appears to stabilize and slightly reverse after 2009. (C) The distribution of cytologic diagnoses by TBSRTC demonstrated decreases in TBSRTC (Bethesda) V (diagonal, striped bar), IV (dotted bar), and I (gray bar) and an increase in Bethesda III (checkered bar) over time. For each time period (1995 to 1998, 1999 to 2002, 2003 to 2006, 2007 to 2010, 2011 to 2014, 2015 to 2017), the rates or each cytologic diagnosis were the following: Bethesda I (10.0%, 7.2%, 5.7%, 6.20%, 6.9%, 4.4%), Bethesda II (67.9%, 65.7%, 68.9%, 72.7%, 73.4%, 69.9%), Bethesda III (4.2%, 3.5%, 5.9%, 6.5%, 7.1%, 11.5%), Bethesda IV (7.6%, 10.7%, 6.8%, 4.5%, 5.0%, 5.6%), Bethesda V (6.4%, 8.6%, 7.5%, 4.6%, 2.6%, 2.7%), and Bethesda VI (3.9%, 4.2%, 5.2%, 5.5%, 5.0%, 5.9%). (D) The percentage of nodules that were malignant among all nodules that underwent surgical resection by time interval (bars) indicates increasing surgical yield for cancer over time.

Limitations to the current study are important to consider. These data represent a single-center experience that may not reflect all populations. However, our clinic is the primary location for referral of nodular disease within our hospital system, which minimizes selection bias. Not all nodules underwent resection to provide a definitive diagnosis. Given the high accuracy of both benign and malignant cytology, we considered it reasonable and clinically relevant to define such nodules based on these findings. Not all potential thyroid cancer risk factors were available for analysis, which may have provided even more precise information. Systems that use multiple sonographic nodule characteristics to classify nodules into categories of malignancy risk have recently been described and improve overall risk stratification. Detailed sonographic characterization was beyond the scope of this study, and differences across the study's 20-year period prevented accurate comparison of certain US features. The inter-rater variability of such systems remains substantial without specific training or experience. Our findings show the value of standard US features to cancer-risk stratification.

The variables included are near-universally available during thyroid nodule assessment, making the current model more generalizable. For indeterminate nodules, final categorization is less certain, and analyses only categorized these nodules based on histopathologic confirmation. Particularly for the TBSRTC III category (AUS/FLUS), TBSRTC categorization was based on the final actionable cytology. Many nodules with initial AUS/FLUS cytology underwent repeat FNA, and nodules with AUS/FLUS cytology that ultimately underwent resection in this cohort did not include those with a repeat UG-FNA showing benign cytology or benign molecular test findings.

In conclusion, this extensive analysis provides insight into the long-term, multidisciplinary evaluation of thyroid nodules. These data demonstrate use of easily

Table 5. Logistic Regression Analyses Defining the RoM in Thyroid Nodules ≥1 cm (n = 20,001)

Predictor		Multivariate Analysis OR (95% CI)	*P* Value
Age, y			<0.0001
	≥52	1 (ref)	
	<52	1.82 (1.63–2.04)	
Sex			<0.0001
	Female	1 (ref)	
	Male	1.68 (1.45–1.93)	
Number of nodules, ≥1 cm	1	1 (ref)	<0.0001
	2	0.69 (0.59–0.79)	<0.0001
	3	0.41 (0.34–0.49)	<0.0001
	4+	0.19 (0.16–0.22)	<0.0001
Nodule diameter, cm	1.0–1.9	1 (ref)	<0.0001
	2.0–2.9	1.30 (1.14–1.49)	<0.0001
	3.0–3.9	1.58 (1.34–1.88)	<0.0001
	≥ 4.0	1.70 (1.42–2.04)	<0.0001
Cystic composition	Predominantly solid	1 (ref)	<0.0001
	Partially cystic	0.43 (0.37–0.50)	<0.0001
	Predominantly cystic	0.21 (0.15–0.28)	<0.0001

Abbreviation: ref, reference.

obtainable and commonly reproducible variables to generate precise RoM for a thyroid nodule to improve personalized discussion of care.

Additional Information

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Disclosure Summary: The authors have nothing to disclose.

Data Availability: Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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