Differential Growth Rates of Benign vs. Malignant Thyroid Nodules

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Context: Thyroid nodule growth was once considered concerning for malignancy, but data showing that benign nodules grow questioned the use of this paradigm. To date, however, no studies have adequately evaluated whether growth rates differ in malignant vs. benign nodules.

Objective: To sonographically evaluate growth rates in benign and malignant thyroid nodules ≥1 cm.

Design: Prospective, cohort study of patients with tissue diagnosis of benign or malignant disease, with repeated ultrasound evaluation six or more months apart.

Main Outcomes: Growth rate in largest dimension of malignant compared with benign thyroid nodules. Regression models were used to evaluate predictors of growth.

Results: Malignant nodules (126) met inclusion criteria (≥6-month nonoperative followup) and were compared with 1363 benign nodules. Malignant nodules were not found to be uniquely selected or prospectively observed solely for low-risk phenotype. Median ultrasound intervals were similar (21.8 months for benign nodules; 20.9 months for malignant nodules). Malignant nodules were more likely to grow >2 mm/y compared with benign nodules [relative risk (RR) = 2.5, 95% confidence interval (CI), 1.6 to 3.1; $P < 0.001$], which remained true after adjustment for clinical factors. The RR of a nodule being malignant increased with faster growth rates. Malignant nodules growing >2 mm/y had greater odds of being more aggressive cancers [intermediate risk: odds ratio (OR) = 2.99; 95% CI, 1.20 to 7.47; $P = 0.03$; higher risk: OR = 8.69; 95% CI, 1.78 to 42.34; $P = 0.02$].

Conclusions: Malignant nodules, especially higher-risk phenotypes, grow faster than benign nodules. As growth >2 mm/y predicts malignant compared with benign disease, this clinical parameter can contribute to the assessment of thyroid cancer risk. **(*J Clin Endocrinol Metab* 102: 4642–4647, 2017)**

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Abbreviations: BWH, Brigham and Women's Hospital; CI, confidence interval; FNA, fine-needle aspiration; FVPTC, follicular variants of papillary thyroid carcinoma; IQR, interquartile range; PTC, papillary thyroid carcinoma; RR, relative risk; SD, standard deviation.

Thyroid nodules are common, and 85% to 90% prove benign (1–3). Assessment with ultrasound and ultrasound-guided fine-needle aspiration (FNA) are the principal means of evaluating thyroid nodules to detect potential cancer (4, 5). Clinical factors, such as age, sex, history of head and neck irradiation, or family history of thyroid cancer, may also influence the risk that a thyroid nodule is malignant. Whereas current integration of clinical, sonographic, and cytology data improves preoperative risk assessment, the ability to identify fully thyroid cancer preoperatively (and in particular, its degree of aggressivity) remains imperfect.

One parameter previously used to assess the risk of thyroid malignancy was nodule growth (6, 7). Once considered predictive of cancer, the clinical significance of growth was called into question by studies demonstrating that growth of benign nodules was common (8–11). Whether there exists a difference in growth rates between benign and malignant nodules is not clear. Prospective observational data have suggested that the growth of papillary thyroid carcinoma (PTC) with nodule size <1 cm (*i.e.*, microcarcinoma) is relatively uncommon and slow (12), but similar assessments in clinically relevant nodules ≥ 1 cm are lacking.

The understanding of the growth rate of malignant nodules compared with benign nodules may prove helpful and further assist in risk stratification and monitoring. Furthermore, different rates of growth in malignant nodules may be associated with the difference in tumor behavior. If such differences exist, then the information could influence clinical decisions related to observation, FNA, and possible surgical resection. A systematic comparison of growth rates in benign and malignant nodules is required to address this issue but is challenging, as those with cytology, suspicious or positive for malignancy, are typically referred for surgical intervention (4).

With the use of a prospective, high-quality database of consecutive patients evaluated over 20 years, we identified a cohort of patients who had repeated ultrasound evaluation of benign nodules and untreated malignant nodules ≥ 1 cm. This study compares the growth rate of benign and malignant nodules to understand further the potential clinical relevance of this variable.

Materials and Methods

We performed a prospective cohort analysis of consecutive patients who underwent FNA of one or more thyroid nodules at the Brigham and Women's Hospital (BWH) Thyroid Nodule Clinic between 1995 and 2014. Clinical care of all patients included thyroid ultrasound evaluation performed by a radiologist with expertise in thyroid sonography, using a 10- to 18-MHz transducer. Nodule location, solid or cystic parenchyma ($<25\%$, 25% to 50%, 50% to 75%, or $>75\%$ cystic), and size in three dimensions were measured. FNA was performed by a thyroidologist under ultrasound guidance, usually using a 25-gauge needle. All aspirates were processed using ThinPrep liquid-based cytology preparation (Hologic, Marlborough, MA), and aspiration specimens were evaluated by a pathologist experienced in thyroid cytopathology. Although the period of this study partially predates the use of the Bethesda System for Reporting Thyroid Cytopathology, cytologic reporting at BWH has used the criteria and terminology later adopted by this classification system (13) throughout the entire study period.

Demographic, sonographic, and pathologic information was obtained from review of medical records. Malignant nodules were defined as those that were histologically confirmed as thyroid cancer. We included for analysis those in which there existed two or more ultrasound assessments ≥ 6 months apart before surgical resection. Benign nodules were defined following confirmation of benign cytology. For the purposes of this study, we included those benign nodules with two or more ultrasound assessments ≥ 1 y apart (14), as this was the recommended follow-up duration specific to that time. Nodules were excluded from analysis if the biopsied nodule could not be clearly identified on all ultrasound examinations or if the nodule could not be correlated with the histopathologic findings.

The nodule growth rate was assessed, as the change in the largest dimension between ultrasound assessments per year (millimeters per year). As 0 to 2 mm has been considered within the range of expected interobserver variability for ultrasound measurement, we considered an increase of >2 mm/y to be evidence of "growth," and a decrease >2 mm/y to be evidence of "shrinking." Therefore, measurement differences that varied from -2 to 2 mm/y were considered stable. We additionally assessed thyroid nodule growth using other definitions (4) of a $>20\%$ increase in two nodule dimensions and separately, a $>50\%$ increase in nodule volume using the ellipsoid formula (length $\times$ width $\times$ depth $\times \pi/6$).

Summary statistics are provided as means $\pm$ standard deviation (SD) for continuous, normally distributed variables; median with range and interquartile range (IQR) for non-normally distributed, continuous variables; or numbers and percentages for categorical variables. Comparison was performed using a two-sample Student's t test for continuous variables and the χ^2 test for categorical variables. Association between nodule growth and clinical variables was assessed using nonparametric tests (Wilcoxon rank sum test, Kruskal Wallis test) with consideration of non-normal distribution of nodule growth in the benign and malignant cohorts. To measure the strength of association between the nodule growth and malignancy rate, we calculated the relative risk (RR) of a malignant nodule in each growth category using Cochran-Mantel-Haenszel statistics. We used the stable growth category (-2 to 2 mm change) as the reference category. A generalized linear model was used to calculate the RR that a nodule with growth >2 mm/y was a malignant nodule, controlling for baseline predictors, such as age, sex, nodule size, and nodule parenchyma. The predictive ability of each nodule growth rate was assessed using receiver-operator characteristic curve analysis. To determine the predictors for growth (>2 mm/y) in malignant nodules, we performed unadjusted and adjusted logistic regression analyses. In this analysis, we included age, sex, nodule size, nodule parenchyma, thyroid cancer risk, and lymph node metastasis to include histopathologic variables

important for clinical management. Analyses were performed using SAS software (SAS Institute, Cary, NC), version 9.4. Statistical significance was defined as a two-tailed $P < 0.05$ value for all analyses. Figures were produced using GraphPad Prism (GraphPad Software, La Jolla, CA) and Adobe Photoshop (Adobe Systems, San Jose, CA). Permission for this study was granted by the Institutional Review Board of BWH.

Results

We identified 135 malignant thyroid nodules, ≥1 cm in diameter, that had repeated ultrasound evaluations before surgical intervention, allowing assessment of growth. Nine of these malignant nodules could not be clearly correlated with ultrasound images or their histopathology specimen and were therefore excluded. For comparison, we identified 1414 benign nodules with repeated ultrasound evaluations, of which 51 nodules had uncertain ultrasound identification, leaving 1363 for evaluation. The median time between the first and the last ultrasound evaluation in these two cohorts was 20.9 months (range, 6.0 to 174.1; IQR, 8.9 to 52.0) and 21.8 months (range, 12.0 to 171.9; IQR, 14.9 to 37.4), respectively ($P = 0.72$).

Patient and nodule characteristics are shown in Table 1. The mean patient age was 48.6 years (±14.5) for malignant nodules compared with 52.2 (±13.6) years for benign nodules ($P < 0.01$). Males accounted for 20 of 126 (15.9%) malignant nodules and 135 of 1363 (9.9%) benign nodules ($P = 0.03$). The median size of benign nodules (17 mm; IQR, 13 to 25 mm) and malignant nodules (17 mm; IQR, 13 to 26 mm) was similar ($P = 0.98$).

Acknowledging that most malignant nodules are resected once identified, we assessed the circumstances leading to ≥6 months duration between repeat ultrasound measurement for the 126 malignant nodules. In this cohort, thyroid cancer was identified, but treatment was deferred in 30 (23.8%) cases, as a result of the patients' separate, higher-priority medical conditions, including pregnancy in five patients. Separately, patients independently chose to delay their surgical evaluation in eight (6.3%) cases, and a repeat ultrasound was obtained preoperatively to assess for interval change. For 33 of 126 other nodules (26.2%), there was simply a delay between the initial ultrasound and subsequent referral for FNA. In 35 of 126 (27.8%) separate nodules, initial cytology was nondiagnostic or indeterminate, and repeat assessment occurred at a delayed time point. Finally, there were 20 of 126 (15.9%) nodules that were seen on the initial ultrasound of a multinodular goiter but were not the initial focus of nodule assessment by FNA. To identify further potential selection bias, clinical variables for the malignant nodules included in the analysis were compared with the malignant nodules that were excluded. There were no statistically significant differences found between these groups in patient age, sex, nodule size, or the amount of cystic component. Together, these data do not identify sources of selection bias influencing these findings.

As shown in Fig. 1, growth rate was more rapid in a higher proportion of malignant thyroid nodules than benign nodules. Specifically, malignant nodules grew >2 mm/y in 33 of 126 cases (26.2%) compared with only 159 of 1363 (11.7%) benign nodules ($P < 0.0001$). In contrast, benign nodules were stable or smaller during follow-up in 1204 of 1363 (88.3%) cases compared with 93 of 126 (73.8%) malignant nodules ($P < 0.001$). Further analysis performed, using a generalized linear regression model and controlling for patient age, sex, initial nodule size, and cystic extent, confirmed that growth >2 mm/y was independently associated with malignancy [RR 1.32; 95% confidence interval (CI), 1.08 to 1.61; $P < 0.01$].

Table 1. Patient and Thyroid Nodule Characteristics

	Benign Nodules (n = 1363)	Malignant Nodules (n = 126)	*P* Value
Patient characteristics			
Age, y (means ± SD)	52.2 ± 13.6	48.6 ± 14.5	<0.01
Sex, n (%)			0.03
Male	135 (9.90)	20 (15.9)	
Female	1228 (90.1)	106 (84.1)	
Nodule characteristics[a]			
Nodule size, mm			0.98
Mean ± SD	20.2 ± 10.1	20.5 ± 11.2	
Median (IQR)	17 (13–25)	17 (13–26)	
Nodule parenchyma, n (%)			0.42
>50% solid	1212 (91.3)	115 (91.3)	
>50% cystic	151 (8.7)	11 (8.7)	
Time (mo) between first and last ultrasound, median (IQR)	21.8 (14.9–37.4)	20.9 (8.9–52.0)	0.72

[a] At the time of initial ultrasound.

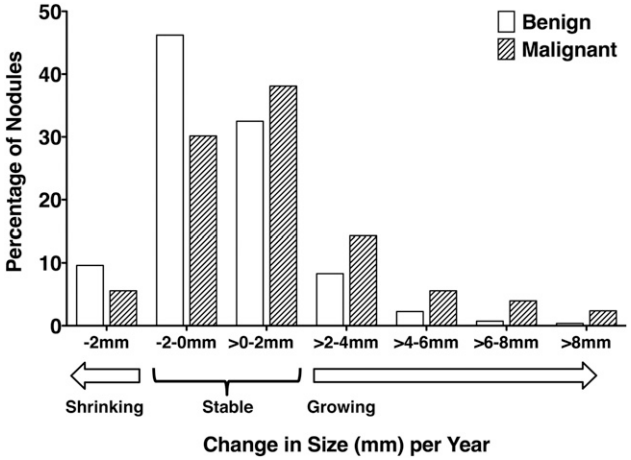

Figure 1. Change in the size (millimeters per year) of benign and malignant thyroid nodules. Nodule reduction by >2 mm/y was defined as shrinking. Nodule measurements that changed between −2 and +2 mm/y was considered stable. Nodule size that increased by >2 mm/y was defined as growth. Bars show the percentage of benign nodules (white bars) and malignant nodules (diagonal, striped bars) present in each growth category.

When growth rates were further stratified, a progressively increasing RR of malignancy was observed as nodules grew faster (Table 2). Compared with stable nodules (−2 to 2 mm/y), nodules growing >2 to 4 mm/y had an RR of malignancy of 1.85 (95% CI, 1.15 to 2.98; $P = 0.01$), whereas nodules growing >8 mm/y demonstrated an RR of malignancy of 5.05 (95% CI, 2.02 to 12.65; $P < 0.01$).

Nodule growth was also evaluated by separate criteria. During similar median follow-up intervals, a >20% change in two or more nodule dimensions was observed in 32 of 126 (25.4%) malignant nodules compared with 194 of 1363 (14.2%) benign nodules ($P < 0.001$). Similarly, using an increase in nodule volume of >50%, we identified 44 of 126 (34.9%) malignant nodules that grew compared with 287 of 1363 (21.1%) benign nodules ($P < 0.001$).

To assess the accuracy of using the nodule growth rate as an isolated variable to predict malignancy in these two cohorts, receiver-operator characteristic curve analysis was performed. The assessment of growth rate demonstrated an area under the curve of 0.63 (95% CI, 0.58 to 0.68; $P < 0.0001$). With the use of a growth cutoff of >2 mm/y to identify malignancy, the specificity, sensitivity, positive predictive value, negative predictive value, and number needed to treat were 0.88 (0.86 to 0.90), 0.26 (0.19 to 0.34), 0.17 (0.12 to 0.23), 0.93 (0.91 to 0.94), and 9.97 (4.50 to 15.54), respectively.

Table 2. Rate of Thyroid Nodule Growth and RR of Malignancy

Category	RR (95% CI)	*P* Value
Shrinking >2 mm/y	0.68 (0.32–1.45)	0.31
No change (−2 to 2 mm/y)	1.00 (reference)	
Growth of >2–4 mm/y	1.85 (1.15–2.98)	<0.05
Growth of >4–6 mm/y	2.48 (1.23–5.00)	<0.05
Growth of >6–8 mm/y	4.49 (2.13–9.45)	<0.01
Growth of >8 mm/y	5.05 (2.02–12.65)	<0.01

To determine if additional factors predicted malignant nodule growth >2 mm/y, we performed logistic regression analysis of clinical, sonographic, and pathologic variables (Table 3). Of the 126 malignant nodules, we classified thyroid cancer as lower risk in 76 cases, which was defined as encapsulated, noninvasive follicular variants of PTC (FVPTC). Cancer was classified as intermediate risk in 42 cases, which included classical PTC, infiltrative FVPTC, and minimally invasive follicular or Hurthle cell thyroid carcinoma. Finally, cancer was classified as higher risk in eight cases, which included medullary thyroid cancer, poorly differentiated thyroid cancer, and columnar and tall cell variants of PTC (Supplemental Table 1). In the multiple logistic regression model, a malignant nodule growth rate of >2 mm/y remained significantly associated with both intermediate- and higher-risk cancers. Intermediate-risk cancers were 2.99 times more likely have a growth rate >2 mm/y (95% CI, 1.20 to 7.47; $P = 0.03$), and higher-risk cancers were 8.69 times more likely have a growth rate >2 mm/y (95% CI, 1.78 to 42.34; $P = 0.02$) compared with lower-risk thyroid cancers. Patient age, sex, nodule size, or cystic content and the presence of lymph node metastases were not associated significantly with nodule growth rate >2 mm/y.

Discussion

In this study, we demonstrate that malignant nodules grow more frequently and more rapidly than benign nodules. Thyroid nodules that were stable or shrinking were significantly more likely to be benign, whereas growth >2 mm/y was associated with malignancy. Furthermore, for every 2 mm/y increment of growth above this threshold, a progressive increase in the RR of malignancy was observed. The relationship between growth >2 mm/y and malignancy remained significant after adjustment for other clinical factors. The analyses also showed that malignant nodules with a growth rate >2 mm/y were more likely to harbor aggressive histopathologic subtypes. Together, these data broadly compare the growth rates of clinically relevant benign and malignant nodules ≥1 cm and support inclusion of thyroid nodule growth as a clinically helpful variable during thyroid nodule evaluation.

The sonographic growth of malignant compared with benign nodules has rarely been reported. Indeed, there is

Table 3. Clinical and Histology Predictors of Nodule Growth Rate >2 mm/y in Malignant Thyroid Nodules

		Univariate Analysis		Multivariate Analysis	
Predictor	**Category**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Age		1.00 (0.98–1.03)	0.78	1.00 (0.97–1.03)	0.85
Sex	Male	1 (reference)		1 (reference)	
	Female	0.80 (0.28–2.28)	0.67	0.83 (0.27–2.61)	0.75
Nodule parenchyma[a]	Cystic	1 (reference)		1 (reference)	
	Solid	0.59 (0.16–2.16)	0.43	0.59 (0.15–2.38)	0.46
Nodule size[a]		1.02 (0.99–1.06)	0.31	1.02 (0.99–1.07)	0.15
Thyroid cancer risk	Lower[b]	1 (reference)		1 (reference)	
	Intermediate[c]	2.69 (1.13–6.42)	0.03	2.99 (1.20–7.47)	0.03
	Higher[d]	8.08 (1.72–38.09)	0.02	8.69 (1.78–42.34)	0.02
Lymph node metastasis	No	1 (reference)		1 (reference)	
	Yes	1.12(0.21–6.08)	0.90	1.20 (0.20–7.33)	0.84

Abbreviation: OR, odds ratio.

[a]At the time of initial ultrasound.

[b]Lower-risk cancers include encapsulated noninvasive follicular variant.

[c]Intermediate-risk cancers include classical PTC and most PTC variants, invasive FVPTC, or minimally invasive follicular or Hurthle cell carcinoma.

[d]Higher-risk cancers include medullary thyroid carcinoma, tall-cell and columnar variants of PTC, and poorly differentiated thyroid cancer.

only one small pilot study of 14 patients, which showed no difference in growth between histologically benign and malignant lesions over a median of 30 months (15). However, the growth of benign nodules alone has been examined more extensively (8, 9, 14, 16, 17). Durante *et al.* (16) recently reported a prospective five-year observational study of cytologically and sonographically benign nodules demonstrating a mean growth rate of nearly 1 mm/y. An increase of 20% in two dimensions occurred in 15.4% of patients, whereas the majority of nodules remained stable. These data are similar to our findings in which 14.2% of benign nodules also met this criterion.

In contrast, studies investigating the growth rate of malignant nodules are rare. Ito *et al.* (12) reported 162 patients with low-risk papillary microcarcinomas (sonographically <1 cm and without lymph node disease) who selected observational therapy. In five years or more of follow-up, only 11% of tumors grew to >10 mm, whereas the majority remained stable. Our data contrast with this finding, demonstrating that 33 of 126 (26.2%) malignant nodules increased >2 mm/y in greatest dimension. It is notable that thyroid nodules in our study were ≥1 cm and relatively unselected. Thus, such differences from prior data may reflect fundamental differences in the biological behavior between the microcarcinomas and malignancy ≥1 cm in diameter.

Our findings may have important implications for clinical practice. Current trends suggest that an increasing number of thyroid nodules are likely to be monitored conservatively, even without prior cytologic assessment. Furthermore, some biopsy-proven thyroid cancers are increasingly being recommended for active observation and follow-up rather than surgical resection. As a consequence, decisions regarding when to perform FNA or when to remove a thyroid malignancy will increasingly depend on observed changes during follow-up. Our data indicate that the nodule growth rate may be an important consideration in thyroid nodules that have not undergone cytologic assessment or observed thyroid cancers. During such follow-up, reduction in nodule size by 2 mm or more per year should suggest a very low risk of a malignancy and thus, may afford the clinician a continued option of conservative management. Conversely, rapid growth of solid nodule tissue should lead to an initial diagnostic FNA or surgical resection of an FNA-proven malignancy, given the association with higher-risk phenotypes found in this analysis. Whereas the rate of nodule growth alone may lack ideal discriminatory value for malignancy, its incorporation into an integrated approach to thyroid nodule evaluation will serve to individualize risk stratification further.

We acknowledge limitations to this study. The cohort of malignant nodules included only those patients with available sonographic reassessment over six or more months. While these patients were not participating in a prospective observational study, this cohort did not appear to show signs of overt selection bias. The finding of several aggressive thyroid cancer histologies in this cohort and the positive correlation between aggressiveness and growth rate suggest that the sample includes a breadth of malignant phenotypes. However, clinical or sonographic factors that favored observation in some patients cannot be excluded. Separately, we acknowledge that benign nodules were defined cytologically, as benign nodules are not typically referred for resection. However, data

confirm the high accuracy of benign FNA cytology (18, 19) and therefore, provide a reasonable and clinically relevant basis for assigning these nodules as nonmalignant.

In conclusion, these data demonstrate that clinically relevant (≥1 cm) cancerous thyroid nodules grow more often and grow faster than clinically relevant (≥1 cm) benign thyroid nodules. Furthermore, aggressive thyroid cancers demonstrated the fastest growth over time. Conversely, nodules that are stable and especially, those decreasing in size are much more likely to prove benign. Together, these data suggest that thyroid nodule growth (and especially rapid nodule growth) should be reintroduced as an important variable in the evaluation and follow-up of thyroid nodules.

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